PROCEDURA DI VALUTAZIONE COMPARATIVA PER LA STIPULA DI N. 1 CONTRATTO DI DIRITTO PRIVATO PER RICERCATORE A TEMPO DETERMINATO, AI SENSI DELL'ART. 24, COMMA 3, LETT. B) DELLA LEGGE 30 DICEMBRE 2010, N. 240, **- SC 06/D1 - SSD MED/11 (Malattie Dell'apparato Cardiovascolare) Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali**

PRESSO L'UNIVERSITA' DEGLI STUDI DI MESSINA

VERBALE 2

(Valutazione preliminare dei candidati e ammissione alla discussione pubblica)

L'anno 2021 il giorno 22 del mese di Dicembre alle ore 18.30 si riunisce al completo, per via telematica, ognuno nella propria sede universitaria, la Commissione giudicatrice, della valutazione comparativa in epigrafe, nominata con D.R. prot. n. 2698 del **05/11/2021 _,** pubblicato sul sito internet dell'Università di Messina, per procedere alla valutazione comparativa dei titoli, dei curricula e della produzione scientifica dei candidati, ivi compresa la tesi di dottorato.

Sono presenti i sotto elencati commissari:

Prof. A.A. Chetta Università di Parma

Prof. C. Vancheri Università di Catania

Prof. A. Micari Università di Messina

Il Presidente della Commissione comunica che sono trascorsi almeno 7 giorni dalla pubblicizzazione dei criteri e che la Commissione può legittimamente proseguire i lavori.

I componenti accedono, tramite le proprie credenziali, alla piattaforma informatica https://pica.cineca.it/ e prendono visione dell'elenco dei candidati che risultano essere:

1. Francesco Costa
2. Giuseppe Dattilo

Ciascun Commissario rende la dichiarazione in ordine all'insussistenza di situazioni di incompatibilità e di conflitto di interessi con i candidati (Allegato A al presente verbale).

La Commissione dà atto dell'esistenza della dichiarazione da parte dei candidati riguardo l'inesistenza di rapporti di parentela o di affinità, fino al quarto grado compreso, con un professore appartenente al Dipartimento che effettua la chiamata, ovvero con il Rettore, con il Direttore Generale o un componente del Consiglio di Amministrazione dell'Università di Messina.

La Commissione procede quindi alla valutazione dei titoli, dei curricula e della produzione scientifica dei candidati, ivi compresa la tesi di dottorato. Vista la consistenza e numerosità dei titoli da esaminare e valutare non conclude i lavori e si riaggiorna a prossima riunione.

La Commissione viene sciolta alle ore 19,45 e si riconvoca per il giorno 11 Gennaio alle ore 12.30 per la valutazione dei titoli e l'ammissione dei candidati.

Letto approvato e sottoscritto seduta stante.

LA COMMISSIONE

Prof. C.Vancheri (Presidente)

Prof. A.A. Chetta (Componente)

Prof. A. Micari (Segretario)

PROCEDURA DI VALUTAZIONE COMPARATIVA PER LA STIPULA DI N. 1 CONTRATTO DI DIRITTO PRIVATO PER RICERCATORE A TEMPO DETERMINATO, AI SENSI DELL'ART. 24, COMMA 3, LETT. B) DELLA LEGGE 30 DICEMBRE 2010, N. 240, PER IL S.C. _06-D1
PROFILO RICHIESTO S.S.D.MED 11- Malattie dell'Apparato Cardiovascolare
DIPARTIMENTO DI BIOMORF
PRESSO L'UNIVERSITA' DEGLI STUDI DI MESSINA

DICHIARAZIONE INSUSSISTENZA INCOMPATIBILITÀ/ CONFLITTO DI INTERESSI

Il sottoscritto Prof. Carlo Vancheri, presso l'Università degli Studi di Catania, nato a Asti (AT) il 09-05-1957, nominato componente della Commissione per la procedura di selezione in epigrafe, consapevole che chiunque rilascia dichiarazioni mendaci è punito ai sensi del Codice Penale e delle leggi speciali in materia, ai sensi e per gli effetti dell'art. 76 D.P.R. n. 445/2000 - dopo aver preso visione dei nominativi dei candidati alla procedura - dichiara:

☒ di non avere rapporti di parentela e affinità entro il quarto grado con alcuno dei candidati e che non sussistono situazioni di incompatibilità tra il sottoscritto e i candidati, così come previsto dagli artt. 51 e 52 c.p.c.;

☒ che non sussistono abituali situazioni di collaborazione professionale, con comunanza d'interessi economici o di vita di particolare intensità, avente i caratteri della sistematicità, stabilità, continuità tali da dar luogo a sodalizio professionale (delibera ANAC n. 1208 del 22 novembre 2017);

☒ che non sussistono situazioni di collaborazione scientifica tra il sottoscritto e i candidati di intensità tale da porsi in contrasto con il rispetto del principio di imparzialità (delibera ANAC n. 1208 del 22 novembre 2017).

In particolare:

☒ di non avere, in relazione all'ambito scientifico relativo alla selezione in oggetto, pubblicazioni in collaborazione con i seguenti candidati:

- Francesco Costa
- Giuseppe Dattilo

☐ di avere, in relazione all'ambito scientifico relativo alla selezione in oggetto, pubblicazioni in collaborazione con i candidati Francesco Costa e Giuseppe Dattilo in numero tale da non costituire situazione di collaborazione scientifica abituale.

In fede,

DATA 22/12/2021

Allegato: documento d'identità

FIRMA

PROCEDURA DI VALUTAZIONE COMPARATIVA PER LA STIPULA DI N. 1 CONTRATTO DI DIRITTO PRIVATO PER RICERCATORE A TEMPO DETERMINATO, AI SENSI DELL'ART. 24, COMMA 3, LETT. B) DELLA LEGGE 30 DICEMBRE 2010, N. 240, PER IL S.C. _06-D1
PROFILO RICHIESTO S.S.D.MED 11- Malattie dell'Apparato Cardiovascolare
DIPARTIMENTO DI BIOMORF
PRESSO L'UNIVERSITA' DEGLI STUDI DI MESSINA

DICHIARAZIONE INSUSSISTENZA INCOMPATIBILITÀ/ CONFLITTO DI INTERESSI

Il sottoscritto Prof. Alfredo Antonio CHETTA, presso l'Università degli Studi di Parma, nato a Melissano (LE) il 10 novembre 1954, nominato componente della Commissione per la procedura di selezione in epigrafe, consapevole che chiunque rilascia dichiarazioni mendaci è punito ai sensi del Codice Penale e delle leggi speciali in materia, ai sensi e per gli effetti dell'art. 76 D.P.R. n. 445/2000 - dopo aver preso visione dei nominativi dei candidati alla procedura - dichiara:

☑ di non avere rapporti di parentela e affinità entro il quarto grado con alcuno dei candidati e che non sussistono situazioni di incompatibilità tra il/la sottoscritto/a e i candidati, così come previsto dagli artt. 51 e 52 c.p.c.;

☑ che non sussistono abituali situazioni di collaborazione professionale, con comunanza d'interessi economici o di vita di particolare intensità, avente i caratteri della sistematicità, stabilità, continuità tali da dar luogo a sodalizio professionale (delibera ANAC n. 1208 del 22 novembre 2017);

☑ che non sussistono situazioni di collaborazione scientifica tra il/la sottoscritto/a e i candidati di intensità tale da porsi in contrasto con il rispetto del principio di imparzialità (delibera ANAC n. 1208 del 22 novembre 2017).

In particolare:

☑ di non avere, in relazione all'ambito scientifico relativo alla selezione in oggetto, pubblicazioni in collaborazione con i seguenti candidati:

- Francesco Costa
- Giuseppe Dattilo

☐ di avere, in relazione all'ambito scientifico relativo alla selezione in oggetto, pubblicazioni in collaborazione con i candidati Francesco Costa e Giuseppe Dattilo in numero tale da non costituire situazione di collaborazione scientifica abituale.

In fede,

Parma, 28 dicembre '21

FIRMA

Allegato: documento d'identità

DICHIARAZIONE INSUSSISTENZA INCOMPATIBILITÀ/ CONFLITTO DI INTERESSI

Il/La sottoscritto/a Prof. Antonio Micari , presso l'Università degli Studi di Messina, nato/a a Messina il 29/08/1976, nominato/a componente della Commissione per la procedura di selezione in epigrafe, consapevole che chiunque rilascia dichiarazioni mendaci è punito ai sensi del Codice Penale e delle leggi speciali in materia, ai sensi e per gli effetti dell'art. 76 D.P.R. n. 445/2000 - dopo aver preso visione dei nominativi dei candidati alla procedura - dichiara:

x□ di non avere rapporti di parentela e affinità entro il quarto grado con alcuno dei candidati e che non sussistono situazioni di incompatibilità tra il/la sottoscritto/a e i candidati, così come previsto dagli artt. 51 e 52 c.p.c.;

x□ che non sussistono abituali situazioni di collaborazione professionale, con comunanza d'interessi economici o di vita di particolare intensità, avente i caratteri della sistematicità, stabilità, continuità tali da dar luogo a sodalizio professionale (delibera ANAC n. 1208 del 22 novembre 2017);

□ che non sussistono situazioni di collaborazione scientifica tra il/la sottoscritto/a e i candidati di intensità tale da porsi in contrasto con il rispetto del principio di imparzialità (delibera ANAC n. 1208 del 22 novembre 2017).

In particolare:

□ di non avere, in relazione all'ambito scientifico relativo alla selezione in oggetto, pubblicazioni in collaborazione con i seguenti candidati:

- Giuseppe Dattilo

□ di avere, in relazione all'ambito scientifico relativo alla selezione in oggetto, pubblicazioni in collaborazione con i candidati (Francesco Costa) in numero tale da non costituire situazione di collaborazione scientifica abituale.

In fede,

DATA 22/12/2021 FIRMA

Allegato: documento d'identità

DICHIARAZIONE DI CONFORMITA'

Il sottoscritto Prof. C. Vancheri dichiara di avere partecipato, in via telematica, alla riunione tenutasi il 22/12/2021 alle ore 18.30 per lo svolgimento dei lavori della procedura di valutazione comparativa per la stipula di n. 1 contratto di diritto privato per ricercatore, a tempo determinato, per il Settore Concorsuale 06/D1 e per il Settore Scientifico Disciplinare Med 11 bandita dall'Università degli Studi di Messina, ai sensi dell'art. 24, comma 3, lettera B) della legge 30 dicembre 2010, n. 240 e di avere preso parte alla stesura del relativo verbale, aderendo al contenuto dello stesso.

data
22/12/2021

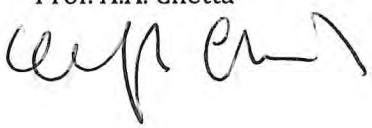
Prof. A. Vancheri

DICHIARAZIONE DI CONFORMITA'

Il sottoscritto Prof. A.A. Chetta dichiara di avere partecipato, in via telematica, alla riunione tenutasi il 22/12/2021 alle ore 18.30 per lo svolgimento dei lavori della procedura di valutazione comparativa per la stipula di n. 1 contratto di diritto privato per ricercatore, a tempo determinato, per il Settore Concorsuale 06/D1 e per il Settore Scientifico Disciplinare Med 11 bandita dall'Università degli Studi di Messina, ai sensi dell'art. 24, comma 3, lettera B) della legge 30 dicembre 2010, n. 240 e di avere preso parte alla stesura del relativo verbale, aderendo al contenuto dello stesso.

data
22/12/2021

Prof. A.A. Chetta



PROCEDURA DI VALUTAZIONE COMPARATIVA PER LA STIPULA DI N. 1 CONTRATTO DI DIRITTO PRIVATO PER RICERCATORE A TEMPO DETERMINATO, AI SENSI DELL'ART. 24, COMMA 3, LETT. B) DELLA LEGGE 30 DICEMBRE 2010, N. 240, **- SC 06/D1 - SSD MED/11 (Malattie Dell'apparato Cardiovascolare) Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali**

PRESSO L'UNIVERSITA' DEGLI STUDI DI MESSINA

VERBALE 2 bis

(Valutazione preliminare dei candidati e ammissione alla discussione pubblica)

L'anno 2021 il giorno 11 del mese di gennaio alle ore 12.30 si riunisce al completo, per via telematica, ognuno nella propria sede universitaria, la Commissione giudicatrice, della valutazione comparativa in epigrafe, nominata con D.R. prot. n. 2698 del **05/11/2021 ,** pubblicato sul sito internet dell'Università di Messina, per procedere alla valutazione comparativa dei titoli, dei curricula e della produzione scientifica dei candidati, ivi compresa la tesi di dottorato.

Sono presenti i sotto elencati commissari:

Prof. A.A. Chetta Università di Parma

Prof. C. Vancheri Università di Catania

Prof. A. Micari Università di Messina

La Commissione procede quindi alla valutazione dei titoli, dei curricula e della produzione scientifica dei candidati, ivi compresa la tesi di dottorato, esprimendo per ciascun candidato, Dott. Francesco Costa e dott. Giuseppe Dattilo un motivato giudizio analitico sui titoli, sul curriculum e sulla produzione scientifica, ivi compresa la tesi di dottorato, sulla base dei criteri stabiliti nella prima riunione (Allegato B al presente verbale). A seguito della valutazione preliminare, sono ammessi alla discussione pubblica i seguenti candidati:

-Dott. Francesco Costa

-Dott. Giuseppe Dattilo

La Commissione viene sciolta alle ore 13,45 e si riconvoca per il giorno 24 Gennaio alle ore 12.30 per la discussione dei titoli e la prova di lingua inglese.

Letto approvato e sottoscritto seduta stante.

LA COMMISSIONE

Prof. C. Vancheri (Presidente)

Prof. A.A. Chetta (Componente)

Prof. A. Micari (Segretario)

ALLEGATO B)

CANDIDATO Francesco Costa

TITOLI E CURRICULUM

Vengono presi in considerazione solo i titoli valutabili secondo i criteri stabiliti durante la prima riunione collegiale in data 22 Dicembre 2022.

a) DOTTORATO DI RICERCA O EQUIPOLLENTI:

• Titolo di Dottore di Ricerca in Scienze Biomediche Cliniche e Sperimentali , conseguito in data 16/11/2020 presso il dipartimento di Scienze Biomediche Cliniche e Sperimentalidell'Università degli Studi di Messina, con una tesi dal titolo "Appraising the counterbalancing ischemia and bleeding risks for dual antiplatelet therapy duration after coronarystenting", relatore Prof. Scipione Carerj (Università degli Studi di Messina).

• Dottorato di Ricerca in "Intravascular imaging and interventional cardiology" l'11/04/2018presso l'Università Erasmus di Rotterdam, Paesi Bassi (Cardiovascular Research SchoolErasmus University Rotterdam – COEUR) con tesi intitolata "Pharmaco-Mechanical Strategiesto Optimize the Balance between Ischemia and Bleeding after Percutaneous CoronaryIntervention". Promotori di tesi dottorale Prof. Felix Zijlstra e Prof. Marco Valgimigli. Tesi didottorato internazionale consultabile presso il repository pubblico dell'Erasmus University di Rotterdam all'indirizzo: https://repub.eur.nl/pub/105339/. Il titolo di "Doctor-PhD" conseguito presso l'università estera stato riconosciuto equipollente al titolo di Dottore di Ricerca dell'ordinamento Universitario Italiano giorno 29/01/2019 dal Ministero dell'Istruzione, dell'Università e della Ricerca (Certificazione del titolo e Decreto di Equipollenza in allegato).

b) DIPLOMA DI SPECIALIZZAZIONE MEDICA O EQUIVALENTE:

- Diploma di specializzazione medica in Malattie dell'apparato cardiovascolare, conseguito in data 11/07/2017 presso l'Università degli Studi di Messina , con una tesi dal titolo "GENESI E VALIDAZIONE DI UN NUOVO SCORE PER PREDIRE IL SANGUINAMENTO IN PAZIENTISOTTOPOSTI AD IMPIANTO DI STENT SEGUITO DA DOPPIA TERAPIA ANTIAGGREGANTE: IL PRECISE-DAPT SCORE ", relatore Prof. Giuseppe Oreto (Università degli Studi di Messina);

c) ATTIVITA' DIDATTICA A LIVELLO UNIVERSITARIO IN ITALIA O ALL'ESTERO:

• Seminario "Evidence supporting the use of Clopidogrel or Prasugrel" del Dipartimento COEUR di Cardiologia e Ricerca Cardiovascolare dell'Università di Rotterdam (27-03- 2015). I seminari sono parte delle attività didattiche per gli studenti del corso di dottorato COEUR e per gli specializzandi in cardiologia.

• Seminario internazionale "Heart and Lung Research Seminars" dell'Università di Messina (24-09-2021). I seminari sono parte delle attività didattiche agli studenti del corso di dottorato internazionale in Medicina e Chirurgia Molecolare Traslazionale e per gli specializzandi di cardiologia e pneumologia.

• Corso di lezioni sul "Trattamento Antitrombotico in Cardiologia" per gli specializzandi in malattie dell'apparato cardiovascolare dell'Università di Messina in collaborazione con il Prof. S. Carerj (AA 2019-2020 e 2020-2021).

• Corso di lezioni in malattie dell'apparato cardiovascolare per gli studenti del corso di laurea in Odontoiatria dell'Università di Messina in collaborazione con il Prof. S. Carerj (AA 2019-2020 e 2020-2021).

• Corso di lezioni in malattie dell'apparato cardiovascolare per gli studenti del corso di laurea in Scienze Infermieristiche dell'Università di Messina in collaborazione con il Prof. S. Carerj (AA 2019-2020 e 2020-2021).

• Co-relatore Tesi Sperimentale di Laurea in Medicina e Chirurgia, Dott. Sara Gulli in collaborazione con il Prof. G. Basile presso l'Università di Messina AA 2020-2021. La tesi di laurea intitolata "Sindrome Coronarica Acuta nell'Anziano in Epoca COVID-19".

• Co-relatore Tesi Sperimentale di Laurea in Medicina e Chirurgia, Dott. Claudio Nicol in collaborazione con il Prof. A. Micari presso l'Università di Messina AA 2020-2021. La tesi di laurea intitolata "Impatto della Sindrome Coronarica Acuta nei Pazienti Giovani".
d) DOCUMENTATA ATTIVIT DI FORMAZIONE O DI RICERCA PRESSO QUALIFICATI ISTITUTI ITALIANI O STRANIERI:
• Research Fellowship da Luglio 2014 ad Agosto 2015 in Cardiologia Interventistica presso il Thoraxcenter, Erasmus Medical Center (Tutor Prof. Valgimigli e Prof. Zijlstra), Rotterdam, Olanda.
• Fellowship clinica in cardiologia interventistica da Dicembre 2015 a Settembre 2016 presso l'Ospedale Umberto I di Siracusa (Tutor Dott. M. Contarini), Italia.
• Research Fellowship da Settembre 2016 a Dicembre 2016 in Cardiologia Interventistica presso Inselspital, Bern University (Tutor Prof. Valgimigli), Berna, Svizzera.
• Fellowship clinica in cardiologia interventistica da Gennaio 2017 a Luglio 2017. presso l'Hospital Virgen de la Victoria Malaga (Tutor Dott. Alonso-Briales), Spagna.
• Fellowship clinica in cardiologia interventistica da Settembre 2017 a Settembre 2018 presso l'Hospital Clinic Barcelona (Tutor Prof. M. Sabat), Spagna.
• Master Universitario in Competenze Mediche Avanzate, Specialità in Trattamento Endoluminale Cardiaco e Vascolare, a Settembre 2018 presso l'Università di Barcellona, Spagna.
• Corso "ICH Good Clinical Practice E6" presso la Global Health Network. 26/09/2017.
• Corso "Statistics in Medicine" presso la Stanford University, CA United States of America.
• Corso "Introduction to Public Speaking" presso la Università of Washington, Seattle, United States of America. Online.
• Corso "Introduction to Negotiation" Universit di Yale, United States of America. Online.
• Internship clinica da Ottobre 2009 a Novembre 2009 presso il reparto di Medicina al Krankenhaus der barmherzigen brüder (Direttore: Prof A. Wechsler), Technische Universitat München, Monaco di Baviera, Germania.
• Internship clinica dal 2 al 30 Settembre 2010 presso il reparto di Cardiologia Virginia Commonwealth University (Direttore: Prof J. Davia), Richmond, U.S.A.
• Intership clinica da Ottobre 2010 a Novembre 2010 presso il reparto di Cardiochirurgia della clinica Padurea Verde (Direttore: Prof. M. Gaspar), Timišoara, Romania.
• Internship clinica dal 5 Settembre al 23 Settembre 2011 in Terapia Intensiva Cardiologiae Laboratorio di Imaging presso gli Spitali Civili (Directore: Prof L. Dei Cas), Brescia,Italia
• Corsi di perfezionamento in cardiologia e cardiologia interventistica: American Collegeof Cardiology congress 2019, NEW ORLEANS, UNITED STATES OF AMERICA.
• Corsi di perfezionamento in cardiologia interventistica: JIM GISE Fellow-Course 2018,Milano, Italia.
• Corsi di perfezionamento in cardiologia interventistica: JIM 2018, Milano, Italia.
• Corsi di perfezionamento in cardiologia interventistica: CTO Course 2018, Barcelona,Spain.
• Corsi di perfezionamento in cardiologia e cardiologia interventistica: American College of Cardiology congress 2016, CHICAGO, UNITED STATES OF AMERICA.• Corsi di perfezionamento in cardiologia interventistica: C3 congress of interventional cardiology 2018, ORLANDO, UNITED STATES OF AMERICA.
• Corsi di perfezionamento in cardiologia interventistica: EuroPCR congress 2015, PARIS,FRANCE.
• Corsi di perfezionamento in cardiologia interventistica: EuroPCR congress 2016, PARIS, FRANCE.
• Corsi di perfezionamento in cardiologia interventistica: EuroPCR congress 2017, PARIS,FRANCE.
Corsi di perfezionamento in cardiologia interventistica: fellow course EAPCI 2017,PARIS, FRANCE.
• Corsi di perfezionamento in cardiologia interventistica: EuroPCR congress 2018, PARIS,FRANCE.
• Corsi di perfezionamento in cardiologia: European Society of Cardiology congress 2017,BARCELONA, SPAIN.
• Corsi di perfezionamento in cardiologia: European Society of Cardiology congress 2018,MUNICH, SPAIN.
• Corsi di perfezionamento in cardiologia interventisica: PCR Peripheral congress 2016,MILANO, ITALIA
• Corsi di perfezionamento in cardiologia interventistica: SCAI Fellow Course 2016, LASVEGAS, UNITED STATES OF AMERICA.

• Corsi di perfezionamento in cardiologia: Oral Antiplatelet Therapies for Acute CoronarySyndromes: State-of-the- Art Management, 2014. Online.
(Documenti allegati: Allegato B pagina 18)

e) DOCUMENTATA ATTIVITA' IN CAMPO CLINICO RELATIVAMENTE AI SC NEI QUALI SONO RICHIESTE TALI SPECIFICHE COMPETENZE:
• Dirigente Medico Cardiologo presso le UOC UTIC e UOSD Cardiologia Interventistica del A.O.U. Policlinico Universitario Gaetano Martino di Messina a tempo pieno dal 1/11/2018. Posizione attualmente ricoperta.
• Specializzazione in Malattie dell'Apparato Cardiovascolare da Luglio 2012 a Luglio 2017
• Master Universitario in Competenze Mediche Avanzate, Specialit in Trattamento Endoluminale Cardiaco e Vascolare, a Settembre 2018 presso l'Universit di Barcelona, Spagna.
(Documenti allegati: Allegato A pagina 5-6)
• Fellowship clinica in cardiologia interventistica presso l'Hospital Clinic Barcelona, Spagna da Settembre 2017 a Settembre 2018.
(Documenti allegati: Allegato A pagina 7-9)
• Fellowship clinica in cardiologia interventistica presso l'Hospital Virgen de la Victoria Malaga, Spagna da Gennaio 2017 a Luglio 2017.
• Fellowship clinica in cardiologia interventistica presso l'Ospedale Umberto I di Siracusa da Dicembre 2015 a Settembre 2016.
(Documenti allegati: Allegato A pagina 10-11)

f) REALIZZAZIONE DI ATTIVITA' PROGETTUALE RELATIVAMENTE AI SC NEI QUALI PREVISTA:
1. Investigatore principale dello studio internazionale PRECISE-DAPT.
2. Investigatore principale e coordinatore scientifico del registro web-based internazionale PRECISE-DAPT. Creazione della piattaforma Web e delle mobile app per il calcolo dello score di rischio PRECISE-DAPT (http://www.precisedaptscore.com/).
3. Investigatore principale e coordinatore dello studio Rotterdam Radial Access Research (R-RADAR). Lo studio stato condotto presso il Thorax center, Erasmus Medical Center dell'Università di Rotterdam, Paesi Bassi.
4. Coordinatore del progetto d'impresa "Cardio App Device" in collaborazione con il Prof. Scipione Carerj,
5. Investigatore principale dello studio prospettico monocentrico BETA-MI presso il Policlinico G. Martino dell'Università di Messina.
6. Investigatore principale dello studio monocentrico YOUNG-MI presso il Policlinico G. Martino dell'Università di Messina.
7. Collaborazione al coordinamento internazionale dello studio randomizzato Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX (MATRIX): coordinamento dell'arruolamento, follow-up e gestione dei dati per il centro di Rotterdam (Paesi Bassi), Zwolle (Paesi Bassi) e Goteborg (Svezia) con i rispettivi PI locali (Marco Valgimigli,
8. Investigatore e coordinamento locale dell'arruolamento e del follow-up del trial clinico randomizzato SUGAR (Second-generatio drUg-elutinG stents in diAbetes: a Randomized trial). (Identifier: SEC-SUG-2016-01) presso l'Hospital Clinic di Barcellona (Spagna) dal 01-09-2017 al 28-03-2018
9. Investigatore e coordinamento locale dell'arruolamento e del follow-up del trial clinico ExoFIS - miRNA (Potential prognostic and therapeutic role of exosomal miRNAs derived from circulating cells in acute coronary syndrome – PI16/00742) presso l'Hospital Clinic di Barcellona (Spagna) dal 01-09-2017 al 31-08-2018
10. Investigatore e coordinamento locale dell'arruolamento e del follow-up del trial clinico internazionale randomizzato GALILEO (A Global Study Comparing a rivAroxaban—based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes). (ClinicalTrials.gov Identifier:

NCT02556203) presso l'Hospital Clinic di Barcellona (Spagna) dal 13-09-2017 al 31-08-2018.
11. Investigatore e coordinamento locale dell'arruolamento e del follow-up del trial clinico internazionale randomizzato AUGUSTUS (An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention)(ClinicalTrials.gov Identifier: NCT02415400) presso l'Hospital Clinic di Barcellona (Spagna) dal
dal 29-11-2017 al 31-08-2018.
12. Investigatore e coordinamento locale dell'arruolamento e del follow-up del trial clinico BIOFREEDOM PK (Biofreedom PK study in patients with CAD who receive the biofreedom Biolimus A9 stent) presso l'Hospital Clinic di Barcellona (Spagna) dal 09-03-2018 al 28-03-2018

g) ORGANIZZAZIONE, DIREZIONE E COORDINAMENTO DI GRUPPI DI RICERCA NAZIONALI E INTERNAZIONALI, O PARTECIPAZIONE AGLI STESSI:
• Coordinatore del gruppo di ricerca internazionale PRECISE-DAPT insieme al Prof. Marco Valgimigli (Università della Svizzera Italiana, Lugano, Svizzera).
• Membro della Task Force per la stesura delle Linee Guida Europee per la Societ Europea di Cardiologia (ESC) e la società Europea di Chirurgia Cardio-toracica (EACTS): focused update on Dual Antiplatelet Therapy in patients with coronary artery disease 2017.
• Membro del gruppo di ricerca internazionale dell'Academic Research Consortium (ARC), in collaborazione con European Cardiovascular Research Institute (ECRI) e la U.S. Food and Drug Administration (FDA), per la task-force sulla non-aderenza terapeutica nelle malattie cardiovascolari (Non-Adherence Academic Research Consortium - NARC).

• Coordinatore di un gruppo di ricerca traslazionale presso l'Università di Messina in collaborazione con il Prof. F. Squadrito e la Dott.ssa N. Irrera del dipartimento di Medicina Clinica e Sperimentale, UOC Tossicologia, Università di Messina.
• Membro del gruppo di ricerca internazionale coordinato dal Dott. Francesco Giannini del GVM Maria Cecilia Hospital di Cotignola.
• Coordinatore di multipli sotto studi nel gruppo di ricerca internazionale del trial randomizzato PRODIGY guidato dal Prof. Marco Valgimigli (Università della Svizzera Italiana, Lugano, Svizzera) (ClinicalTrials.gov NCT00611286)
• Membro del gruppo di ricerca internazionale nell'ambito del trial randomizzato ZEUS (ClinicalTrials.gov NCT01385319) guidato dal Prof. Marco Valgimigli (Università della Svizzera Italiana, Lugano, Svizzera)
• Membro del gruppo di ricerca internazionale coordinato dal Prof. Matthrew Roe ed il Dott. Guillaume Marquis Gravel (Università Duke, Duhram, USA)
• Coordinatore del gruppo di ricerca internazionale insieme al Prof. Christopher Cannon (Harvard University, Boston, Stati Uniti) per lo studio di validazione del PRECISE-DAPT score
• Membro del gruppo di ricerca internazionale coordinato dal Prof. Patrick Serruys (Imperial College London, London, United Kingdom), Prof. Stephan Windecker (Universit di Berna, Svizzera) e Prof. Hector Manuel Garcia-Garcia (Università di Georgetown, Washington DC, USA) nell'ambito degli studi clinici SYNTAX (ClinicalTrials.gov NCT00114972) RESOLUTE (ClinicalTrials.gov NCT01443104) e LEADERS (ClinicalTrials.gov NCT00617084)
• Membro del gruppo di ricerca internazionale coordinato dal Prof. Pierluigi Tricoci, il Prof Kenneth Mahaffey (Università Duke, Duhram, USA) ed il Prof Marco Valgimigli (Universit della Svizzera Italiana, Lugano, Svizzera) nell'ambito dello studio clinico TRACER (ClinicalTrials.gov NCT00527943)
• Coordinatore del sottostudio nell'ambito del trial clinico internazionale randomizzato

EXAMINATION (ClinicalTrials.gov NCT00828087) guidato dal Prof. Manel Sabat (Universit di Barcellona, Spagna)
• Coordinazione del gruppo di ricerca nazionale con il Prof. Sergio Leonardi ed il Dott. Marco Ferlini dell'Universit di Pavia.
• Collaborazione scientifica con il Dott. Pierre Sabouret dell'Università Sorbonne di Parigi da Gennaio 2019 ad oggi.
• Membro del gruppo di ricerca internazionale coordinato dal Dott. Fabrizio D'Ascenzo dell'Universit Vita e Salute di Torino nell'ambito del registro multicentrico RAIN (veRy thin stents for patients with left mAIn or bifurcatioN in real life)
• Membro del gruppo di ricerca internazionale della societ europea di cardiologia interventistica (EAPCI) ed il European bifurcation club (EBC) coordinato dal Dott. M. Zimarino per la stesura del documento di consenso riguardante la terapia antitrombotica ottimale dopo angioplastica coronarica per lesioni in biforcazione.
• Coordinatore del gruppo dei giovani interventisti italiani afferenti all'European Association of Percutaneous Cardiovascular Intervention (EAPCI) come EAPCI National Ambassador per l'Italia dal 01-01-2016 al 01-01-2018.
• Membro del gruppo di ricerca nazionale della società italiana di cardiologia interventistica coordinato dal Prof. Giuseppe Tarantini (Università di Padova) ed il Dott. Francesco Saia (Università di Bologna, Italia) focalizzato alla definizione dei criteri di una certificazione nazionale in cardiologia interventistica.
• Membro del gruppo di ricerca internazionale coordinato dal Prof. Harvey White (Aukland city hospital, Nuova Zelanda) ed il Prof Marco Valgimigli (Università della Svizzera Italiana, Lugano, Svizzera) nell'ambito dello studio clinico PRISM
• Partecipazione alle attivit di ricerca di un gruppo di ricerca con collaborazioni a livello nazionale e internazionale: IDIBAPS dell'Università degli studi di Barcellona, dal 01-09-2017 al 01-09-2018.

h) TITOLARITA' DI BREVETTI RELATIVAMENTE AI SETTORI CONCORSUALI NEI QUALI PREVISTA:
_non valutabile_____

i) RELATORE A CONGRESSI E CONVEGNI NAZIONALI E INTERNAZIONALI:
• Relatore al Congresso internazionale dell'American College of Cardiology (San Diego, United States of America 2015): "Impact of Clinical Presentation on Ischemic and Bleeding Outcomes in Patients Receiving 6 or 24 Month Duration of Dual Antiplatelet Therapy After Stent Implantation. A Pre-specified Analysis From the (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) PRODIGY Trial" (2015) dal 15-03-2015 al 15-03-2015.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2015): "Rotterdam radial access research: echo-based radial artery evaluation for diagnostic and therapeutic coronary procedures: the R-RADAR study" (2015) dal 20-05-2015 al 20-05-2015.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2015) Hot Line Session: "Anatomical location and bleeding risk as potential drivers of DAPT duration: insights from PRODIGY trial." (2015) dal 21-05-2015 al 21-05-2015.
• Relatore al Congresso nazionale della Societ Italiana di Cardiologia (Roma, Italia 2015): "Impact of Clinical Presentation on Ischemic and Bleeding Outcomes in Patients Receiving 6 or 24 Month Duration of Dual Antiplatelet Therapy After Stent Implantation" (2015) dal 13-12-2015 al 13-12-2015.
• Relatore al Congresso internazionale dell'American College of Cardiology (Chicago, United States of America 2016): "Tradeoff Between Myocardial Infarction Versus Bleeding Types on Mortality After Acute Coronary Syndrome: Lessons From the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary

Syndrome (TRACER) Randomized Trial" (2016) dal 03-04-2016 al 03-04-2016.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2016): "Impellent Impeller" (2016) dal 15-05-2016 al 15-05-2016.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2016): "Impact of greater than 12-month DAPT duration on mortality: drug specific or a class- effect?" (2016) dal 15-05-2016 al 15-05-2016.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2016): "Impact of protonpump inhibitors on clinical outcomes in patients treated with a six-month or 24-month DAPT duration: insights from the PRODIGY trial" (2016) dal 20-05-2016 al 20-05-2016.
• Relatore al Congresso nazionale dell'Associazione Nazionale Medici Cardiologi Ospedalieri ANMCO (Rimini, Italia 2016): "Il valore incrementale del crusade risk score nella predizione di eventi emorragici in pazienti trattati con una doppia terapia antiaggregante di 6 o 24 mesi dopo stenting coronarico." (2016) dal 03-06-2016 al 03-06-2016.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia Interventistica GISE (Genova, Italia 2016): "Il ruolo dell'ambasciatore EAPCI Young" (2016) dal 14-10-2016 al 14-10-2016.
• Relatore al Congresso nazionale della Societ Italiana di Cardiologia sezione Sicilia (Messina, Italia 2016): "Tradeoff Between Myocardial Infarction Versus Bleeding Types on Mortality After Acute Coronary Syndrome." (2016). Vincitore Premio Giovane Ricercatore dal 19-11-2016 al 19-11-2016.
• Faculty e Relatore al congresso internazionale Cardiology in Practice 2017 What to know and how to apply knowledge (Madrid, Spain 2017). "One valve more, two vessels less" (2017) dal 24-02-2017 al 24-02-2017.
• Faculty al Congresso nazionale della Societ Italiana di Cardiologia Interventistica ThinkHeart GISE (Firenze, Italia 2017) dal 20-04-2017 al 21-04-2017.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2017): "A novel risk score to predict out-of-hospital bleeding on DAPT" (2017) dal 16-05-2017 al 16-05-2017.
• Faculty al Congresso internazionale European Society of Cardiology (Barcelona, Spain 2017) dal 26-08-2017 al 30-08-2017.
• Faculty e Live Operator al Congresso internazionale Coronary and Structural Course (CSC) 2017 Madrid, Live from H.Clinic Barcelona Session: "Left main stenting"
o Operatori: Ana Mar a Serrador Frutos, Victoria Martin Yuste and Francesco Costa
o dal 01-10-2017 al 01-10-2017
• Faculty e Live Operator al Congresso internazionale Coronary and Structural Course (CSC) 2017 Madrid, Live from H.Clinic Barcelona Session: "Left atrial appendage occlusion" Operators: Ignacio Cruz Gonz lez, Ander Regueiro Cueva and Francesco Costa dal 02-10-2017 al 02-10-2017.
• Faculty al Congresso nazionale della Societ Italiana di Cardiologia Interventistica GISE (Genova, Italia 2017) dal 10-10-2017 al 13-10-2017.
• Faculty e Relatore al Congresso nazionale TaoHeart 2.1 (Giardini Naxos, Italy 2017): "Il rischio cardiovascolare dopo sindrome coronarica acuta, luci ed ombre" (2017).
o dal 10-11-2017 al 10-11-2017.
• Faculty e Relatore al Congresso nazionale Italian Society of Cardiology Regional Congress (Catania, Italy 2017): "DAPT a lungo termine in pazienti con pregresso infarto del miocardio" (2017) dal 17-11-2017 al 17-11-2017.
• Faculty e relatore al Congresso internazionale Ischemic Heart Disease 2018 International Symposium (Santiago de Compostela, Spain 2018): "Las guias ESC 2017 contadas por los protagonistas (DAPT)" (2018) dal 21-04-2018 al 21-04-2018.
• Faculty e relatore al Congresso internazionale Ischemic Heart Disease 2018 International Symposium (Santiago de Compostela, Spain 2018): "Individualizar el periodo de DAPT tras PCI en SCA: el PRECISE-DAPT score." (2018) dal 21-04-2018 al 21-04-2018.

• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2018): "Global use and implementation of the PRECISE-DAPT score in clinical practice in 2017. A website and mobile app based survey" (2018) dal 23-05-2018 al 23-05-2018.
• Relatore al Congresso internazionale EuroPCR (Parigi, Francia 2018): "Does large vessel size still justify the use of BMS for PCI? Insights from the EXAMINATION trial" (2018) dal 24-05-2018 al 24-05-2018.
• Relatore al Congresso internazionale European Society of Cardiology (Munich, Germany 2018): "Exploring the value of the PRECISE-DAPT score after complex percutaneous coronary intervention to inform dual antiplatelet therapy duration decision-making." (2018). Vincitore del premio miglior poster-moderato (PDF allegato) dal 28-08-2018 al 28-08-2018.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia Interventistica GISE (Milano, Italia 2018): "My experience as a Member of the PCRonline Editorial Team" (2018) dal 16-10-2018 al 19-10-2018.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia (Roma, Italia 2018): "Triple vs dual antithrombotic therapy" (2018) dal 14-12-2018 al 17-12-2018.
• Faculty al Congresso internazionale Change in Cardiology (Torino, Italia 2019).
o dal 17-01-2019 al 19-01-2019.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia SIC (Roma, Italia, 2019) “DAPT dopo SCA per quanto tempo e per quali pazienti”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia Interventistica GISE (Milano, Italia, 2019) “Is it possible to stop antiplatelet agents 12 months after PCI?”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia SIC (Roma, Italia, 2019) “Quando sospendere l’aspirina dopo la PCI”.
Faculty e Relatore al Webinar Internazionale della Societ Europea di Terapia Intensiva Cardiologica ACCA (Nizza, Francia, 2020) “Decision-making principles of dual antiplatelet therapy duration in acute coronary syndrome”.
• Relatore al Congresso internazionale American Heart Association (Philadelphia, USA 2019) "Triple Antithrombotic Therapy With Warfarin or Dual Therapy With Dabigatran According to the Precise-Dapt Score in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: Insights From the Re-Dual Pci Trial".
• Faculty e Relatore al Congresso nazionale Transcatheter Innovations in Practice (Web 2020) “Long term Antiplatelet therapy is mandatory in the vast majority of MI patients”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia Interventistica GISE (Web 2020) “Long term DAPT clinical trials and guidelines”.
• Faculty e Relatore al Congresso nazionale della Consulta delle Societ Cardiologiche HCF,ANMCO, AICPR, SIMG, SIT (Web 2020) “L’importanza della DAPT a lungo termine: novit dalle Linee Guida ESC 2019”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia SIC (Web 2020) “Pazienti NSTEMI niente pi pretrattamento?”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia SIC (Web 2020) “Short DAPT, long DAPT, monoterapia, de-escalation dopo angioplastica percutanea: come orientarsi alla luce degli ultimi trial clinici”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia SIC (Web 2020) “I farmaci antiaggreganti iniettabili”.
• Faculty e Relatore al Congresso nazionale della Societ Italiana di Cardiologia SIC (Web 2020) “Paziente con SCA intollerante alle statine”.
• Faculty e Relatore al Congresso nazionale “Fibrillazione atriale discutiamone con..” (Web 2021) relazione “il paziente con fibrillazione atriale e SCA sottoposto a PCI”.
• Presentazione di poster al Congresso internazionale dell'American College of Cardiology (San Diego, United States of America 2015): "Exploring the Incremental Value of CRUSADE Score as Clinical Guidance for the Decision-Making of Dual Antiplatelet

Therapy Duration. A Retrospective Analysis From the (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) PRODIGY Trial" (2015) dal 16-03-2015 al 16-03-2015.
• Presentazione Poster al congresso internazionale American College of Cardiology (San Diego, United States of America 2015) “Exploring the Incremental Value of CRUSADE Score as Clinical Guidance for the Decision-Making of Dual Antiplatelet Therapy Duration. A Retrospective Analysis From the (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) PRODIGY Trial
• Presentazione Poster al congresso internazionale: EuroPCR (Paris, France 2015). Impact of a 24 ratherthan 6-month DAPT with clopidogrel in patients with left main or proximal left anterior descending coronary artery disease: a post hoc analysis from the PRODIGY trial.
• Presentazione Poster al congresso nazionale: ANMCO (Rimini, Italy 2016) La presentazione clinica al momento dello stenting coronarico come fattore determinante la durata della doppia terapia antiaggregante.
• Presentazione Poster al congresso internazionale: EuroPCR (Paris, France 2018) “Global use and implementation of the PRECISE-DAPT score in clinical practice in 2017. A website and mobile app based survey”.
• Presentazione Poster al congresso internazionale: American College of Cardiology (New Orleans, United States of America 2019) “Comparison of bleeding risk prediction models with dual anti-platelet therapy treatment among patients with acute coronary syndromes treated medically without revascularization.”
j) PREMI E RICONOSCIMENTI NAZIONALI E INTERNAZIONALI PER ATTIVIT DI RICERCA:
1. Nominato Young National Ambassador per l'Italia della societ Europea di interventistica cardiaca percutanea (EAPCI) per il biennio 2016-2018.
dal 01-01-2016 al 01-01-2018
(Documenti allegati: Allegato A pagina 16)
2. Vincitore del premio Unime Start Cup 2016 (Messina, Italy 2016) per il progetto di impresa pi innovativo nella competizione Start Up: “Cardio App Device”
(Documenti allegati: Allegato A pagina 17)
3. Vincitore del premio del Consorzio Universitario Siciliano StartCup 2016 (Palermo, Italia 2016) per il progetto di impresa pi innovativo nella competizione Start Up: “Cardio App Device” con particolare menzione per l'impatto sociale. (Documenti allegati: Allegato A pagina 18)
4. Invitato per la fase finale del premio nazionale dell’innovazione 2016 nella categoria Lifescience PNI Cube e Universit di Modena (Modena, Italy 2016) con il progetto “Cardio App Device”.
(Documenti allegati: Allegato A pagina 19)
5. Finalista nazionale nel concorso Premio Giovane Ricercatore della Societ Italiana di Cardiologia (SIC) (Roma, Italy 2015).
6. Vincitore premio Giovane Ricercatore della Societ Italiana di Cardiologia (SIC) sezione Sicilia. (Messina, Italia 2016) il 19-11-2016
(Documenti allegati: Allegato A pagina 20)
7. Vincitore del training grant della societ Europea di Cardiologia (ESC) anno 2017.
(Documenti allegati: Allegato A pagina 21)
8. Vincitore del research and training grant della societ Europea di interventistica percutanea cardiaca (EAPCI) anno 2017
(Documenti allegati: Allegato A pagina 22)
9. Vincitore del premio per il miglior poster-moderato al congresso internazionale della Societ Europea di Cardiologia (ESC): "Exploring the value of the PRECISE-DAPT score after complex percutaneous coronary intervention to inform dual antiplatelet therapy duration decision-making". dal 25-08-2018 al 29-08-2018
(Documenti allegati: Allegato A pagina 23)
10. Nominato Fellow della Societ Europea di Cardiologia (FESC) per meriti scientifici

(Scientific Excellence Track - 2019) (Parigi, Francia, 2019)
(Documenti allegati: Allegato A pagina 24)
11. Nominato Fellow della Societ Italiana di Cardiologia (SIC) (Roma, Italia, 2019)
(Documenti allegati: Allegato A pagina 25)
12. Abilitazione Scientifica Nazionale a Professore di II Fascia per il Settore Concorsuale 06/D1 Malattie dell'Apparato Cardiovascolare e Malattie dell'Apparato Respiratorio (dal 02/09/2019 al 02/09/2028) da parte del Ministero dell'Istruzione, Universit e Ricerca (MIUR).
k) DIPLOMA DI SPECIALIZZAZIONE EUROPEA RICONOSCIUTO DA BOARD INTERNAZIONALI, RELATIVAMENTE A QUEI SETTORI CONCORSUALI NEI QUALI PREVISTA:

L) autore di 72 pubblicazioni valutabili , indexate. Tutte valutabili. Allegato 1

MOTIVATO GIUDIZIO ANALITICO SUI TITOLI, SUL CURRICULUM E SULLA PRODUZIONE SCIENTIFICA IVI COMPRESA LA TESI DI DOTTORATO

GIUDIZI INDIVIDUALI

Prof. A.A.Chetta

Ial Candidato Francesco Costa ha conseguito la Laurea e il titolo di Dottorato di Ricerca presso l'Università degli studi di Messina. La tesi di Dottorato è stata giudicata totalmente coerente con il SSD MED/11. Il Candidato ha comunque svolto periodi di studio e Ricerca presso qualificati Enti di Ricerca all'estero migliorando la sua formazione verso il Settore delle Malattie Cardiovascolari.
La produzione scientifica risulta ottima, testimoniata da 72 pubblicazioni ISI coerenti con il settore concorsuale.
Ha svolto attività didattica certificata, anche all'estero.
Le tematiche della ricerca sono congruenti con il SSD MED/11 e l'IF risulta di ottimo livello, con un H index di 20.
Si evince una buona autonomia nell'attività di ricerca, testimoniata dalla posizione di primo ultimo o autore corrispondente nella maggior parte dei lavori presentati.
Il candidato risulta pertanto idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale della lingua inglese, ai fini della presente valutazione comparativa.

Prof. C. Vancheri

Il Dott. Francesco Costa si è laureato in Medicina e chirurgia all'Università di Messina e ha conseguito il Titolo di Dottore di Ricerca in Scienze Biomediche Cliniche e Sperimentali , conseguito in data 16/11/2020 presso il dipartimento di Scienze Biomediche Cliniche e Sperimentali dell'Università degli Studi di Messina, con una tesi dal titolo "Appraising the counterbalancingischemia and bleeding risks for dual antiplatelet therapy duration after coronarystenting", relatore Prof. Scipione Carerj (Università degli Studi di Messina).
Ha presentato 72 pubblicazioni su riviste internazionali con Impact Factor, numerose comunicazioni e poster a congressi nazionali e internazionali, in cui ha partecipato anche come relatore e o faculty.
L'IF delle riviste risulta di buon livello con un H index pari a 20 con numero totale di citazioni 3347
Ha una discreta attività di didattica.
Il Candidato ha una buona autonomia di nell'attività di ricerca.
Il candidato risulta pertanto idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale della lingua inglese, ai fini della presente valutazione comparativa.

Prof.Antonio Micari

Il Dott. Francesco Costa si è laureato in Medicina e chirurgia all'Università di Messina e ha conseguito il Titolo di Dottore di Ricerca in Scienze Biomediche Cliniche e Sperimentali , conseguito in data 16/11/2020 presso il dipartimento di Scienze Biomediche Cliniche e Sperimentali dell'Università degli Studi di Messina, con una tesi dal titolo "Appraising the counterbalancingischemia and bleeding risks for dual antiplatelet therapy duration after coronarystenting".

Ha presentato 72 pubblicazioni su riviste internazionali, numerose comunicazioni e poster a congressi nazionali e internazionali, in cui ha partecipato anche come relatore e o faculty.

L'IF delle riviste risulta di buon livello con un H index pari a 20 con numero totale di citazioni 3347

Ha svolto una discreta attività di didattica.

Il Candidato ha una ottima autonomia di nell'attività di ricerca.

Il candidato risulta pertanto idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale della lingua inglese, ai fini della presente valutazione comparativa.

GIUDIZIO COLLEGIALE

Il candidato Francesco Costa ha conseguito la laurea e il Dottorato di Ricerca congruenti con il SSD MED/11. Ha svolto attività di ricerca sia in Italia che all'estero, riuscendo a realizzare numerose collaborazioni. L'attività di ricerca è documentata da un congruo numero di pubblicazioni su riviste internazionali ottenendo un buon indice bibliometrico cosi come da citazioni.

L'attività didattica è stata svolta nell'ambito delle discipline del SSD MED/11.

La Commissione sulla base dei giudizi individuali espressi, giudica il candidato, ai fini della presente valutazione comparativa, idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale che accerti la conoscenza della lingua inglese.

CANDIDATO Giuseppe Dattilo

TITOLI E CURRICULUM

Vengono presi in considerazione solo i titoli valutabili secondo i criteri stabiliti durante la prima riunione collegiale in data 22 Dicembre 2022.

a) DOTTORATO DI RICERCA O EQUIPOLLENTI:

• Dottorato di Ricerca presso l'Università Degli Studi di Messina, Facolt di Medicina e Chirurgia in "Metodologie e Tecniche di Imaging Cardiovascolare" il 28/03/09 con discussione tesi in < Un nuovo approccio diagnostico non invasivo nello studio della cardiopatia ischemica: Ecostress-Dipiridamolo associato a 2D Strain versus TC Coronarica > Tutor: Prof S. Carerj. Coordinatore: Prof F. Arrigo

b) DIPLOMA DI SPECIALIZZAZIONE MEDICA O EQUIVALENTE:

- Specializzazione quadriennale in Cardiologia, ai sensi del D. Lgs 08-08-1991 n 257, il 27 Ottobre 2005 presso l'Universit degli Studi di Messina, Direttore Professore Giuseppe Oreto, con votazione 50 e lode/50; tesi di specializzazione: Un nuovo Test nello studio della Cardiopatia Ischemica: Test Ecodobutamina-Handgrip. Risultati preliminari , relatore Prof. Scipione Carerj.

c) ATTIVITA' DIDATTICA A LIVELLO UNIVERSITARIO IN ITALIA O ALL'ESTERO:

• Collaboratore nelle Lezioni Frontali e Docente nelle Lezioni Professionalizzanti del Corso integrato di Malattie Cardiovascolari e Respiratorie nell'anno accademico 2005/06, 2006/07 e 2007/08 presso Università degli Studi di Messina, Facoltà di Medicina e Chirurgia, Corso di Laurea in Medicina e Chirurgia.

- Docente a Corsi di Ecocardiografia: ETT, ETE, Eco-Stress, TCD (Accreditati ECM) svolti nei mesi di Giugno e Luglio 2007 e nei mesi di Ottobre e Novembre presso U.O.S. di Diagnostica Strumentale Cardiovascolare non Invasiva, Università degli Studi di Messina, Facoltà di Medicina e Chirurgia, Policlinico Universitario G. Martino Messina
- Docente (dal 2012 al 31/10/2018) di Malattie dell'Apparato Cardiovascolare presso Università à degli Studi di Messina, Dipartimento di Medicina Clinica e Sperimentale, Corso di Studi di Dietistica (II anno), Infermieristica (III anno), Corso di Laurea in Medicina e Chirurgia e nella Scuola di Specializzazione in Cardiologia.
- Dal 01/10/2016 al 31/10/2018 Coordinatore del corso integrato "Scienze Interdisciplinari cliniche" nel Corso di Studi di Infermieristica, Università degli studi di Messina.
- Docente nel corso di Dottorato di Ricerca in "Scienze Biomediche Cliniche e Sperimentali XXXIII ciclo"
- In qualità di Docente Universitario Componente o Relatore di diverse Sedute di Laurea e di diverse Commissione di Esami

d) DOCUMENTATA ATTIVIT DI FORMAZIONE O DI RICERCA PRESSO QUALIFICATI ISTITUTI ITALIANI O STRANIERI:

e) DOCUMENTATA ATTIVITA' IN CAMPO CLINICO RELATIVAMENTE AI SC NEI QUALI SONO RICHIESTE TALI SPECIFICHE COMPETENZE:

• Medico di Continuità Assistenziale per mesi 8, dal Luglio 2001 a Gennaio 2004, tra ASL n 5 di Crotone ed AUSL n 5 di Messina.

• Da ottobre 2004 a dicembre 2005 esperienza pratico professionale presso VIGI s.a.s. Diagnostica Cardiologica (accreditato SSN), V.le della Pace VV, eseguendo come primo operatore Ecocardiogramma transtoracico (n 549), Test-ergometrico (n 240), Tilt-test (n 7) e refertando n 432 holter ecg e n 309 holter PA. Da dicembre 2005 a febbraio 2007 il rapporto continuato come prestazioni medico-specialistiche fornite alla VIGI s.a.s.

• Da novembre 2005 a tutto oggi 62 h di sostituzione specialistica cardiologica ambulatoriale presso l'AUSL n 5 di Messina (ECG e visita cardiologica – Ecocardiografia – Medicina dello Sport).
• Da gennaio 2006 a giugno 2007 prestazioni specialistiche libero-professionali presso il servizio di Cardiologia del Centro Catanese di Medicina e Chirurgia, via Battello 48 Catania, effettuando un numero di prestazioni pari a: 1.121 visita cardiologia ed ECG con inquadramento diagnostico e terapeutico; 971 esami ecocardiografici; 72 Test-Ergometrici; e refertando n 50 holter ecg e n 45 holter PA. Il rapporto si protratto sino a dicembre 2007.
• Da marzo 2006 al 31/07/2008 (28 mesi) attività assistenziale (Medico di guardia, ambulatorio di Ecocardiografia, Ergometria, Holteristica, Visita cardiologica interni – esterni e post-infarto) presso U.T.I.C del Policlinico Universitario G. Martino Messina, come parte integrante del Dottorato di Ricerca.
• Dal 11/08/2008 al 21/09/09 (13 mesi) Assunzione a Tempo Determinato come Dirigente Medico di Cardiologia presso U.O. di Cardiologia e U.T.I.C. AUSL 5 Messina.
• Dal 22/09/09 al 31/10/2012 (37 mesi) Assunzione a Tempo Indeterminato in qualit di Dirigente Medico di Cardiologia presso l'Unità Operativa di U.T.I.C. e Cardiologia del Presidio Ospedaliero "Santa Maria della Misericordia" di Urbino, Zona Territoriale n.2, ASUR MARCHE.
• Oltre ad occuparsi prevalentemente di diagnostica cardiologica non invasiva, la costante frequenza della sala di elettrofisiologia come Dirigente Medico di Cardiologia presso l'Unit Operativa di U.T.I.C. e Cardiologia del Presidio Ospedaliero "Santa Maria della Misericordia" di Urbino, ha consentito l'acquisizione di una buona professionalità diagnostica (studio elettrofisiologico transesofageo ed endocavitario) ed interventistica, effettuando come secondo operatore 31 impianti tra mono e bicamerali, biventricolari ed ICD e come primo ed unico operatore ha effettuato 40 impianti tra PM monocamerali, bicamerale ed ICD.
• Dal 01/11/2012 Assunzione come Ricercatore a Tempo Determinano ed a regime di tempo pieno, presso l'Università Degli Studi Di Messina, Facoltà di Medicina e Chirurgia, Settore Scientifico Disciplinare MED/11 (Malattie Apparato Cardiovascolare) con attivit assistenziale (01/04/2013 - 30/06/2018) come Dirigente Medico presso l'U.O.C. di Terapia Cardiologica Intensiva ed Interventistica e l'U.O.C. di Cardiologia.
• Diversi incarichi di Facente Funzioni Direttore dell'Unità Operativa Complessa di Cardiologia con UTIC, presso l'AOU Policlinico G Martino Messina
• Dal 01/07/2018 Assunzione a Tempo Indeterminato come Dirigente Medico di Cardiologia presso l'Unità Operativa Complessa di Cardiologia con UTIC, dell'AOU Policlinico G Martino Messina

f) REALIZZAZIONE DI ATTIVITA' PROGETTUALE RELATIVAMENTE AI SC NEI QUALI PREVISTA:
Ha partecipato ad attività progettuale concordante con il settore Scientifico come si evince da allegato 2.
g) ORGANIZZAZIONE, DIREZIONE E COORDINAMENTO DI GRUPPI DI RICERCA NAZIONALI E INTERNAZIONALI, O PARTECIPAZIONE AGLI STESSI:
Ha partecipato a diversi gruppi di ricerca in collaborazione internazionale come evidente da studi pubblicati con Inpact Factor.(allegato 2)

h) TITOLARITA' DI BREVETTI RELATIVAMENTE AI SETTORI CONCORSUALI NEI QUALI PREVISTA:
_non valutabile_____

i)RELATORE A CONGRESSI E CONVEGNI NAZIONALI E INTERNAZIONALI:

-L'utilizzo dell'ecoscopio nell'attività formativa degli specializzandi in cardiologia. XLIX Convegno Scientifico Regionale "Società Italiana di Cardiologia - Sezione Siciliana Messina 21-22 Novembre 2003".
- La ricerca della vitalità nella disfunzione ischemica.II Convegno di Ecografia cardiovascolare "Reggio Calabria 1-3 luglio 2004".
- Valutazione funzionale mediante eco-stress del paziente rivascolarizzato. "Congresso di Cardiologia Clinica e Riabilitativa. Sidereo 14-15-16 ottobre 2004".
- Uso dell'ecoscopio nell'U.T.I.C. LI Convegno Scientifico "Società Italiana di Cardiologia - Sezione Regionale Siciliana Palermo 6-7-8 Novembre 2005".

- Componente del Comitato Scientifico e Discussants ufficiale del IX Convegno Internazionale Di Ecocardiografia. Taormina 3-5 ottobre 2006
- Degenerazione Caseosa Dell'Anello mitralico: Approccio Diagnostico Integrato. LII Convegno Scientifico "Società Italiana di Cardiologia – Sezione Regionale Siciliana Messina 6-7 Novembre 2006
- Confronto ECO TT – ECO TE - Doppler TC nello studio del Forame Ovale Pervio
LII Convegno Scientifico "Societ Italiana di Cardiologia – Sezione Regionale Siciliana Messina 6-7 Novembre 2006
- Ruolo dell'Ecocardiografia nella Terapia di Resincronizzazione Cardiaca Le Bizzarrie del Cuore – Augusta 2007. 2 Corso Teorico Pratico di Aritmologia Clinica, Sala conferenze Dip. Marina Militare, Augusta 9-novembre-2007
- Displasia Aritmogena del Ventricolo Destro (Tecniche di Imaging "Eco e RM")
Le Bizzarrie del Cuore – Augusta 2007. 2 Corso Teorico Pratico di Aritmologia Clinica, Sala conferenze Dip. Marina Militare, Augusta 9-novembre-2007.
- Confronto tra ECO Transesofageo, Eco Doppler Transuranico, ed Eco Transtoracico con contrasto nell'identificazione del Forame Ovale Pervio. 68 Congresso Nazionale della Società Italiana di Cardiologia "Roma 15-18 Dicembre 2007 Hotel Cavalieri di Hilton"
- Cases From The Crypt Asymptomatic Mass on the Heart. International Meeting of Cardiology. April 18 – 19, 2008 Congress Center – Polyclinic Hospital University of Messina (Italy).
- Coronary Artery Disease and Psoriasis. Corso Formativo ANMCO "Aggirnamenti in Cardiologia Interventistica 2013" Palermo, Villa Alliata Cardillo 24 – 25 Giugno 2013
- L'ecostress nella diagnosi della Cardiopatia Ischemica. Corso Formativo "Percorso diagnostico nella cardiopatia Ischemica" Messina, Palacultura Viale Boccetta 07/06/2014
- Multimodality imaging in TAVI and mitraclip. XIII International Meeting of Echocardiography. Hilton Giardini Naxos October 09 – 11 ottobre 2014 (Moderatore)
- Il coinvolgimento del Cardiologo. Corso pso cube "La Psoriasi: da patologia della pelle a patologia infiammatoria multiorgano" A.O.U. Policlinico G. Martino 5 dicembre 2014
- Vitamina D e Malattie Cardiovascolari. Corso di aggiornamento ECM "Vitamina D e Osteopatie Metaboliche" A.O.U. Policlinico G. Martino 13 dicembre 2014
- XIV International Meeting of echocardiography. Hilton Giardini Naxos October 06 – 08 ottobre 2016 (Speaker)
- La Malattia di Anderson-Fabry. Cardiologi e Neurologi a Confronto. Cardiomiopatie Rare e Scompenso Cardiaco. Cosa sapere e come trattarle. Hilton Giardini Naxos 31/3 - 1/4 2017. (Docente)
Partecipazione a convegni, congressi ed eventi formativi
- Focus sulla Fibrillazione Atriale "L'imaging integrato nella fibrillazione atriale" Hotel Villa deodoro Taormina, Messina 4/5 dicembre 2017. (Moderatore)
- Corso Share 2.0 "Il paziente con Insufficienza Cardiaca tra tradizione e nuove oppurtunit terapeutiche". 28/04/2018 Messina. (Docente)
- Advisory Board: Il ruolo di edoxaban nella gestione del paziente con TEV. Messina 20/11/2018 (Relatore)
- Gruppo di miglioramento "La gestione del paziente complesso con psoriasi con situazioni infettive e rischio cardiovascolare". Enna 7 novembre e 17 dicembre 2019 (Docente)
- Webinar 25/06/2020 NAO CONTEST: Anticoagulazione diretta nella real life. "Prevenzione del Tromboembolismo e scenari particolari. I DOAC sono sempre indicati?" Premio come migliore relazione (Relatore)
- Webinar 29/06/2020 Gestione del paziente Psoriaco con Comorbilit . " Psoriasi e rischio cardiovascolare ". (Relatore)
- VII Convegno Internazionale di Ecocardiografia " Grande Albergo Capotaormina, Taormina 1-3 Giugno 2002".
- XLIX Convegno Scientifico Regionale "Societ Italiana di Cardiologia-Sezione Siciliana Messina 21-22 Novembre 2003".
- Riunione Scientifica Regionale: " L'Endocardite Infettiva " S.I.E.C. 2-Aprile-2004 Hotel Hellenia di Giardini Naxos-Taormina
- Riunione Scientifiche Regionali: "Il Ruolo dell'Ecocardiografia nel Paziente con Ictus Cardioembolico" S.I.E.C. Catania 2-Marzo-2005
- Riunione Scientifica Regionale: "Linee guida AIAC per il trattamento della fibrillaziona atriale". Messina 23 Settembre 2006.
- 8 European Round Table on Fabry Disease. Rome, Italy – octobre 12 – 13, 2007.
- Cardiovascular forum. 2 forum nazionale sul rischio e la prevenzione cardiovascolare. Il continum cardiovascolare: dai fattori di rischio allo scompenso cardiaco. Marriot Park Hotel 16-17 novembre 2007.
- La Gestione Multidisciplinare del Paziente Portatore di Defibrillatore. Messina 10 Maggio 2008. Policlinico Universitario "G. Martino" Messina.

- Scompenso Cardiaco - da Cardiosource. Evento organizzato da Infomedica, in collaborazione con l'American College of Cardiology (9 crediti ECM 2009)
- JACC online 2009. Progressi recenti nel campo della rianimazione cardiopolmonare: rianimazione cardiocerebrale - Vol. 53 n. 2, 13 gennaio 2009 (21 crediti ECM 2009)
- La Fibrillazione atriale, aspetti gestionali. 19 Novembre 2010, Palazzo Montani Antaldi, Pesaro
- Paths to Treatment, 13 - 14 Settembre 2013, Hotel Royal Continental, Napoli.
22
- l CORSI DI AGGIORNAMENTO DELLA SIC. Sindrome Coronarica Acuta - Strategia mirata alla riduzione degli eventi cardiovascolari. ROMA 21-22 settembre 2017
- Updates and best practice in HF "Esperienze a confronto", 10 - 11 Novemnbre 2017, Pero, Milano.
- Gestione dell'Insufficienza cardiaca in Sicilia, 3 Marzo 2018, Caltanissetta.
- Idee per la Cardiologia del nuovo Millennio. 23 Novembre 2018, Urbino
- Venice Arrhythmias 2019.October 3/4/5 2019 Venezia

j) PREMI E RICONOSCIMENTI NAZIONALI E INTERNAZIONALI PER ATTIVIT DI RICERCA:
Scholar in Cardiologia (14/12/2018): riconoscimento di merito che la Societ Italiana di Cardiologia riserva a Soci che si siano distinti per originali contributi nel campo della ricerca in Cardiologia ed il cui prestigio sia riconosciuto dalla Comunit Scientifica Internazionale
- Premio come migliore relazione (25/06/2020): Webinar NAO CONTEST: Anticoagulazione diretta nella real life. "Prevenzione del Tromboembolismo e scenari particolari. I DOAC sono sempre indicati?"

k) DIPLOMA DI SPECIALIZZAZIONE EUROPEA RICONOSCIUTO DA BOARD INTERNAZIONALI, RELATIVAMENTE A QUEI SETTORI CONCORSUALI NEI QUALI PREVISTA:Specializzazione quadriennale in Cardiologia, ai sensi del D. Lgs 08-08-1991 n 257, il 27 Ottobre 2005 presso l'Università degli Studi di Messina, Direttore Professore Giuseppe Oreto, con votazione 50 e lode/50; tesi di specializzazione: Un nuovo Test nello studio della Cardiopatia Ischemica: Test Ecodobutamina-Handgrip. Risultati preliminari , relatore Prof. Scipione Carerj.

L) autore di 102 pubblicazioni valutabili , indexate. Allegato 2

MOTIVATO GIUDIZIO ANALITICO SUI TITOLI, SUL CURRICULUM E SULLA PRODUZIONE SCIENTIFICA IVI COMPRESA LA TESI DI DOTTORATO

GIUDIZI INDIVIDUALI

Prof. A.A.Chetta

Il Candidato Giuseppe Dattilo ha conseguito la Laurea e il titolo di Dottorato di Ricerca e la specializzazione presso l'Università degli studi di Messina. La tesi di Dottorato è stata giudicata totalmente coerente con il SSD MED/11. Il Candidato non ha svolto periodi di studio e Ricerca presso qualificati Enti di Ricerca all'estero.

La produzione scientifica risulta buona, testimoniata da 102 pubblicazioni Indicizzate coerenti con il settore concorsuale.

Ha svolto attività didattica certificata.

Le tematiche della ricerca sono congruenti con il SSD MED/11 e l'IF risulta di ottimo livello, con un H index di 21.

Si evince una buona autonomia nell'attività di ricerca, testimoniata dalla posizione di primo ultimo o autore corrispondente in un buon numero di lavori presentati.
Il candidato risulta pertanto idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale della lingua inglese, ai fini della presente valutazione comparativa.

Prof. C. Vancheri

Il Dott. Giuseppe Dattilo si è laureato in Medicina e chirurgia all'Università di Messina e ha conseguito il Titolo di Dottorato di Ricerca presso l'Università Degli Studi di Messina, Facoltà di Medicina e Chirurgia in "Metodologie e Tecniche di Imaging Cardiovascolare" il 28/03/09 con discussione tesi in Un nuovo approccio diagnostico non invasivo nello studio della cardiopatia ischemica: Ecostress-Dipiridamolo associato a 2D Strain versus TC Coronarica Tutor: Prof S. Carerj. Coordinatore: Prof F. Arrigo .

Ha presentato 102 pubblicazioni su riviste internazionali la maggiorparte con Impact Factor, numerose comunicazioni e poster a congressi nazionali e internazionali, in cui ha partecipato anche come relatore e o faculty.
L'IF delle riviste risulta di buon livello con un H index pari a 21 con numero totale di citazioni 959
Ha una buona attività di didattica.
Il Candidato ha una buona autonomia di nell'attività di ricerca.
Il candidato risulta pertanto idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale della lingua inglese, ai fini della presente valutazione comparativa.

Prof. Antonio Micari

Il Dott. Giuseppe Dattilo si è laureato in Medicina e chirurgia all'Università di Messina e ha conseguito il Dottorato di Ricerca presso l'Università Degli Studi di Messina, Facoltà di Medicina e Chirurgia in "Metodologie e Tecniche di Imaging Cardiovascolare" il 28/03/09 con discussione tesi in Un nuovo approccio diagnostico non invasivo nello studio della cardiopatia ischemica: Ecostress-Dipiridamolo associato a 2D Strain versus TC Coronarica Tutor: Prof S. Carerj. Coordinatore: Prof F. Arrigo .

Ha presentato 102 pubblicazioni su riviste internazionali, numerose comunicazioni e poster a congressi nazionali e internazionali, in cui ha partecipato anche come relatore e o faculty.
L'IF delle riviste risulta di buon livello con un H index pari a 21 con numero totale di citazioni 959
Ha svolto una buona attività di didattica.
Il Candidato ha una buona autonomia di nell'attività di ricerca.
Il candidato risulta pertanto idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale della lingua inglese, ai fini della presente valutazione comparativa.

GIUDIZIO COLLEGIALE

Il candidato Giuseppe Dattilo ha conseguito la laurea, la specializzazione e il Dottorato di Ricerca congruenti con il SSD MED/11. Ha svolto attività di ricerca, riuscendo a realizzare numerose collaborazioni. L'attività di ricerca è documentata da un congruo numero di pubblicazioni su riviste internazionali ottenendo un buon indice bibliometrico cosi come da citazioni.
L'attività didattica è stata svolta nell'ambito delle discipline del SSD MED/11.
La Commissione sulla base dei giudizi individuali espressi, giudica il candidato, ai fini della presente valutazione comparativa, idoneo alla discussione pubblica dei titoli, delle pubblicazioni e la contestuale prova orale che accerti la conoscenza della lingua inglese.

PRODUZIONE SCIENTIFICA

Il candidato è autore di **72** pubblicazioni scientifiche in riviste internazionali (**41** come primo o secondo autore, **8** come ultimo autore o corresponding author), **6** capitoli in libro di testo (tutti come primo, ultimo o unico autore), **19** abstract su riviste internazionali e **2** tesi dottorali (1 con valenza internazionale).

Il candidato presenta i seguenti indici bibliometrici (fonte Scopus al 15/09/2021):
Citazioni totali: 3347
H-Index: 20
H-Index$_{10}$: 30

PUBBLICAZIONI SCIENTIFICHE SU RIVISTE INTERNAZIONALI:

2013

1. Francesco Costa, Scipione Carerj, Simona Cammaroto, Maurizio Cusma Piccione, Giuseppe Oreto, Paolo Girlanda and Concetta Zito
Concurrent Pulmonary and Cerebral Embolism: Is Tricuspid Valve Endocarditis the Culprit?
Int J Cardiovasc Res 2013, 2:2

2014

2. Giuseppe Andò, Francesco Costa, Ilaria Boretti, Olimpia Trio, Marco Valgimigli
Benefit of radial approach in reducing the incidence of acute kidney injury after percutaneous coronary intervention: A meta-analysis of 22,108 patients
International Journal of Cardiology /2014; 179C:309-311.

2015

3. Eliano Pio Navarese, Felicita Andreotti, Volker Schulze, Michalina Kołodziejczak, Antonino Buffon, Marc Brouwer, Francesco Costa, Mariusz Kowalewski, Gianfranco Parati, Gregory Y H Lip, Malte Kelm, Marco Valgimigli
Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials.
BMJ 01/2015; 350:h1618

4. Gabriele Crimi, Sergio Leonardi, Francesco Costa, Sara Ariotti, Matteo Tebaldi, Simone Biscaglia, Marco Valgimigli
Incidence, prognostic impact, and optimal definition of contrast-induced acute kidney injury in consecutive patients with stable or unstable coronary artery disease undergoing percutaneous coronary intervention. insights from the all-comer PRODIGY trial
Catheterization and Cardiovascular Interventions 02/2015; DOI:10.1002/ccd.25822

5. Francesco Costa, Pascal Vranckx, Sergio Leonardi, Elisabetta Moscarella, Giuseppe Ando, Paolo Calabro, Giuseppe Oreto, Felix Zijlstra, Marco Valgimigli
Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial
European Heart Journal 02/2015; DOI:10.1093/eurheartj/ehv038

6. Marco Valgimigli, Sara Ariotti, Francesco Costa
Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus?
European Heart Journal 03/2015; DOI:10.1093/eurheartj/ehv053

7. Carlos M Campos, Francesco Costa, Hector M Garcia-Garcia, Christos Bourantas, Pannipa Suwannasom, Marco Valgimigli, Marie-Angele Morel, Stephan Windecker, Patrick W Serruys
Anatomic Characteristics and Clinical Implications of Angiographic Coronary Thrombus: Insights From a Patient-Level Pooled Analysis of SYNTAX, RESOLUTE, and LEADERS Trials
Circulation Cardiovascular Interventions 04/2015; 8(4).

8. Marianna Adamo, Francesco Costa, Pascal Vranckx, Sergio Leonardi, Eliano P Navarese, Hector M Garcia-Garcia, Marco Valgimigli
Does smoking habit affect the randomized comparison of 6 versus 24-month dual antiplatelet therapy duration? Insights from the PRODIGY Trial
International journal of cardiology 04/2015; 190:242-245.

9. Francesco Costa, Sara Ariotti, Marco Valgimigli, Philippe Kolh, Stephan Windecker
Perspectives on the 2014 ESC/EACTS Guidelines on Myocardial Revascularization : Fifty Years of Revascularization: Where Are We and Where Are We Heading?
Journal of Cardiovascular Translational Research 05/2015; DOI:10.1007/s12265-015-9632-6

10. Marco Valgimigli, Francesco Costa, Robert Byrne, Michael Haude, Andreas Baumbach, Stephan Windecker
Dual antiplatelet therapy duration after coronary stenting in clinical practice: results of an EAPCI survey
EuroIntervention 05/2015; 11(1):68-74. DOI:10.4244/EIJV11I1A11

11. Sara Ariotti, Francesco Costa, Marco Valgimigli

Coronary stent selection and optimal course of dual antiplatelet therapy in patients at high bleeding or thrombotic risk: navigating between limited evidence and clinical concerns
Current opinion in cardiology 07/2015; 30(4):325-332.

12. Monica Lunetta, Francesco Costa, Marcello La Gattuta, Salvatore Novo
Transesophageal Contrast Echocardiography is Not Always the Gold Standard Method in the Identification of a Patent Foramen Ovale: A Clinical Case
J Cardiovasc Echography 2015;25:86-9

13. Francesco Costa, Marianna Adamo, Sara Ariotti, Giuseppe Ferrante, Eliano Pio Navarese, Sergio Leonardi, Hector Garcia-Garcia, Pascal Vranckx, Marco Valgimigli
Left Main or Proximal Left Anterior Descending Coronary Artery Disease Location Identifies High-risk Patients Deriving Potential Greater Benefit from Prolonged Dual Antiplatelet Therapy Duration.
EuroIntervention. 2016 Feb;11(11):e1222-30

14. Francesco Costa, Marco Valgimigli
Impact of Clinical Presentation on Dual Antiplatelet Therapy Duration: Let's Re-Evaluate Our Priorities.
J Am Coll Cardiol. 2015 Sep 8;66(10):1203-4

15. Francesco Costa, Marco Valgimigli
Impact of greater than 12-month Dual Antiplatelet Therapy Duration on Mortality: Drug-specific or a Class-effect? A Meta-analysis
Int J Cardiol. 2015 Dec 15;201:179-81

16. Giuseppe Andò, Francesco Costa
Bleeding risk stratification in acute coronary syndromes. Is it still valid in the era of the radial approach?
Advances in Interventional Cardiology 08/2015.

17. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee, C. W., Mauri, L., Valgimigli, M., Park, S. J., Montalescot, G., Sabatine, M. S., Braunwald, E., Bhatt, D. L.
Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials.
European Heart Journal, 08/2015.

18. Francesco Costa, Marco Valgimigli
Long-term use of ticagrelor in patients with prior myocardial infarction
The New England journal of medicine.2015;373(13):1271-2.

19. Costa F, Tijssen JG, Ariotti S, Giatti S, Moscarella E, Guastaroba P, De Palma R, Andò G, Oreto G, Zijlstra F, Valgimigli M.
Incremental Value of the CRUSADE, ACUITY, and HAS-BLED Risk Scores for the Prediction of Hemorrhagic Events After Coronary Stent Implantation in Patients Undergoing Long or Short Duration of Dual Antiplatelet Therapy.
J Am Heart Assoc. 2015 Dec 7;4(12)

2016

20. Giuseppe Gargiulo, Francesco Costa, Sara Ariotti, Simone Biscaglia, Gianluca Campo, Giovanni Esposito, Sergio Leonardi, Pascal Vranckx, Stephan Windecker, Marco Valgimigli
Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: insights from the PRODIGY trial
Am Heart J. 2016 Apr;174:95-102

21. Costa F, van Leeuwen MA, Daemen J, Diletti R, Kauer F, van Geuns RJ, Ligthart J, Witberg K, Zijlstra F, Valgimigli M, Van Mieghem NM.
The Rotterdam Radial Access Research : Ultrasound-Based Radial Artery Evaluation for Diagnostic and Therapeutic Coronary Procedures.
Circ Cardiovasc Interv. 2016 Feb;9(2):e003129

22. Ariotti S, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini M, Vranckx P, Valgimigli M.
Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial.
JACC Cardiovasc Interv. 2016 Mar 14;9(5):426-36

23. Crimi G, Leonardi S, Costa F, Adamo M, Ariotti S, Valgimigli M.
Role of stent type and of duration of dual antiplatelet therapy in patients with chronic kidney disease undergoing percutaneous coronary interventions. Is bare metal stent implantation still a justifiable choice? A post-hoc analysis of the all comer PRODIGY trial.
Int J Cardiol. 2016 Jun 1;212:110-7

24. Andò G, Costa F, Trio O, Oreto G, Valgimigli M.
Impact of vascular access on acute kidney injury after percutaneous coronary intervention.
Cardiovasc Revasc Med. 2016 Mar 10. pii: S1553-8389(16)30060-4

25. De Paolis M, Felix C, van Ditzhuijzen N, Fam JM, Karanasos A, de Boer S, van Mieghem NM, Daemen J, Costa F, Bergoli LC, Ligthart JM, Regar E, de Jaegere PP, Zijlstra F, van Geuns RJ, Diletti R.
Everolimus-eluting bioresorbable vascular scaffolds implanted in coronary bifurcation lesions: Impact of polymeric wide struts on side-branch impairment.

Int J Cardiol. 2016 Jun 25;221:656-664 doi: 10.1016/j.ijcard.2016.06.153

26. Adamo M, Ariotti S, Costa F, Curello S, Moschovitis A, de Vries T, White HD, Windecker S, Valgimigli M.
Phosphate- or Citrate-Buffered Tirofiban Versus Unfractionated Heparin and its Impact on Thrombocytopenia and Clinical Outcomes in Patients With Acute Coronary Syndrome: A Post Hoc Analysis From the PRISM Trial.
JACC Cardiovasc Interv. 2016 Aug 22;9(16):1667-76. doi: 10.1016/j.jcin.2016.05.031

27. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, WallentinL, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, Van de Werf F, Harrington RA, Mahaffey KW, and Tricoci P
Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event
5 Reduction in Acute Coronary Syndrome (TRACER) randomized tria
European Heart Journal (2016) 00, 1–8 doi:10.1093/eurheartj/ehw525

2017

28. Di Giorgio A, Costa F, Virga V, Saporito F.
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TESI DI DOTTORATO:

1. **Dottorato di Ricerca Internazionale in "Intravascular imaging and interventional cardiology" presso l'Università Erasmus di Rotterdam, Paesi Bassi.**

   Titolo: Pharmaco-Mechanical Strategies to Optimize the Balance between Ischemia and Bleeding after Percutaneous Coronary Intervention – Navigating between Scylla and Charybdis.

   Repository: Tesi di dottorato consultabile presso il repository pubblico dell'Erasmus University di Rotterdam all'indirizzo: https://repub.eur.nl/pub/105339/

   Pubblicazione: La tesi dottorale comprende 21 articoli pubblicati in riviste scientifiche internazionali. L'articolo conclusivo della tesi è stato pubblicato sulla Rivista Internazionale "The Lancet": *Costa et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017 Mar 11;389(10073):1025-1034*

2. **Dottorato di Ricerca Scienze Biomediche Cliniche e Sperimentali presso l'Università di Messina, Italia.**

   Titolo: Appraising the counter-balancing ischemia and bleeding risks for dual antiplatelet therapy duration after coronary stenting.

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Handgrip exercise associated with dobutamine stress echocardiography

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Abstract

Background: Stress echocardiography is today the best possible imaging choice in the field of noninvasive diagnosis of coronary artery disease. Dobutamine stress echocardiography (DSE) and Dobutamine-atropine stress echocardiography (DASE) have been studied. Handgrip (HG) exercise has been rarely studied in stress echocardiography. Aim of the study was to investigate the safe, feasibility and efficacy of use of HG associated with DSE and if it may lead to improved diagnostic capacity of the test.
Methods: DSE was performed in 96 consecutive patients. Seventy-seven patients reached their target heart rate age-adjusted and were excluded. To 19 patients who have not reached their target hr age-adjusted, HG at 50% maximum effort was applied for a minute and 16 patients reached the maximum heart rate.
Results: Of these 16 patients, 8 were positive for myocardial ischemia induced. Of the 3 other patients, 2 were positive for myocardial ischemia before reaching the target hr. One patient, without reaching the max hr and without being positive for myocardial ischemia, refused other investigations. Therefore, a total of 10 patients presented an inducible myocardial ischemia. Coronary angiography revealed a significant coronary artery disease in all these 10 patients (10/10 patients, 100%).
Discussion: Our study concludes for the safe, feasibility and efficacy of use of HG with DSE and that it may lead to improved diagnostic capacity of the test. Large studies need to be done to confirm these preliminary results but our study is very encouraging for the application and validity of this type of test mixture.

Keywords: Heart rate; Stress echocardiography; Coronary artery disease

1. Text

In spite of its dependence upon operator's training, stress echocardiography is today the best (most cost-effective and risk-effective) possible imaging choice to achieve the still elusive target of sustainable cardiac imaging in the field of noninvasive diagnosis of coronary artery disease [1]. Dobutamine [2–5] and vasodilators (at appropriately high doses) are equally potent ischemic stressors for inducing wall motion abnormalities in presence of a critical coronary artery stenosis [6] and although vasodilators may have advantages for assessment of myocardial perfusion, dobutamine is preferred when the test is based on assessment of regional wall motion [7]. Muscle sympathetic nerve activity (MSNA) and handgrip (HG) exercise has been rarely studied also in heart failure [8] and in stress echocardiography [9–11]. Use of isometric HG exercise with dobutamine-atropine stress echocardiography (DASE) decreases time to target heart rate, recovery time, overall study time, and mean dosage of dobutamine and atropine [9]. Adjunctive isometric exercise in the form of sustained submaximal HG to peak of

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Table 1
Age, average heart rate increase, average systolic blood pressure increase, average diastolic blood pressure increase, average double product increase.

	N	Mean	SD
Age	19	66.68	10.90
Average heart rate increase	19	15.21	6.11
Average systolic blood pressure increase	19	9.16	6.55
Average diastolic blood increase	19	5	9.43
Average double product increase	19	24	11.21

dobutamine stress echocardiography (DSE) without atropine results in a modest increase in MVO2, primarily by an increase in end-systolic wall stress [10] and can significantly lower the fractional flow reserve (FFR) and potentially improve its ability to detect physiologically significant stenoses [11].

2. Aim of the study

Aim of the study was to investigate the safe, feasibility and efficacy of use of isometric HG exercise with DSE and if it may lead to improved diagnostic capacity of the test.

3. Materials and methods

DSE was performed in all consecutive patients (n 96) admitted to the Clinical and Experimental Department of Medicine and Pharmacology. University of Messina, Messina (Italy) from April 2005, to September 2005 (during 5 months). All patients were without previous AMI and heart failure. The main initial exclusion criteria included to reach at least 85% of maximum heart rate (hr) age-adjusted. All patients were subjected to the following protocol: in the pre-test was assessed the maximum isometric muscular effort performed by the patient through HG measured in kg, followed by infusion of dobutamine intravenously at progressively increasing doses of 5, 10, 20, 30 and 40 γ/kg/min. every 3 min. Registration echocardiography was performed in basal conditions and at the end of each step. The detection of blood pressure (PA) and ECG monitoring chart was made at each step. Of all patients, 77 patients reached their target hr age-adjusted. Therefore, the final population of our study consisted of 19 patients out of 96 (20%), 12 males (63%) and 7 females (37%) average age 66.6 years(Table 1) who have not reached their target hr age-adjusted. At the end of the step, to our final population of 19 patients, HG at 50% maximum effort was applied, obtained in basal conditions, for a minute under continuous monitoring by echocardiography, ECG and monitoring of the PA at the beginning and the end of isometric effort. We chose the application of 50% of maximum effort that the patient can do for two reasons: 1) to have a unique parameter for all patients, and 2) not to cause excessive muscle fatigue in patients who have undermined the possibility of keep the load constant for the entire minute.

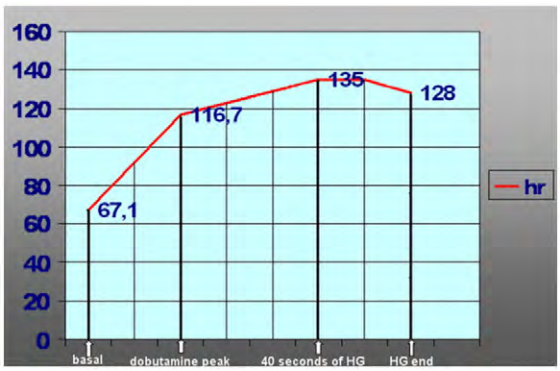

Fig. 1. Average heart rate (hr) increase.

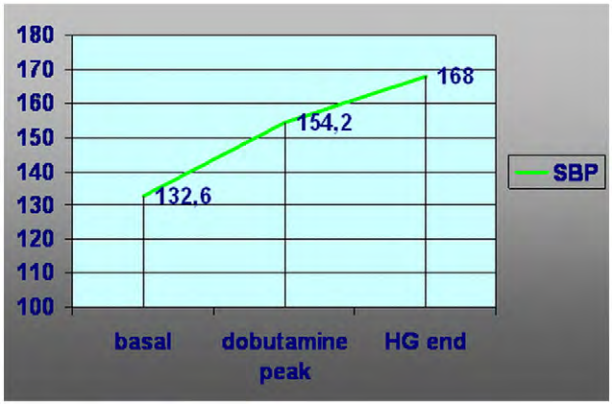

Fig. 2. Average systolic blood pressure (SBP) increase.

4. Results

Of the 19 patients evaluated according to this protocol, 16 (84%) reached the maximum heart rate after adjunctive HG application and they have a peak in terms of average increase in heart rate of 15.2% within 40 sec after adjunctive HG application with plateau later (Fig. 1), an average increase of 9.2% of systolic blood pressure (Fig. 2) (Table 1) and 4.4% of pressure diastolic) (Table 1), an increase of double product of 24% (Fig. 3) (Table 1). Of the 16 patients, 8 (50%) presented a dobutamine DSE+HG positive for myocardial ischemia induced. Of the 3 other patients, 2 were positive for myocardial ischemia before reaching the target hr and the test was stopped. One patient, without reaching the max hr and without being positive for myocardial ischemia, refused other investigations. Therefore, a total of 10 patients presented an inducible myocardial ischemia. Coronary angiography revealed a significant coronary artery disease in all these 10 patients c/10/10 patients, 100%) with an inducible myocardial ischemia.

5. Discussion

DASE is a reasonably safe method for detection of coronary artery disease [1,6,7] in the hospital or in an ambulatory basis. However disturbances of cardiac rhythm and conduction [12], an acute cardiac rupture [13,14], a neurological syndrome [15], hypotensive response [5], splenic artery aneurysm rupture [16] have been reported. In an experience of 4033 consecutive studies, reported in literature, major test-related cardiac complications occurred in 10 (0.25%) patients and included 1 ventricular fibrillation, 1 case of myocardial infarction, and 8 cases of sustained ventricular tachycardia, Atropine poisoning was observed in 5 (0.12%) patients and no deaths occurred as a direct or indirect consequence of DASE [17]. DASE, however, can increase test duration and a patient's exposure to large doses of dobutamine. New protocols, including the early injection of atropine during dobutamine stress echocardiography (EA-DSE), have been proposed to decrease test duration and a lower incidence of minor adverse effects than did DASE but a similar rate of major adverse effects have been reported

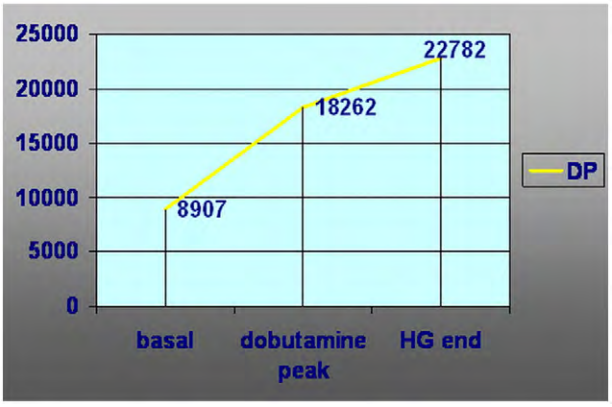

Fig. 3. Average double product (DP) increase.

[18]. It has been reported that early DASE in emergency department triage of low-risk patients with acute chest pain (ACP) is safe and reduces costs of care compared to electrocardiographic exercise testing (EET) [19]. Adjunctive isometric exercise in the form of sustained submaximal HG to peak of DSE results in a modest increase in MVO2, primarily by an increase in end-systolic wall stress [10] and can significantly lower the fractional flow reserve (FFR) and potentially improve its ability to detect physiologically significant stenoses [11]. It, allowed in 84% of our patients to achieve the theoretical maximum heart rate expected for age, without any significant side effects. Another aspect to the benefit of the combined stress (pharmacological and physical) with HG is significant increase in the average value of double-registered product (from 18,262 to 22,782 with an average increase of 24% Fig. 3 and Table 1 ") that determines an increase of MVO2, which is certainly more similar to the one has MVO2 during exercise. By use of atropine the increase in the double product is mainly due to an increase in heart rate with values of the PA virtually unchanged. From the pathophysiological point of view the increase in double product with the test-atropine ecodobutamina is less similar to what usually occurs during exercise. Another advantage of the test mixture (dobutamine-HG), is the reduction of total dose infusion of dobutamine compared to traditional testing with atropine. Moreover, coronary angiography revealed a significant coronary artery disease in all these 10 patients (10/10 patients,100%) with an inducible myocardial ischemia. Our study concludes for the safe, feasibility and efficacy of use of isometric HG exercise with DSE and that it may lead to improved diagnostic capacity of the test. Large studies need to be done to confirm these preliminary results but our study is very encouraging for the application and validity of this type of test mixture.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [20].

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Combination therapy with aliskiren versus ramipril or losartan added to conventional therapy in patients with type 2 diabetes mellitus, uncontrolled hypertension and microalbuminuria

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Abstract

Hypothesis/Introduction: The aim of this study was to assess the antihypertensive efficacy and safety of aliskiren versus ramipril or losartan in hypertensive patients with type 2 diabetes mellitus, microalbuminuria and uncontrolled hypertension, despite the use of optimal conventional antihypertensive therapy.

Materials and methods: In this open-label active comparator study, 126 patients were randomly assigned to receive 24 weeks of additional therapy with aliskiren (Group A) or either losartan or ramipril (Group B), according to whether a patient was already treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, respectively.

Results: After 24 weeks, both treatment groups experienced a significant reduction of systolic blood pressure (–11.37% and –8.47%, respectively; both p <0.001 *vs.* baseline) and diastolic blood pressure levels (–10.67% and –9.28%, respectively; both p <0.001 *vs.* baseline), with a greater reduction of mean systolic values in Group A compared with Group B (p <0.001). Furthermore, after six months microalbuminuria was significantly decreased in both treatment groups (–67.62% and –49.1%, respectively; both p <0.001), with a reduction rate in Group A significantly higher than in Group B (p<0.001).

Conclusions: The addition of aliskiren to optimal conventional therapy provided a higher reduction of blood pressure and urinary albumin excretion when compared with the addition of losartan or ramipril.

Keywords

Direct renin inhibitors, angiotensin receptor blockers, renin–angiotensin–aldosterone system, hypertension, angiotensin-converting enzyme inhibitors

Introduction

It is well established that the renin–angiotensin–aldosterone system (RAAS) plays a central role in the development of arterial hypertension. Angiotensin II (AngII) plasma levels are clearly involved in vascular endothelium alterations and atherogenesis, and contribute to the progression of target organ damage.[1–8] Drugs inhibiting the RAAS, such as angiotensin-converting enzyme inhibitors (ACE-is) and angiotensin receptor blockers (ARBs), have been shown to be effective in reducing blood pressure (BP) and hypertension-associated target organ damage,[9] particularly heart failure (HF),[10–12] coronary artery disease (CAD),[13,14] left ventricular hypertrophy (LVH)[15,16] and chronic kidney disease

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(CKD).[17] A treatment that includes an ACE-i or an ARB can contribute to cardiorenal protection effects; however, these drugs act by blocking the RAAS at different levels. In addition, they are not able to completely block RAAS activity because of the reactive rise in renin release induced by the withdrawal of the feedback inhibition exerted by AngII (the so-called short feedback loop), as evidenced by a reactive increase in plasma renin activity (PRA), a well-established cardiovascular risk marker,[18] providing an incomplete cardiorenal protection.[19]

The central role of the RAAS in the pathogenesis of diabetic nephropathy is accepted because several studies have shown that ACE-is and ARBs can significantly reduce diabetic nephropathy.[20–25] Blockade of the RAAS with ACE-is or ARBs may be delayed; however, this delay does not avoid the progression of diabetic nephropathy towards end-stage renal disease (ESRD).[24,26,27] Dual blockade with ACE-is and ARBs offers no additional benefit in patients with hypertension as well as normal renal and left ventricular function; indeed, PRA increases consistently with the dual blockade.[19] The ONTARGET study showed that the combination of telmisartan and ramipril, despite reducing BP by a few millimetres of mercury more than therapy with either ramipril or telmisartan, was associated with more adverse events.[28,29] More recently, a new antihypertensive class, the direct renin inhibitors (DRIs), was introduced;[30] In fact, renin is the first and primary enzyme involved in the RAAS cascade. Since the early 1980s, several compounds have been synthesized to test the effects of a blockade of renin enzyme activity (e.g. enalkiren, ramikiren and zankiren). However, none of these reached the clinical arena, because of their low inhibiting activity, lack of oral bioavailability and short half-life. Aliskiren (Novartis) is the first DRI suitable for oral administration, and it has been available since 2008.[18] Aliskiren is a powerful renin inhibitor which is highly specific for human renin. It inhibits the enzyme activity of renin at the onset of the conversion cascade of the RAAS, thus avoiding the activation of angiotensinogen into angiotensin I and consequently into AngII.[31]

By blocking the first and rate-limiting step in the RAAS, aliskiren reduces PRA by at least 70% and buffers the compensatory increase in PRA observed with ACE-is and ARBs.[19] The combination of a DRI and an ARB or an ACE-i is an effective approach for lowering BP and available data indicate that such combinations favourably affect proteinuria, left ventricular mass index and brain natriuretic peptide levels in patients with albuminuria, LVH and HF.[15,19,24,32]

Four different trials evaluated the potential cardiorenal effects of aliskiren on morbidity and mortality.[33] One of these, the ALTITUDE, was halted by the recommendation of its Data Monitoring Committee (DMC) because of a higher event rate.[34] The recently published ASTRONAUT trial reported post-discharge mortality and HF readmissions among patients with acute HF and reduced left ventricular ejection fraction treated with aliskiren or placebo in addition to standard therapy.[35]

The ATMOSPHERE trial is currently evaluating the effects of an additional treatment with aliskiren in patients with chronic HF.[36] The APOLLO trial (to date at phase 3) will provide new information regarding the role of aliskiren administered with or without additional therapy with a diuretic or a calcium channel blocker (CCB) in elderly subjects (≥65 years) with systolic BP (SBP) from 130 to 159 mmHg. The trial is designed to assess the ability of DRI to prevent major cardiovascular (CV) events, as well as its impact on global measures of physical, executive and cognitive function (ClinicalTrials.gov identifier: NCT01259297). Ongoing outcome studies will clarify which subclass of patient will derive benefit from the combination therapy of aliskiren with an ACE-i or an ARB.

The aim of the present study was to evaluate the impact on BP and on urinary albumin excretion of a dual RAAS blockade strategy in hypertensive patients with type 2 diabetes mellitus (T2DM), impaired renal function (IRF), microalbuminuria (MA) and uncontrolled hypertension, despite the administration of an optimal antihypertensive therapy, already including an ACE-i or an ARB; the study design included the addition of aliskiren to a conventional therapy with an ACE-I or an ARB, compared with the addition of ramipril or losartan to a therapy already including an ARB or an ACE-I, respectively. Furthermore, the short-term safety of these dual blockade strategies was also evaluated.

We want to underline that our study was completed before Novartis announced the termination of the ALTITUDE study due to the unexpected increased incidence of renal impairment, non-fatal stroke, hyperkalaemia and hypotension. Moreover, the patients enrolled in the ALTITUDE study presented with adequate BP levels.

Materials and methods

Study population

From June 2009 to June 2010, 1107 outpatients presented at the Hypertension Care Centre of the University of Messina, Italy. Each patient underwent a complete history and physical examination, blood sampling for routine blood chemistry, 24 h urine collection (to measure creatinine clearance and albumin excretion), electrocardiography and echocardiography. Patients with secondary hypertension, acute cardiovascular (myocardial infarction (AMI) or unstable angina) or cerebrovascular (transient ischemic attack (TIA) or stroke) disease, which occurred within the previous 12 months, were excluded from the study. We also excluded patients with left ventricular dysfunction (ejection fraction ≤40%), creatinine clearance (CrCl) ≤40 ml/min, urinary albumin excretion ≤30 mg/24 h or ≥300 mg/24 h, or with serum potassium levels ≥5.5 mEq/l. Glycosylated haemoglobin was also assessed.

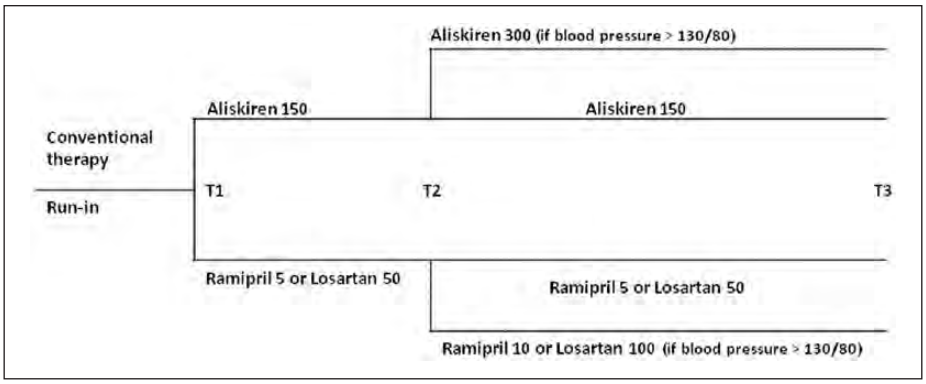

Figure 1. Study design.

We included 126 hypertensive patients (65 males and 61 females, mean age 66.8 ± 8.9 years), with T2DM, IRF and MA, defined as urinary albumin excretion ≥30 mg/24h but ≤300 mg/24 h, and BP values higher than recommended by ESC-ESH guidelines (>130/80 mmHg).[37]

All patients included in the study were receiving the maximum tolerated dosage of any ACE-i or any ARB for at least six months before inclusion. During the study period, the subjects were allowed to continue their previous pharmacological treatment with their antihypertensive drugs, eventually including diuretics, β-blockers, CCBs, or any other antihypertensive drug, without dose adjustment. Biometric parameters, including weight and height, were measured in the morning under fasting conditions; accordingly, the body mass index (BMI) was estimated. All patients provided written informed consent, and the study protocol was approved by local ethical review boards. The study was conducted in accordance with good clinical practice and in accordance with the Declaration of Helsinki (2002) of the World Medical Association.

Study design

The aim of the study was to assess and compare the efficacy and safety of add-on therapy with aliskiren versus losartan (ARB) or ramipril (ACE-i) in hypertensive patients with a very high cardiovascular risk profile, due to concomitant presence of T2DM, IRF and uncontrolled hypertension, despite the current administration of optimal antihypertensive therapy, which included ACE-is or ARBs. See Figure 1. Patients were randomly assigned to receive 24 weeks of treatment with aliskiren (Group A; 63 patients), or losartan or ramipril (Group B; 63 patients), according to whether a patient was already receiving treatment with an ACE-i or an ARB, respectively. In Group A, we added aliskiren 150 mg to the previous therapy (T0), while in Group B we added ramipril 5 mg or losartan 50 mg. Drug up-titration was mandatory for SBP or diastolic BP (DBP) values ≥130 or ≥80 mmHg. Aliskiren was increased from 150 to 300 mg, ramipril from 5 to 10 mg and losartan from 50 to 100 mg; no further dose adjustments were allowed until the end of the observation period. If the glomerular filtration rate (GFR) estimated by CrCl decreased by more than 30% from baseline within four weeks after initiation of aliskiren, we would have decreased or discontinued ACE-i or an ARB.[38] The dosage of oral antidiabetic drugs or insulin was adjusted as needed. BP values, MA, CrCl and clinical chemistry were evaluated at baseline and after four (T1), 12 (T2) and 24 (T3) weeks.

Blood pressure measurement

Clinical BP measurement was performed at our hospital in the morning between 8:00 and 10:00; it was taken in the supine position after at least 10 min of rest. Three measurements were performed with a mercury sphygmomanometer and averaged, according to current recommendations.[38]

Evaluation of CrCl and albuminuria

Each enrolled patient underwent a 24 h urine collection to evaluate CrCl and MA. CrCl was calculated according to the standard formula: (urinary creatinine × 24h urinary volume)/(serum creatinine × 1440); MA was evaluated by standard immunoturbidimetric assay.

Statistical analysis

The Kolmogorov Smirnov test verified that several variables had a non-normal distribution; consequently, given also the relatively small size of our sample, we chose a permutation test-based analysis. This subset of non-parametric statistics, widely used in biomedical research, is considered preferable to the classic non-parametric approach[39] since it is based on more realistic foundations; furthermore, it is intrinsically robust and the resulting inferences are credible because they estimate the entire data distribution and exploit all information contained in the sample.[40] Accordingly, data were expressed as mean ± standard deviation (SD). Comparisons were conducted

Table 1. Baseline characteristics of study groups.

	All hypertensives	Group A	Group B	*p*
Number	126	63	63	NS
Gender (m/f)	65/61	33/30	32/31	NS
Age (years)	66.8±8.9	67.2±8.6	66.4±9.2	NS
BMI (kg/m²)	27.7±4.3	28.6±4.8	26.8±3.6	= 0.02
SBP (mmHg)	153.3±5.7	153.5±5.4	153.5±5.4	NS
DBP (mmHg)	83.6±8.0	83.7±7.5	83.5±8.6	NS
EF (%)	59.4±6.0	59.2±6.0	59.6±6.1	NS
HR (beats/min)	76.7±9.7	77.4+9.7	76+9.7	NS
sCr	0.97±0.2	0.96±0.2	0.99±0.2	NS
CrCl (ml/min)	74.17±19.8	75.30±19.8	73.0±19.8	NS
MA (mg/24h)	103.4±53.3	103.4±56.8	103.4±50.0	NS
K+ (mEq/l)	4.0±0.4	4.03±0.6	4.04±0.5	NS
HbA1c (%)	7.5±1.7	7.5±1.6	7.6±1.3	NS
Smokers (%)	27	26	28	NS
LHDL-C (%)	34	35	33	NS
AMI (%)	10	9.5	11.1	NS
CAD (%)	18	19	17	NS
Stroke (%)	13	11	12	NS
TIA (%)	17	17	16	NS
RPs (%)	14	14	14	NS
LVH (%)	46	47	45	NS
IRF (%)	24	24	25	NS
mCVRFs	4.8±1.8	4.8±1.7	4.7±1.9	NS
Drugs	2.6	2.56	2.64	NS

Values are calculated as mean ± SD.
LHDL-C: low high-density lipoprotein cholesterol; AMI: acute myocardial infarction; CAD: stable coronary artery disease; TIA: transient ischaemic attack; RP: revascularization procedure; LVH: left ventricular hypertrophy; IRF: impaired renal function; BMI: body mass index; EF: ejection fraction; K+: serum potassium levels; SBP: systolic blood pressure; DBP: diastolic blood pressure; mCVRF: mean cardiovascular risk factor; sCr: serum creatinine; CrCl: creatinine clearance; MA: microalbuminuria (mg/24h); HbA1c: glycosylated haemoglobin.

with the Nonparametric Combination test (NPC-test), which is based on a simulation or resampling procedure that is conditionally dependent on the data; thus, it provides a simulated estimate of the permutation distribution of any statistic.[41]

Moreover, in order to verify the results obtained with this approach, we integrated the statistical analysis with a traditional non-parametric approach (median and IQR); consequently, the comparisons between the variables were conducted with the Mann–Whitney *U* test. Comparisons between different observation times were carried out with the Wilcoxon test. The correlations among the variables were assessed with Spearman's test. To perform the statistical analyses, we used the SPSS statistical package (SPSS V. 17.0, Chicago, IL), and the NPC test 2.0 (Statistical software for multivariate permutation tests; Methodologica srl, Treviso).

Results

Patient characteristics

Table 1 presents the characteristics of the study population at baseline. Besides age, gender and biometric parameters, in the table are reported adjunctive CV risk factors (CVRFs), such as smoking habit and low high-density lipoprotein cholesterol (HDL-C) plasma levels, and comorbidities/complications such as history of CAD, previous AMI, TIA, stroke, history of coronary revascularization procedures, and the prevalence of LVH and of IRF. No significant differences could be found in regard to the age, gender, heart rate and CVRF prevalence. Group A had a higher BMI compared with Group B (28.6 ± 4.8 *vs*. 26.8 ± 3.6; $p < 0.05$). At baseline, patients were receiving an average of 2.4 antihypertensive drugs.

Four patients dropped out the study before its conclusion because of adverse events: one in Group A (diarrhoea) and three in Group B (two for cough, and one for angina pectoris). The direct causal relationship of adverse events with drugs in use and/or with pre-existing conditions was not further evaluated.

Changes in BP, MA, CrCl and serum potassium

Tables 2 and 3 present the mean changes in BP, MA, CrCl and serum potassium levels. At T1 (four weeks) in both groups there was a significant reduction of SBP (–9.08 mmHg and –5.33 mmHg, respectively; both $p < 0.001$)

and DBP (–4.36 mmHg, $p < 0.001$; and –2.55 mmHg, $p < 0.003$, respectively).

At T1, 35 patients from Group A (~55%) and 41 patients from Group B (~65%) still exhibited inadequate control of BP; therefore, and according to the study design, drug uptitration was prescribed. In detail, from the fifth week of treatment until the end of the observation, 35 of 63 patients in group A took aliskiren 300 mg daily, whereas 27 continued with 150 mg daily; in Group B, 22 out of 30 patients who were taking ramipril 5 mg switched to 10 mg per day, and 19 out of 33 patients who were taking losartan 50 mg switched to 100 mg per day.

Figure 2 presents SBP, DBP, MA, CrCl and serum potassium level variation during the observation period.

At the conclusion of the study (T3) both treatments provided a significant reduction of SBP (–11.4 mmHg and –8.5 mmHg, respectively; both $p < 0.001$) and DBP levels (–10.7 mmHg and −9.3 mmHg, respectively; both $p < 0.001$) versus baseline. The reduction rate of SBP in Group A was significantly higher than in Group B ($\Delta = –2.9\%$; $p < 0.01$); furthermore, the DBP reduction rate reached statistical significance ($\Delta = –1.4\%$; $p = 0.05$) (Figure 2(a) and (b)).

Table 2. Percentage of changes of BP, creatinine clearance, microalbuminuria and serum potassium levels at the end of observation in Group A and Group B.

Δ%	Group A	Group B	Difference	*p*
SBP	–11.4	–8.5	–2.9	<0.001
DBP	–10.7	–9.3	–1.4	<0.05
CrCl	+13.1	+19.4	–6.3	NS
MA	–67.6	– 49.1	–18.5	<0.001
K±	+19.3	+16.8	+2.5	NS

Statistical difference was tested with the Mann–Witney *U* test.
SBP: systolic blood pressure; DBP: diastolic blood pressure; CrCl: creatinine clearance; MA: microalbuminuria (mg/24h); K±: serum potassium levels

At T3 both treatments provided a significant increase of CrCl (+13.1 ml/min and +19.4 ml/min, respectively; both $p < 0.001$). There was no significant difference between the groups (*p*: NS) (Figure 2(c))

MA levels remained substantially unchanged after the first four weeks in both groups; a significant urinary albumin excretion reduction was observed after 12 weeks of treatment (T2) in both the treatment groups, and it decreased further after 24 weeks (T3) ($p < 0.001$ for both groups compared with baseline). The MA reduction rate was significantly higher in Group A compared with Group B ($\Delta = –18.5\%$; $p < 0.001$) (Figure 2(d)).

During follow-up, we observed a slight, progressive increase of serum potassium levels when compared with baseline (+ 0.78 mEq/l and + 0.68 mEq/l, respectively; both $p < 0.001$) (Figure 2(e)) without a significant difference between the groups ($\Delta = + 0.1$ mEq/l; 2.5%; $p = 0.51$, NS). Five patients experienced a mild increase of serum potassium levels (K+ > 5.5 but < 6.0 mEq/l) and they were managed with dietary potassium restriction. None of these patients were discontinued from the trial because of increase of serum potassium levels, or increase in baseline plasma creatinine > 30%.

Discussion

Patients enrolled in our study are those that are termed ‘complicated’. We usually define ‘complicated’ patients as hypertensive subjects with diabetes, MA and previous CV events. In fact, these conditions increase the risk of new CV events and accelerate the progression of target organ damage, such as end-stage renal disease; moreover, low numbers of patients at very high CV risk achieve the BP target levels.[37]

At the conclusion of the study, we observed a reduction of BP and MA in all patients. This result is likely due to the addition of a RAAS antagonist to the previous standard

Table 3. Percentage of changes of blood pressure, creatinine clearance, albuminuria and serum potassium levels between baseline and T3.

		Baseline	T3	Δ%	*p*
Group A	**SBP (mmHg)**	153.5±5	136.0±7.7	–11.4	<0.001
	DBP (mmHg)	83.7±7.6	74.5±7.9	–10.7	<0.001
	CrCl (ml/min)	75.3±19.8	85.2±20.3	+13.1	<0.001
	MA (mg/24h)	103.4±57	33.5±16	–67.6	<0.001
	K± (mEq/l)	4.03±0.45	4.81 ± 0.62	+19.3	<0.001
Group B	**SBP (mmHg)**	153.2±6	140.2±7.8	–8.47	<0.001
	DBP (mmHg)	83.5±8.6	75.7±8.3	–9.28	<0.001
	CrCl (ml/min)	73.0±19.8	87.2±20.1	+19.4	<0.001
	MA (mg/24h)	103.5±5	52.6±44.2	– 49.1	<0.001
	K± (mEq/l)	4.04± 0.5	4.72 ± 0.7	+16.8	<0.001

Data are mean ± standard deviation. Δ between group after 24 weeks. *P*: two-tailed *Z*-test for significance (Wilcoxon).
T3: 24 weeks after treatment; SBP: systolic blood pressure; DBP: diastolic blood pressure; CrCl: creatinine clearance; MA: microalbuminuria (mg/24h); K±: serum potassium levels

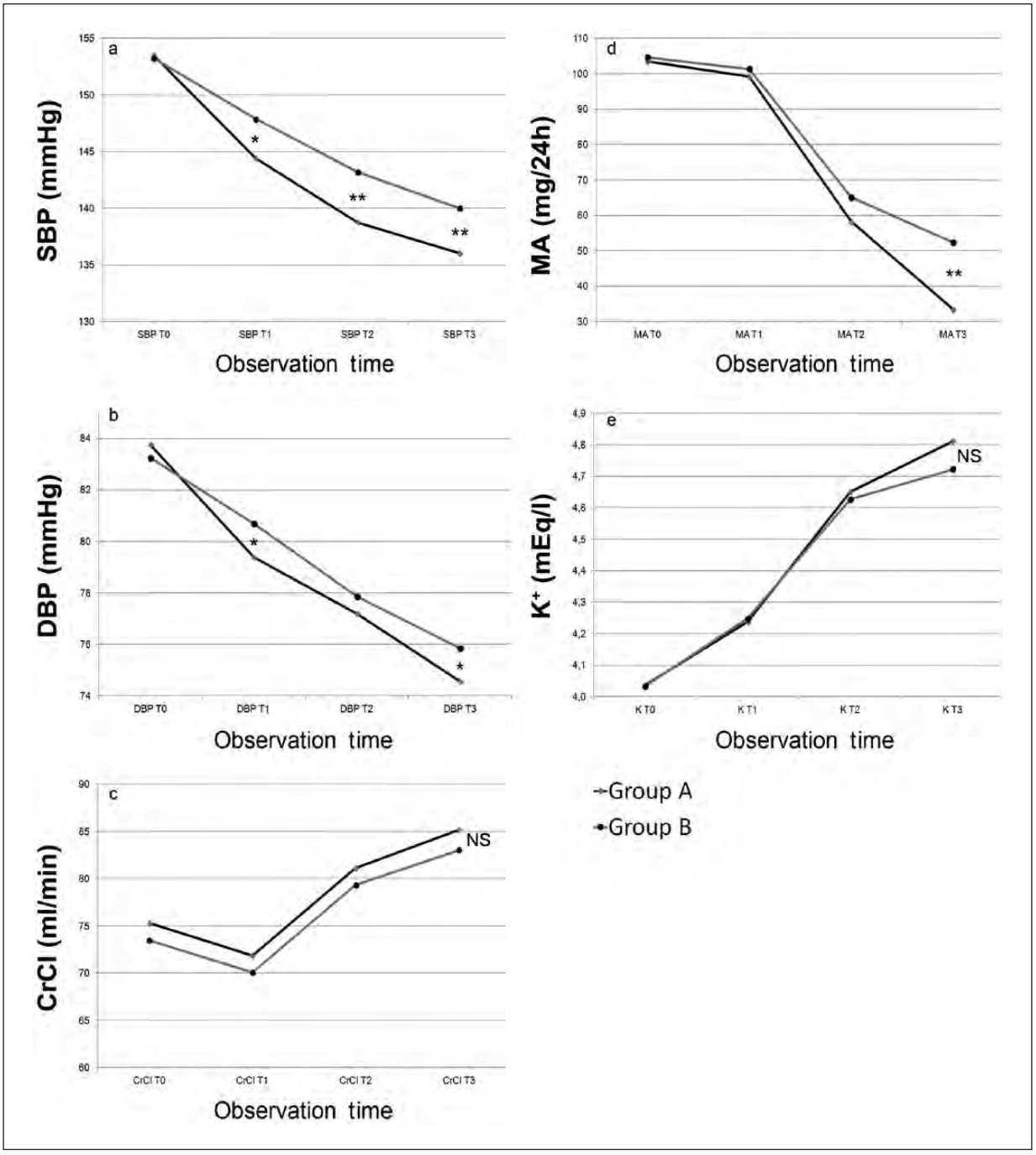

Figure 2. Variation of systolic blood pressure (SBP) (a), diastolic blood pressure (DBP) (b), creatinine clearance (CrCl) (c), microalbuminuria (MA) (d), serum potassium (K+) (e) during observation period (four (T1), 12 (T2) and 24 (T3) weeks).

treatment. Notably, in this study, both treatments showed an adequate safety and tolerability profile. In fact, we actually had a low dropout incidence due to an increase of serum potassium levels: we had five cases of mild hyperkalaemia, which were managed with dietary potassium restriction. None of these patients were discontinued from the trial because of hyperkalaemia, or an increase in baseline plasma creatinine > 30%. Furthermore, our study showed that the addition of aliskiren to a previous conventional antihypertensive treatment that included a RAAS antagonist, either an ACE-i or an ARB, had a greater effect in reducing SBP than the addition of either ACE-i or ARB; further reduction of SBP by approximately 4 mmHg was found with the former regimen.

No difference was observed in DBP reduction between the two groups.

However, our results are in agreement with the findings of other clinical trials.[42–44] An eight-week, double-blind, multicentre trial[45] assessed whether the combination of aliskiren and ramipril in patients with diabetes and hypertension was safe and effective in lowering BP when compared with the respective monotherapies. In this study aliskiren showed higher SBP reduction with ramipril. Moreover, when used in combination with ramipril, aliskiren provided a significant additional reduction in both SBP and DBP. Another eight-week, randomized, controlled trial[42] compared valsartan, aliskiren and their combination at the maximum dose (320/300 mg) in patients with mild to moderate hypertension. This study showed that the combination of aliskiren and valsartan at maximum recommended dosages provides greater reduction in BP values compared with monotherapy with valsartan or aliskiren alone.

We must stress that these results were obtained in a clinical setting of mild to moderate residual hypertension in T2DM patients, where a significant degree of pressure reduction is hard to achieve, especially in a limited timeframe. A recent 24-week, open-label, single-arm study showed that the combination therapy of aliskiren and a RAAS blocker in CKD patients who were already being treated with ACE-is or ARBs for more than six months had a favorable effect on reducing residual proteinuria and BP reduction.[44] Another recent study[43] confirmed the efficacy and safety of aliskiren in a real-life setting. Aliskiren is approved for treatment of hypertension, but has also shown renoprotective potential in normotensive patients with T2DM and albuminuria.[24,25,46] All patients included in the study were receiving the maximum dosage of an ACE-i or ARB for at least six months before inclusion. To date, this is the optimal treatment to reduce albuminuria and delay the progression of CKD.[38] After 24 weeks we observed a significant reduction of urinary albumin levels in both groups. In Group A, we observed a higher reduction of MA compared with group B (–67.6% *vs*. −49.1%, respectively; versus basal, additional reduction –18.5%; $p< 0.001$); furthermore, in both study groups we observed, after an initial decrease at four weeks, a significant improvement of GFR estimated with CrCl at 24 weeks with respect to baseline (+13.1 ml/min and +19.4 ml/min, respectively; both $p < 0.001$); however, no difference was detected in CrCl variation between the two groups. Adjunctive therapy with aliskiren appeared to provide a more beneficial improvement of diabetic nephropathy in hypertensive patients, as marked by urinary albumin excretion, compared with other treatment protocols that are considered to be the gold standard.[38] The renal protective effects of aliskiren could be related to its organ-specific mechanism of action.[18] A direct renin inhibition with aliskiren provides a greater intrarenal protective effect than other RAAS antagonists.[47] The results of our study show that the multi-level blockade of the RAAS represents a good therapeutic strategy, and confirms the efficacy and safety of aliskiren. These results are consistent with those of other and larger randomized clinical trials. The AVOID study recruited 599 patients with hypertension, T2DM and proteinuria who were already receiving the maximum recommended renoprotective treatment with losartan (100 mg daily) and exhibited an optimal management of hypertension; enrolled patients were randomized to receive adjunctive treatment with aliskiren (300 mg daily) or placebo. In the group treated with aliskiren, a significant reduction of albuminuria, compared with placebo, was observed. This benefit appeared to be independent of systemic BP reduction.[24] Adjunctive therapy with aliskiren appears to be a unique opportunity for patients at high cardiovascular risk. These patients usually show a poor response to conventional antihypertensive treatment. It is likely that the double blockade of RAAS with DRI and an ACE-i or an ARB can help us to better understand the pathogenesis of hypertension. If so, it would provide a more effective therapeutic strategy in preventing hypertension-related diseases; consequently, it would delay the progression towards the end-organ damage. More long-term data are needed to confirm the efficacy and safety of this regimen in these patient populations. The ASPIRE HIGHER programme was undertaken to evaluate potential cardiorenal effects of aliskiren over a spectrum of conditions in 14 different studies involving more than 35,000 patients.[33] Three of these studies (AVOID, ALLAY and ALOFT) evaluated surrogate endpoints and confirmed the favourable effects of adding aliskiren to standard treatment. The ASPIRE HIGHER programme also included four morbidity and mortality trials.[33] One of these, the ALTITUDE, was halted by a recommendation from its DMC.[34] The basis of the DMC recommendation was futility (i.e. no prospect of demonstrating the treatment benefit anticipated in the protocol), as well as safety concerns. These concerns included renal dysfunction and hyperkalaemia. Doubling of serum creatinine occurred in 4.8% of the aliskiren group *vs.* 5% of the placebo group (p= NS). ESRD or renal death occurred in 2.8% of the aliskiren group *vs.* 2.5% of the placebo group (p= NS). Hyperkalaemia occurred in 39% of the aliskiren group *vs.* 29% of the placebo group, and severe hyperkalaemia was observed in 21% *vs.* 16%. It was assessed that there were no cases where the increase in potassium needed dialysis, but there was one case where raised potassium levels were specified as the cause of death. Other main concerns were hypotension and an excess of non-fatal strokes. In response to these findings, it has been recommended that dual aliskiren and ACE-i/ARB therapy not be used in patients with both hypertension (the current indication for aliskiren) and diabetes or moderate to severe renal dysfunction. The recently-published ASTRONAUT trial[35] reported that the addition of aliskiren to standard therapy in patients with acute HF and reduced left ventricular ejection fraction (LVEF) appeared to improve post-discharge outcomes and biomarker profiles; it was

generally well-tolerated in non-diabetic patients. In contrast, diabetic patients receiving aliskiren appeared to have poorer post-discharge outcomes.

The ATMOSPHERE trial is currently being conducted on patients with chronic HF.[36,48] We want to stress that, in the population enrolled in ALTITUDE, BP was well-controlled at baseline, and patients were randomized to receive aliskiren 150 mg or placebo in addition to their conventional treatment (including a maximum dose of ACE-i or ARB). After four weeks of treatment, the patients were force-titrated to receive aliskiren 300 mg. In contrast, all of the patients enrolled in our study had poor BP control at baseline, and aliskiren was up-titrated to 300 mg only if the BP target was not achieved at the fourth week. This study design allowed a low dropout rate and a lower incidence of side effects compared with other studies.

Further larger clinical studies are ongoing, and they may add further insight regarding aliskiren safety and efficacy; furthermore, they may increase understanding regarding the mechanisms underlying its cardiorenal protective potential. The APOLLO Trial should provide new information regarding the role of aliskiren (with or without additional therapy with a diuretic or a CCB) in elderly subjects (≥ 65 years; with SBP 130 to 159 mmHg) in preventing major CV events and on global measures of physical, executive and cognitive function (ClinicalTrials.gov identifier: NCT01259297). Moreover, we hope that a subanalysis of ALTITUDE, and the outcomes of the other long-term studies (ATMOSPHERE, ASTRONAUT and APOLLO) will help us to identify the subgroup of patients that could obtain an advantage from dual RAAS blockade with DRI and ACE-I or ARB.

Study limitations

The major limitation of our study is the small sample size that limits our ability to determine statistical significance.

Conclusions

The addition of aliskiren to the standard therapy provides greater reduction of BP and urinary albumin excretion than adding an ACE-i (ramipril) to an ARB and vice versa (losartan to ACE-i). The dual blockade of RAAS can be associated with an increased risk of hyperkalaemia compared with monotherapy; therefore, we recommend that this therapeutic strategy requires closer monitoring of renal function and serum potassium levels.

Conflict of interest

The authors have no conflicts of interest to declare.

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ORIGINAL PAPER

Arterial stiffness as a predictor of recovery of left ventricular systolic function after acute myocardial infarction treated with primary percutaneous coronary intervention

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Abstract Left ventricular ejection fraction (LVEF) and pulse wave velocity (PWV) are acknowledged as independent risk factors in different high-risk populations. We investigated the effects of arterial stiffness on LV function at 3 and 6 months after acute myocardial infarction. Changes in LVEF were evaluated in 136 consecutive patients who were diagnosed with ST-segment elevation coronary syndrome and treated with primary percutaneous coronary intervention. Doppler guided by 2D ultrasound was used to measure carotid-femoral PWV. According to tertiles of arterial stiffness, a significant correlation between higher PWV and worse recovery in LVEF was found (3 months EF change: 9.9 ± 5.0 % vs 5.9 ± 3.4 vs 3.8 ± 1.6; $p < 0.001$ and 6 months EF change: 18.5 ± 7.0 % vs 11.5 ± 5.2 vs 7.3 ± 3.0; $p = 0.002$). In the multivariate analysis PWV showed the ability to predict the outcome in terms of EF recovery at 3 and 6 months also after any correction for age and other variables ($\beta = -0.566$, $p < 0.001$). Arterial stiffening may result in a less effective recovery of LV function after acute myocardial infarction.

Keywords Arterial stiffness · Pulse wave velocity · Left ventricular systolic function · Myocardial infarction · STEMI

Introduction

Left ventricular (LV) systolic function is a useful indicator of in-hospital [1] and long-term [2] prognosis in patients with acute myocardial infarction (MI). Some authors described a variable degree of recovery that may occur early (i.e., within the first 24 or 48 h after admission) or during the ensuing period (i.e., several weeks or months after MI) [3], related to restoration of LV stunning and/or the effect of medical and mechanical therapies. Indeed, recovery of LV function can improve the clinical outcome. On the other hand, increased pulse wave velocity (PWV), a non-invasive index of arterial stiffness [4], predicts cardiovascular event in different clinical conditions [5, 6]. Increased arterial stiffness negatively affects both cardiac structure and function [4], leading to left ventricular hypertrophy, a powerful independent marker of mortality [7], and associates with systolic and diastolic abnormalities [8], putting the emphasis on arterial-ventricular coupling. To the best of our knowledge, no study on the relationship between PWV and improvement of LV ejection function (EF) in patients with acute MI has been reported. The aim of the present study was to state whether the value of PWV after acute myocardial infarction may predict the change in LVEF in the medium term.

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Methods

Subjects and measures

One-hundred-thirty-six consecutive acute coronary syndrome (ACS) patients were recruited from January to June 20 [1] 4 during their hospitalization in our Department of Cardiology for ST-Elevation Myocardial Infarction (STEMI). Patients were eligible if they met the criteria for ACS, proposed by the Joint European Society of Cardiology/American College of Cardiology Committee [9], and if they underwent to immediate coronary revascularization procedures (primary percutaneous coronary intervention, pPCI). Exclusion criteria were: previous ACS or current ACS without ST elevation, PCI following coronary artery bypass graft surgery (CABG), cardiogenic shock, atrial fibrillation, peripheral artery disease, severe cardiac valve disease and the presence of a prosthetic aorta. Patients with: age >75 years, EF < 35 %, or underwent to pPCI > 240 min were not included in the study. Patients with persistent not hemodynamically stable after 24 h from pPCI were also excluded. Blood pressure and heart rate values as well as echocardiographic study were achieved in all participants at baseline and as two fixed time points at 3 and 6 months during follow-up. Echocardiograms were performed in double by two experienced ultrasonographers, before PCI procedure and at follow-up, using a VIVID 7 Pro ultrasound machine (GE Technologies, Milwaukee, WI, USA) as recommended by the American Society of Echocardiography [10]. A standard imaging protocol was used, based on apical 4- and 2-chamber views; two-dimensional echocardiograms of the LV short axis were recorded from the left parasternal region at three levels: mitral valve, mid-papillary muscle level and apex. M-mode echocardiographic features were used for measurement of LV and left atrial dimension, while LV ejection fraction and LV volumes were estimated from apical four chamber view, using the biplane modified Simpson method [11]. The peak early transmitral filling velocity during early diastole (E), late diastole (A) and deceleration time (DT) were imaged in the apical 4-chamber view at the tip of the mitral leaflets. Color-coded tissue Doppler imaging (TDI) was applied to the apical 4-chamber view to determine mean early (E′) and late (A′) velocity at the septal mitral annulus. Changes in LV function at time points was defined as $\Delta(\%) = [(EF_{xmonths}–EF_{baseline})/EF_{baseline}] \times 100$. According to the method published in detail elsewhere [12], a pulsed Doppler ultrasound with a linear array probe, synchronized with ECG, was used to measure carotid-femoral PWV in all participants. We performed three recordings of the common carotid artery and three recordings of the femoral artery at the groin. Each recording involved at least three cardiac cycles. Transit time (TT), was estimated by the time from the R wave of QRS to the foot of the ultrasound waveforms at each site. To determine PWV, the ratio between the distance (measured from the sternal notch to the femoral artery at the groin) and TT was calculated, according to the formula: PWV = distance/(T2−T1). Standard echocardiography and PWV assessment were performed when patients were hemodynamically stable, however within 48 h following PCI.

To evaluate the reproducibility of the Simpson's method and PWV estimation, we evaluated the variability of individual methods between two observers, and between two analyses by the same observer. Inter-observer variability was studied by comparing pairs of results analyzed by two observers. Intra-observer variability was studied by comparing pairs of results from the repeated analyses by the same observer. Intra- and inter-observer agreements in Simpson's method were assessed by linear regression with Bland–Altman analysis, showing a correlation of 0.91 and 0.88, respectively. The same analysis was performed to assess intra- and inter-observer agreement in PWV evaluation, with a correlation coefficient of 0.89 and 0.87, respectively. A written informed consent was obtained from each participant before initiating any study-related procedure. The study protocol was approved by the research review board of the participating hospital units.

Statistical analysis

Data are presented as means, standard deviations, and frequency of occurrence (%). Continuous variables were compared with the paired or unpaired Student's *T* test, ANOVA with post hoc Tukey test, or with simple Pearson correlation as appropriate. Test for normality was carried out on all variables by Kolmogorov–Smirnov test, and non-normally distributed variables (as PWV and EF) has been transformed for the purpose of regression analysis. In order to assess independent predictors of Δ (%) EF of LV function we performed a dependence analysis by multiple regression model adjusted for age, sex and body mass index. The SPSS 20 statistical software was used for the analysis (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

Table 1 shows the characteristics of the population at the time of enrolment. Table 2 compares the characteristics of the patients divided by tertiles of baseline PWV. Patients with higher values of PWV were older and had higher systolic and diastolic BP ($p < 0.001$); however, no significant difference was found as regards multi-vessel coronary artery disease, burden of coronary disease, time-to-balloon,

Table 1 Baseline characteristics

	All patients (136)
Male sex (%)	52.0
Age (year)	63.1 ± 11.3
Body-mass index (kg/m^2)	27.5 ± 5.1
Smokers/hypertension/diabetes mellitus (%)	64.0/52.0/14.0
Systolic/diastolic BP (mmHg)	131.5 ± 19.3/71.2 ± 11.4
Heart rate (beats/min)	74.9 ± 9.8
Killip Class I/II/III/IV	70.1/25.2/5.1/0.0
Pulse wave velocity (m/s)	10.5 ± 4.5
Multivessel coronary artery disease (%)	85.6
Burden of coronary artery disease (%)[†]	24.6 ± 6.5
Time to balloon (min)	146.8 ± 53.9
Stent implantation/patient (n°)	1.3 ± 0.5
Glycoprotein IIb/IIIa Inhibitors (%)	58.4
Total Cholesterol (mg/dl)	190.7 ± 38.9
HDL Cholesterol (mg/dl)	41.2 ± 7.7
Triglyceride (mg/dl)	135.4 ± 59.5
Fasting glucose (mg/dl)	90.6 ± 14.8
Creatinine (mg/dl)	0.8 ± 0.1
C reactive protein (mg/dl)	7.1 ± 3.7
Peak creatine kinase (U/L)	1724.5 ± 477.3
Peak MB creatine kinase (U/L)	133.9 ± 43.4
Peak high sensitive troponine-T (μg/L)	3.0 ± 1.6
End-diastolic volume (mL/m^2)	59.0 ± 13.9
End-systolic volume (mL/m^2)	20.4 ± 7.8
Index LV mass (g/m^2)	111.2 ± 25.0
Basal ejection fraction (%)	51.5 ± 6.4
Wall motion score index	1.83 ± 0.16
E/A	0.9 ± 0.4
E/E′ ratio	8.0 ± 2.9

[†] Calculated as the ratio between stenosis degree and the number of vessels

final TIMI flow grade, LV mass index. Wall motion score index was similar among the groups, but E/E′ ratio appears to gradually increase ($p < 0.001$) according to tertiles, and EF to decrease ($p < 0.001$). No patient has died during the follow-up period; there was no significant difference in therapy among the groups as regards ACE inhibitors/Angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, statins, and dual antiplatelet therapy (Table 2), both at the discharge and at 3 and 6 months. Hemodynamic parameters were likewise distributed in the tertiles of PWV; EF appeared to be significantly improved both after 3 and 6 months in all patient groups with respect to baseline values. The change of LV function from baseline to 3 and 6-months follow-up, assessed as previous described (Δ %), is shown in Fig. 1. An inverse correlation ($r = -0.621$; $p < 0.001$) between baseline PWV and EF change at 6 months was found in the whole study population (Fig. 2). Table 3 compares the difference of PWV and EF according to age. Figure 3 compares the PWV values of the patients divided by steps of 5 % recovery of LV function at 6 months. However, the adjusted recovery rate after 3 and 6 months was significantly lower in the tertile of patients with higher values of PWV (1.7 ± 0.7 %; 3.3 ± 1.4 %) compared to the first one (5.6 ± 2.7 %; 10.4 ± 3.7 %; $p = 0.045$ and $p = 0.002$, respectively). Moreover, multiple regression analysis performed to assess the contribution of each variable on Δ(%) EF showed that PWV ($p < 0.001$), together with baseline EF and E/E′ ratio, appeared to be independently associated also after the adjustment for confounders (Table 4).

Discussion

Our study shows, for the first time, a worse and late recovery in LV function after MI in patients with increased arterial stiffness. Although previous studies have already reported the relationship between other variables and progressive improvement in LV function within weeks or months following MI, our study provides new insights about this focus. Our data in fact suggest that PWV values recorded within 48 h after acute MI is able to predict LVEF change at 6 months from ACS. It is noteworthy that age was confirmed as a major determinant of PWV; age in fact appeared to be significantly associated with PWV and EF values recorded after AMI, and also with EF change over the time. However, PWV maintained its significance in predicting the outcome in terms of EF recovery at 6 months also after any correction for age.

The first potential mechanism might be that baseline cardiac work load and systolic stress were increased by ejection into the stiffened vasculature, limiting the adaptive responses to ischemia.

In particular, when the heart ejects into the abnormally compliant systemic vasculature, acute coronary occlusion could be more tolerated, with only modest changes in diastolic and systolic pressures. However, when heart is subjected to the same occlusion while ejecting into the stiff aortic conduit, acute cardio-depression could be greatly exacerbated and adaptive responses compromised, with increased myocardial vulnerability to widespread ischemia [13]. Indeed, heart ejecting into a low-compliance vascular system could generate a wide pulse pressure, simultaneously increasing systolic chamber wall stress while lowering diastolic coronary perfusion pressure [14]. A compelling and plausible explanation for the relationship between arterial stiffness and LV dysfunction invokes high blood pressure, chronic pulsatile hemodynamic loading on

Table 2 Differences of variables according to tertiles of pulse wave velocity

	PWV < 7.9 (45 pts)	8 < PWV <10.9 (46 pts)	PWV > 11 (45 pts)	*p**
Male sex (%)	50.0	52.3	53.6	ns
Age (year)	58.3 ± 8.8	63.5 ± 12.4	67.4 ± 10.9	0.001
Body-mass index (kg/m^2)	27.4 ± 3.7	27.1 ± 3.7	27.9 ± 7.2	ns
Smokers/hypertension/diabetes mellitus (%)	61.9/50.0/11.9	64.3/52.4/14.3	65.8/53.7/14.6	ns
Baseline systolic BP (mmHg)	121.4 ± 10.9	131.6 ± 12.3	141.6 ± 25.9	0.000
3-months systolic BP (mmHg)	119.5 ± 9.5	129.7 ± 9.2	137.5 ± 19.9	0.000
6-months systolic BP (mmHg)	117.2 ± 7.4	127.5 ± 7.7	132.5 ± 14.5	0.000
Baseline diastolic BP (mmHg)	64.1 ± 6.6	71.4 ± 9.3	78.3 ± 12.9	0.000
3-months diastolic BP (mmHg)	63.4 ± 7.1	70.6 ± 10.1	75.8 ± 11.8	0.000
6-months diastolic BP (mmHg)	62.4 ± 5.3	70.2 ± 8.7	77.1 ± 12.7	0.000
Baseline Pulse Pressure (mmHg)‡	57.4 ± 11.2	60.2 ± 12.2	63.3 ± 19.9	ns
3-months Pulse Pressure (mmHg)‡	56.0 ± 9.4	59.1 ± 10.4	61.6 ± 16.3	ns
6-months Pulse Pressure (mmHg)‡	65.8 ± 6.4	57.3 ± 9.6	55.4 ± 11.2	ns
Baseline Heart rate (beats/min)	73.8 ± 10.0	74.6 ± 8.0	76.5 ± 11.4	ns
3-months Heart rate (beats/min)	73.2 ± 9.8	72.7 ± 7.0	75.1 ± 11.2	ns
6-months Heart rate (beats/min)	72.2 ± 10.1	72.3 ± 7.3	74.1 ± 12.0	ns
Killip Class I/II/III/IV (%)	75/25/0/0	81/19/0/0	57/33/10/0	ns
Multivessel coronary artery disease (%)	83.3	85.7	87.8	ns
Burden of coronary artery disease (%)†	24.1 ± 5.2	24.2 ± 7.5	25.6 ± 6.5	ns
Time to balloon (min)	145.3 ± 43.9	147.1 ± 57.8	148.2 ± 60.1	ns
Stent implantation/patient (n°)	1.2 ± 0.4	1.3 ± 0.6	1.5 ± 0.5	ns
Final TIMI flow grade 3 (%)	100.0	97.6	95.1	ns
Glycoprotein IIb/IIIa Inhibitors (%)‡	57.1	59.5	58.5	ns
Total Cholesterol (mg/dl)	191.2 ± 54.0	187.8 ± 38.8	193.3 ± 23.4	ns
HDL Cholesterol (mg/dl)	42.7 ± 8.6	40.2 ± 8.4	40.6 ± 5.8	ns
Triglyceride (mg/dl)	135.9 ± 56.8	134.5 ± 45.9	135.8 ± 76.6	ns
Fasting glucose (mg/dl)	86.6 ± 15.8	90.8 ± 12.4	94.4 ± 15.4	ns
Creatinine (mg/dl)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	ns
C reactive protein (mg/dl)	6.9 ± 3.9	7.1 ± 3.7	7.2 ± 3.5	ns
Peak creatine kinase (U/L)	1727.2 ± 578.1	1722.5 ± 446.9	1723.9 ± 398.7	ns
Peak MB creatine kinase (U/L)	134.8 ± 32.9	134.1 ± 36.5	132.8 ± 58.1	ns
Peak high sensitive troponine-T (μg/l)	2.9 ± 1.3	3.2 ± 1.6	2.9 ± 1.8	ns
End-diastolic volume (mL/m^2)	59.5 ± 14.9	60.1 ± 14.6	57.5 ± 11.8	ns
End-systolic volume (mL/m^2)	18.3 ± 5.7	20.5 ± 741	22.3 ± 9.5	ns
LV mass index (g/m^2)	101.6 ± 24.5	112.2 ± 18.0	119.9 ± 28.6	ns
Wall motion score index	1.56 ± 0.15	1.45 ± 0.16	1.63 ± 0.13	ns
Baseline EF (%)	57.0 ± 2.4	52.8 ± 5.6	44.4 ± 1.8	0.000
3-months EF (%)	62.6 ± 2.9	56.0 ± 6.1	46.1 ± 2.3	0.000
6-months EF (%)	67.4 ± 2.4	59.0 ± 6.8	47.7 ± 2.7	0.000
E/A	1.1 ± 0.5	1.0 ± 0.4	0.7 ± 0.1	0.000
E/E′ ratio	6.8 ± 2.6	7.2 ± 2.6	10.0 ± 2.6	0.000
Dual antiplatelet therapy (%)	100.0	100.0	100.0	ns
Statins (%)	100.0	100.0	100.0	ns
Diuretics (%)	25.2	27.4	29.7	ns
ACE-i/ARBs (%)	95.2	97.6	100.0	ns
Beta-blocker (%)	97.6	95.2	95.1	ns

* p values for ANOVA; †calculated as the ratio between stenosis degree and the number of vessels. ‡ $p < 0.05$ for independent T test between the first and the last tertiles of PWV

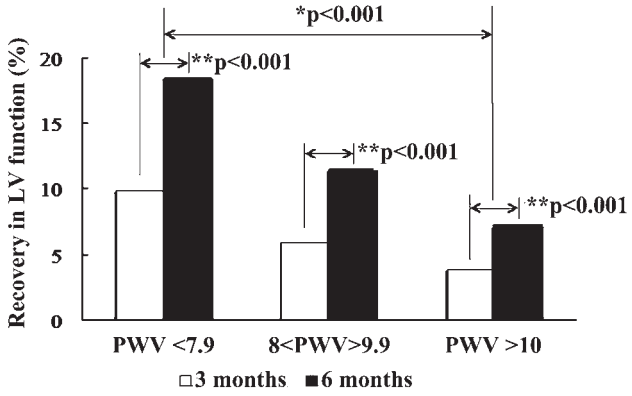

Fig. 1 Change % in left ventricular function at 3 and 6 months follow-up according to tertiles of pulse wave velocity (PWV). **p* value for ANOVA; ***p* values for paired *T* test

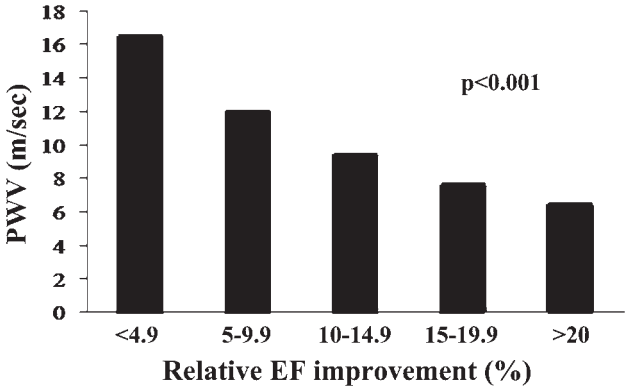

Fig. 3 Differences of PWV according to steps of 5 % of 6 months ΔEF

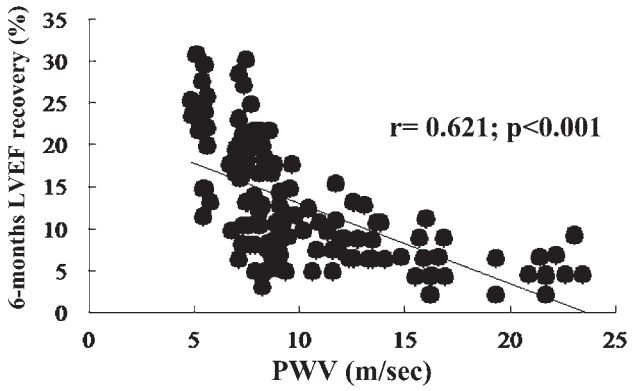

Fig. 2 Correlations between PWV and left ventricular ΔEF after 6 months. Correlation coefficient (*R*) is showed with its significance (*p*)

Table 4 Multiple regression analysis for EF

	ΔEF (%)	
	β	*P*
Male sex (%)	0.125	ns
Age (year)	−0.015	ns
Systolic BP (mm Hg)	−0.191	ns
Diastolic BP (mm Hg)	−0.214	ns
Pulse pressure (mm Hg)	−0.117	ns
Heart rate (beats/min)	−0.133	ns
Pulse wave velocity (m/s)	**−0.566**	**<0.001**
Time to balloon (min)	−0.047	ns
Peak creatine kinase (U/L)	0.089	ns
Baseline EF (%)	**0.457**	**0.013**
E/E′ ratio	**−0.283**	**0.029**
Glycoprotein IIb/IIIa inhibitors (%)	0.178	ns
Diuretics (%)	0.041	ns
ACE inhibitor (%)	0.083	ns
Beta-blocker (%)	0.012	ns

the LV, and subsequent ventricular hypertrophy predisposing to impaired function.

Interestingly, we found that arterial compliance was directly associated with late recovery function even after adjustment for systolic and pulse pressure, BP-lowering drugs, LV geometry and filling pressure. This finding is in line with recent work demonstrating that concurrent vascular and ventricular stiffening can advance even in the absence of cardiac hypertrophy [15]. In agreement with this hypothesis, patients with higher PWV had higher E/E′ ratio. The augmentation of the central aortic systolic BP together with the reduction in central aortic diastolic BP, may compromise coronary perfusion and enhance subendocardial ischemia. This can further impair myocardial relaxation and promote myocardial fibrosis, leading to diastolic dysfunction. However, we cannot exclude that ventricular and vascular stiffening occur in parallel, driven

Table 3 Differences of PWV and EF according to age

	Age < 55 (47 pts)	56 < Age < 69 (50 pts)	Age > 70 (39 pts)	*p**
PWV (m/s)	8.8 ± 2.4	9.9 ± 3.9	12.8 ± 5.8	0.000
Baseline EF (%)	54.1 ± 5.6	51.7 ± 5.3	48.6 ± 7.0	0.000
3-months EF (%)	58.1 ± 6.0	55.3 ± 7.9	51.4 ± 8.4	0.001
6-months EF (%)	61.1 ± 7.2	59.5 ± 9.0	53.6 ± 9.7	0.000

p values for ANOVA

by the same molecular mechanisms. Several scientific reports remarked that compromised arterial-ventricular coupling affects cardiovascular reserve function [16]. In a recent study, Patrianakos et al. showed that increased aortic stiffness is correlated with LV function and reduced exercise capacity in dilated cardiomyopathy [17]. It's known that in dilated heart disease, myocardial hypertrophy serves as a compensatory mechanism in response to excessive loading conditions to initially normalize wall stress. Likewise, in our hypothesis, inadequate LV adaptation (e.g. quasi-normal LV mass but increased LV wall stress), alters supply-to-demand balance by increasing myocardial oxygen consumption and reducing coronary blood flow, particularly in the subendocardium, with repetitive stunning [18] that might contribute to the irreversible impairment of regional LV function. Another implication of combined ventricular–arterial stiffening is that cardiac relaxation is delayed when the heart is exposed to elevated systolic pressure during ejection (i.e., increased afterload), as it occurs when arteries are stiffened and/or systemic resistance is increased [19]. Finally, it is well known that left ventricular function may change during the months after myocardial infarction, by mechanisms such as remodeling and gradual relief of stunning [20]. Thus, the complex relation between arterial stiffness and recovery of LV function could be related not only to the balance between necrosis and viability but also to plausible histological and biochemical changes in viable myocytes that might be responsible for delayed recovery of the function.

Study limitations

The study presents several limitations. The aim of the present study was to state whether the value of PWV after acute myocardial infarction may provide additional information on the ability of predict the recovery of systolic function within the following 6 months; consistently, we evaluated PWV at baseline, and LVEF, together with BP and HR values, at each time-point. However, to state potential relationships between PWV and LVEF at the following time-points was not the purpose of the study. Also, in our study population, we measured LVEF at 6 months, and some reports have suggested ongoing remodeling also beyond this period [21]. Moreover, we had no data on the extent of stunned but functionally viable myocardium in the infarct zone, as it can be estimated by other imaging studies [22]. Also we did not study the possible influence of other factors such as a better anticoagulant regimen or improvements in PCI procedure such as thrombo-aspiration; these therapeutic innovations might result in a greater portion of viable myocardium and consequently in a greater potential for recovery in LV systolic function. Finally, we acknowledge that our results were obtained in selected patients, predominantly male with acute MI and variable degree of baseline EF, and that any extrapolation to patients with other type of ventricular dysfunction should be made with caution, also taking into account the effects of the numerous confounders beyond statistical adjustments. On the other hand, our very homogeneous study population allows an easy estimation of residual LV dysfunction prior to discharge and of its recovery subsequently. Finally, we considered as "baseline" EF the value recorded after 24–48 h from myocardial infarction; we are unaware about the EF of each patient before ACS, consistently we can observe the change in systolic function, as evaluated by EF, with respect to this start point.

Conclusions

To the best of our knowledge, this is the first echocardiographic and Doppler study investigating the interrelationships between LV ejection fraction and arterial stiffness in patients with acute MI treated with pPCI. This study showed, for the first time, that by measuring PWV values after acute MI, important information could be obtained about LV function recovery during the follow-up.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Ischemic heart disease and early diagnosis. Study on the predictive value of 2D strain

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ABSTRACT

Introduction: Two-dimensional strain echocardiography (2D-SE) quantifies left ventricular global longitudinal strain (GLS) and global circumferential strain (GCS). Our aim was to test 2D-SE during dipyridamole stress echocardiography (Dipy-Stress) in patients with non-diagnostic result, checking by way of coronary CT angiography (CCTA) the possible presence of coronary artery disease (CAD).

Methods: Over twenty-four months 65 consecutive patients with non-diagnostic Dipy-Stress were studied by 2D-SE and by CCTA. GCS and GLS at rest and after stress were compared according to data derived from CCTA.

CAD was graded as significant (stenosis ≥50%), mild (stenosis between 15 and 50%) or absent (stenosis <15%). CCTA was defined as "positive" in presence of mild CAD and "negative" in absence of stenoses. Furthermore, Δ strain was defined as follows: [(stressS − restS) / restS] × 100.

Results: GCS at rest and after stress was similar in CCTA-positive (26 ± 5% and 27 ± 5% respectively) and CCTA-negative groups (27 ± 3% and 28 ± 3% respectively). GLS at rest was significantly reduced ($P < 0.0001$) in CCTA-positive (23 ± 3%) compared to CCTA-negative group (25 ± 2%). GLS after stress was lower ($P < 0.0001$) in CCTA-positive group (20 ± 3%) than CCTA-negative one (26 ± 2%).

A significant reduction ($P < 0.0001$) of GLS at rest versus after stress was found in positive-CCTA group. ΔGLS showed a significant decrease ($P < 0.0001$) in CCTA-positive (−10 ± 8%) compared to CCTA-negative (4.4 ± 5.8%) group.

ROC analysis of ΔGLS showed high accuracy (area under the ROC curve 0.916, 95% CI: 0.820–0.970) in distinguishing positive and negative CCTA groups.

Conclusions: 2D-SE during Dipy-Stress allows, in case of non-diagnostic test, identification of mild-CAD with high sensitivity and specificity.

1. Introduction

Ischemic heart disease is a major cause of death with a growing clinical and economic impact [1].

An early identification of coronary artery disease (CAD) and its correction by appropriate medical treatment and/or coronary revascularization reduces the incidence of cardiac events and improve the prognosis [2].

A non-invasive provocative test is generally required for the detection of myocardial ischemia in patients with multiple cardiovascular risk factors but also in those ones without history of ischemic heart disease or left ventricle (LV) dysfunction [3,4]. Dipyridamole stress echocardiography (Dipy-Stress) is a test widely recognized to unmask CAD in patients with moderate cardiovascular risk. Particularly Dipy-Stress has an excellent negative predictive value [5–7].

Recently two-dimensional strain echocardiography (2D-SE) has been introduced as a valid method to quantify both left ventricular (LV) longitudinal (L) and circumferential (C) deformation [8–16].

An early impairment of LV deformation, often without clinical signs of disease, has been observed in many heart diseases [17].

2D-SE is able to detect even minimal abnormalities of systolic function [15,16] improving the ability to quantitatively assess regional LV function [18].

Coronary CT angiography (CCTA) is a non-invasive diagnostic procedure for the direct identification of significant (≥50%) and not significant (<50%) coronary stenoses [19–24].

Previous studies investigated the clinical value of stress echocardiography to detect abnormalities of LV deformation due to significant CAD [25–27]. No previous studies instead investigated if mild coronary stenoses (<50%) could have an effect on LV deformation.

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The aim of our study was to test the usefulness of 2D-SE during Dipy-Stress in a group of patients with a non-diagnostic test result (no wall motion abnormalities or significant electrocardiographic changes in presence of atypical symptoms), checking through CCTA the presence of CAD Fig. 1.

2. Methods

2.1. Study population

Over twenty-four months we enrolled 71 consecutive patients [60 ± 6 years old, 34 (48%) female] with: 1) atypical chest pain, 2) no previous heart diseases, 3) no mechanical alterations during Dipy-Stress (wall motion score index, WMSI = 1) and 4) no electrocardiographic alterations during and after Dipy-Stress [28]. Baseline characteristics and cardiovascular risk factors as age, gender, estrogen status, diabetes mellitus, hypercholesterolemia, obesity, current or prior cigarette smoking, arterial hypertension, and a positive family history of CAD were collected before Dipy-Stress examination. According to these cardiovascular risk factors a Morise score [29] was quantified for each patient. Clinical characteristics are summarized in Table 1.

Everyone was then studied by 2D strain echocardiography "off-line" and by coronary CT angiography. Patients presenting with a) abnormal wall motion during stress echocardiography, b) kinetic abnormalities due to left bundle branch block and/or pacemaker stimulation, c) ejection fraction inferior to 50% at rest, or d) chronic coronary artery disease, arrhythmias, previous cardiac surgery, cardiomyopathies or moderate to severe valve disorders were excluded from the study (Fig. 1). Our local ethics committee reviewed the study and approved the investigation, judging it compliant to the principles outlined in the Helsinki Declaration. Written informed consent was obtained from all the subjects.

Table 1
Study population (clinical characteristics).

Variable	All patients (n = 65)
Age (years)	60 ± 6
Male	37
BMI (kg/m^2)	27 ± 3
SBP (mm Hg)	130 ± 16
DBP (mm Hg)	85 ± 11
HR (beats/min)	76 ± 13
Coronary risk factors (%)	
Arterial hypertension	74
Smoke	55
Hypercholesterolemia	58
Family history of cardiovascular disease	46
Diabetes mellitus	46
CRF	6
Morise score	15 ± 2
Drugs (%)	
ACE inhibitors/ARB	65
β-Blockers	46
Calcium antagonists	23
Diuretics	31
Aspirin	58
Statins	58
Insulin therapy	3
Oral hypoglycemic agents	43

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CRF = chronic renal failure; Morise score = clinical score to estimate the probability of coronary artery disease; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

2.2. Echocardiography data acquisition

Two-dimensional echocardiographic images were acquired using an ultrasound equipment (My Lab ALFA, Esaote, Florence, Italy) with a 2.5-

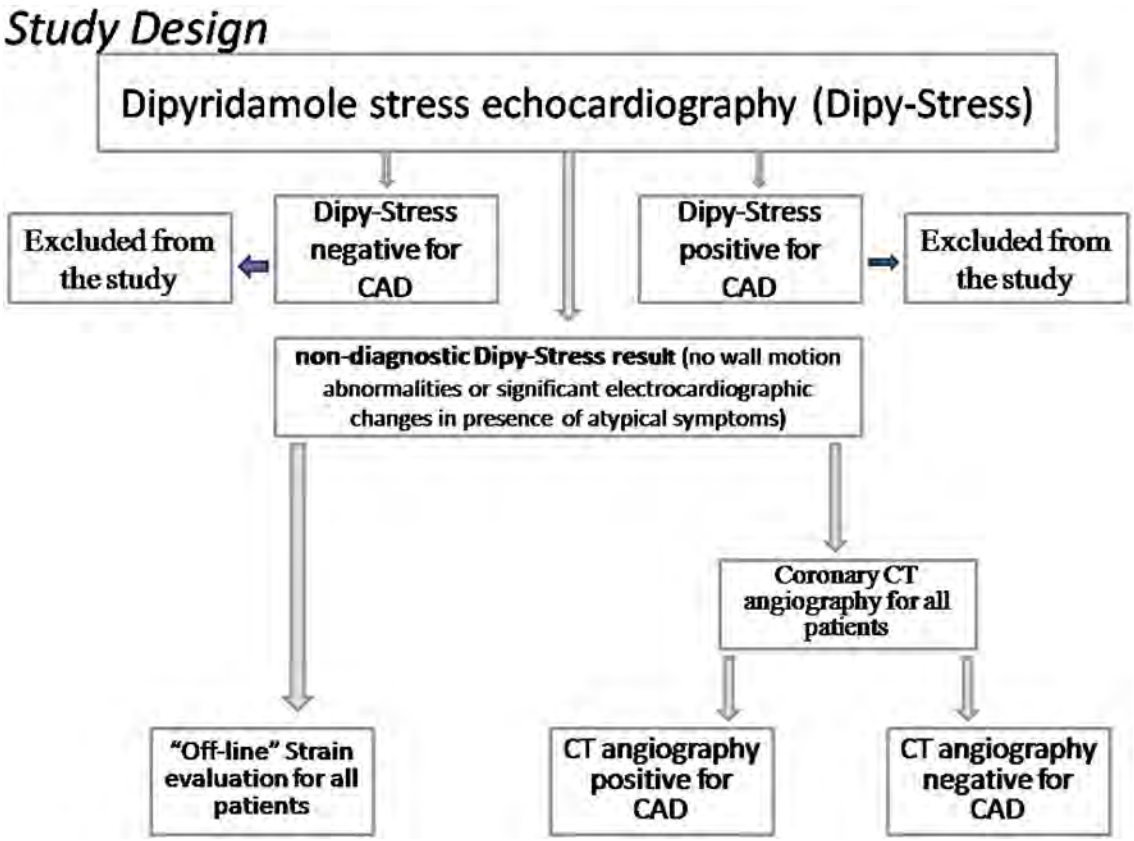

Fig. 1. Study design.

MHz phased-array transducer. 2D data acquisitions were obtained with parasternal long axis and short axis views and the three standard apical views, according to the recommendations of the American Society for Echocardiography, for the analysis of wall motion, end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) [30].

2.3. Dipyridamole stress echocardiography and protocol

All enrolled patients undergoing to intravenous dipyridamole pharmacologic stress avoided caffeinated beverages, foods and medications containing methylxanthine for at least 12–24 h before the test. Dipyridamole was given intravenously at the dose of 0.84 mg/kg in 6 min. One-lead ECG continuous monitoring was performed during the test up to 7 min after the end of the infusion. 12-lead ECG and blood pressure measurement have been performed at rest, at the beginning of the infusion, at the end of infusion, 4 min after infusion and at 7 min after infusion. Echocardiographic evaluation was performed at rest, after 3 min from the beginning of infusion, at the end of infusion, at 4 and at 7 min after the end. Acquisition of 2D images for the evaluation of circumferential and longitudinal strain in "off-line" modality was performed for each scanning section during an apnea period of 5 heart cycles, acquiring 3 of them. These acquisitions were all performed at rest and within 2 min from the infusion end Fig. 2.

2.4. Speckle-tracking analysis by 2D echocardiography

A dedicated software package (XStrain™, Esaote, Florence, Italy) was used for an "off-line" quantification of circumferential and longitudinal strain. The LV was divided according to the 16-segment model (6 basal, 6 mid-level, and 4 apical). Short-axis views images, obtained at the mitral valve, papillary muscles and apical levels, were used to compute circumferential strain (CS). Longitudinal strain was calculated using standard apical 4-, 3-, and 2-chamber views. Global Strain was defined as the mean value of 16 segments Fig. 3. In all patients it was calculated the Global Circumferential Strain (GCS) and the Global Longitudinal Strain (GLS) at rest and within 2 min after stress. It was also evaluated the percentage of variation of GCS (ΔGCS) from rest to the end of the test, according to the following formula: $\Delta GCS = [(\text{stress GCS} - \text{rest GCS}) / \text{rest GCS}] \times 100$. Similarly it was calculated the percentage of variation of the GLS (ΔGLS). Strain "off-line" analysis was done by an investigator unaware of coronary CT angiography results.

2.5. Reproducibility analysis

Intra-observer and inter-observer variabilities of 2D Strain data were evaluated blindly in 20 randomly subjects by two sonographers.

2.6. Computed tomography data acquisition

All patients enrolled in the study were studied with coronary CT angiography. CT examination was performed by using a 64-slice CT scanner (Sensation 64 Cardiac; Siemens, Berlin, Germany). Computed Tomography Coronary Angiography (CCTA) was performed by means of 64×0.6 mm collimation, 0.33 s of gantry rotation time, a tube voltage of 120 kV and a tube current of 900 mA. Nonionic iodinated contrast material (Iomeprole 400 mg/ml; Bracco, Milan, Italy) was injected in an antecubital vein with bolus tracking technique [31] (100 ml of contrast agent followed by a 50 ml of isotonic saline bolus, with a flow rate of 4–5.5 ml/s).

Sublingual nitroglycerin (0.3 mg) was administered to patients with a systolic blood pressure >100 mm Hg in order to better visualize small coronary arteries.

CCTA images were acquired during a 10–12 s inspiratory breathhold. End-diastolic and end-systolic phases were used to reconstruct data

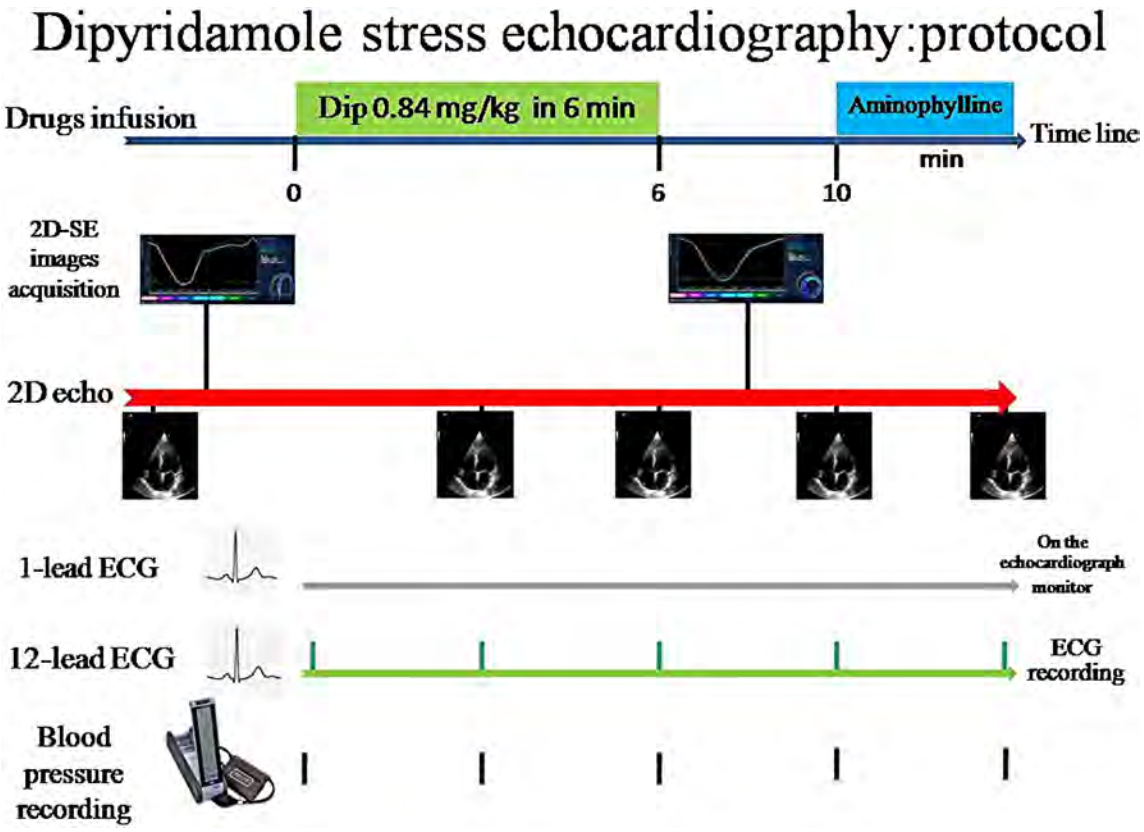

Fig. 2. Protocol of dipyridamole stress echocardiography combined with acquisition of 2D images for the "off-line" evaluation of circumferential and longitudinal strain. Acquisitions were performed at rest and within 2 min from the infusion end.

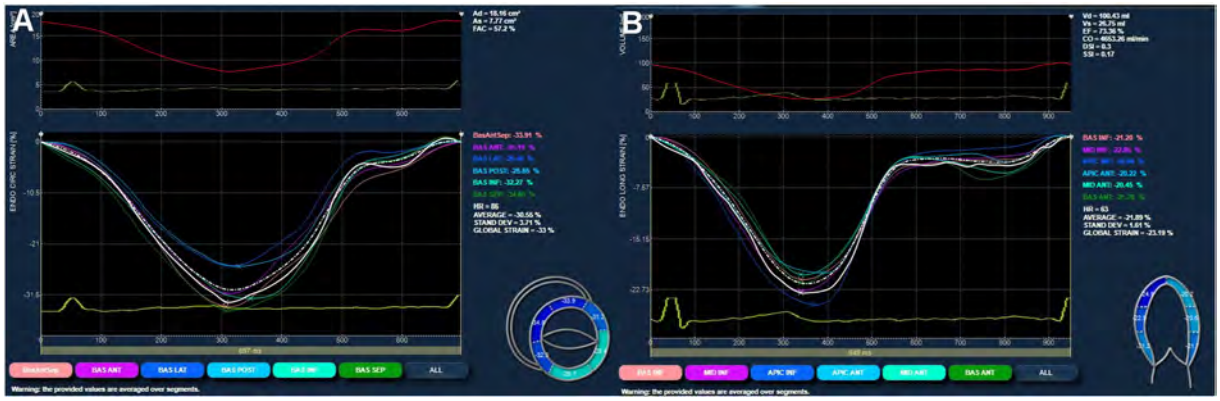

Fig. 3. Curves obtained by speckle-tracking analysis. Panel A: Circumferential strain evaluation obtained by a short-axis image. Panel B: Longitudinal strain evaluation from an apical image.

with a retrospective ECG gating. All data were evaluated and post-processed in a dedicated workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany).

CCTA scans were visually evaluated in consensus by two experienced cardiologist blinded to others clinical and/or electrocardiographic and/or echocardiographic data.

Readers evaluated the eventual presence of coronary stenosis as significant CAD (stenosis ≥50%), mild CAD (coronary stenosis between 15 and 50%) and no CAD (coronary stenosis <15% to no coronary stenosis).

2.7. Statistical analysis

Continuous variables were expressed as mean ± 1 SD and categorical variables were expressed as percentages. One-way analysis of variance (ANOVA) was used to compare data between the two groups (positive CCTA and negative CCTA).

Receiver Operating Characteristic (ROC) curves were constructed, and areas under the curves were measured to determine cut-off values of ΔGLS for optimal sensitivity and specificity to identify those patients positive and those ones negative for CAD.

For any statistical comparison a P-value < 0.05 was considered significant.

Statistical analyses were carried out using SPSS version 12 (SPSS Inc., Chicago, IL, USA). And MedCalc 6.00.014 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Patients characteristics

Among the 71 screened subjects 5 patients were excluded due to the poor image quality on strain analysis and one was excluded because CCTA showed a CAD with a stenosis greater than 80%.

A total of 65 patients (female 28) were included in the final population. Among these, according to CCTA results, were categorized two groups: a group of 37 patients with coronary stenosis between 15% and 50% (positive CCTA) and a group of 28 patients without coronary disease (negative CCTA).

As showed on Table 2 no differences were found regarding clinical parameters, cardiovascular risk factors and treatment between CCTA negative group and CCTA positive group.

3.2. Echocardiographic results

Echocardiographic parameters at rest and after stress were compared between them and also with those ones derived from CCTA. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (EF), both at rest and after stress, in comparison with CCTA results didn't show significant statistical differences Table 3. Also the analysis of variation percentage between rest and after stress (ΔFE, ΔLVEDV, ΔLVESV) didn't show statistical significant differences.

3.3. Comparison between 2D strain values and coronary CT angiography

GCS and GLS at rest and after the test were compared between them and with the data derived from CCTA. The values of GCS at rest and after stress were similar in CCTA positive and CCTA negative groups Fig. 4A. Thirty two patients (82%) in CCTA positive group showed an increase of GCS. The ΔGCS showed only a mild increase, without significant difference (P = 0.87), in CCTA positive (1 ± 13%) compared to negative group (0.6 ± 4.7%).

Although in normal range and with an overlapping of value, GLS at rest showed a significant reduction (P < 0.0001) in CCTA positive group in comparison to GLS at rest in CCTA negative group (Fig. 4B).

Table 2
Comparative clinical characteristics.

Variable	Positive CCTA (n.37)	Negative CCTA (n.28)	P-value
Age (years)	61 ± 6	59 ± 4	NS
BMI (kg/m^2)	28 ± 3	26 ± 4	NS
SBP (mm Hg)	132 ± 16	128 ± 14	NS
DBP (mm Hg)	88 ± 10	84 ± 12	NS
HR (beats/min)	80 ± 10	74 ± 14	NS
Coronary risk factors (%)			
Arterial hypertension	76	72	NS
Smoke	54	57	NS
Hypercholesterolemia	62	54	NS
Family history of cardiovascular disease	46	46	NS
Diabetes mellitus	49	43	NS
CRF	8	4	NS
Morise score	15.4 ± 1.9	14.8 ± 1.3	NS
Drugs (%)			
ACE inhibitors/ARB	68	60	NS
β-Blockers	46	46	NS
Calcium antagonists	24	21	NS
Diuretics	35	25	NS
Aspirin	62	54	NS
Statins	62	54	NS
Insulin therapy	5	4	NS
Oral hypoglycemic agents	43	40	NS

Positive CCTA = Coronary Computed Tomography Angiography positive for CAD; negative CCTA = Coronary Computed Tomography Angiography negative for CAD; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CRF = chronic renal failure; Morise score = clinical score to estimate the probability of coronary artery disease; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Table 3
Comparative echocardiographic characteristics.

	positive CCTA (n.37)	negative CCTA (n.28)	P-value
Rest			
EF (%)	56 ± 5	57 ± 4	0.191
LVEDV (ml)	101 ± 5	103 ± 5	0.191
LVESV (ml)	44 ± 4	44 ± 5	0.516
Stress			
EF (%)	55 ± 5	58 ± 4	0.022
LVEDV (ml)	100 ± 4	102 ± 5	0.056
LVESV (ml)	44 ± 5	43 ± 5	0.146

Positive CCTA = Coronary Computed Tomography Angiography positive for CAD; negative CCTA = Coronary Computed Tomography Angiography negative for CAD; EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

Similarly, GLS during stress was lower ($P < 0.0001$) in CCTA positive group compared to CCTA negative one Fig. 4B.

Comparing value of rest versus stress was found a significant reduction ($P < 0.0001$) of GLS in patients with positive CCTA; on the contrary in negative CCTA group was found a no significant increase of GLS.

The ΔGLS showed a significant decrease ($P < 0.0001$) in CCTA positive ($-10 \pm 8\%$), with respect to CCTA negative group ($4.4 \pm 5.8\%$).

Thirty-five patients (95%) of the positive CCTA group had a reduction of GLS after stress. In CCTA negative group only 2 patients (7%) showed a reduction of GLS at stress compared to rest.

ROC analysis of ΔGLS showed a high accuracy (area under the ROC curve was 0.916, 95% CI: 0.820–0.970) to distinguish positive and negative CCTA groups Fig. 5. A ΔGLS cut-off point of ≤0 yielded the best result in terms of combined sensitivity (94.6%) and specificity (92.9%) for the diagnosis of positive CCTA.

3.4. Reproducibility analysis

The intra-class correlation coefficient for inter- and intra-observer reproducibility was 0.91 (95% confidence interval [CI] 0.89 to 0.94) and 0.93 (95% CI 0.90 to 0.97) for longitudinal strain, 0.88 (95% CI 0.85 to 0.92) and 0.910 (95% CI 0.87 to 0.94) for circumferential strain.

4. Discussion

The main results of the present study are:

1) GLS is reduced but remaining within the normal range at rest and after Dipy-Stress test in patients with mild CAD; 2) the difference between stress and rest, called ΔGLS, is the best parameter to identify mild CAD; 3) circumferential deformation is not impaired neither at rest nor after dipyridamole infusion.

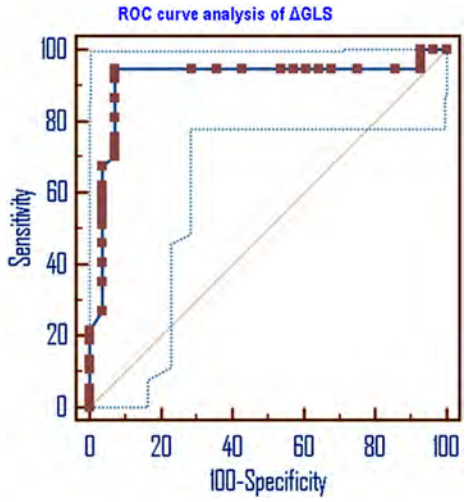

Fig. 5. ROC curve analysis of ΔGLS shows high accuracy in distinguishing between positive and negative CCTA groups.

Of interest is the fact that these results were obtained in patients without previous diagnosis of heart disease and without electrocardiographic or wall motion abnormalities after dipyridamole infusion but in presence of mild CAD (stenosis >15% and <50%) detected by CCTA. This shows that alterations in myocardial strain are early, preceding contractile abnormalities both at rest and after Dipy-Stress. Previous studies in many different heart diseases using tissue Doppler imaging and/or speckle tracking echocardiography have shown early LV deformation abnormalities despite preserved EF. Early abnormalities on LV deformation using strain echocardiography both at rest and after dipyridamole infusion have been found in patients with ischemic heart disease.

Yang et al. [32] performed a study by 2D speckle tracking echocardiography on 85 patients without regional wall motion abnormalities, comparing results with coronary angiography. They evaluated left ventricle relaxation using the strain imaging diastolic index at rest, demonstrating it can predict coronary artery stenoses. Authors conclude: "This method might be useful for detecting CAD without the need for a stress test".

Although their data seem to be attractive we believe that larger multicenter studies are needed before overcoming the use of provocative tests for unmasking CAD.

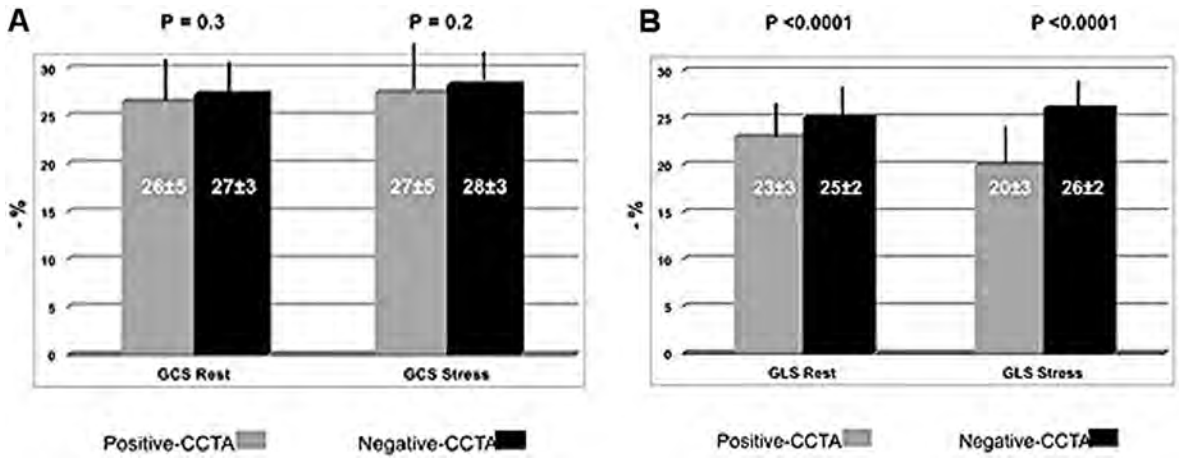

Fig. 4. Panel A: Comparative values of GCS between CCTA positive group and CCTA negative group, at rest and after test end. Panel B: Comparative values of GLS between CCTA positive group and CCTA negative group, at rest and after test end.

Our study showed a significant increase in sensitivity and specificity by Dipy-Stress echocardiography without significantly increased risk and no increase in health care costs.

Bolognesi et al. [26] observed, in patients with obstructive CAD, an impairment of LV longitudinal shortening despite normal LVEF.

Data published by Edvardsen et al. [27] showed an impairment of LV systolic function in relation to the presence of coronary atherosclerosis in patients without history of CAD and with normal LVEF.

Nucifora et al. [33] demonstrated, on 182 patients without known coronary artery disease or overt left ventricular systolic dysfunction, that GLS could be useful for predicting the presence of obstructive CAD (Duke Clinical Score) verified by CCTA [34]. In accord with these Authors our results, showing early abnormalities of longitudinal function at rest, are similar. However, differently from previous studies, we included patients without significant CAD, suggesting that atherosclerotic disease, also without hemodynamically significant coronary artery stenosis, is related with early cardiac function abnormalities. In particular we found that ΔGLS is able to identify patients with mild stenosis demonstrated by CCTA. Interesting is the fact that, in these subsets of patients, GLS after dipyridamole infusion is mostly lower than rest. This contributes to have a minus sign of ΔGLS in patients with mild CAD; on the contrary in patients without CAD the infusion of dipyridamole shows an increase of longitudinal function (positive sign of ΔGLS).

When a ΔGLS cut-off value ≤0 was used, sensitivity for mild CAD was 94.6% and specificity was 92.9%. Therefore ΔGLS may be considered a potential marker during dipyridamole stress echocardiography to identify patients with mild CAD.

Interpretation of these results can be very challenging but we think that LV anatomy, function and perfusion have a role. Longitudinal function is mainly driven by deformation of the subendocardial fibers, which are the most vulnerable and most sensitive to perfusion changes. In this subclinical stage of LV systolic dysfunction mesocardium and epicardium's fibers could be involved in a compensation function, resulting in normal circumferential mechanics with relatively preserved LV pump function and, therefore, normal EF [35–37].

One aspect of our study that remains unexplained is why in our selected population, despite a comparable risk profile for CAD in both groups, only 57% of subjects had coronary atherosclerosis. Although this doesn't constitute an objective of the study it is probably explained by the fact that, while clinical scores are made on large populations, the individual phenotypic expression may vary both temporally and quantitatively.

Finally our study showed the feasibility of an early diagnosis of mild CAD by Dipy-Stress. We think that our results can be applied to better stratify the patient's CAD risk and its management.

4.1. Limitations

The major limitations of the present study were the small number of subjects and the lack of invasive assessment of atherosclerotic plaques by intravascular ultrasound (IVUS), optical coherence tomography (OCT) or Fractional Flow Reserve. However these invasive techniques require cardiac catheterization, which is not appropriate in our patients. In fact they are characterized by preserved EF with neither WM nor electrocardiographic abnormalities after stress, CCTA demonstrating only mild CAD. Finally another limitation is the absence of a clinical follow-up.

5. Conclusions

Use of 2D SE during Dipy-Stress allows identification of mild CAD which is not identified by the conventional non-diagnostic test result. This subset of patients needs an accurate analysis of atherosclerotic burden and further diagnostic investigation during follow-up for better stratification of early ischemic damage. Further data in larger sample size are needed to better identify the evolution and the clinical role of our results.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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Myocardial Deformation in Acute Myocarditis With Normal Left Ventricular Wall Motion

– A Cardiac Magnetic Resonance and 2-Dimensional Strain Echocardiographic Study –

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Background: The aim of our study was to assess longitudinal (L), circumferential (C) and radial (R) strain (S) of the left ventricle (LV) in patients with acute myocarditis and preserved LV wall motion.

Methods and Results: Of the 26 male patients that were enrolled, 13 patients (26±8 years) suffered from acute myocarditis and 13 (25±2 years) were healthy participants (controls). Both patients and controls underwent cardiac magnetic resonance (CMR) and 2-dimensional S imaging (2D-S) echocardiography on the same day. Myocardial strains (RS, LS and CS) were quantified by 2D-S. In patients with myocarditis, a delayed enhancement (DE) CMR study was performed to identify damaged myocardial segments. In the myocarditis group there was a significant LS reduction compared with controls (–25±7 vs –20±7, P<0.0001), whereas no difference was found between the 2 groups concerning CS and RS. Subepicardial DE areas were found in 12 of 13 patients. Segments with DE showed a significantly lower LS in comparison with segments without DE (–19±4 vs –23±6, P<0.0001). In contrast, no difference in CS and RS was found when comparing segments with DE vs segments without DE.

Conclusions: In patients with acute myocarditis, evidence of subepicardial damage and no wall motion abnormalities, longitudinal deformation is diffusely impaired, whereas circumferential impairment is regionally sited in the areas of subepicardial damage. (*Circ J* 2010; **74:** 1205–1213)

Key Words: Magnetic resonance imaging; Myocarditis; Tissue Doppler imaging

Ventricular contractile function depends on a complex longitudinal, circumferential and radial deformation that is deeply dependent on myocardial fiber architecture.[1–3] Regional myocardial deformation can be assessed by many techniques such as sonomicrometry, tagging cardiac magnetic resonance (CMR) and tissue Doppler imaging (TDI) echocardiography. One of the most recent techniques aimed at quantifying myocardial deformation is 2-dimensional strain imaging (2D-S), a new non-invasive and accurate method.[4–9]

A transmural heterogeneity of left ventricular (LV) wall deformation has been documented in healthy patients: longitudinal and circumferential strain is higher in subendocardial than subepicardial layers, and a base to apex strain gradient exists, with longitudinal, circumferential and radial strain higher at the apex than at the base.[10,11] In myocardial infarction, the distribution of strain impairment reveals the extent of necrosis: a transmural infarction is characterized by reduced longitudinal, circumferential and radial strain, while in subendocardial necrosis only the longitudinal and radial strain are reduced, and the circumferential strain is preserved.[8,9,12]

Acute myocarditis is characterized by inflammatory myocardial damage that can result in severe LV dysfunction.[13] In acute focal myocarditis, however, the myocardial damage is mainly circumscribed to the subepicardial layers, whether or not it is associated with any wall motion abnormality.[14–15] Focal myocarditis thus may be a suitable model for assessing the abnormalities of myocardial deformation induced by selective damage of the subepicardial layer.

CMR associated with the delayed enhancement (DE) technique reveals the location, size and transmural extent of myocardial damage. This technique shows the compromised

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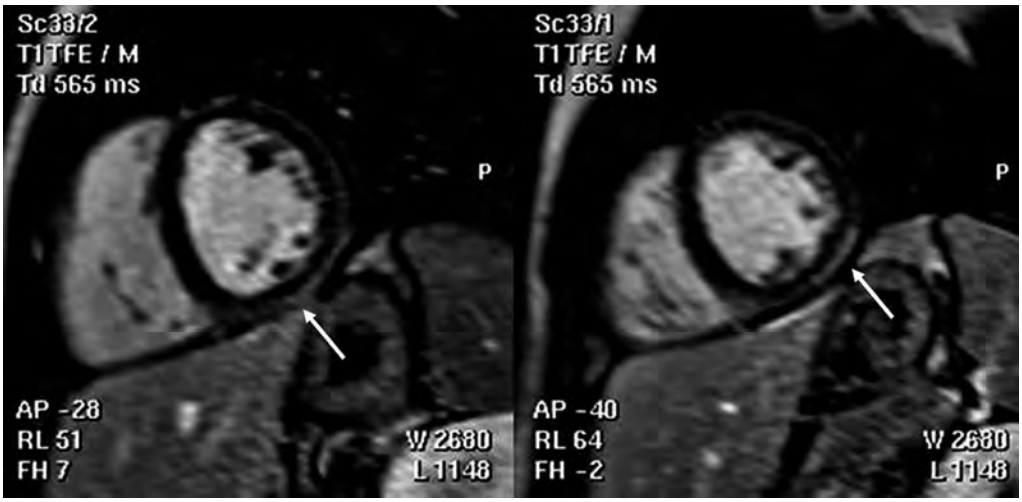

Figure 1. Delayed enhancement-cardiac magnetic resonance images of 2 contiguous mid short-axis views of the left ventricle in a patient with acute myocarditis. White arrows indicate the myocardial damage (hyperenhancement areas) involving the subepicardial layers of the inferior and inferolateral walls.

myocardium as a hyperenhanced area that always involves the endocardial layer in myocardial infarction, whereas in focal myocarditis subepicardial layers are predominantly affected.[14–17] The hypothesis of the present study was that LV strain abnormalities can be a subliminal sign of subepicardial damage in patients with acute myocarditis, as documented by DE-CMR, in absence of wall motion abnormalities. The aim of this study was to analyze global and regional 2D myocardial strain in patients with acute focal myocarditis in the presence of epicardial damage but without wall motion abnormalities.

Methods

Patients

From February 2007 to October 2008, 27 male patients were enrolled. Fourteen consecutive patients (mean age: 27±9 years) had a diagnosis of suspected acute myocarditis based on the following criteria: (A) history of flu-like symptoms within 8 weeks before admission (14/14); (B) 1 of the following symptoms: fatigue/malaise (4/14), chest pain (14/14), dyspnea (2/14), palpitation (4/14); (C) 1 of the following ECG patterns: ST-segment elevation (14/14), T wave abnormalities (5/14); and (D) increase of inflammation markers (14/14) and cardiac enzymes (14/14).

Thirteen healthy male participants (mean age: 25±2 years) without a history of heart disease and with normal ECG and transthoracic echocardiogram were enrolled as the control group. Both patients and controls were free from any other concomitant disorder (hypertension, dyslipidemia, diabetes, obesity). Both patients and controls underwent a standard transthoracic echocardiogram study, 2D-S evaluation and CMR on the same day and in random order. Coronary angiography was performed to rule out coronary artery disease on the basis of the DE pattern.

The study was approved by the local ethics review committee and the investigation conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

CMR Data Acquisition and Analysis

CMR was performed using a 1.5-T system (Gyroscan NT; Philips Medical Systems, Best, The Netherlands) with a cardiac phased-array coil and vectorcardiogram synchronization. A breath-hold balanced fast field echo sequence was used to evaluate wall motion and global LV function. Sequence parameters were: TR 3.8 ms, TE 1.92 ms, flip angle 60°, slice thickness 8 mm, matrix 192×512, field of view 500 mm, FOV 50% and number of phases 30. In each patient, depending on LV volume, a total of 9–14 short-axis views and 2 long-axis views (4-chamber view and 2-chamber view, respectively) were acquired.

DE images by a gradient echo inversion recovery sequence were obtained within 10–20 min after bolus injection of 0.2 mmol/kg of gadobutrol (Gadovist®, Schering, Germany); a 2D-T1-weighted turbo-field-echo technique was used in the same short and long axis views. Sequence parameters were: TR 4.3 ms, TE 1.54 ms, flip angle 15°, slice thickness 10 mm, matrix 208×512 and field of view 350 mm, FOV 80%). Inversion time (200–320 ms) was optimized to a null signal from normal myocardium. DE images were obtained only in patients with suspected myocarditis. LV volumes, mass and ejection fraction (EF) were measured using a previously validated software (EasyVision, version 4.0; Philips Medical Systems, Best, The Netherlands).

As reported in a previous study,[18] the areas of DE were assessed by visual approach with a scheme based on the transmural extent of DE within each quartile (0–25%, 26–50%, 51–75% or >75%). According to the literature, patients were labeled as suffering from myocarditis if myocardial damage was evident on the LV wall but involvement of the endocardial layer was absent (**Figure 1**).[14–17]

The 2-Dimensional Echocardiography Data Acquisition and Analysis

Echocardiographic images were obtained using a commercial ultrasound machine (My Lab 50, Esaote, Florence, Italy) equipped with a 2.5-MHz phased array transducer. Parasternal short axis views at the basal, mid and apical levels and 3

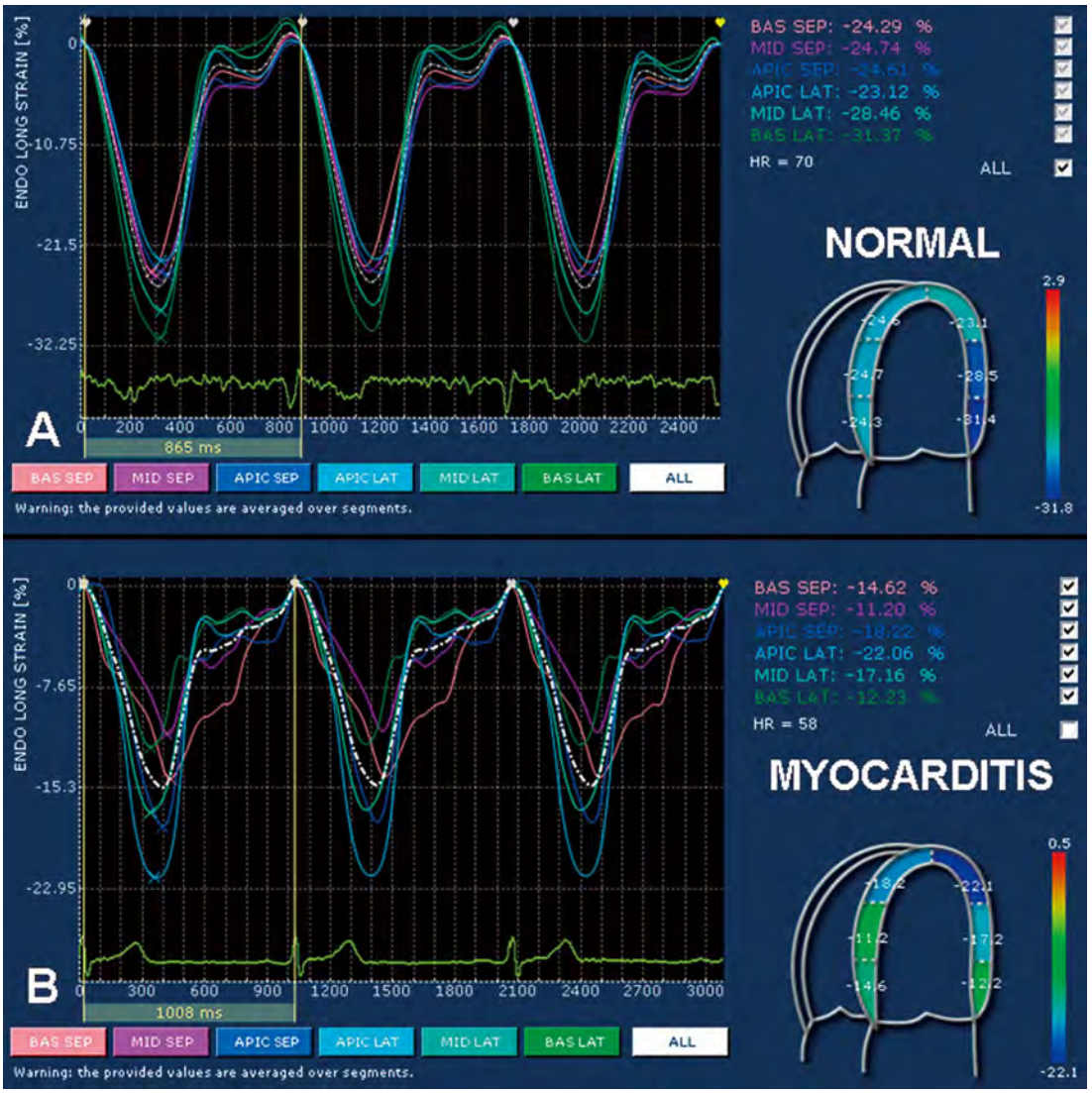

Figure 2. Longitudinal strain curves of left ventricle in a (**A**) normal subject and (**B**) patient suffering from myocarditis.

standard apical views (4-chamber, 2-chamber and long-axis) were acquired. LVEF was calculated by biplane Simpson's method; LV diastolic function was quantified by the ratio between the E wave velocity of the pulsed wave Doppler mitral flow image and the early diastolic velocity of the septum at the mitral annulus level (E' wave) on TDI.[19] A 16-segment model was used to divide the LV.[20]

A dedicated software package (XStrain™, Esaote, Florence, Italy) was used for an off-line quantification of circumferential, radial and longitudinal strain. This software provides angle-independent 2D strain based on speckle tracking.[21–23] For the quantification of radial and circumferential strain, the software was applied on parasternal short-axis views, while for the quantification of longitudinal strain, the same software was applied on apical views. More specifically, XStrain[24] relies on a "feature tracking" algorithm and, in order to improve the border tracking results, it combines speckle tracking based with other information such as tissue-to-blood border detection, the periodicity of the cardiac cycle and the fact that the cardiac borders maintain their own "overall spatial coherence" over time. All data were elaborated with the aid of Fourier techniques that ensure a higher accuracy using the periodicity of the heart motion. The software asks the user to identify the initial border position by identifying a sequence of points on an arbitrary single frame of the acquired loop. Then the border is automatically followed frame by frame, by searching for each single point and the maximum likelihood in the greyscale pattern over its neighbourhood in the following frames. Strain is obtained by comparing displacements of the speckles in relation to each other along the endocardial contour/border for quantify circumferential and longitudinal strain or between endocardial and epicardial contours/borders for radial strain. Frame by frame displacement of these points was automatically evaluated by generating strain curves (**Figure 2**).

Only images with good quality and adequate frame rates (50–70 frames/s) were used. The tracking quality was verified for each segment and subsequent manual adjustments were

Table 1. Demographic and Echocardiographic Characteristics

	Controls (n=13)	Myocarditis (n=13)	P value
Age (years)	25±2	26±8	NS
Male gender (%)	100	100	NS
LV mass (g)	161±28	164±38	NS
LVEDD (mm)	50±3	50±4	NS
LVESD (mm)	32±3	32±3	NS
LVEDV (ml)	77±15	80±8	NS
LVESV (ml)	27±6	30±4	NS
LVEF (%)	65±4	62±2	0.04
LA area (cm^2)	14±2	14±2	NS
RA area (cm^2)	16±2	16±2	NS
E/E'	4±2	4±1	NS

LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LA, left atrium; RA, right atrium.

performed when required.

All images used for quantification of longitudinal and circumferential strain were independently analyzed off-line by 2 cardiologists (G.D.B. and C.Z.) who were unaware of the clinical condition. Inter-observer variability was assessed.

Follow-up

The follow-up was performed by history, clinical evaluation and a 2D-S echocardiographic study. The events evaluated were: a new occurrence of acute myocarditis or a new hospitalization for any cardiac reason, heart failure and sudden death.

Statistical Analysis

Continuous variables were expressed as mean±1 SD and categorical variables were expressed as percentages. An unpaired t-test was used to assess the differences between the myocarditis and control groups.

One-way analysis of variance (ANOVA) and Bonferroni post hoc tests, when appropriate, were used to compare data between the three groups (No-DE vs DE 1–25% vs DE >25%).

Receiver-operating characteristic (ROC) curves were constructed, and areas under the curves were measured to determine cut-off values of strain for optimal sensitivity and specificity. The ROC analyses were set to identify the segments of the myocarditis group compared with the controls.

Interobserver and intraobserver variability were assessed using the Bland-Altman method. For any statistical comparison, a P-value <0.05 was considered significant. Statistical analyses were performed using SPSS version 12 (SPSS Inc, Chicago, IL, USA).

Results

All participants underwent transthoracic echocardiogram, 2D-S and CMR within 48 h from admission. Of the 14 patients suffering of acute myocarditis, only 1 patient (7%) showed an akinesia of apical LV segments with a LV dysfunction (EF was 37%). This patient had a non-ischemic localization of DE (epicardial layer of inferior and anterior wall and midwall of septum) and an impairment of longitudinal (–14±5), circumferential (–13.6±4.4) and radial (15±4.4) strain. Thus the 13 remaining patients with acute myocarditis and preserved wall motion and EF were labeled as the myocarditis group. Table 1 shows that no significant difference is present

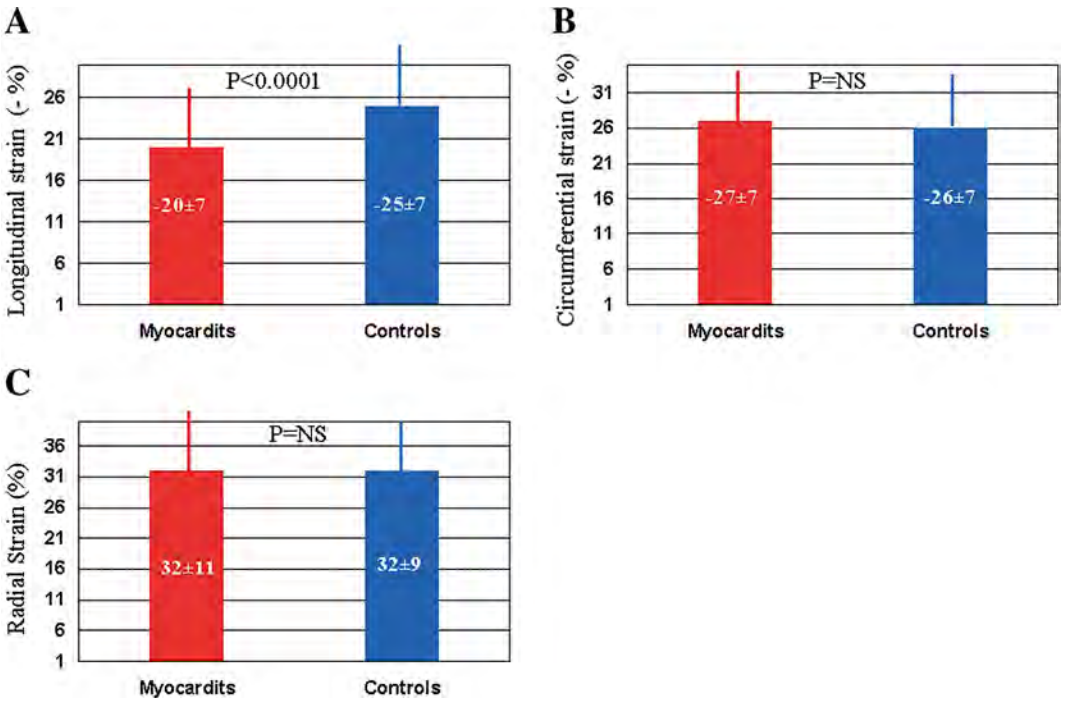

Figure 3. (A) Longitudinal, (B) circumferential and (C) radial strain in patients with myocarditis and in controls.

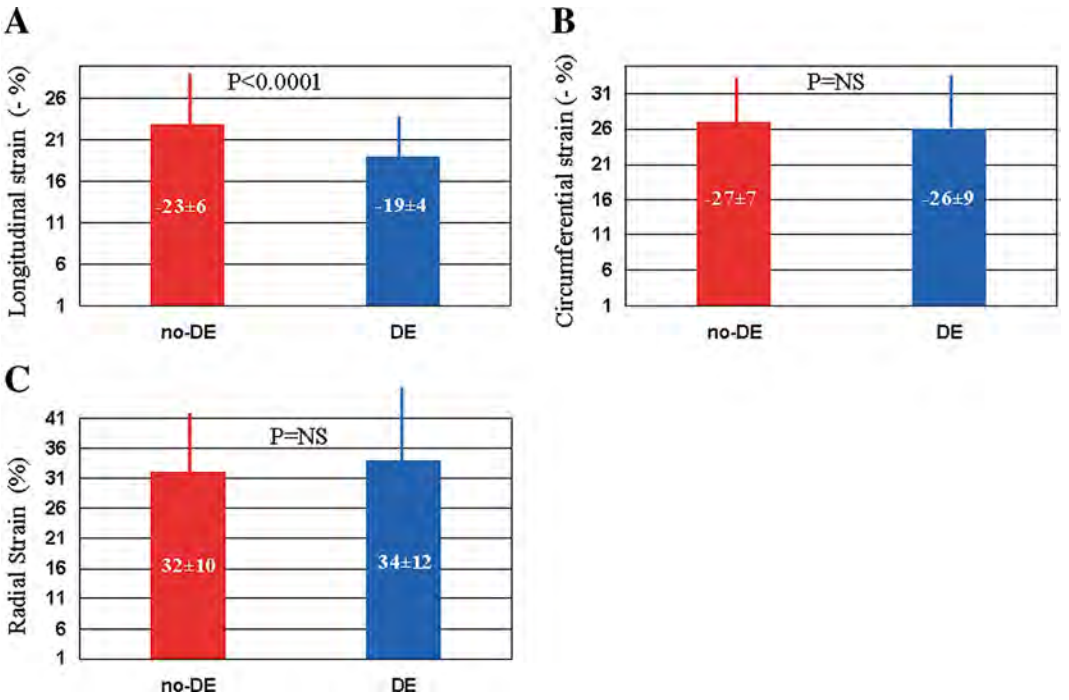

Figure 4. (**A**) Longitudinal, (**B**) circumferential and (**C**) radial strain in myocardial segments without (no-DE) and with (DE) delayed enhancement (data relative to the whole population, including both patients and controls).

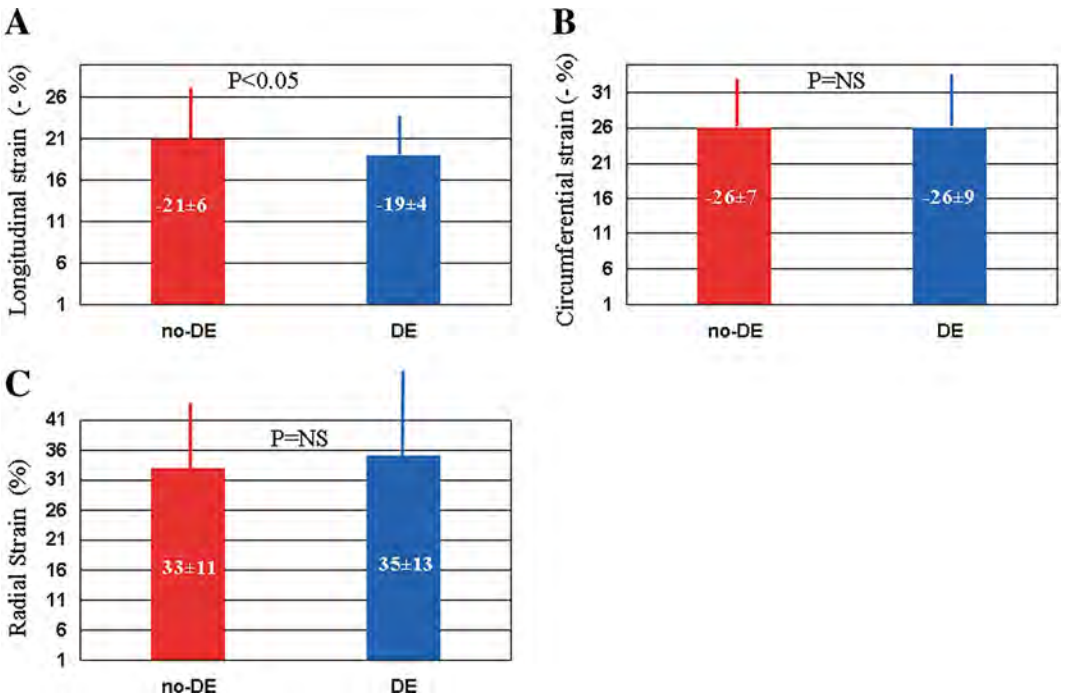

Figure 5. (**A**) Longitudinal, (**B**) circumferential and (**C**) radial strain in myocardial segments without (no-DE) and with (DE) delayed enhancement (data relative to patients with myocarditis).

Table 2. Longitudinal, Circumferential and Radial Strain of Left Ventricle Walls

	Longitudinal strain			Circumferential strain			Radial strain		
	Controls (n=13)	Myocarditis (n=13)	P value	Controls (n=13)	Myocarditis (n=13)	P value	Controls (n=13)	Myocarditis (n=13)	P value
Anterior wall (%)	–26±5	–20±5	<0.0001	–27±6	–26±7	NS	32±7	36±14	NS
Lateral wall (%)	–24±6	–20±6	0.001	–28±7	–25±7	0.02	31±10	33±11	NS
Inferior wall (%)	–29±8	–22±5	<0.0001	–27±6	–25±8	NS	34±12	30±9	NS
Septal wall (%)	–23±6	–20±5	<0.0001	–27±6	–26±9	NS	32±8	31±12	NS

Lateral wall includes all anterolateral and inferolateral segments of the left ventricle. Septal wall includes all anteroseptal and inferoseptal segments of the left ventricle.

Table 3. Longitudinal, Circumferential and Radial Strain in Segments Without DE (No DE), With DE Transmural Extent of 1–25% (DE 1–25%) and With DE Transmural Extent >25% (DE>25%)

	No DE	DE 1–25%	DE>25%	P value	P value*	P value**
Longitudinal strain (%)	–23±6	–20±4	–19±4	0.04	0.001	NS
Circumferential strain (%)	–27±7	–28±3	–24±6	NS	NS	NS
Radial strain (%)	32±10	39±12	34±14	NS	NS	NS

P value, No DE vs DE 1–25%; P value*, No DE vs DE>25%; P value**, DE 1–25% vs DE>25%.
DE, delayed enhancement.

between the myocarditis and control groups concerning LV size, volume and mass, atrial areas and diastolic LV function. In the myocarditis group, LVEF was within the normal range but significantly lower than in normal participants (P=0.04).

CMR: Functional Parameters

The 2 groups (myocarditis and control) did not show any significant difference concerning diastolic and systolic LV volume (156±21 ml vs 170±33 ml, P=NS; 68±12 ml vs 71±15 ml, P=NS); LV mass was almost identical in both groups (105±27 g vs 103±45 g, P=NS). LVEF, although in the normal range, was lower in the myocarditis than in the control group (55±3 vs 59±1, P=0.02).

CMR: DE

Areas of DE were found in 12 of the 13 patients in the myocarditis group. One patient without DE underwent coronary angiography, which did not show any coronary artery disease. A total of 54 (26%) out of 208 LV segments had DE with subepicardial distribution. The location of DE was: the inferior wall (2 patients; 17%), the infero-lateral wall (4 patients; 33%), the antero-lateral wall (3 patients; 25%) and both antero-lateral and infero-lateral walls (3 patients; 25%). Therefore, the 83% of segments with DE were located in the anterolateral and inferolateral wall.

The transmural extent of DE did not exceed 75% of the LV wall thickness in any segment. The subepicardial DE extent was 1–25% in 26 segments (48.2%), 26–50% in 24 segments (44.4%) and only 51–75% in 4 segments (7.4%).

Segments with a subepicardial transmural DE extent >26% (28 segments) were mainly located in the antero-lateral and infero-lateral walls (22 segments, 79%).

Longitudinal, Circumferential and Radial Strain

Longitudinal strain was measured in 379 segments (91%), circumferential strain in 337 segments (81%) and radial strain in 261 segments (63%). The remaining segments were excluded because of poor echocardiographic image quality. The myocarditis patients had a significant global longitudinal LV strain decrease in comparison with normal participants (–20±7% vs –25±7%, P<0.0001), while global circumferential strain and radial strain did not show any difference between the 2 groups (P=NS) (**Figure 3**).

Considering all participants together (both the myocarditis and control groups), analysis of segments with DE (49 segments) showed that these had a significantly lower global longitudinal strain (P<0.0001) than segments without DE (330 segments). In contrast, no significant difference in global circumferential strain and radial strain was found between segments with and without DE (**Figure 4**). Considering the myocarditis group only, longitudinal strain was significantly lower (P=0.04) in segments with DE (49 segments; –19±4%) than in those without DE (162 segments, –21±6%), while no difference in circumferential strain and radial strain was observed in segments with DE, when compared to those without DE (**Figure 5**).

Analysis of myocardial deformation, performed separately for each LV wall, revealed that patients had: (1) a significant longitudinal strain decrease in each wall; (2) a significant decrease in circumferential strain only in the lateral wall; (3) no difference in radial strain (**Table 2**); (4) longitudinal strain impairment in all segments with DE, independent of DE transmurality (**Table 3**); and (5) circumferential strain lower in segments with >25% transmural DE extent, with respect to segments with or without DE transmural extent <25% (**Table 3**).

Longitudinal strain showed a moderate predictive value (area under the ROC curve was 0.73, 95%CI: 0.66–0.79) that distinguished the 2 groups. A longitudinal strain cut-off point of ≤–21% yielded the best result in terms of combined sensitivity (69%) and specificity (65%). However, using a longitudinal strain value ≤–21% in 2 or more contiguous segments, as a marker of longitudinal LV dysfunction, sensitivity was 100%, specificity was 62%, diagnostic accuracy was 81%, positive predictive was 72% and negative predictive value was 100% for the diagnosis of acute myocarditis.

Follow-up Data

Ten of the 13 patients (77%) in the myocarditis group were included in the follow-up evaluation. The average duration of follow up was approximately 23±11 months. Mainly, our follow-up data showed that: (1) no patients had any clinical

event recurrence; and (2) the evaluation of myocardial deformation by 2D-S showed no significant recovery of segmental longitudinal deformation between acute phase myocarditis (–20±7%) than follow-up myocarditis (–19±5). Furthermore, circumferential and radial deformations were similar between the acute phase and follow-up (–27±7 vs –26±5 and 32±11 vs 32±14, respectively).

Reproducibility

There was good inter-observer agreement concerning longitudinal (mean –2.1%, SD 11.7), circumferential (mean –0.4%, SD 4.6) and radial strain (mean 4.6 %, SD 20). Intra-observer agreement of longitudinal (mean –4.4%, SD 14), circumferential (mean –1%, SD 6) and radial strain (mean 4.7 %, SD 28) was also good.

Discussion

The main results of this study showed that both longitudinal and circumferential myocardial strain were impaired in patients with acute myocarditis with preserved wall motion and evidence of subepicardial damage. Particularly, longitudinal strain was reduced in all myocardial walls independently from the presence or absence of subepicardial damage, although segments with subepicardial DE had a greater impairment of longitudinal strain than those without DE. This suggests that subepicardium contributes together with subendocardium to longitudinal strain.

In the normal human heart, longitudinal strain is higher in endocardium than in epicardium.[25] This is likely to depend on LV geometry and tissue incompressibility: accordingly, systole concentric shells of myocardium have proportionally greater changes in dimension with decreasing radius.[26,27] The relevant contribution of subendocardium to longitudinal strain is also confirmed by myocardial infarction, since subendocardial infarctions have a longitudinal strain reduction almost identical to that of transmural infarctions.[8,9] The contribution of both subendocardium and subepicardium to longitudinal function can be explained by the complex orientation of myocardial fibers. These are predominantly longitudinal in the subendocardial region (right-handed helix), become circumferential in the mid-wall, and resume a longitudinal orientation at the subepicardial surface (left-handed helix).[28–30] During ejection, the ventricular volume is reduced as a result of contraction of both the subendocardial and subepicardial layers.[1–3] Whenever one of these is damaged (subendocardium in myocardial infarction, subepicardium in focal acute myocarditis), longitudinal function is impaired. On the other hand, the functional recovery of viable sub-epicardial regions is an important mechanism for the improvement of longitudinal regional function in patients with myocardial infarction.[31]

Longitudinal strain was globally reduced in patients with uncomplicated diabetes, normal LV volumes, regional wall motion and EF.[32,33] This is thought to be an early, diffuse and subclinical response to myocardial accumulation of connective tissue and insoluble collagen due to diabetes.

Myocarditis shows a macroscopic damage (ie, DE on MRI) usually located in the epicardial layer of the lateral wall; however, acute myocarditis is a systemic disease as a consequence of a direct viral damage or as consequence of an immune reaction, mediated by T-lymphocytes and antibodies directed against pathogens and similar endogenous heart epitopes, involving, although without clinical sequels, all of the myocardium.[34–36] These latter findings added with the results of De Cobelli, showing a positive septal biopsy for acute myocarditis without septal DE on MRI,[15] can explain our findings that also segments without DE, but having longitudinal dysfunction.

Circumferential strain was reduced in those segments with a DE transmural extent higher than 25%. The link between the reduction of circumferential strain and the DE transmural extent is likely to depend on the localization of the circumferential fibers mainly located in the mid-myocardium.

Accordingly, circumferential strain is preserved in subendocardial infarction; on the contrary, it is impaired in transmural infarction.[9]

In contrast to longitudinal and circumferential strain, radial function was unaffected in isolated subepicardial damage because it strongly depends on the shortening of subendocardial longitudinal fibers.[1,37–41]

Study Limitations

A major limitation to this research is the relatively small number of young male patients with myocarditis and normal LV wall motion. However, the study reflects a single center experience, based on a series of selected consecutive patients with a rare disease collected over approximately 2 years. The annual incidence of myocarditis is estimated at 10–17 per 100,000 in the population, and in these patients a preserved wall motion can be found in no more than 40%.[14,15,42,43]

Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, but in patients without wall motion abnormalities and preserved EF, this approach is unnecessary or even contraindicated.[44] Therefore, CMR is the primary tool for non-invasive assessment of myocardial inflammation in patients with acute myocarditis and normal systolic function.

A further limitation of the present study is that 2D myocardial strain is a new, not well standardized tool in cardiovascular disease; chiefly this method still suffers from reproducibility issues partly from the need for manual tracings of the myocardium.

Additionally, approximately 9% longitudinal, 19% circumferential and 37% radial segments were not analyzable by 2D strain echocardiography because of poor image quality.

In the present study, we did not use tagging MRI, which is the referral non-invasive research tool to quantify segmental deformation. However, it is not widely used in clinical practice due to the complexity of the technique (reduced availability of the sequence to acquire images, and image acquisition and post-processing analysis is time consuming).

The DE technique was not performed in normal participants. However, in this group of young participants who had no history or symptoms of heart disease, and normal ECG and echocardiogram, it was very unlikely to find a scar on DE-CMR.

Conclusion

The present study demonstrates the effect of acute myocardial inflammation on LV deformation.

In acute myocarditis with evidence of subepicardial damage and without wall motion abnormalities, longitudinal deformation is diffusely impaired, whereas circumferential impairment is regionally sited in the areas of subepicardial damage and, in particular, in those segments with a higher transmural extent of DE. Impaired longitudinal and circumferential function in the absence of wall motion abnormalities may represent a useful additional diagnostic finding to

support the diagnosis of acute focal myocarditis; however, further investigations with a larger sample size are required to confirm the clinical role of 2D myocardial strain in acute myocarditis.

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Disclosure

All authors declare no conflict of interest.

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REVIEW

The mosaic of the cardiac amyloidosis diagnosis: role of imaging in subtypes and stages of the disease

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Cardiac amyloidosis is a rare, infiltrative cardiomyopathy that presents with thickened ventricular walls and progressive heart failure. The morphological findings and clinical features are shared with many other diseases (i.e. hypertrophic cardiomyopathy, 'athlete's heart,' Fabry disease, and hypertensive cardiomyopathy), and misdiagnosis occurs frequently. Cardiologists have many instruments that can help reach a correct diagnosis in a relatively short time. As tiles of a mosaic are placed to create an image, thoughtful and smart use of the different diagnostic tools available allows the opportunity to identify amyloid infiltration of the myocardium. When the myocardium is involved, prognosis is poor, so identification of its involvement is crucial for disease management. The diagnostic process begins with an accurate evaluation of clinical elements and includes cardiovascular imaging (echocardiography, magnetic resonance, and nuclear medicine), electrocardiography, serological assays, and myocardial biopsy; only the appropriate integration of these instruments can reveal the diagnosis to an expert physician. The latest improvements in non-invasive diagnostic techniques with increased diagnostic power have reduced the need for biopsy.

Keywords Cardiac amyloidosis • Cardiac magnetic resonance • Echocardiography • Nuclear medicine imaging

Introduction

Amyloidosis is a systemic or localized disease characterized by deposition of anomalous fibrillar proteins in a variety of tissues causing structural alterations and functional impairment. Fibrils originate from the misfolding of an altered precursor protein that precipitates in the extracellular matrix where it assumes a proteolytic resistant beta-sheet structure; the amorphous material generated is called 'amyloid'. To date, 28 precursor proteins have been identified; however, subtypes light chain amyloidosis (AL), transthyretin (TTR) amyloidosis, systemic secondary amyloidosis, and systemic senile amyloidosis are the most common.[1–5] Amyloidotic deposition can affect myocardium, valves, and coronary vessels, leading to structural and functional alterations.[3]

Diagnostic process: from clinical presentation to myocardial biopsy

Clinical presentation

Close to 90% of patients with amyloidosis experience fatigue, weight loss, and present with edema. The clinical presentation depends on the amyloid deposit in the vessels, kidneys, liver, nerves, and heart.[6–9]

Cardiac involvement is frequent in AL, systemic senile, and TTR amyloidosis but rare in the systemic secondary variant. Cardiac amyloidosis begins with a subclinical stage due to initial amyloid deposition that is characterized by mild and unspecific cardiac symptoms.[10] Observations in this phase include focal deposition of amyloid [atria, atrioventricular valves, intramural left ventricular (LV) deposition], mild LV wall thickness (<15 mm), mild diastolic dysfunction, and an impairment of only LV longitudinal function (subclinical stage). Progression of amyloid deposition causes a marked thickening of the LV wall (>15 mm) and the typical stage is characterized by heart failure (HF) with preserved systolic function, sometimes with a restrictive diastolic pattern (typical 'hypertrophic' stage). The disease evolves to end-stage congestive HF with biventricular systolic impairment and arrhythmias (end-stage). Angina could be present because of amyloid infiltration of the small intramyocardial vessels. Syncope is common and a consequence of both autonomic failure and arrhythmias; when activity-related syncope occurs, prognosis is poor. The most frequent arrhythmias are atrial fibrillation, sinus

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dysfunction, and atrioventricular blocks.[9,11] The degree of cardiac involvement, clinical presentation, and prognosis are strongly related to the particular subtypes of cardiac amyloidosis. Particularly, wild-type TTR has less cardiac involvement and a good prognosis with respect to mutant TTR. On the contrary, AL cardiac amyloidosis has a very poor prognosis with respect to wild-type TTR and mutated TTR.[1,3]

Electrocardiography

The most common electrocardiogram (ECG) finding of cardiac amyloidosis is represented by low QRS voltages (*Figure 1*). The diagnosis of low voltages is correct when the sum of three peripheral lead voltages is $\leq$0.15 mV. Other cardiac amyloidosis findings are poor R-wave progression in precordial leads and pseudonecrotic Q waves, atrial fibrillation, and atrioventricular block.[9,11]

Circulating biomarkers

Brain natriuretic peptide (BNP) is the active molecule obtained from the cleavage of the N-amino terminal fragment (NT-proBNP). NT-proBNP is an inactive element but produced in equimolarity to active BNP. BNP and NT-proBNP are widely recognized as markers of HF. Although the elevation of ventricular filling pressure is the main cause for the release of BNP, it is possible that direct damage of the ventricular myocites could increase the level of BNP in patients with cardiac amyloidosis.[12,13] Cardiac troponin is the most sensitive biomarker of myocardial injury. Recently, several studies demonstrated that high levels of cardiac troponin T and I have a strong predictive power in diagnosis and prognosis of cardiac amyloidosis.[14]

Histological assay

Abdominal fat biopsy is a highly sensitive (<70% of AL amyloidosis) and specific instrument to diagnose amyloidosis. Other tissues that allow relatively non-invasive biopsy procedures are minor salivary glands, gingiva, rectum, and skin.[1,2,4] Despite imaging development, endomyocardial biopsy remains the gold standard technique to diagnose cardiac amyloidsosis in patients with HF.[14]

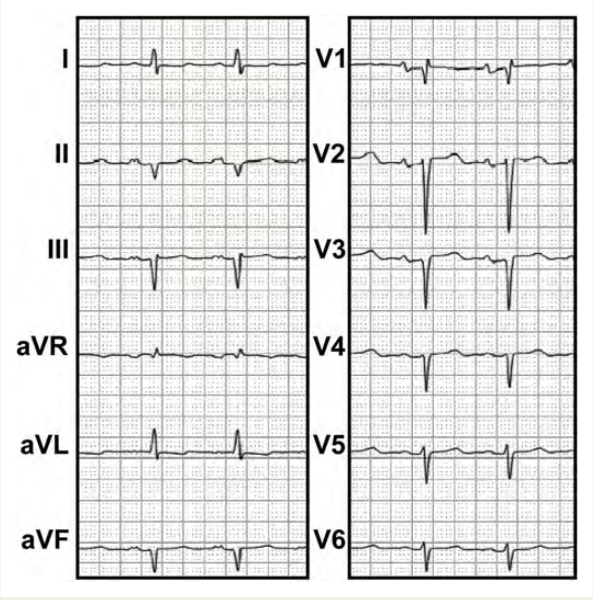

Figure 1: Electrocardiogram showing low voltages of QRS in the peripheral leads and a poor precordial R-wave progression with inferior pseudonecrotic Q-waves.

Need for cardiac imaging

Although clinical evaluation and extracardiac biopsy allow the diagnosis of systemic amyloidosis, accurate evaluation of myocardial involvement in patients with amyloidosis is extremely complex, particularly at the subclinical phase. Imaging techniques were introduced with the aim to identify with high accuracy specific forms of cardiac amyloidosis (i.e. ^{99m}Tc-3,3,-diphosphono-1,2-propanodicarboxylic acid [^{99m}Tc-DPD] to diagnose TTR cardiac amyloidosis) and to evaluate early structural [i.e. focal delayed contrast enhancement (DCE) at cardiac magnetic resonance (CMR)] or mechanical (i.e. longitudinal strain) abnormalities. Only an appropriate use of these techniques guides the clinician towards the proper management of these patients.

Nuclear medicine techniques

Although different features of heart involvement can be assessed by nuclear medicine techniques, the most useful information in patients with amyloidosis is obtained through the imaging of myocardial innervation by ^{123}I-metaiodobenzylguanidine (^{123}I-mIBG) or by using radiopharmaceuticals that image amyloid deposits.

Myocardial defects in ^{123}I-mIBG activity seem to correlate with impaired cardiac sympathetic nerve endings due to amyloid deposits and with clinical severity of disease. Namely, ^{123}I-mIBG heart-to-mediastinum ratio is reduced and washout rate is increased in patients with cardiac amyloidosis. Moreover, it has been demonstrated that ^{123}I-mIBG scintigraphy can detect cardiac denervation in TTR amyloidosis in early stage, before signs of amyloidosis are evident on echocardiography.[15] Furthermore, in a recent study evaluating the prognostic value of ^{123}I-mIBG scintigraphy in 143 patients with TTR amyloidosis, Coutinho *et al.*[16] found that heart-to-mediastinum ratio is an independent prognostic predictor of survival.

At present, nuclear medicine imaging of cardiac amyloid deposition is predominantly accomplished with bone-seeking radiotracers (panel C in *Figures 2* and *3*), such as ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-hydroxymethylene-diphosphonate (^{99m}Tc-HDP), and ^{99m}Tc-DPD, which may differentiate AL from TTR cardiac amyloidosis with significant implications for prognosis, therapy, and genetic counselling. In particular, using ^{99m}Tc-PYP imaging, Bokhari *et al.*[17] found that subjects with TTR cardiac amyloidosis had a significantly higher semiquantitative cardiac visual score as well as a higher quantitative score than those in the AL cohort. They reported that using a heart-to-contralateral chest ratio >1.5, consistent with intensely diffuse myocardial tracer retention, had a 97% sensitivity and 100% specificity for identifying TTR cardiac amyloidosis. Rapezzi *et al.*[18] found ^{99m}Tc-DPD accumulation in 45/45 cases of TTR cardiac amyloidosis, no radiotracer uptake in 15/15 unaffected controls, and only a mild degree of radiotracer uptake in 11 of 34 patients with AL-related cardiac amyloidosis. As a further positive issue, it has been demonstrated that both ^{99m}Tc-DPD and ^{99m}Tc-HDP scintigraphy are capable to identify amyloid deposition

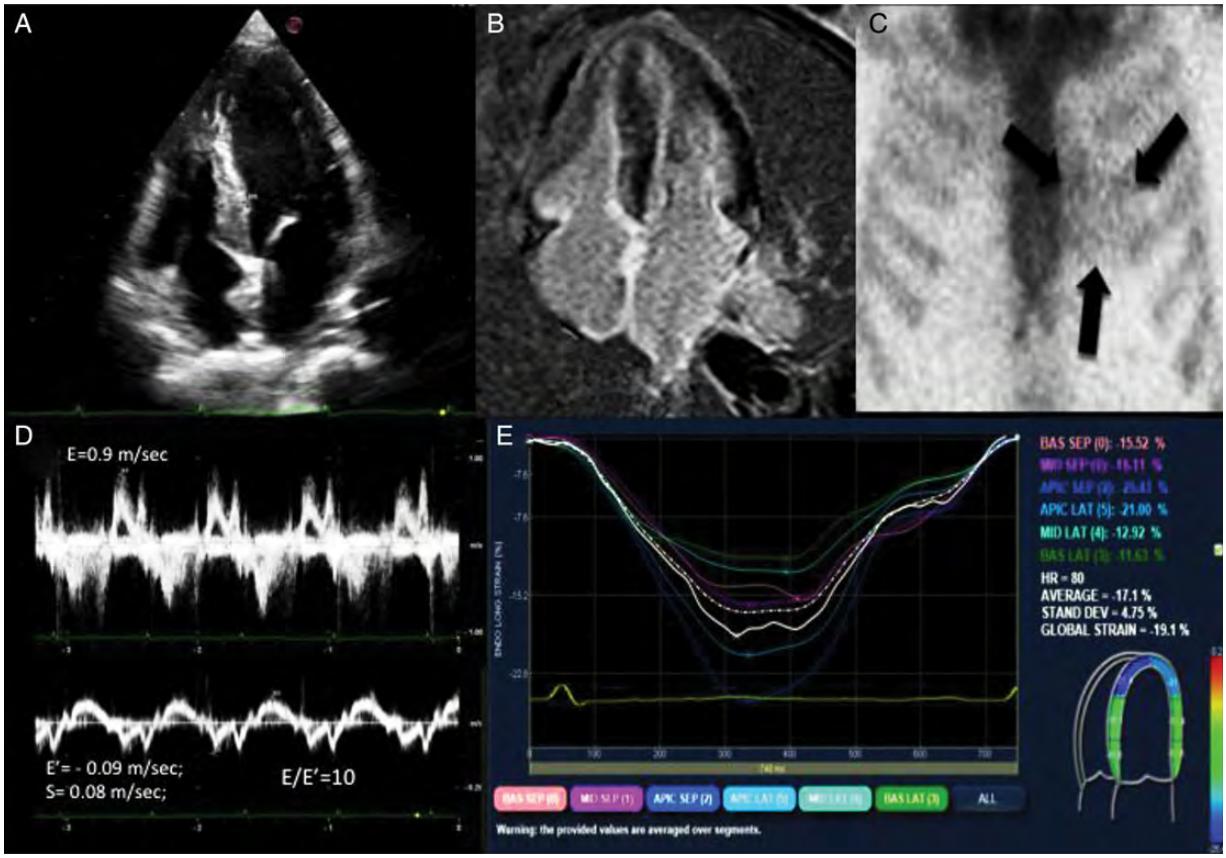

Figure 2: Case 1. Subclinical stage. A 42-year-old woman with somatic polyneuropathy, no cardiac symptoms, and positive results of genetic testing for transthyretin familial amyloid polyneuropathy (Thr49Ala). Echocardiographic findings show a mild increase of LV thickness (12 mm) on four chambers view (*A*), a normal longitudinal function (S wave 0.08 cm/s) on TDI (*D*) and a moderate diastolic dysfunction (pseudonormal E/A pattern and E/E′ 10). Longitudinal deformation by 2D strain imaging (*E*) shows a very mild impairment of global longitudinal deformation (-19.1, normal value > -19.7). Furthermore, a lower deformation in basal segments with respect to apical segments can be found. MRI with late gadolinium enhancement in horizontal long-axis view (*B*) shows focal enhancement of right atrium and left atrium (with arrow). Technetium-99m-diphosphonate scan shows faint cardiac radiotracer uptake (arrows).

in the myocardium of patients with TTR cardiac amyloidosis (i.e. TTR- familial amyloid polyneuropathy and systemic senile amyloidosis) across a wide spectrum of morphologic/functional cardiac involvement allowing an early diagnosis of the disease, even before the appearance of echocardiographic abnormalities.[19–21] Moreover, in a recent study by Minutoli *et al.*,[22] LV segmental extension of myocardial amyloid deposition as demonstrated by ^{99m}Tc-DPD imaging was often larger than that revealed by visual analysis of DCE-CMR. Indeed, although ^{99m}Tc-DPD imaging and DCE-CMR have similar capability to identify patients with myocardial amyloid deposition, cardiac amyloid infiltration burden can be significantly underestimated by visual analysis with DCE-MRI with respect to ^{99m}Tc-DPD imaging. Finally, myocardial uptake of bone-seeking radiotracers is correlated with disease severity[20,21] and has been demonstrated to be a prognostic determinant of "cardiac" outcome in TTR cardiac amyloidosis, either alone or in combination with LV wall thickness.[19]

The clinical use of positron emission tomography, which has the advantages of absolute quantification and higher resolution, probably will be gained by the increasing investigation of tracers that sensitively and specifically binds to amyloid fibrils.[23]

Echocardiography

The main 2D echocardiographic findings observed in the typical 'hypertrophic' stage of cardiac amyloidosis include: symmetric LV and right ventricular (RV) thickening, dilated atria, pericardial effusion, valvular thickening (particularly in wild-type or mutant TTR cardiac amyloidosis), and 'granular sparkling' appearance (Supplementary data online, *Video S1*).[9,11]

Although these findings are common in the typical stage of cardiac amyloidosis, they have low accuracy in the early stage of cardiac amyloidosis and in discriminating cardiac amyloidosis from other causes of LV hypertrophy.

In order to obtain an early and definite diagnosis of cardiac amyloidosis, it is necessary a multiparametric evaluation, which also includes data of segmental systolic function (longitudinal, radial, and circumferential), right ventricular, and ventricular diastolic function.

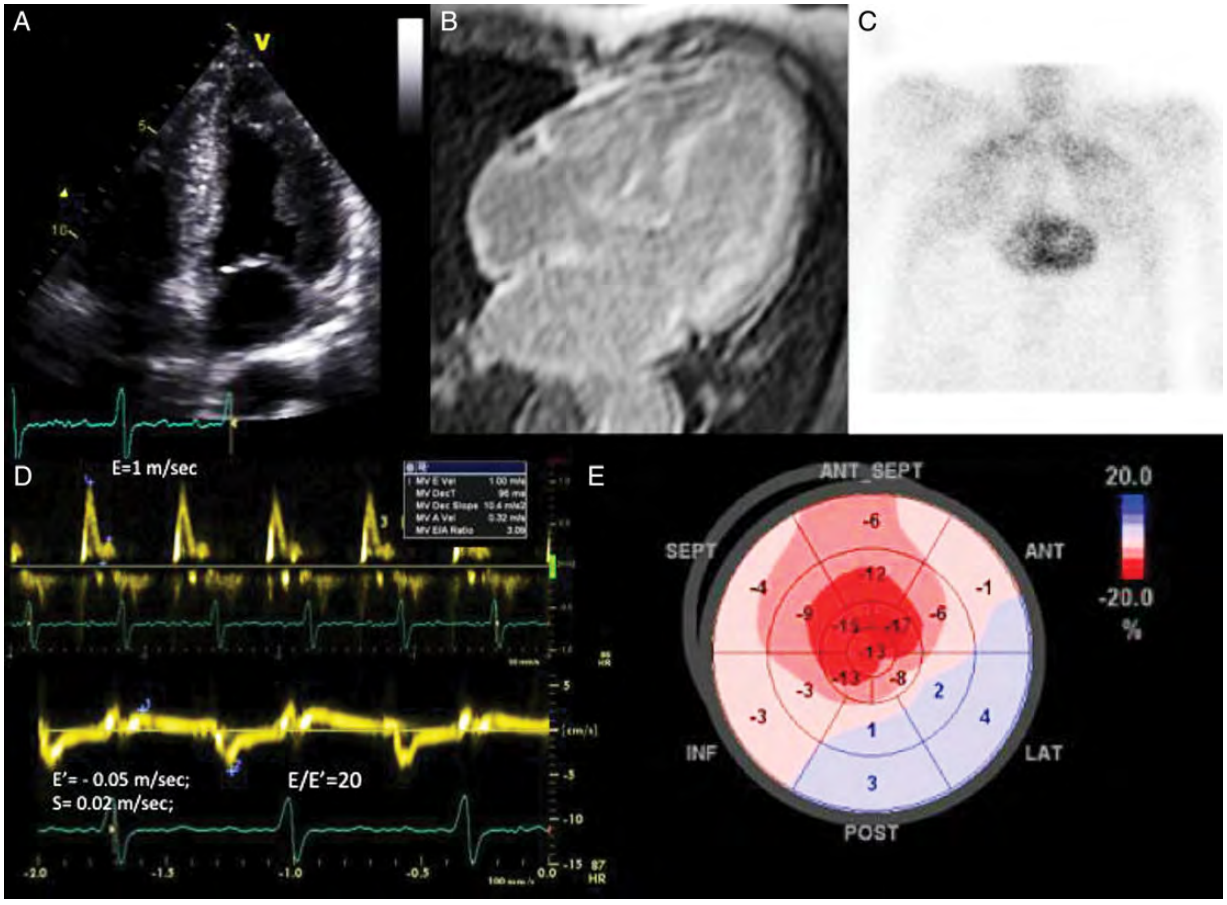

Figure 3: Case 2. Typical stage. A 56-year-old woman with somatic polyneuropathy, NHYA III, and positive results of genetic testing for transthyretin familial amyloid polyneuropathy (Glu89Gln). Echocardiographic findings show a moderate increase of LV thickness (19 mm) on four chambers view (*A*), a severe longitudinal dysfunction (S wave 0.02 cm/s) on TDI (*D*) and a severe (restrictive) diastolic dysfunction (E/A>2 and E/E′ 20). Longitudinal deformation by 2D strain imaging (*E*) shows a severe impairment of global longitudinal deformation (−7, normal value > −19.7) with a lower deformation in basal segments with respect to apical segments. MRI with late gadolinium enhancement in the horizontal long-axis view (*B*) shows a diminished T1 difference between myocardium and blood pool, and a myocardial enhancement distributed over the entire subendocardial circumference (global subendocardial circumference-DCE). Technetium-99m-diphosphonate SPECT image shows intense cardiac radiotracer uptake.

Tissue Doppler and two-dimensional strain rate and strain imaging

The analysis of segmental myocardial deformation derived by tissue Doppler imaging (TDI) and 2D strain imaging (2D-S) plays a crucial role in early diagnosis and prognostic evaluation of patients with cardiac amyloidosis.[24]

Serial investigations revealed that longitudinal deformation detected by TDI is impaired early in patients with cardiac amyloidosis.[25] Porciani *et al.*[25] observed a strong correlation between LV thickness and longitudinal dysfunction investigated by TDI in patients with cardiac amyloidosis and mild amyloid infiltration. Lindqvist *et al.*[26] found that TDI was accurate in the detection of myocardial involvement in familial amyloidotic polyneuropathy patients with no clinical signs of HF. These data were further confirmed by Koyama *et al.*,[27,28] who showed a lower longitudinal function, derived by TDI, in patients with typical stage of cardiac amyloidosis compared with amyloidotic patients without heart involvement.

Particularly, longitudinal myocardial deformation at the base and mid LV was significantly decreased in asymptomatic cardiac amyloidosis patients with and without increased wall thickness.[28]

The clinical relevance of longitudinal dysfunction detected by TDI is confirmed by an adverse outcome in patients with depressed longitudinal peak systolic septal deformation.[29]

All these observations support the notion that impairment of longitudinal function by TDI plays a major role in the pathophysiology of cardiac amyloidosis and may be present even before congestive HF occurs and sometimes even in subjects without increased LV wall thickening.

However, TDI has many of the typical limitations of techniques based on Doppler effect, including angle dependence and noise interference.

The introduction of speckle tracking analysis allowed limitations linked to deformation analysis performed by TDI to be overcome. Speckle tracking permits evaluation of the myocardial deformation

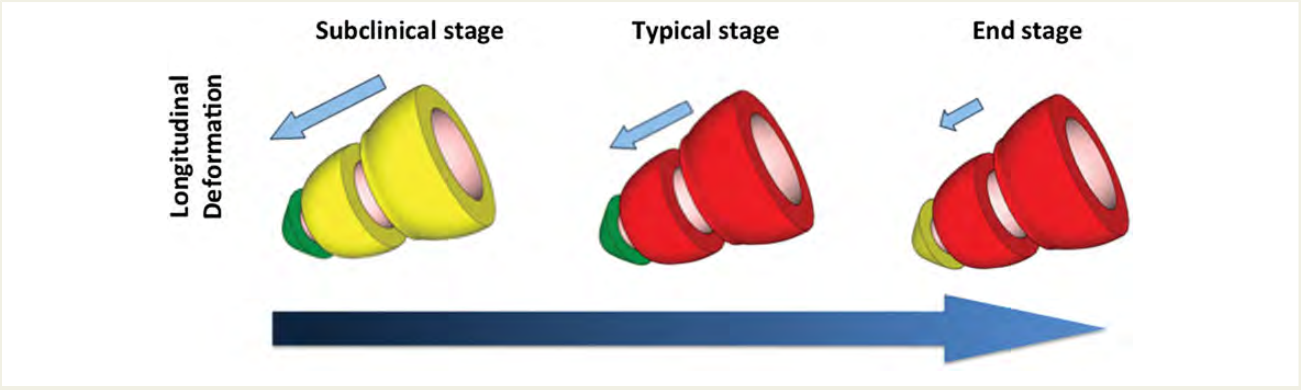

Figure 4: Myocardial deformation in different stages of cardiac amyloidosis. Green = normal strain; yellow = mild–moderate strain impairment; red = severe strain impairment). Note the longitudinal dysfunction in mid and basal LV segments both in subclinical (longitudinal mild dysfunction <19%) and typical stage.

thanks to the analysis of acoustic interferences created by interaction between ultrasounds and tissues (speckles). The dedicated software is able to evaluate not only longitudinal function but also the radial and the circumferential ones. Twist, untwist, and torsion are other parameters of deformation connected to the opposite rotation of the base of the heart and apex.

Sun *et al.*[30] reported that global longitudinal, circumferential, and radial deformations detected by 2D strain were significantly lower in patients with advanced cardiac amyloidosis compared with controls, hypertrophic cardiomyopathy (HCM), and hypertensive heart disease. Di Bella *et al.*[31] showed that epicardial circumferential strain was significantly lower in patients with TTR cardiac amyloidosis than in patients with HCM.

Recently Quarta *et al.*,[32] analysing myocardial deformation by 2D-S in patients with AL and TTR cardiac amyloidosis, observed that despite a preserved LV ejection fraction, longitudinal deformation was severely impaired at basal and mid LV segments while apical longitudinal strain was preserved irrespective of the etiology of CA and the degree of wall thickening. Interesting, systemic senile amyloidosis (wild type TTR) was characterized by greater LV wall thickness and lower ejection fraction with respect to AL and mutated TTR. However, patients with systemic senile amyloidosis had a similar prognosis with respect to mutated TTR and a longer survival with respect to AL cardiac amyloidosis.

An interesting study carried out by Baccouche *et al.*[33] compared late gadolinium enhancement evaluated by CMR with three-dimensional strain by echocardiography; they found that radial strain was strongly correlated with the severity of the myocardial involvement.

The more severe infiltration of the basal segments determined a clear basoapical gradient ('inverse pattern'), with lower deformation in basal segments with respect to apical segments. This condition has been observed in CA and could be used to differentiate it from other causes of LV hypertrophy. Patients with HCM had a reduced, but still preserved, basoapical gradient. Therefore, the basoapical radial strain gradient displayed oppositional characteristics in cardiac amyloidosis and HCM, suggesting a 'function pattern-based' differentiation with a sensitivity of 83% versus the CMR-derived diagnosis.[33]

Left ventricular rotational mechanics, investigated in patients with systemic amyloidosis, showed that LV twist and untwist rate enhances before LV hypertrophy is developed.[34]

Data from both TDI and 2D-S highlight that patients with cardiac amyloidosis show a greater impairment of basal segments than apical ones.

Finally, in clinical practice, the greater impairment of basal segments with respect to apical ones from TDI and/or 2D-S can help clinicians in diagnosing cardiac amyloidosis (*Figure 4*).

For the most part, the studies highlighted that strain is useful in the distinction between cardiac amyloidosis and other diseases characterized by LV hypertrophy, myocardial deformation is usually more reduced in cardiac amyloidosis than in other forms of cardiac hypertrophy, and, moreover, the greater impairment of basal segments with respect to apical ones can further help clinicians in differential diagnosis of cardiac amyloidosis. However, larger studies are needed to determine clear and reliable reference values.

Left ventricular diastolic dysfunction

Cardiac amyloidosis is usually described as a typical example of 'restrictive cardiomyopathy' characterized by high filling pressures and restrictive mitral inflow pattern. Recently, many authors revealed that these findings are common only in advanced cardiac amyloidosis. In this stage, a markedly increased wall thickness associated with a restrictive filling pattern characterized by markedly shortened deceleration time and high early (E-wave) velocity and relatively low atrial (A-wave) velocity is usually observed.

Many studies revealed that in cardiac amyloidosis, the degree of amyloid infiltration is related to diastolic dysfunction, which progresses from an abnormal relaxation pattern in the early stage, through a pseudonormal pattern, to a restrictive filling pattern in the late stage (E/A>2, deceleration time <150 ms).[27,28,35] The onset of a restrictive pattern is an important and independent prognostic indicator of (poor) outcome in cardiac amyloidosis.[35]

Interestingly, although diastolic dysfunction is a common finding, restrictive filling pattern is unusually observed in cardiac amyloidosis. Rapezzi *et al.*[3] have studied diastolic function, using both invasive haemodynamic measures and Doppler echocardiography, of the

three main systemic types of cardiac amyloidosis (AL, TTR-familial amyloid polyneuropathy, and TTR wild-type); they observed that the majority of patients in each group did not display restrictive filling pattern. Particularly, groups showed relevant haemodynamic differences, with AL patients most often displaying abnormal values in the different measures of diastolic function.

Many studies showed that peak early diastolic velocity (E′) by TDI already is decreased in patients with systemic amyloidosis and normal wall thickness (early stage) and further decreases with the advent of LV thickening (typical stage) and in the late phase of cardiac amyloidosis (end-stage).

Another clinical application of TDI to the evaluation of diastolic function is the ability of E′ to discriminate cardiac amyloidosis (marked reduced) with respect to constrictive pericarditis (normal or mild reduced).[36]

Some authors described a higher sensitivity of TDI in comparison with the strain rate in detecting the decrease of the E′ velocity in patient with advanced cardiac amyloidosis.[24,37]

Therefore, in clinical evaluation of cardiac amyloidosis, diastolic dysfunction is a common finding but the restrictive mitral pattern is observed only in the few cases with massive deposition of amyloid in the end-stage phase of cardiomyopathy; parameters derived from TDI are more accurate in detecting the alteration of the diastolic function in the early stage of the disease.

Recently, Liu *et al.*[38] tried to combine data from strain imaging and diastolic function to obtain a more accurate differentiation between cardiac amyloidosis and other causes of concentric LV hypertrophy. He observed that combination of systolic septal longitudinal base-to-apex strain gradient (septal apical to basal LSsys ratio >2.1) with a shortened diastolic deceleration time of early filling wave (<200 ms) aids in differentiating cardiac amyloidosis from other causes of concentric LV hypertrophy.

Particularly, diastolic dysfunction can be an important independent prognostic indicator of (poor) outcome in cardiac amyloidosis.[35]

Finally, in clinical evaluation of cardiac amyloidosis, diastolic dysfunction is a common finding but the restrictive pattern is observed only in the few cases with severe deposition of amyloid, typical, and end-stage phases of cardiomyopathy.

Right ventricular dysfunction

It has been reported that RV dysfunction is common in cardiac amyloidosis and indicates poorer outcome.[39,40] Reduced tricuspid annular plane systolic excursion was associated with more severe LV involvement, higher NT- pro-BNP peptide levels, and poorer survival.[41] Right ventricular dysfunction in patients with cardiac amyloidosis using both TDI and strain imaging was significantly reduced in cardiac amyloidosis compared with controls and was a significant independent predictor of poor prognosis.[42]

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging, having higher spatial resolution than nuclear medicine and echocardiography, is an excellent tool to obtain a detailed view of morphofunctional (volumes, ejection fraction, and mass) parameters of LV and RV as well as of atrial and ventricular thickness.[22,43] Delayed contrast enhancement CMR obtained 10–20 min after injection of gadolinium is a robust tool to identify myocardial damage (scar, fibrosis) in many heart diseases. Delayed contrast enhancement occurs as a result of altered gadolinium washout kinetics in the damaged myocardium (slow washout) with respect to normal surrounding tissue (fast washout). Therefore, myocardial damage appears as a hyperintense area due to the presence of gadolinium, while normal myocardium appears as a hypointense area.

To better identify myocardial damage (hyperintense area), it is needed to find a specific inversion time (usually 200–300 ms) to null the normal myocardial signal. This technical approach allows identification of normal myocardium as 'nulled signal' (hypointense), showing strong differing signal intensities with respect to myocardial damage and cavities.[44] The DCE areas can be observed both in ischaemic heart disease and in many cardiomyopathies such as HCM and Fabry disease. Usually, HCM shows a patchy DCE area located in the mid-wall of the hypertrophic segments; Fabry disease shows DCE in the basal inferolateral segment of the LV.[43]

On the contrary, DCE images show atypical signal intensity in cardiac amyloidosis, determined by the distribution and severity of myocardial amyloid deposition and the faster clearance of gadolinium from the blood pool (*Figure 3B*). The peculiar gadolinium kinetics in amyloid heart walls are defined by the following patterns: (i) a diminished T1 difference between damaged myocardium and blood pool, and (ii) many myocardial DCE patterns due to the slow washout of gadolinium from interstitial space that is infiltrated and expanded by amyloid proteins. The diminished T1 difference causes similar signal intensities between myocardium and blood pool, causing difficulty in distinguishing myocardium cavities. To confirm this, the CMR protocol for cardiac amyloidosis calls for the acquisition of multiple images using different inversion times (i.e. 80–350 ms with a 30 ms increment). Further DCE CMR patterns include a myocardial enhancement distributed over the entire subendocardial circumference (global subendocardial circumference-DCE), a 'zebra pattern' consisting of a subendocardial and subepicardial DCE and a diffuse homogeneous myocardial enhancement sometimes with focal regions of higher DCE areas.[45,46]

Furthermore, DCE CMR is able to identify areas of hyperintensity due to amyloid deposition in RV, atrioventricular valves, and thickened atria.[43]

Vogelsberg *et al.*[46] reported that global subendocardial circumference-DCE pattern is the most frequent pattern observed in patients with biopsy-proven cardiac amyloidosis and shows high accuracy to detect cardiac amyloidosis. Others authors have shown that the 2 min post-gadolinium intramyocardial T1 difference between the subepicardium and subendocardium predict mortality; particularly, the lower the difference, the worse the prognosis.[47] Further main findings in cardiac amyloidosis are that DCE areas are not limited to the LV but usually involve the RV and atria.[43]

Di Bella *et al.*[43] studied 16 TTR patients with familial amyloid polyneuropathy and showed unusual findings of cardiac amyloidosis. Particularly, the typical subendocardial circumferential-DCE pattern was observed only in one patient with advanced HF; asymptomatic patients with cardiac amyloid deposition detected by ^{99m}Tc-DPD scintigraphy showed a patchy intramural focal enhancement located in basal segments of inferolateral and inferior wall and areas of DCE in atria, atrioventricular valves, and RV.

Similarly, Syed *et al.*[47] observed both the typical subendocardial circumferential-DCE pattern and intramural focal DCE pattern in

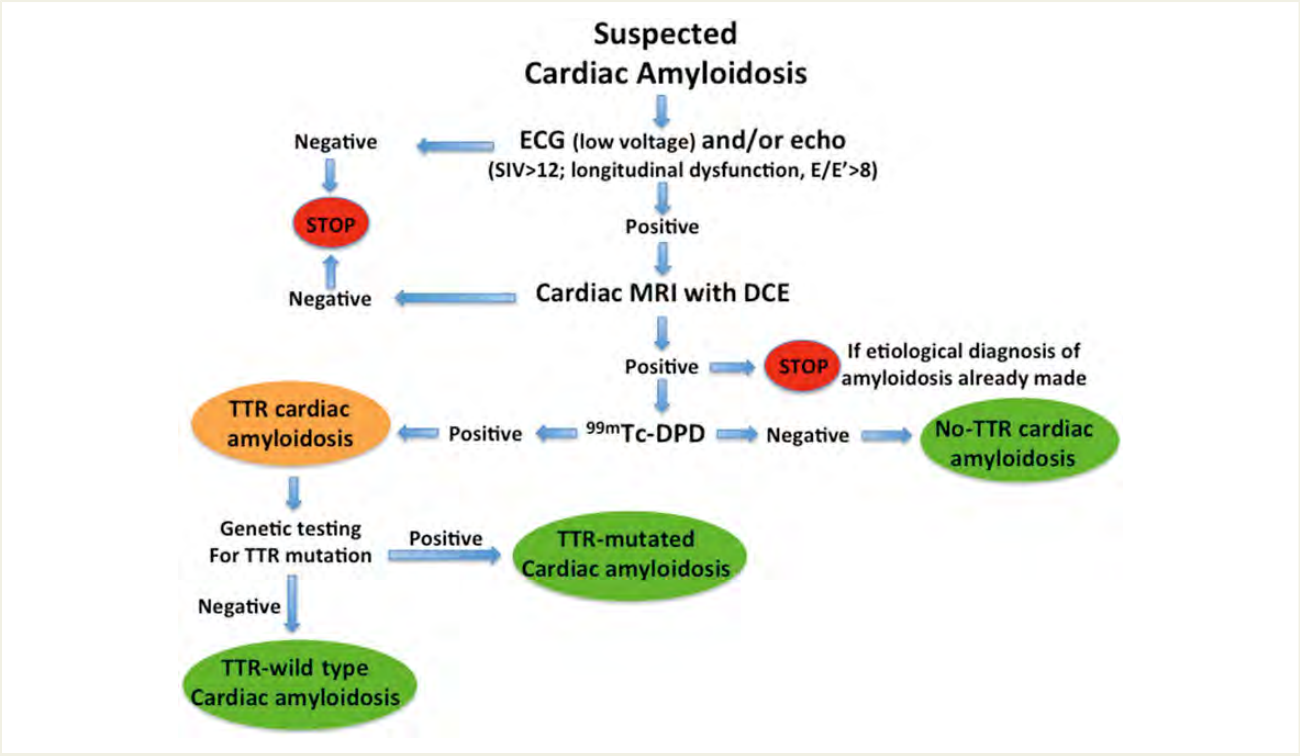

Figure 5: Suggested workflow diagram in the non-invasive diagnostic imaging workup of suspected cardiac amyloidosis. Note that non-TTR cardiac amyloidosis includes many diseases (multiple myeloma, non-Hodgkin lymphoma, Waldenstrom macroglobulinemia, monoclonal gammopathy of unknown significance, chronic arthritis, ankylosing spondylitis, Crohn's disease, hereditary periodic fevers and acquired or inherited immunodeficiencies, chronic renal failure, and long-term history of haemodialysis). After finding evidence of cardiac amyloidosis using cardiac imaging, if there are no etiological data, a large series of examinations are needed to confirm systemic amyloidosis and to diagnose the aetiology of cardiac amyloidosis.

35 patients with cardiac amyloidosis; particularly, NYHA functional class, low voltage and pseudoinfarct pattern on ECG, LV and RV thickness, and cardiac troponin T and BNP levels were higher in patients with global subendocardial circumferential-DCE with respect to those with patchy intramural focal enhancement. These data support that the patchy intramural focal enhancement and DCE of atria, RV, and valves represent an early phase of myocardial amyloid deposition.

Recently, Dungu *et al.*[48] highlighted the different CMR features in TTR and AL cardiac amyloidosis. Particularly, they showed an improved survival despite increased LV mass and more extensive LV and RV DCE in TTR with respect to AL cardiac amyloidosis.

Areas of DCE in atria and RV, typically found in asymptomatic TTR patients, are not observed in HCM and Fabry disease.[43] Although subendocardial circumferential-DCE has high specificity in the identification of cardiac amyloidosis, the focal pattern cannot be considered specific. Therefore, the differential diagnosis has to include many other heart diseases; however, it is highly probable that the combined presence of focal LV-DCE and the involvement of other chambers or structures are due to cardiac amyloidosis.

T1 mapping is an interesting application of T1-weighted imaging. T1 mapping requires acquisition of multiple images with different T1 to derive the T1 recovery curve. This approach permits acquisition of quantitative data of T1 tissue characterization; particularly, T1 mapping permits one to obtain, without use of gadolinium-based contrast agents (non-contrast or native T1 mapping), information about changes of myocytes and interstitium and, after gadolinium administration (contrast T1 mapping), information about the size of the extracellular space (myocardial interstitial disease).

Myocardial native T1 mapping has been shown to be accurate in detecting early cardiac involvement in both AL and TTR cardiac amyloidosis; furthermore, native T1 mapping can be used to track amyloidotic deposition.[49,50]

An important limitation of DCE technique is represented by the risk of nephrogenic systemic sclerosis in patients with renal impairment. Furthermore, CMR allows identification of both pericardial and pleural effusion (Supplementary data online, *Video S1*). These latter findings, usually, are observed in cardiac amyloidosis rather than in other cardiomyopathies with hypertrophic phenotypes.

Practical application of cardiac imaging techniques

In clinical practice, several clinical scenarios may occur in diagnosing cardiac amyloidosis.

SCENARIO A, patients with a definite diagnosis of systemic amyloidosis (e.g. positive fat biopsy) and no other possible causes of

abnormal cardiac findings: in this case, the evidence of abnormal ECG (i.e. low voltage) and/or LV wall thickening (>12 mm), longitudinal dysfunction, E/E′ >8 are satisfactory to diagnose cardiac amyloidosis.

SCENARIO B, patients with a definite diagnosis of systemic amyloidosis and other possible causes of increased LV thickness (e.g. hypertension): in this scenario, CMR (including DCE imaging) is needed. Scintigraphy using bone-seeking radiopharmaceuticals may be additionally performed in patients with TTR-related amyloidosis and non-conclusive CMR findings because of its high sensitivity in revealing amyloid deposition.[22]

SCENARIO C, patients with high risk to develop cardiac amyloidosis: this scenario includes subjects with a positive genetic test for TTR gene mutation or a disease carrying amyloid deposition, e.g. multiple myeloma, non-Hodgkin lymphoma, Waldenstrom macroglobulinemia, monoclonal gammopathy of unknown significance, chronic arthritis (particularly rheumatoid arthritis), ankylosing spondylitis, Crohn's disease, hereditary periodic fevers and acquired or inherited immunodeficiencies, chronic renal failure, and long-term history of haemodialysis (non-TTR amyloidosis). Cardiac imaging using CMR and/or scintigraphy maybe used to reveal amyloid deposition.

SCENARIO D, patients with clinical and/or laboratory ECG and echocardiographic findings compatible with cardiac amyloidosis and without any known condition related to the development of amyloidosis: this scenario is very challenging, and it can be observed during echocardiographic examinations. Because of the heterogeneity of causes leading to amyloid deposition, diagnostic algorithm, and the need for imaging should be addressed by careful clinical evaluation. As far as cardiac imaging is concerned, when echocardiography and strain imaging reveal cardiac abnormalities, CMR with DCE should be the main diagnostic tool. Indeed, it is a 'one stop shop' technique that may disclose specific findings without radiation exposure. Scintigraphy using bone-seeking radiopharmaceuticals may be used as a non-invasive method to individuate TTR-related amyloidosis (*Figure 5*). Both CMR and nuclear medicine techniques allow prognostic evaluation. Biopsy should be considered in patients with HF when clinical features and cardiac imaging findings are not conclusive for cardiac amyloidosis.

Conclusions

Cardiac amyloidosis is a rare infiltrative cardiomyopathy resulting from a broad range of genetic, neoplastic, inflammatory, and autoimmune causes. The diagnostic process requires an accurate clinical evaluation, electrocardiography, serological assays, cardiac imaging, and biopsy. Although endomyocardial biopsy is the gold standard modality to diagnose cardiac amyloidosis, it is recommended in patients presenting with HF. Conversely, conventional echocardiography is the first line imaging modality in patients with clinical suspicion for cardiac amyloidosis and for follow-up patients. Advanced imaging, namely strain echocardiography, DCE CMR, and nuclear medicine techniques, is effective to non-invasively diagnose both early and advanced phases of cardiac amyloidosis.

Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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Left Atrial Morphology, Size and Function in Patients With Transthyretin Cardiac Amyloidosis and Primary Hypertrophic Cardiomyopathy

– Comparative Strain Imaging Study –

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Background: We sought to assess left atrial (LA) morphology and function in patients with transthyretin cardiac amyloidosis (TTR-CA) and hypertrophic cardiomyopathy (HCM). Primarily, longitudinal deformation (reservoir) and pump function were the focus of vector-velocity strain echocardiography imaging.

Methods and Results: The study group comprised 32 patients (mean age 57.7±15.4 years, 16 in each group), and 15 healthy controls. Diagnosis of TTR-CA was based on echocardiography and either gadolinium-enhanced (LGE) cardiac magnetic resonance (cMRI) or radionuclide imaging. At baseline, there were no differences in age, body surface area, blood pressure and risk factors among the groups. Left ventricular (LV) mass was greater in patients than in controls, and slight LA dilatation was found in the TTR-CA group. LA reservoir was 14.1±4.7% in TTR-CA, 20.0±5.6% in HCM, and 34.0±11.8% in controls (<0.001). In addition, LA pump function chiefly was impaired in the former group, irrespective of LA chamber size and LV ejection fraction. LGE in the atrial wall was seen in 9/10 TTR-CA versus 0/8 HCM patients undergoing cMRI (P<0.001). LA reservoir ≤19% and pump function ≤–1.1% best discriminated TTR-CA from HCM patients in the receiver-operating characteristic analysis.

Conclusions: LA reservoir and pump function were significantly impaired in both TTR-CA and HCM patients compared with controls, but mainly in the former group, irrespective of LA volume and LV ejection fraction, likely caused by a more altered LA wall structure. (*Circ J* 2016; **80:** 1830–1837)

Key Words: Amyloidosis; Atrial function; Hypertrophic cardiomyopathy; Strain echocardiography

Strain echocardiography (strain) imaging is a modern and valuable technique for recognizing left ventricular (LV) dysfunction in several cardiomyopathies, including rare diseases such as cardiac amyloidosis (CA) and hypertrophic cardiomyopathy (HCM).[1–3]

Despite the absence of software tailored for the atria, recent studies suggest this technique is a powered detector of left atrial (LA) mechanics, and both speckle tracking and vector-velocity (feature tracking) modalities have been used for that purpose.[4–6]

CA represents a cause of LV wall thickening and dysfunction, gradually leading to heart failure as a consequence of amyloid deposits in intramural coronary arteries and endomyocardium. However, noninvasive diagnostic tools of cardiac involvement are challenging when the clinical diagnosis is deficient, and misdiagnoses can be potentially harmful in some patients, because of a failure to differentiate CA from overlapping cardiomyopathies, with different prognosis.[7–9]

Among all the subtypes of CA, there is a variant caused by mutations in the genes encoding for transthyretin (TTR), a tetrameric protein rich in β-strands highly present in human serum and tissues. Both familial and acquired (wild-type or senile variant) TTR-amyloidosis account for 8–10% of all forms. The familial variant approximately involves 1:100,000 individuals of the general population in the USA, but it is more frequent in some geographic areas, such as Italy.

Clinical expression varies from initial (isolated polyneuropathy without cardiac involvement) to advanced (amyloid deposits into myocardial wall, TTR-CA), the latter usually considered at poor prognosis. Hence, the early identification of the cardiac involvement is a crucial issue in the clinical management of such patients.[7–10]

Furthermore, HCM represents a dramatic, potentially fatal, cardiac disease often complicated by myocardial fibrosis and

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subsequent functional impairment, in which the fibers' disarray, microvasculature impairment, abnormal collagen deposits, ischemic spots and chronic LV pressure overload are, in turn, important prognosticators.[11,12]

In both conditions, there would be a clinical advantage in recognition of functional impairment of the LA, probably earlier than LV dysfunction, and recent studies indicate strain imaging as the most valuable noninvasive technique to disclose subclinical atrial dysfunction.[8,13] LA morphofunctional changes are emerging as prognosticators in various cardiac diseases, but only scanty literature is available on comparative strain studies between TTR-CA and HCM patients, being all cardiac chambers target organs for either amyloid deposits or interstitial fibrosis.[6,13–16]

In the present study we sought to evaluate and compare the distinctive features of LA size and function in these 2 clinical conditions using vector-velocity strain imaging.

Methods

Patient Population

All patients consecutively admitted to the University Hospital of Messina for TTR-CA or primary HCM from January 2013 to May 2015 were enrolled. Fine acoustic window for ultrasound investigation was a stringent inclusion criterion, and the exclusion conditions were as follows: (a) systemic hypertension; (b) previous myocardial infarction, ischemic heart disease or stroke; (c) dilated or endstage cardiomyopathy; (d) permanent/persistent atrial fibrillation; (e) severe mitral regurgitation; (f) aortic valve stenosis; (g) chronic lung disease; and (h) severe renal or hepatic dysfunction.

Diagnosis of TTR-amyloidosis had been made 39±13 months before the cardiac study, on the basis of neurological stadiation and genomic testing in all patients. Also, green birefringence under cross-polarized light following Congo red staining was demonstrated in biopsied fat pad tissues in 10 of them (62%). Cardiac involvement was then investigated by Doppler echocardiography in the whole study population in combination with either cardiac magnetic resonance imaging (cMRI) or ^{99m}TC-diphosphono-1,2-proponodicarboxylic acid (^{99m}Tc-DPD) scintigraphy.

Nobody from this group had evidence of monoclonal protein in the serum or urinalysis, nor monoclonal population in the plasma cells or in the bone marrow, thus excluding light-chain amyloidosis. All subjects had clinical evidence of polyneuropathy.

Primary HCM was established according to current ACCF/AHA guidelines,[11] using family history, electrocardiography, echocardiography, and cMRI if necessary. Stringent echocardiographic criteria were LV wall thickness of ≥15 mm (≥17 mm for posterior septum) in a non-dilated LV chamber, without any possible hemodynamic cause of hypertrophy. All patients complaining of angina or equivalent symptoms underwent exercise ECG or stress-echocardiography in order to rule out underlying active coronary artery disease.

Study Design

This was a single-center, case-control imaging study aimed at evaluating LA morphology and function in patients with TTR-CA and primary HCM, comparing findings with 15 apparently healthy control subjects, matched for age, body surface area (BSA) and blood pressure (BP). Ultrasound studies were interpreted by a skilled cardiologist, blinded to the subjects' grouping.

Because of budget restrictions in the original proposal, cMRI and ^{99m}Tc-DPD scintigraphy were performed only in some TTR-CA patients, especially when echocardiography was not conclusive.

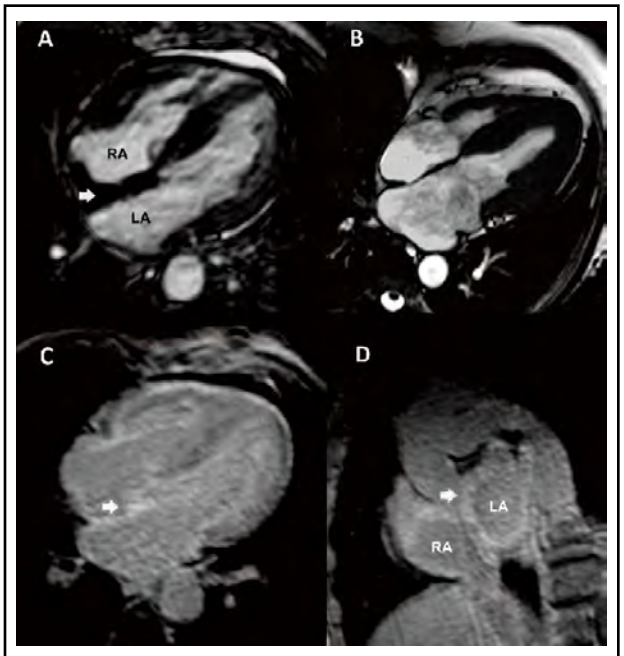

Figure 1. Cardiac magnetic resonance imaging by cine modality (**A**,**B**) and T1-weighted (**C**,**D**) in a patient with TTR-CA (**A**,**C**,**D**) or HCM (**B**). Note the greater atrial septal thickness (**A**) as well as the strong gadolinium enhancement in the TTR-CA patient (**C**,**D**: arrows). HCM, hypertrophic cardiomyopathy; LA, left atrium; RA, right atrium; TTR-CA, transthyretin cardiac amyloidosis.

cMRI was also carried out in HCM patients highly suspected of having myocardial fibrosis (severe LV hypertrophy on echocardiography, repetitive ventricular beats and/or non-sustained tachycardia).

Enrolment of patients complied with the Declaration of Helsinki and informed consent was given by all participants. Data were collected anonymously according to the Italian Health System regulation.

Echocardiography

All subjects underwent high-resolution ultrasound study. Quantitative findings were indexed to BSA, according to our laboratory protocols and current guidelines.[12,17] LV end-diastolic and systolic volumes were achieved by both 4- and 2-chamber apical views, and ejection fraction (EF) was calculated with the biplane Simpson rule method. LA systolic (maximum) and diastolic (minimum) volumes were measured as a mean value from both 4- and 2-chamber apical views, and fractional emptying calculated as follows: (maximum–minimum)/maximum volume percent change. LA volume index ≤29 ml/m^2 was considered as the upper normal limit, in both men and women. LV diastolic function was evaluated by PW Doppler sampling at the mitral valve inflow (E/A velocity ratio, E-wave deceleration time) and by tissue Doppler velocity (E' velocity) at the lateral annulus, expected to be less impaired in hypertrophied patients, and the E/E' ratio calculated. More than mild diastolic dysfunction was defined as LA volume >34 ml/m^2, E/A ratio ≥2, E-wave deceleration time ≤150 ms and E/E' ratio >12.[17,18]

Table 1. Demographic and Clinical Characteristics of the Study Population

	TTR-CA (n=16)	HCM (n=16)	Controls (n=15)	P value
Male	13 (81)	12 (75)	8 (53.3)	NS
Age (years)	57.7±9.8	57.6±19.9	57.9±12.7	NS
BSA (m^2)	1.83±0.22	1.79±0.18	1.79±0.16	NS
Heart rate (beats/min)	75.1±9.6	69.6±8.7	68.1±7.0	NS
SBP (mmHg)	129±7	132±12	132±6	NS
DBP (mmHg)	74±6	79±9	77±5	NS
NYHA functional class	1.6±0.8	1.4±0.5	1.0±0.0	<0.01
LDL-C >130 mg/dl	3 (19)	3 (19)	2 (13)	NS
β-blockers	2 (12)	10 (62)	0	<0.01
ACEI	2 (12)	4 (25)	0	NS
Aspirin	0	6 (37)	0	<0.05
Other drugs	3 (19)	4 (25)	0	NS

Values are mean ± SD or number and percent (%). ACEI, angiotensin-converting enzyme inhibitor; BSA, body surface area; CV, cardiovascular; DBP, diastolic blood pressure; HCM, hypertrophic cardiomyopathy; LDL-C, low-density lipoprotein cholesterol; NS, not significant; SBP, systolic blood pressure; TTR-CA, transthyretin cardiac amyloidosis.

Quantitative Assessment of LA Function

Vector-velocity strain imaging was performed using a commercial ultrasound unit and with a dedicated Mylab platform system (Esaote, Florence, Italy) that allowed measurement of both LV and LA mechanics in an offline modality on digitally stored images.

Global longitudinal strain (ε_{sys}) was achieved by average measurements from the 4- and two-chamber apical views, as suggested.[1–3] LA strain was accomplished by clockwise point-to-point placement on the endocardial border from a foreground apical view of the atrial chamber. Pointing was manually adjusted in order to avoid interference of empty areas like pulmonary vein ostia. Typically, global ε_{sys} was a negative value from the LV and positive from the LA chamber. (Hereinafter, peak LA ε_{sys} (PALS) will be termed "reservoir".) Potential interference of heart rate (HR) on strain measurements was also limited by normalizing LA ε_{sys} to RR cycle. Atrial pump (contractile) function was identified as the small negative peak velocity following the conduit phase.[1,4–6]

cMRI and Radionuclide Imaging

cMRI was performed on a 1.5-Tesla cardiac-dedicated clinical system (Gyroscan NT; Philips Medical Systems, Best, The Netherlands) with phased-array coil and vectorcardiogram synchronization. Breath-hold sequenced parameters were: time repetition/time echo 3.8/1.92 ms; slice thickness 8 mm; matrix size 192/512; field of view 300 mm, rectangular field of view 80%; number of phases 30. The late gadolinium-enhanced (LGE) protocol consisted of a functional study devoted to acquiring ECG-gated T1 and T2 analyses and steady-state free-precession cine-imaging, and 3 standard long-axis slices and a stack of contiguous short-axis slices (10 mm each, 30 phases/RR-interval) were acquired. Delay enhancement within the LV and LA myocardium was recognized. In the TTR-CA patients, subendocardial circumferential enhancement was considered a highly sensitive finding for the identification of amyloid deposits, whereas focal patterns were considered to be more specific for HCM. Thickened atrial wall (>3 mm) was also considered a sign of TTR deposits or fibrosis (**Figure 1**).

^{99m}Tc-DPD accumulation was evaluated on a whole-body scan (anterior and posterior projections) using a dual-headed gamma camera (Millennium VG; GE Healthcare, Milwaukee, Wisconsin), detected 3 h after intravenous injection of 740 MBq of ^{99m}Tc-DPD. Moreover, a thoracic single-photon emission computed tomography scan was attained soon after the whole-body scan using the same machine.

Statistical Analysis

Values are reported as mean ± standard deviation (SD) or number and percent (%).

The distribution of qualitative variables was checked by chi-square, whereas continuous variables were investigated at ANOVA testing for independent groups. A post-hoc Scheffé analysis was also performed for between-group differences.

Receiver-operating characteristic (ROC) curves were generated to identify cut-off values for both LA reservoir and negative peak strain in order to discriminate patients in the 2 study groups and between both hypertrophic phenotypes and controls.

The null hypothesis was rejected at 2 tails for $P<0.05$. Statistical analysis was performed by SPSS release 15 (SPSS Inc, Chicago, IL, USA) and MedCalc 6.00.014 (MedCalc Software, Mariakerke, Belgium).

Results

Patients' Characteristics

Of the 20 TTR-CA and 30 HCM patients initially examined, only 16 in each group met the inclusion criteria; 2 TTR-CA (10%) and 3 HCM (10%) patients were excluded because of systemic hypertension; chronic respiratory insufficiency was found in 2 and 3 patients, respectively; permanent atrial fibrillation in 4 HCM (13%) patients and active coronary artery disease in 4 more HCM patients. Therefore, the study population consisted of 32 patients, mean age 57.7±15.4 years, and their demographic and clinical characteristics are summarized in **Table 1**. Overall, there were no significant differences in age, sex, BSA and office BP measurements among the groups. However, TTR-CA patients were more symptomatic than HCM patients and both groups more than controls. A higher proportion of HCM patients were on β-blockers, angiotensin-converting enzyme inhibitors and aspirin.

On gene mapping, all TTR-CA patients were carriers of exon 3 mutations, as defined by protein amino acid (and DNA nucleotide) changes according to the standard nomenclature of the Human Genomic Variation Society[19] as follows:

Table 2. Cardiac Morphofunctional Indices on Echocardiography in the Study Groups

	TTR-CA (n=16)	HCM (n=16)	Controls (n=15)	P value*
LV end-diastolic diameter index (mm/m²)	23.1±4.0	24.9±3.2	26.7±1.9	<0.02
LV end-systolic diameter index (mm/m²)	17.2±3.5	14.4±3.3*,†	17.3±1.9	NS
LV anterior septal thickness (mm)	16.4±2.8	18.7±2.8*	10.4±1.4	<0.001
LV posterior wall thickness (mm)	13.3±2.3	10.7±2.3	7.8±1.7	<0.001
LV lateral wall thickness (mm)	13.8±4.5	11.8±1.3	9.2±0.8	<0.01
LV mean wall thickness (mm)	14.1±2.9	13.1±1.0	8.5±1.6	<0.001
LV mass index (g/m²)	152.2±46.6	149.6±33.3	85.5±19.7	<0.001
LV end-diastolic volume (ml)	74.5±23.4	65.1±17.5‡	77.3±12.6	NS
LV end-diastolic volume index (ml/m²)	40.8±11.7	36.6±10.3‡	43.0±5.2	NS
LV ejection fraction	0.56±0.09§	0.68±0.08	0.63±0.05	<0.05
LV ejection fraction <0.55	5 (31.2)	1 (6.2)	0	NS
Mitral E/A ratio	1.35±0.71	1.07±0.59	1.20±0.38	NS
E-wave deceleration time (ms)	151.4±56.9	205.7±59.8*	188.2±25.6	0.05
Mitral E/septal E' ratio	15.6±7.6	10.4±4.1	7.3±1.2	<0.01
> Mild LV diastolic dysfunction	8 (50)	3 (18.7)	0	0.05
LV outflow tract obstruction	0	4 (25)	0	NS
Mitral regurgitation (++/+++)	2 (12.5)	4 (25)	0	NS
Global LV ε_{sys} (%)	−11.5±3.2	−13.0±3.4	−19.3±1.6	<0.001
Atrial morphology and function				
LA max volume (ml)	69.4±22.4	67.1±24.9	52.2±8.3	<0.05
LA max volume index (ml/m²)	38.0±10.6	37.5±13.4	29.1±4.1	<0.05
LA fractional emptying (%)	40.1±16.3‡	46.3±18.6	51.9±15.0	NS
LA ε_{sys} (reservoir phase) (%)	14.1±4.7§	20.0±5.6	34.0±11.8	<0.001
HR-normalized LA ε_{sys} (%)	0.50±0.17§	0.68±0.19	1.15±0.42	<0.001
LA pump function (%)	−0.92±0.56	−1.76±1.17	−2.21±0.90	<0.01

Values are mean±SD or number and percent (%). ANOVA comparison between study groups and controls. Post-hoc Scheffe analysis: *P<0.05 vs. TTR-CA; †P<0.01 vs. controls; ‡P=0.05 vs. controls; §P<0.01 vs. HCM. LA, left atrium/atrial; LV, left ventricle/ventricular; ε_{sys}, longitudinal strain; PALS, peak LA longitudinal strain/reservoir. Other abbreviations as in Table 1.

Glu89Gln (c.325G>C) in 8 patients (50%), Phe64Leu (c.250T>C) in 6 (37%) and Thr49Ala (c.205A>G) in 2 more patients (12%).

Diagnosis of HCM was based on individual family history and confirmed by both electrocardiographic and echocardiographic findings in 100% of cases. cMRI was carried out in half of the patients, but no genomic study was performed.

Accumulation of ^{99m}Tc-DPD on scintigraphy was detected in 6 TTR-CA patients.

LV Morphology and Function on Echocardiography

LV end-diastolic diameters, but not volumes, were mildly lower in both groups than in controls. As expected, LV wall thickness and mass index were significantly greater in patients (Table 2). There was a difference in the site of the greatest hypertrophy, being the posterior wall more thickened in TTR-CA than in HCM patients, and vice-versa for the ventricular septum. Systolic function was mildly reduced in the TTR-CA group because of 5 patients (31%) presenting with LVEF <0.55, compared with 1 patient (6%) in the HCM group and none of the controls.

More than mild LV diastolic dysfunction was disclosed in 8 TTR-CA and 3 HCM patients. LV ε_{sys} was significantly impaired (≤−14%) in both groups (Table 2).

LA Morphology and Function

Compared with the controls, LA systolic volumes were greater in TTR-CA and HCM patients, even if volume fractional emptying was preserved (Table 2). LA reservoir was significantly impaired in the TTR-CA group compared with HCM and controls, but also the HCM patients had poorer values than the controls (Figure 2). It was <19% in 15 TTR-CA (94%) vs. 5 HCM patients (31%), but in none of the controls (P<0.001).

The same statistical difference was observed after excluding patients with mildly impaired LVEF (Figure 2) and HR-normalized LA reservoir confirmed such a trend in the TTR-CA group (Table 2).

Likewise, pump function was more depressed in TTR-CA patients than in HCM patients and controls (P<0.01).

Matching LA size to strain measurements, both the reservoir phase and pump function were lower in TTR-CA patients, irrespective of whether the LA chamber size was normal or dilated (Figure 3).

Using ROC curve analyses, LA reservoir ≤20.05% (AUC=0.906; 95% confidence interval (CI) 0.785–0.972, P<0.0001) and pump function ≤−1.4% (AUC=0.777; 95% CI 0.632–0.885, P<0.0001) were the best cut-offs discriminating hypertrophic phenotype from controls, whereas the values of 19% and −1.1%, respectively, distinguished TTR-CA from HCM patients (Figure 4).

Comparison of cMRI and Strain Imaging

Table 3 shows the characteristics of both subgroups undergo-

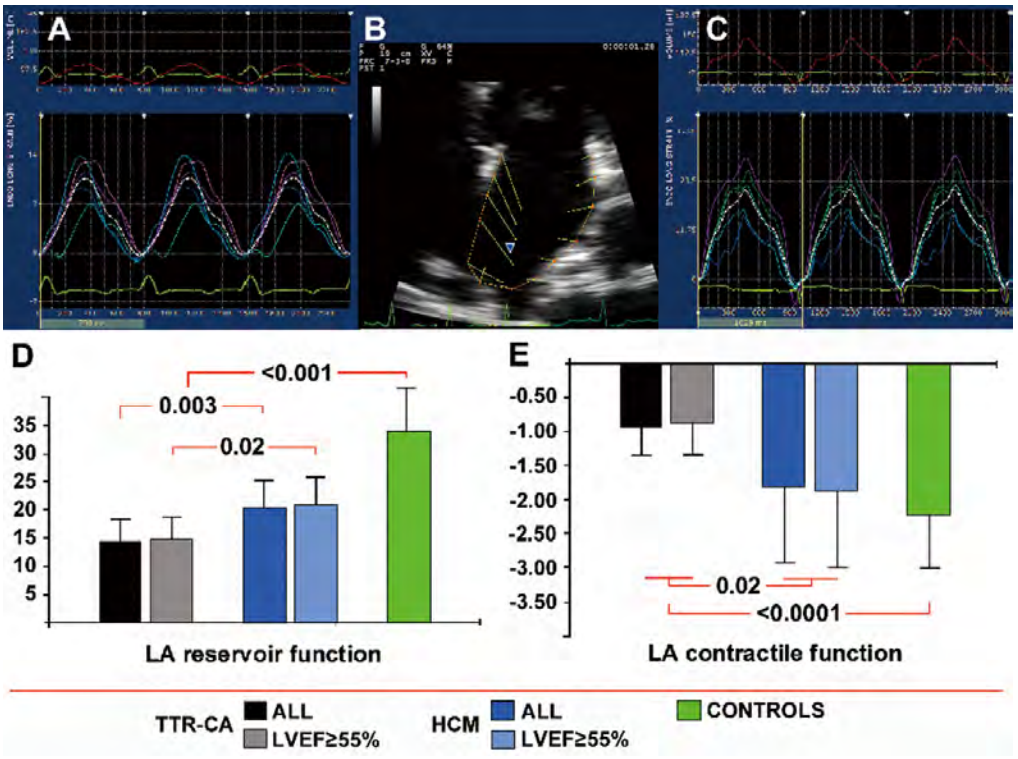

Figure 2. Strain measurement of the atrial wall in a patient with TTR-CA (**A**) or HCM (**C**). (**B**) Graphical vector-velocity imaging. Columns reporting average values of (**D**) LA ε_{sys} (reservoir) and (**E**) pump function in panel E, in each study group (ALL) and in patients with preserved left ventricular ejection fraction (LVEF ≥55%). HCM, hypertrophic cardiomyopathy; LA, left atrium; TTR-CA, transthyretin cardiac amyloidosis.

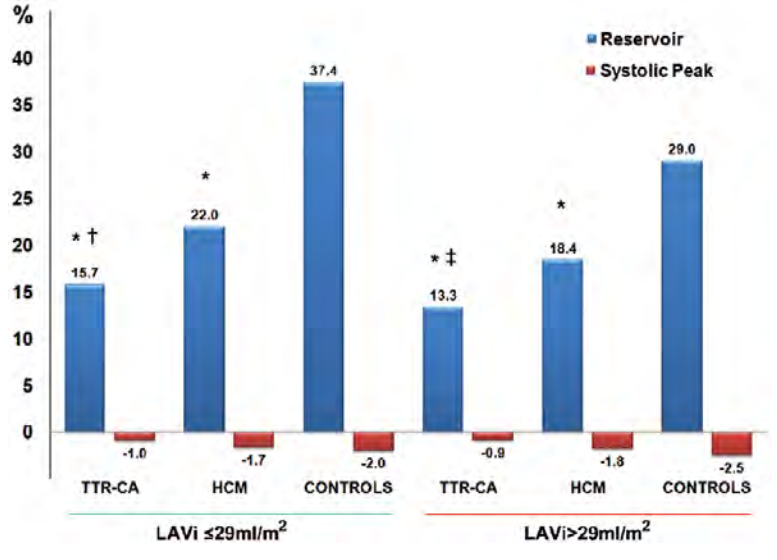

Figure 3. Comparison of atrial functional characteristics among the study groups, related to normal-sized (LAVi ≤29 ml/m^2) or dilated (LAVi >29 ml/m^2) LA chamber. *P<0.05 (TTR-CA vs. HCM and HCM vs. controls); †P<0.01 and ‡P<0.001 (TTR-CA vs. controls). HCM, hypertrophic cardiomyopathy; LAVi, left atrial volume index; TTR-CA, transthyretin cardiac amyloidosis.

ing cMRI. Typical endocardial LGE distribution was found in 90% of patients with TTR-CA, whereas there were intramural spots in 62% of those with HCM. Moreover, LGE in the LA wall was present in the former group, together with wall thickening occurring in 70% vs. 12% of cases, respectively.

Patients from the TTR-CA subgroup were confirmed to have much lower values for LA reservoir and atrial pump function, as well as lower LVEF.

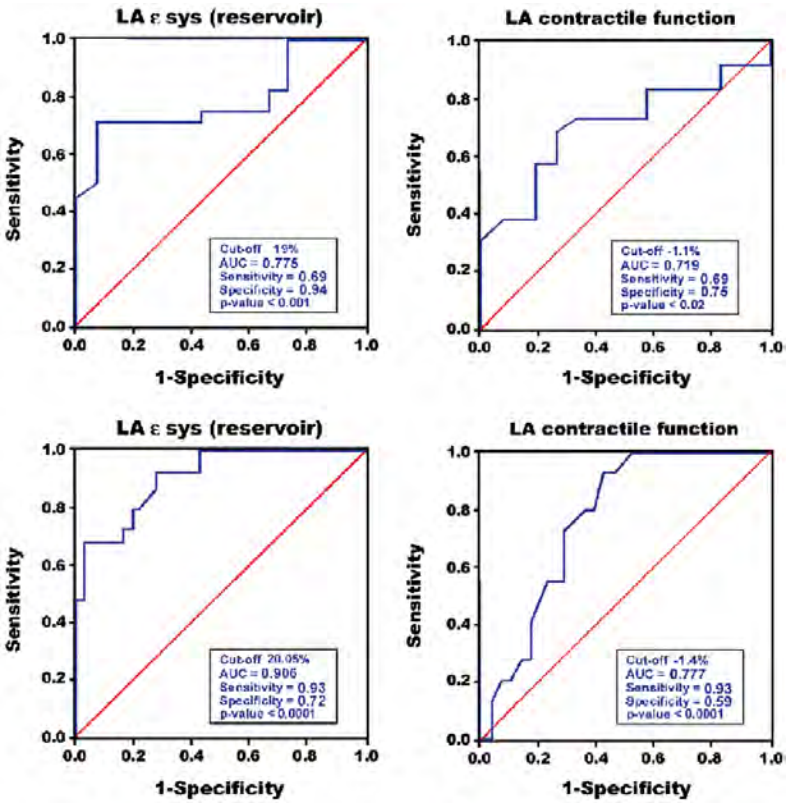

Figure 4. Receiver-operating characteristic (ROC) curves identifying cut-off values for LA reservoir and contractile (pump) functions between TTR-CA and HCM patients (**Top panels**), and between both groups and controls (**Bottom panels**). AUC, area under the curve; HCM, hypertrophic cardiomyopathy; LA, left atrium; TTR-CA, transthyretin cardiac amyloidosis.

Table 3. Characteristics of Hypertrophic Patients Undergoing Cardiac MRI

	TTR-CA (n=10)	HCM (n=8)	P value
Cardiac MRI findings			
LV LGE* [n (%)]	10 (100)	5 (62)	–
LA LGE [n (%)]	9 (90)	0	<0.001
LA wall thickening [n (%)]	7 (70)	1 (12)	<0.05
Ultrasound findings			
LV mass index (g/m^2)	156.1±57.2	160.8±42.1	–
LV ejection fraction	0.59±0.06	0.69±0.05	<0.005
LA volume index (ml/m^2)	34.5±11.3	39.9±15.2	–
LA ε_{sys} (reservoir phase) (%)	15.1±4.1	20.8±6.4	<0.05
LA pump function (%)	–0.87±0.37	–1.17±0.43	0.05

Values are mean±SD or number and percent (%). ANOVA comparison between study groups and controls. *Considering different LGE patterns in TTR-CA and HCM patients (see text). LGE, late gadolinium enhancement; MRI, magnetic resonance imaging. Other abbreviations as in Tables 1,2.

Discussion

The main findings from the present study indicate that LA dysfunction can be found in a large proportion of patients with a hypertrophic phenotype from either TTR-CA or HCM, but a greater impairment occurs in the former group, irrespective of body mass index, LV mass and function, and LA fractional empting.

Strain echocardiography can been confirmed as a significantly helpful technique to investigate advanced atrial functional components such as reservoir phase and booster pump work (contractile performance), which are otherwise difficult to investigate noninvasively.[4–6,14–16]

Also, our study indicates that both markers are greatly impaired in the TTR-CA patients irrespective of LA size and LVEF.

In the ROC curve analyses, LA reservoir ≤19% best discriminated between the 2 groups of patients. In fact, it was found in approximately 94% of TTR-CA patients vs. 31% of HCM patients, respectively, but not in controls.

We have already demonstrated adverse LA remodeling in patients with amyloidosis, possibly related to increased wall stiffness as a consequence of the continuing dumping of insoluble amyloid fibrils in the atrial wall, as well as the ventricular

wall, indicating cMRI as the gold standard for detecting deposits by LGE technique.[6] On the other hand, interstitial fibrosis has been demonstrated to occur in a variable proportion of HCM patients, but with a different pathogenesis being LGE as the consequence of reiterate microcirculatory injuries, often limited to the ventricular myocardium, at least in the initial stages of the cardiomyopathy.

In view of the relationships among myocardial structure, function and mid-term outcomes, a large body of literature indicates LV fibrosis as an additional cardiovascular prognosticator in HCM patients, particularly in those otherwise classified at a lower risk.[11,13,20–22]

More recently, Hen et al[22] found that progression of LGE on cMRI was related to increased wall thickness, decreased contractility, and reduced intraventricular pressure gradient in a Japanese population. The same group also demonstrated a greater incidence of atrial fibrillation in such patients, underlying a possible relationship between LA function and LV disarray.[23]

Just recently the attention of clinicians has been placed on the atrial chambers. The clinical effect of LA dilatation has been already shown by Losi et al[24] in HCM patients, in whom either systolic volume >27 ml/m^2 and/or a fast dilating atrial chamber were predictors of unfavorable outcomes.

Badran et al,[14] using vector-velocity strain imaging, found that LA reservoir and conduit functions were more impaired in HCM than in hypertensive patients, leading to different clinical outcomes. However, LA reservoir was much higher in their HCM patients (25±15%) than in ours (20±6%), even if their patients had greater LA size and LV ε_{sys} impairment, likely suggesting a variability in apparently similar cardiac diseases.

LA reservoir is a marker of LV diastolic function, and its impairment indicates a rise in LV stiffness, harbinger of the upstream transmission of LV chamber filling pressure to the lung venous system, often commensurate with clinical deterioration. However, when considering the interplay of atrial and ventricular chambers because of displacement of the shared atrioventricular plane, it is not easy to ascertain which chamber is first impaired in patients with hypertrophied hearts.

Also of interest, we did not find relevant differences in LA function when excluding patients with LVEF <55%. This can be explained by considering that a greater diastolic dysfunction is expected in patients with impaired LA reservoir, but such an assumption is not obvious in those presenting with mildly reduced LVEF caused by variable ventricular stiffness adaptation.[12–16,25–27]

In our patients undergoing cMRI, LA function significantly correlated with the wall structure, because LGE was more frequent in TTR-CA patients than in HCM patients. This likely suggests that amyloid deposits in CA patients occur earlier (or are heavier) than fibrosis in HCM patients. Moreover, it could also be hypothesized that in uncomplicated HCM patients, such as the nonobstructive variant, free of interstitial fibrosis and severe mitral regurgitation, an increased LA pump and conduit function may be valid compensatory mechanisms in order to preserve LA function, at least in the early stages of the disease. In contrast, in patients with severe disarray of the wall structure these features might be lacking, matching the high levels of NT-proBNP previously demonstrated in CA patients.[6–9]

This study also demonstrates that a preclinical LA dysfunction may occur in both groups irrespective of chamber dilatation, with poorer values in TTR-CA patients. It is not easy to give true mechanistic insights on this finding, but it could be theorized that the quality and/or density of tetrameric proteins resulting in amyloid deposits may vary significantly among the patients, being more toxic or fast-storing in those with rapid impairment of atrial function even in the absence of dilatation. This could be leading to higher NT-proBNP serum levels, untested in this but found in previous studies.[8,10] Furthermore, it has to be considered that some of our patients were evaluated in the early stage of CA, when LA dilatation cannot yet be present. Therefore, wider studies on atrial chamber adaptation to infiltrative storage diseases should be encouraged.

The present findings must be interpreted in the light of previous studies on the prognostic effect of LA dysfunction. For instance, in 312 individuals from a general population Cameli et al[28] showed that a severely reduced LA reservoir (<18.8%) was an independent predictor of cardiovascular events, including atrial fibrillation and stroke, with 78% sensitivity and 85% specificity. Approximately the same value (19%) discriminated between the more and less compromised patients in our series.

This likely indicates that TTR-CA patients, and also those with HCM with low ε_{sys} values, may be at risk of arrhythmic disorders, such as atrial fibrillation. In fact, Habibi et al found that hypertensive patients with LA enhancement were more inclined to persistent or permanent atrial fibrillation.[29]

Therefore, our study adds to the current knowledge by providing new functional issues in patients with similar LV hypertrophy, but different pathophysiology, in an attempt to improve the therapeutic approach to these difficult conditions.

Study Limitations

Several limitations should be considered in the interpretation of the present study. First of all, familial TTR is such a rare variant of amyloidosis, compared with other forms, that it involved a limited sample in the present study, also related to our stringent inclusion criteria. Thus, our results might not be representative of the general patient population suffering from CA.

It is not surprising that multiple determinants can impair LA reservoir and pump function in hypertrophic patients, such as LA chamber dilatation, myocardial stretching in response to pressure overload, dynamic and fixed obstruction to outflow and mitral valve regurgitation,[1–3,11,14,16] but not all these factors were investigated.

Among many possible markers of atrial dysfunction, we just studied the reservoir phase and contractile function, based on the most significant clinical studies.[4–6,14–16,26] Therefore, we cannot exclude a discriminant role also for the LA conduit phase.

Regarding technical limitations, strain studies of LA function are affected by the fact that available software packages are dedicated to LV not LA chamber analysis. Discrepancies are then expected to be found in view of such differences, as well as the methods used for digital acquisition. It is worth remarking that vector-velocity strain imaging allows detection of LA wall deformation by sparing empty areas such as the pulmonary vein outlet and thin or floating atrial septa. In contrast, the speckle-tracking technique is more valuable for recognizing global chamber deformation, but blank areas are usually included.[1,2,5,16,28]

Of note, it should be considered that our MRI algorithms were not appropriately powered enough for detecting LA fibrosis in HCM patients, and the most recent T1 mapping techniques are more promising for this purpose.[30]

Finally, large studies are needed in order to confirm the

present cut-off values for both LA reservoir phase and pump function as discriminators between less and more compromised patients, as well as whether such values are case-sensitive or limited to hypertrophic cardiomyopathies.

Conclusions

The present study results indicate that the LA reservoir phase and contractile function are impaired in a high proportion of TTR-CA and HCM patients in comparison with healthy controls. Greater functional impairment was demonstrated in the former group, likely because of amyloid deposits in the atrial wall being more significant than fibrosis in HCM, irrespective of LA chamber size. Further study is encouraged in order to better ascertain the mechanistic difference among the various infiltrative disorders and whether strain-derived functional markers can be endorsed from experimental models to an integrated individual care management and treatment approach.

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Disclosures

No conflicts of interest declared.

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Cardiovascular Risk and Psoriasis: A Role in Clinical Cardiology?

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Psoriasis is a chronic inflammatory disease. Classic manifestations are erythematous patches of skin with periods of exacerbation and remission.[1,2] The inflammatory process is evidenced by the increase in several markers such as cell adhesion molecules, cytokines, chemokines, and other molecules of the acute phase such as fibrinogen, C-reactive protein (CRP), and serum amyloid A protein.[3,4] C-reactive protein levels correlate with an increase in potential cardiovascular (CV) risk predictors based on evidence obtained in experimental animals, which have demonstrated a role of toll-like receptor (TLR) type 2 and 4 in the development and progression of atherosclerosis.[5,6] C-reactive protein promotes endothelial dysfunction by reducing endothelial nitric oxide synthetase expression and activity, reducing prostacyclin release from endothelial cells, increasing plasminogen activator inhibitor 1 expression and activity, endothelin 1 and interleukin 1 release, and by promoting cellular adhesion between endothelial cells and monocytes with increase in the size of atherosclerotic plaques[4,7]; moreover a novel marker of endothelial dysfunction, endocan, was recently proposed to stratify CV risk in patients with psoriasis, since serum endocan levels correlated with the Psoriasis Area and Severity Index (PASI), CRP, and carotid intima–media thickness.[8] It follows that psoriasis alone, or in combination with other risk factors, may play a role in the development and progression of CV disease but its exact contribution is not clear. Therefore, we performed a search of the literature, selecting the publications that we thought to be of interest.

We carried out a systematic search in PubMed and Embase using the keywords "psoriasis," "autoimmune disease," "cardiovascular disease," "diabetes," "hypertension," "high blood pressure," "dyslipidaemia," "metabolic syndrome," and "obesity." We found 231 articles of interest but we selected only 19 as the most representative.

Several authors have highlighted the association between coronary heart disease (CHD) and psoriasis. However, there is no single definition of the parameters of severity of the psoriasis[9] or a homogeneity of patient selection in different studies.[9,10]

In 1978, McDonald and Calabresi studied 323 hospitalized patients with psoriasis and showed an association with arterial and venous vascular diseases.[11] Further studies[12-15] have revealed a correlation between this disease and atherosclerosis, focusing on CHD. The main limitation of these studies was that they could not conclusively define a significant correlation between the 2 conditions mainly because they did not sufficiently take into account the presence of confounding factors, such as the presence of CV risk factors.[9] This correlation, however, was established by Gelfand et al in 2006. Their objective was to "determine within a population-based cohort if psoriasis is an independent risk factor for acute myocardial infarction (AMI)." They studied 130 976 patients with psoriasis of whom 3827 had a severe form (ie, on systemic therapy). Patients were matched with 556 995 controls and followed for a mean of 5.4 years. There was an increased risk of AMI in patients with moderate and severe psoriasis. The authors concluded that psoriasis may be considered as an independent risk factor for AMI.[16] A subsequent study in 2008 examined 2 large US databases and showed an increase in CV risk in patients with mild psoriasis.[17]

In 2009, Prodanovich et al[18] in an observational study of 3236 patients with psoriasis reported a higher prevalence of traditional CV risk factors (diabetes mellitus, hypertension, dyslipidemia, and smoking) compared with controls. This association was known from previous studies but the new element was the association of psoriasis with an increased prevalence not only of myocardial ischemia but also of cerebrovascular and peripheral arterial disease. The conclusion was that psoriasis is associated with atherosclerosis.[18]

A study published in 2012 compared the severity of psoriasis (PASI score) with coronary flow reserve (CFR). In patients with reduced CFR (<2.5) psoriasis was more severe (higher PASI score). According to the authors in young

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patients, in the absence of known CHD, the reduction in CFR supports an early dysfunction of the microcirculation which may be a consequence of the sustained systemic inflammatory state. The dysfunction of the cardiac microcirculation would be present regardless of the extent and severity of psoriasis.[19] Ahlehoff et al in 2011 assessed the prognosis of patients with previous myocardial infarction and concluded that the presence of psoriasis leads to a worse prognosis.[20] In 2013, Yiu et al demonstrated in 70 patients with psoriasis without additional CV risk factors, the important role played by inflammation in the early onset of coronary atherosclerosis.[21] On the basis of this evidence, the results published later in 2013 by Maradit-Kremers et al seem unexpected.[22] They performed a series of analyses of historical cohort and case–cohort study (Olmsted County, Minnesota Study), examining the risk and determinants of AMI, heart failure, and cardiac death in patients with psoriasis.[22] They concluded that for new-onset psoriasis, although it is not possible to exclude a modest increase in CV risk, their investigation appears not to confirm an excess of incidence and prevalence of AMI (when restricted to validated hospital admission; there was an increased risk of AMI when restricted to diagnostic codes), heart failure, or cardiac death.[22] These results contrast with those reported in the literature.[12-15] However, they may reflect the young age of the patients with psoriasis and the fact that only a small number had severe disease.

We agree with Prey et al[9] and Vena et al[10] that the discrepancies in the literature may be due to the lack of stratification of participants based on severity and duration of psoriasis. Therefore, there is a need to define the severity of psoriasis and plan for adequate follow-up periods. Dermatologists are usually the first to see patients with psoriasis and they need to know when they should request a cardiology assessment and stratification of CV risk.[22-24] In this context, there is emerging evidence that severe psoriasis is not only associated with CV risk factors[25] but also with worse left ventricular performance index even in the absence of cardiac diseases[26]; moreover, a link between psoriasis and aortic arterial stiffness (a predictor of CV disease[27]) was recently proposed.

Psoriasis is probably a ''complementary'' CV risk factor due to the associated inflammatory state. From the review of the literature, we cannot confirm that mild psoriasis independently increases the risk of CV events but such an increase may occur when associated with other known CV risk factors. However, severe psoriasis could assume the role of an independent CV risk factor. Studies with adequate follow-up periods are needed to resolve these issues.

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Psoriasis and Cardiovascular Risk: Correlation Between Psoriasis and Cardiovascular Functional Indices

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Abstract

Evidence suggests that psoriasis together with other cardiovascular (CV) risk factors is associated with increased vascular morbidity, but it is not clear whether psoriasis is an independent risk factor. Consecutive patients (n = 33; 35.6 ± 5.7 years; 13 females) with mild psoriasis (Psoriasis Area and Severity Index <10) without comorbidities and 33 healthy participants (36.3 ± 5.9 years; 15 females) were enrolled. Both groups underwent echocardiography, speckle tracking (2-dimensional strain echocardiography [2D-SE]), and pulse wave velocity (PWV) testing. Clinical and conventional echocardiographic characteristics were comparable between both groups. Global longitudinal strain (GLS) was significantly lower ($P = .002$) in the psoriasis group (22.39% ± 2.28%) than in controls (24.15% ± 2.17%). The PWV was significantly lower ($P = .004$) in controls (8.06 ± 1.68 m/s) than in the psoriasis group (9.23 ± 1.53 m/s). Significant correlations between GLS and disease duration ($r = -.66$, $P < .0001$) and between GLS and patient age at diagnosis ($r = .48$, $P = .0043$) were found. Psoriasis may be an independent CV risk factor, causing cardiac and vascular impairment. Both 2D-SE and PWV may be useful tools for the screening of CV risk in these patients.

Keywords

psoriasis, cardiovascular risk, speckle tracking echocardiography, arterial stiffness, pulse wave velocity

Introduction

Psoriasis is a chronic immune-mediated inflammatory disease of the skin, affecting the 1% to 3% of the population.[1,2] Several studies highlighted an association between psoriasis and coronary artery disease (CAD).[3,4] Evidence suggests that a combination of psoriasis with other cardiovascular (CV) risk factors leads to an increased incidence of CAD,[5,6] but whether psoriasis is an independent risk factor for CAD has not been established.

The systemic inflammatory response in psoriasis is regulated by T helper 1 and T helper 17 lymphocytes, which play a key role in its pathogenesis,[7-10] leading to endothelial damage with premature progression to atherosclerosis.[11,12] Currently, there are few data about the development of subclinical myocardial dysfunction and vascular changes in patients with mild psoriasis. Two-dimensional strain echocardiography (2D-SE) is a valid tool to quantify both left ventricular (LV) longitudinal and circumferential deformations, allowing the detection of subclinical changes in systolic function and providing a quantitative assessment of regional LV function.[13-17] Arterial stiffness has been identified as an independent prognostic factor for patients with CV disease (CVD).[18-21] An increased pulse wave velocity (PWV), a noninvasive index of arterial stiffness, predicts CV events in different clinical conditions.[22-24] Increased arterial stiffness negatively affects cardiac structure and function with systolic and diastolic abnormalities.[22,25,26]

The aim of our study was to test cardiac performance and vascular stiffness in patients with mild psoriasis in the absence of other CV risk factors or drug treatment. Cardiac function was assessed by echocardiography both with conventional

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indexes, according to the guidelines of the American Society of Echocardiography,[27] and through new technologies (speckle tracking analysis with evaluation of longitudinal and circumferential strain [CS]). For the evaluation of vascular stiffness, carotid–femoral PWV was measured by Doppler ultrasound.

Materials and Methods

Enrolled Population

Consecutive patients (n = 33; 35.6 ± 5.7 years; 13 [40%] females) with mild psoriasis were enrolled and compared with 33 healthy controls (36.3 ± 5.9 years; 15 [45%] females). Only patients with mild psoriasis with no CV risk factors and no systemic drug therapy were enrolled. Disease severity was assessed by a dermatologist using the Psoriasis Area and Severity Index (PASI) score: A score <10 was used to classify psoriasis as mild. We excluded participants with (1) PASI ≥ 10, (2) any drug therapy, (3) smoking, (4) hypertension, (5) diabetes mellitus, (6) renal failure, (7) LV kinetic abnormalities due to left bundle branch block and/or pacemaker stimulation, (8) LV ejection fraction <50%, (9) chronic CAD, (10) arrhythmias, (11) previous cardiac surgery, (12) cardiomyopathies, (13) moderate-to-severe valve disorders, and (14) poor acoustic window. Physical examination of all patients was carried out by a qualified dermatologist. All echocardiographic scans and Doppler data of carotid–femoral PWV were acquired by an experienced cardiologist and processed "off-line" by another cardiologist blinded for participant diagnosis. Clinical characteristics are summarized in Table 1.

Our local ethics committee approved the investigation, judging it compliant with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants.

Patients were enrolled from the Department of Dermatology where they attended for periodic follow-up. We evaluated 232 patients affected by psoriasis attending the Department of Dermatology during 15 months; 162 (70%) patients were affected by psoriasis in a degree from moderate to severe and were already on drug therapy: Among them, 68% were also affected by other CV risk factors and 9% had a previous episode of CAD. Thirty-seven (16%) patients had mild psoriasis but were already receiving pharmacological therapy because of concomitant CV risk factors (7 were hypertensive; 10 hypertensive and smokers; 8 hypertensive and dyslipidemic; 6 diabetic; 3 diabetic and dyslipidemic; and 3 diabetic, hypertensive, and smokers). The final 14% (33 patients) represents the population enrolled for our study. The control group consisted of healthy volunteers enrolled between the staff members of both the Departments of Cardiology and Dermatology.

Table 1. Demographic and Clinical Data for Cases With Psoriasis and Controls.[a]

	Patients With Psoriasis (n = 33)	Normal Controls (n = 33)	P[b]
Age, years	35.6 ± 5.7	36.3 ± 5.9	.66
Male, n (%)	20 (60.6)	18 (54.5)	.8
BMI, mean (SD)	24.0 ± 3.0	23.2 ± 2.4	.21
HR, b/m	65.0 ± 8.3	67.6 ± 10.6	.26
SBP, mm Hg	123.5 ± 10.2	123.0 ± 10.7	.86
DBP, mm Hg	74.2 ± 8.3	74.7 ± 8.5	.83
Creatinine, mg/dL	0.78 ± 0.12	0.76 ± 0.11	.23
eGFR, mL/min	132 ± 23.6	133.6 ± 24.2	.38
Family history of CAD, n	13	11	.33
Glucose, mg/dL	98 ± 5	96 ± 6	.14
Total cholesterol, mg/dL	185 ± 13	184 ± 11	.27
Triglyceride, mg/dL	100 ± 23	99 ± 14	.38
HDL-cholesterol, mg/dL	52 ± 8	52 ± 10	.40
LDL-cholesterol, mg/dL	113 ± 15	111 ± 17	.33
Disease duration, years	5.6 ± 1.7	NA	-
Age at diagnosis, years	30.3 ± 6.4	NA	-
PASI score	7.3 ± 1.8	NA	-

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; SBP, systolic blood pressure; LDL, low-density lipoprotein; NA, not applicable; PASI, Psoriasis Area Severity Index.

[a]Data are presented as mean ± standard deviation (SD), number (percentage), or median (interquartile range).

[b]*t* test for continuous variables, cross-tabulations, and 2-test for categorical variables.

Echocardiographic Measurements

Two-dimensional echocardiographic images were acquired using ultrasound equipment (MyLab Alpha, Esaote, Florence, Italy) with a 2.5-MHz phased array transducer. The 2D data measurements were obtained, according to the recommendations of the American Society for Echocardiography, by parasternal long and short axes and by 3 standard apical windows. An analysis of wall motion, end-diastolic volume, end-systolic volume, and ejection fraction (EF) was carried out as well as the measurement of peak A, E and E′ waves, E deceleration time (Dt), and isovolumetric relaxation time (IVRT). Diastolic function was assessed by the ratio of early and late diastolic mitral inflow velocities (E/A ratio), the Dt, the IVRT, and by the E/E′ ratio.

Speckle Tracking Analysis by 2D Echocardiography

A dedicated software package (XStrain; Esaote) was used for an "off-line" quantification of circumferential (Figure 1A) and longitudinal strain (Figure 1B). The LV was divided according to the 16-segment model (6 basal, 6 mid-level, and 4 apical). Short-axis scans were obtained at the mitral valve, papillary muscles, and apical levels and used to assess CS. Longitudinal strain (LS) was calculated using standard apical 4-, 3-, and 2-chamber scans. Global strain was defined as the mean value of all the 16 segments. In all patients, the global CS (GCS) and the global LS (GLS) were calculated.

Evaluation of PWV

Carotid–femoral PWV was measured using pulsed wave Doppler analysis synchronized with electrocardiogram with a linear probe. We performed 3 recordings from the common carotid

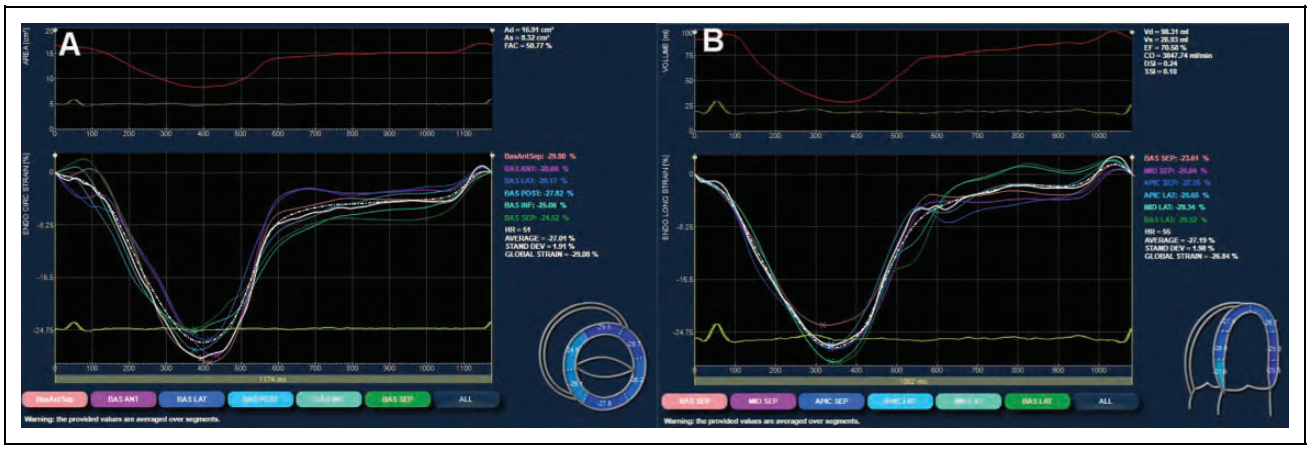

Figure 1. Two-dimensional (2D) acquisitions for the "off-line" evaluation of circumferential and longitudinal strain. A, Evaluation of circumferential strain. B, Evaluation of longitudinal strain.

artery and 3 from the femoral artery at the groin region. Each recording involved at least 3 cardiac cycles. Transit time (TT) was estimated by the time from the R wave of QRS to the foot of the waveforms at each site. In order to determine PWV, the ratio between the distance measured from the sternal notch to the femoral artery at the groin and TT was calculated, according to the following formula: PWV = distance/(T2 − T1).

Data Analysis

Data were assessed for equality of variance and distribution. Descriptive statistics with means and median, as appropriate, and proportions were used to describe continuous and categorical variables. Unpaired *t* tests were used to test differences in demographic and clinical characteristics and to test cardiac and echocardiographic parameter differences between cases and controls. The association between categorical variables was evaluated using the χ^2 test. Correlation analyses were performed by means of the nonparametric Spearman rank correlation test. All statistical tests were 2 sided, and a $P < .05$ was considered significant. Statistical tests were conducted using the statistical software package SigmaPlot (version 11.0; Systat Software, Inc., San Jose, California) and SAS (version 9.0; SAS Institute Inc, Cary, North Carolina).

Results

Demographic and Clinical Characteristics

We studied a total of 33 patients with psoriasis and 33 normal controls from February 2015 to May 2016. The characteristics of the cases and controls are listed in Table 1. The mean psoriasis duration was 5.6 ± 1.7 years, and the disease severity was PASI 7.3 ± 1.8. Patients and controls were well matched with regard to demographic characteristics. The mean age did not differ significantly between the patients with psoriasis and controls. Just over half were males. Body mass index did not differ significantly between the patients with psoriasis and control participants. In addition, there were no significant differences in systolic blood pressure, diastolic blood pressure, and heart rate. None of the participants in either group had other conditions that are known to or could reasonably be expected to affect cardiac function, echocardiographic characteristics, and arterial stiffness. Specifically, no participant in either group was affected by any conventional CV risk factor (eg, arterial hypertension, diabetes mellitus, dyslipidemia, smoke, or chronic kidney disease).

Table 2. Echocardiographic Characteristics in Patients With Psoriasis and Controls.

	Patients With Psoriasis (n = 33)	Normal Controls (n = 33)	*P*
IVSD, mm	9.21 ± 1.64	9.03 ± 1.16	.44
LVEDD, mm	46.85 ± 1.45	45.31 ± 2.65	.15
LVPWD, mm	9 ± 1.54	8.76 ± 1.06	.46
LVEDV, mL	105.1 ± 6.5	106.5 ± 6.58	.36
LVESV, mL	37.58 ± 4.44	39.12 ± 3.24	.11
EF, %	62.55 ± 5.67	63.12 ± 2.84	.6
E, cm/s	76.06 ± 7.74	78.36 ± 8.21	.25
A, cm/s	61.18 ± 6.81	63.12 ± 7.07	.26
E/A	1.25 ± 0.1	1.25 ± 0.12	.99
DT, ms	183.4 ± 17.5	182.3 ± 17.38	.8
IVRT, ms	80.82 ± 8.9	81.64 ± 8.81	.71

Abbreviations: A, late diastolic mitral inflow; DT, deceleration time; E, early diastolic mitral inflow velocity; E/A, ratio; EF, ejection fraction; IVRT, isovolumetric relaxation time; IVSD, interventricular septum diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVPWD, left ventricular posterior wall diameter.

Echocardiographic Characteristics

Comparisons of the echocardiographic conventional indexes between patients with psoriasis and controls are summarized in Table 2. No significant differences were observed in LV end-diastolic diameter, interventricular septum, and posterior wall thickness. There were no significant differences in LV end-diastolic volume, LV end-systolic volume, and EF.

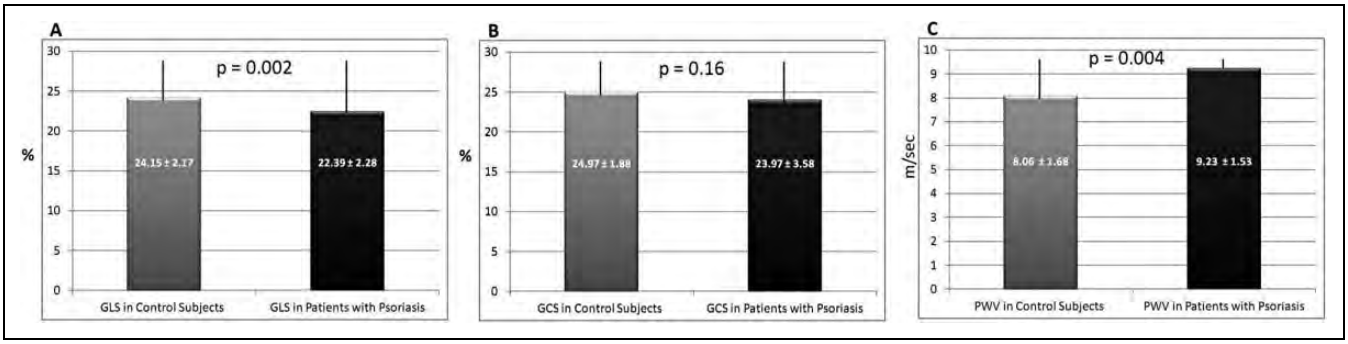

Figure 2. Comparative values of speckle tracking analysis and of pulse wave velocity between patients with psoriasis and the control group. A, Comparative values of global longitudinal strain (%). B, Comparative values of global circumferential strain (%). C, Comparative values of pulse wave velocity (m/s).

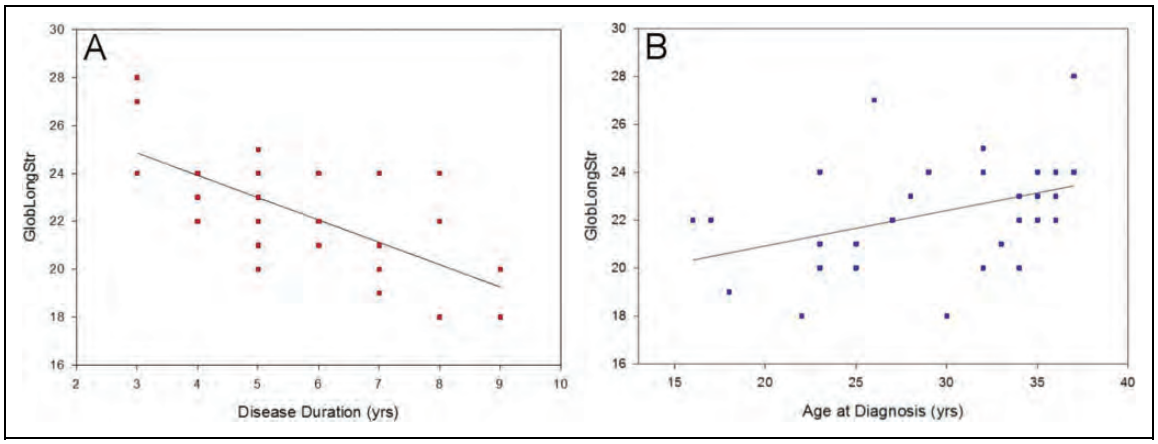

Figure 3. A, Correlation between global longitudinal strain (GlobLongStr) and disease duration ($r = -.66$, $P < .0001$). B, Correlation between global longitudinal strain (GlobLongStr) and patient age at which the diagnosis was made ($r = .48$, $P = .0043$).

Furthermore, early diastolic mitral inflow velocity (E), late diastolic mitral inflow (A), the E/A ratio, Dt, and IVRT did not differ significantly between the patients and the controls.

Speckle tracking analysis showed that GLS values were significantly lower ($P = .002$) in patients with psoriasis (22.39% ± 2.28%) than in controls (24.15% ± 2.17%; Figure 2A); for GCS, there were no significant differences ($P = .16$; Figure 2B).

A correlation between the GLS and disease duration ($r = -.66$, $P < .0001$; Figure 3A) and a correlation between the GLS and the patient age at which the diagnosis was made ($r = .48$, $P = .0043$; Figure 3B) were also observed. No other correlations were found. In particular, no correlations between GLS and PASI, age, or gender were observed.

Pulse Wave Velocity Characteristics

Analysis of the PWV characteristics showed values of arterial stiffness significantly lower ($P = .004$) in controls (8.06 ± 1.68 m/s) than in patients with psoriasis (9.23 ± 1.53 m/s; Figure 2C).

Discussion

Our main findings are:

1. Global longitudinal strain was significantly lower in patients with psoriasis than in controls.
2. Global circumferential strain was not significantly different between the 2 groups.
3. There was a significant correlation between GLS and disease duration.
4. There was a significant correlation between GLS and patient age at first diagnosis.
5. Arterial stiffness values were significantly higher in patients with psoriasis compared to controls.

These results were obtained in patients with untreated mild psoriasis and without any other condition affecting cardiac function, echocardiographic characteristics, and arterial stiffness. Specifically, none of the participants in both groups was affected by conventional CV risk factors.

There is evidence that links the presence of psoriasis, in association with other CV risk factors, with an increased prevalence of myocardial ischemia, cerebrovascular disease, and

peripheral artery disease.[28-32] Other studies concluded that psoriasis leads to a worse prognosis in patients with previous myocardial infarction.[33] However, another study did not confirm an increase in incidence and/or prevalence of myocardial infarction in patients with psoriasis, although it was not possible to exclude a modest increase in CV risk.[34] Because of this evidence, psoriasis, alone or in combination with other CV risk factors, could play a role in the development and progression of myocardial ischemia, but its exact contribution is not completely clear, especially when considered as a "stand-alone" risk factor.

Our results suggest that psoriasis, in the absence of other CV risk factors, is associated with subclinical alterations in both cardiac function and arterial stiffness.

Guven et al reported comparable LV dimensions, wall thickness, and EF between patients with psoriasis and healthy controls.[35] Similarly, Ardic et al showed no differences in LV diameters or EF.[36] Also, the results of our study show that all conventional echocardiographic parameters are comparable between patients with mild psoriasis and controls.

Cardiac function abnormalities were observed by 2D-SE, a technique that can detect minimal abnormalities in systolic and regional LV function.[17,37-39] In our patients, the GLS values were significantly lower compared to controls, suggesting subclinical reductions in longitudinal function. Furthermore, a recent study demonstrated (using 2D strain imaging) that patients with psoriasis have lower LV function.[40] In the same study, there were also significant differences in some parameters of diastolic function. These differences were not present in our study probably because their patients were older than ours (41.1 $\pm$ 3.8 years) with a greater PASI score (15.8 $\pm$ 7.7).

We did not find significant differences in terms of GCS. Interpretation of these results can be very challenging, but we think that LV anatomy, function, and perfusion play a role. Longitudinal function is mainly driven by deformation of the subendocardial fibers, which are the most vulnerable and most sensitive to perfusion changes.[14-15] In this subclinical stage of LV systolic dysfunction, mesocardium and epicardium fibers could be involved in a compensation mechanism, resulting in normal circumferential mechanics and pump function and, therefore, in normal GCS and EF.[14-17]

In this study, we found that LV dysfunction correlated with the duration of the disease. A possible explanation is that patients with longer disease duration could have developed more inflammatory damage than those ones with a shorter duration. Furthermore, the novelty that emerges from our results is that cardiac functional impairment was more severe in younger patients, irrespective of duration and severity. These data agree with those of Sunbul et al.[41] However, the main difference with their study is that they included patients with various degrees of psoriasis (PASI 13.7 $\pm$ 8.9), treated with topical and/or systemic drugs (including retinoids, photochemotherapy, methotrexate, cyclosporine, etanercept, or infliximab), while our patients had mild psoriasis (PASI < 10) and were not treated for psoriasis nor for other diseases. Our results suggest that psoriasis is independently associated with an arterial stiffness, which is significantly higher in affected patients than in controls.

The chronic systemic inflammation related to psoriasis could be involved in the damage of the vascular endothelium and in its function, leading to greater arterial stiffness. This hypothesis is consistent with other studies.[42-44] There are several important clinical implications deriving from our work. We studied a relatively young patient group (mean age 35.6 years) with mild psoriasis, without any evidence of CVD, other concomitant conditions, and without any pharmacological treatment.

We demonstrated that assessment of cardiac performance parameters, by 2D-SE, and assessment of arterial stiffness parameters, by PWV, may be used as markers for screening CV risk. In this context, dermatologists should pay attention to CV risk when managing patients with mild psoriasis, allowing them to benefit from early intervention.

Our study has several limitations. First, there is no follow-up in order to evaluate the incidence of major CV events related to the risk deriving from psoriasis. Inflammation biomarkers were not sampled even if we hypothesized a central role for chronic inflammation[45] in the worsening of cardiac performance and of vascular stiffness in mild psoriasis. However, this was only an assumption made retrospectively, the main aim being to measure any functional cardiac and/or vascular modification in the absence of other confounding factors (comorbidities and/or therapies). This objective was reached demonstrating that these patients have significant reduction in GLS and significant rise in PWV compared to healthy controls.

Psoriasis, in its mild form, may be an independent CV risk factor associated with impairment of cardiac performance and increased vascular stiffness even in the absence of other risk factors. Impairment of cardiac function is greater with longer disease duration and as patient age is lower. Both 2D-SE and PWV may be used as tools for screening CV risk.

Further studies are required to fully understand the underlying mechanisms of CV dysfunction to evaluate the incidence of major CV events and to identify proper strategies for slowing down CV damage progression in these patients.

Authors' Note

All authors contributed to (1) substantial conception, design, acquisition of data, analysis, and interpretation of data; (2) drafting of the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Subclinical impairment of myocardial and endothelial functionality in very early psoriatic and rheumatoid arthritis patients: Association with vitamin D and inflammation

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ABSTRACT

Background and aims: Cardiovascular (CV) morbidity is increased in inflammatory joint diseases (IJD), as rheumatoid (RA) and psoriatic arthritis (PsA). Whereas increased prevalence of subclinical atherosclerosis has been reported in these conditions, whether an early myocardial functionality is also impaired remains unknown. The aim of this study was to evaluate the myocardial functionality by speckle-tracking echocardiography (STE) in recent onset RA and PsA patients and its potential associations with the levels of circulating $CD34^+$ cells, vitamin D, and with disease activity.

Methods: STE was used to assess the myocardial functionality in patients with very early RA ($n = 41$) and PsA ($n = 35$) without traditional CV risk factors, and 58 matched healthy controls (HC). Global longitudinal and circumferential strain (GLS and GCS) was estimated. Pulse wave velocity (PWV) and carotid intima-media thickness (cIMT) were measured as surrogate markers of atherosclerosis. Circulating $CD34^+$ counts were evaluated by flow cytometry and vitamin D levels were quantified by HPLC. Disease activity was assessed by Disease Activity Score-28 (DAS28).

Results: RA patients exhibited impaired GLS and GCS (both $p < 0.001$) as compared to HC, GLS being also altered in PsA ($p = 0.020$ *vs.* HC). DAS28 was correlated to GLS ($r = 0.908$, $p < 0.001$) and GCS ($r = 0.868$, $p < 0.001$) in RA, these findings being confirmed by multivariate regression analyses adjusted for confounders and Principal Component Analyses. GLS and GCS were impaired in PsA patients with high disease activity as compared to HC, and GLS was found to be a predictor of cIMT in this condition. On the other hand, vitamin D was negatively associated with cIMT in HC ($r = -0.308$, $p = 0.026$) but not in PsA or RA, although decreased levels were observed (both $p < 0.001$). Vitamin D was an independent predictor of decreased $CD34^+$ levels in PsA and RA. $CD34^+$ counts negatively correlated DAS28, GLS and GCS in RA.

Conclusions: Subclinical myocardial dysfunction is observed in IJD patients with preserved left-ventricular function and without traditional CV risk factors. Subclinical myocardial dysfunction was found to be a very early event in IJD. Disease activity was the main predictor of myocardial strain impairment. Interestingly, myocardial function was altered and associated with cIMT also in PsA patients with high disease activity.

1. Introduction

Patients with inflammatory joint diseases (IJD), including rheumatoid arthritis (RA) and psoriatic arthritis (PsA), exhibit increased rates of cardiovascular disease (CVD) morbidity and

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mortality [1,2], especially heart failure and myocardial infarction. Traditional CV risk factors cannot fully account for this increased risk, and chronic inflammation and immune dysregulation are thought to play a substantial role [3,4].

The involvement of traditional and non-traditional CV risk factors in IJD has two main consequences. First, the CVD have a premature development in these patients. Second, the assessment of CV risk solely based on traditional CV risk factors, as implemented for the general population, is obviously insufficient. Therefore, there is a clear need for early and appropriate methods for CV risk assessment in IJD [5,6], which may benefit patient stratification and facilitate the establishment of earlier therapeutic interventions, in order to improve clinical outcomes.

Several non-invasive imaging techniques allows an adequate estimation of CV risk by evaluating atherosclerosis burden and cardiac function. Although most of the studies have focused on atherosclerosis, less attention has been paid to myocardial systolic functionality. Two dimensional speckle tracking echocardiography (STE) is a recent method for detecting ventricular dysfunction by echocardiographic assessment of myocardial deformation (strain). Strain refers to the deformation or the relative change of muscle from its original length, expressed as a percentage of change. This technique provides information about both regional and global myocardial function. It is a very sensitive, load- and angle-independent technique, which make it superior to angle-dependent 2D Doppler echocardiography [7,8]. Moreover, strain abnormalities have been reported in a broad range of CV conditions, from heart failure with preserved EF to myocardial infarction and ischemia-reperfusion lesions [9–12]. Therefore, impaired ventricular strain can be suited for early detection of CVD in PsA and RA [7,13].

The involvement of non-traditional risk factors in IJD is supported by mechanistic insights and may represent a source of biomarkers and therapeutic targets. Common immune mediators [14–17] drive both atherosclerosis and joint progression. Chronic activation of immune pathways leads to endothelial dysfunction, vascular repair failure [18], atherosclerotic plaque formation and, ultimately, CVD development. Among reparative mechanisms, the case of circulating proangiogenic haematopoietic cells ($CD34^+$) must be noted. $CD34^+$ precursors are bone marrow-derived, multipotent cells with the ability to differentiate into different cell types [19,20] that participate in the turnover of damaged endothelium, likely delaying CVD development [20]. $CD34^+$ cells have been described to improve myocardial neovascularization and function [21,22], and their number is associated with LV remodeling [23]. Several factors are known to modulate the number and activity of progenitor cells in rheumatic diseases [18]. Recently, vitamin D receptor has been detected in progenitor $CD34^+$ cells [23], and vitamin D3 has been described to promote the functionality of endothelial colony-forming cells [24], hence pointing to a role for the vitamin D-$CD34^+$ cells axis in CV homeostasis. Actually, vitamin D levels have been related to arterial stiffness and progenitor cell numbers in RA [25].

Whether myocardial dysfunction can be detected in patients with IJD free of traditional CV risk factors already in the early phases of the disease remains unknown. Moreover, although circulating $CD34^+$ cells and vitamin D have been related to ventricular remodeling [23,26] and have been described to be altered in rheumatic conditions, the associations between STE, circulating $CD34^+$ cells and vitamin D in IJD have not been investigated so far. Therefore, in the present study, we aimed (i) to evaluate the subclinical myocardial dysfunction by STE, as well as surrogate markers of subclinical CVD, in patients with very early IJD without traditional CV risk factors, (ii) to evaluate the associations of STE markers with disease activity, and (iii) to analyze the associations between myocardial dysfunction and the levels of circulating $CD34^+$ cells and vitamin D.

2. Materials and methods

2.1. Ethics statement

Written informed consent was obtained from all subjects according to the Helsinki declaration and the retrospective observation was approved by the Ethics Committee of the University of Messina (Prot. N. 11/17).

2.2. Subjects

Between October 2015 and May 2016, 514 outpatients were examined for the first time at the Rheumatology Division of the University of Messina and were referred for a clinical and instrumental screening.

To be selected for the study, subjects needed to fulfill the following inclusion criteria: (i) to be newly diagnosed, (ii) not being exposed to immunomodulatory treatments, (iii) to be free of traditional CV risk factors, and (iv) to meet the classification criteria for PsA or RA [27,28]. Extended definition of traditional CV risk factors and exclusion criteria can be found in the Supplementary Materials. After applying inclusion and exclusion criteria, only 35 subjects with PsA and 41 RA patients were considered eligible for this study. A group of 58 gender- and age-matched healthy subjects were enrolled (institution-based recruitment) using identical inclusion and exclusion criteria (where applicable) and were studied as the healthy control (HC) group.

Patients undergone a complete clinical examination during the clinical appointment, including DAS28-CRP calculation. In PsA patients, cutaneous lesions were examined and the Psoriasis Area and Severity Index (PASI) was calculated to assess the severity [29]. The cut-off for low disease activity was established in 2.9 according to the literature [30].

At the first clinical evaluation, patients and controls underwent blood sampling by venipuncture and instrumental examination. Extensive chemical analyses were performed at the medical center after an overnight fasting in all subjects. Plasma lipids, glucose, fibrinogen, rheumatoid factor (RF) and ACPA were determined by routine methods. CRP was determined by a commercially available ELISA kit. The levels of 25-hydroxyvitamin D3 (25-OH D) were measured by using high-performance liquid chromatography (Bio-Rad).

2.3. $CD34^+$ cell count

Flow cytometry was used for the quantification of $CD34^+$ frequency in peripheral blood samples as previously described [25,29]. Briefly, 50 μL of peripheral blood was incubated with 10 μL of PE-conjugated anti-human CD34 antibody (BD) in TRUCOUNT tubes (BD) for 15 min. Sample acquisition and analysis were performed by in a FACSCalibur cytometer using CELLQuest as software. Non-viable cells were excluded according to 7-amino-actinomycin D (7-AAD; BD Pharmingen) staining. Circulating cells that expressed the stem cell antigen CD34 were defined as progenitor haematopoietic $CD34^+$ cells, and estimated and counted (cells/μL) as absolute count as previously described [25,29].

2.4. Measurement of cIMT and arterial stiffness indices

Carotid echo Doppler scan and arterial stiffness assessments were performed using a Vivid 3 Expert ultrasound machine equipped with a 7–15 MHz linear array transducer (GE Healthcare)

according to ESC/ESH guidelines [31] (Supplementary Materials). The intraobserver/interobserver variability of IMT and PWV measurements were 1.13/3.51% and 1.23/3.86%, respectively. Intraclass Correlation Coefficient (ICC) for PWV yielded a value of 0.993 (95% CI: 0.991–0.995).

2.5. Echocardiography study

Echocardiography examination was performed using a VIVID-7 ultrasound machine (GE Vingmed Ultrasound) equipped with a phased-array transducer, and stored on a dedicated workstation (EchoPAC, version 8.0.0) for off-line analyses. All measurements (LV, E/A ratio, LVMI and LV mass) were performed according to the recommendations of the American Society of Echocardiography on three averaged cardiac cycles [29] (see Supplementary Materials for detailed definitions). To complete the analysis of LV systolic function, myocardial deformation was assessed by speckle tracking echocardiography and automated function imaging for the evaluation of global and regional longitudinal (GLS) and circumferential (GCS) strain, as previously described [29]. Automated function imaging was performed on apical long-axis, 4-chamber, and 2-chamber views, following an on-screen guided workflow. The results are presented as a bull's-eye display showing color-coded and numeric values for peak systolic GLS and GCS. A detailed technique was previously described [29]. A frame rate >70 fps was employed. Strain analysis was performed offline by using Echopac. Endocardial border was manually traced from apical views, automatically obtaining the calculation of a region of interest comprised between endocardial and epicardial layers. Tracking quality was verified for each segment and low quality images were excluded. Global values of longitudinal strain from each apical view were calculated through an Automated Function Imaging analysis. LV twist was defined by the difference (in degrees) between apical rotation and basal rotation at isochronal time points. The intraobserver/interobserver variability of GLS and GCS measurements were 0.90/3.49% and 1.78/5.97%, respectively. ICC analyses for GLS yielded a value of 0.982 (0.975–0.987) whereas that of GCS was 0.971 (0.960–0.979).

2.6. Statistical analysis

Variables were summarized as mean ± standard deviation or n (%), unless otherwise stated. Variables were checked for normality by the Kolmogorov-Smirnov test, and non-parametric tests (Mann-Withney U and Kruskal-Wallis tests) were used to analyze differences among groups. Correlations were assessed by the Spearman's test. Multivariate regression analyses were performed to assess the contribution of different independent covariates to the dependent variable. Non-normal variables were log-transformed prior to be included in the models. A Principal Component Analysis (PCA) was performed as an integrative approach to avoid any potential collinearity bias and to retain the maximum of the variance from the demographical, clinical and traditional risk-related variables. The number of components (correlation method) retained was based on eigenvalues (>1) and loadings greater than 0.5 were used to identify the variables comprising a component. Principal component scores were calculated for each patient and used for multivariate regression analysis. Intraclass Correlation Coefficients (ICC) were computed to further assess the reproducibility of the imaging parameters made by different observers. ICC estimates and their 95% confident intervals were calculated based on a mean-rating (k = 3), absolute-agreement, two-way mixed-effects models. A $p < 0.050$ was used to denote statistical significance. SPSS 17.0 and R v. 3.3.1 statistical packages were used to perform statistical analyses.

3. Results

3.1. Subclinical CV disease and myocardial dysfunction in early RA and PsA

The characteristics of the subjects recruited for this study are summarized in Table 1. No differences were observed in age ($p = 0.170$), gender ($p = 0.130$) or BMI ($p = 0.787$) among study groups. Although slight differences in HDL-cholesterol in RA, the total/HDL-cholesterol ratio (atherogenic index) did not differ among groups and all individuals were free of previously diagnosed traditional CV risk factors (hypercholesterolemia/dyslipidemia, hypertension, diabetes, smoking habit and obesity). Similarly, no differences in creatinine levels and estimated GFR were noted. Finally, both PsA and RA patients were recruited at onset and they were not exposed to any medication at the time of sampling.

cIMT was found to be increased in RA (Table 1): 25 (60.9%) of the RA patients exhibited a cIMT>0.90 mm, compared to 4 (11.4%) and 8 (13.7%) of the PsA and HC groups, respectively ($p < 0.0001$). Additionally, the PWV was found to be impaired in both PsA and RA (Table 1). Moreover, PWV was correlated with DAS28 ($r = 0.322$, $p = 0.055$), CRP ($r = 0.446$, $p = 0.007$) and BASDAI ($r = 0.340$, $p = 0.049$) in PsA. Similarly, it was found to parallel DAS28 ($r = 0.371$, $p = 0.017$), ESR ($r = 0.456$, $p = 0.003$), CRP ($r = 0.384$, $p = 0.013$) and duration of the symptoms ($r = 0.337$, $p = 0.036$) in the RA group.

Finally, RA patients exhibited a significant impairment of GLS and GCS compared to HC, whereas GLS was also altered in PsA. Importantly, DAS28 was positively correlated to GLS ($r = 0.908$, $p < 0.001$) and GCS ($r = 0.868$, $p < 0.001$) in RA. Similar associations were retrieved for ESR, CRP and fibrinogen (data not shown). Of note, although GCS was not significantly different in PsA compared to HC, a positive correlation with DAS28 ($r = 0.438$, $p = 0.008$) was observed. Notably, standard echocardiographic examination showed no differences in LV diameters, volumes, wall thickness and EF among individuals (Table 1).

Overall, all these results confirm an increased prevalence of subclinical CV disease and myocardial dysfunction in the early stages of inflammatory joint diseases in the absence of established traditional CV risk factors. Surrogate markers of subclinical CV disease and myocardial dysfunction were strongly associated with the inflammatory burden, hence suggesting a role for inflammation in this scenario.

3.2. Subclinical myocardial dysfunction: role for disease features

Further analyses were conducted to evaluate the associations between the subclinical myocardial dysfunction and disease features in PsA and RA.

Because of the previous findings in relation to the disease activity, PsA patients were classified as low (DAS28 < 2.9) or high (DAS28 > 2.9) disease activity (Table 2). High disease activity was associated with altered GCS and PWV. Moreover, a trend towards an impaired GLS was also noted. PsA patients with high disease activity exhibited differences in GCS, GLS and PWV when compared to HC, but these differences were not observed in their low disease activity-counterparts. Interestingly, GLS was found to be a predictor of cIMT in PsA patients (B [95% CI], p: 0.019 [0.002, 0.035], $p = 0.027$) after adjusting for age, BMI, disease activity and inflammation parameters (ESR, CRP and fibrinogen), PWV and vitamin D.

Equivalent results were obtained when RA patients were stratified according to disease activity (Supplementary Table 1). The association between disease activity and subclinical myocardial dysfunction was analyzed by multivariate regression analyses

Table 1
Characteristics of the subjects recruited in the present study.

	HC (n = 58)	PsA (n = 35)	RA (n = 41)	$p^{\#}$	*p* (Dunn-Bonferroni)		
					C *vs.* PsA	C *vs.* RA	PsA *vs.* RA
Age, median (range)	45 (24–66)	45 (23–59)	46 (32–62)	ns			
Gender, f/m	35/23	26/9	32/9	ns			
CV risk-related parameters							
BMI, kg/m^2	24.79 ± 2.73	24.70 ± 2.61	25.15 ± 3.71	ns			
Total cholesterol, mg/dl	181.84 ± 20.88	185.00 ± 22.84	198.05 ± 36.43	ns			
HDL-cholesterol, mg/dl	50.41 ± 9.91	58.00 ± 19.81	58.00 ± 12.87	0.020	0.070	0.021	1.000
LDL-cholesterol, mg/dl	114.00 ± 20.88	106.29 ± 34.94	116.56 ± 35.53	ns			
Total/HDL-cholesterol ratio	3.73 ± 0.80	3.12 ± 0.89	3.62 ± 0.85	ns			
Glucose, mg/dl	88.00 ± 7.04	89.50 ± 10.76	89.00 ± 14.09	ns			
Creatinine, mg/dl	0.66 ± 0.14	0.71 ± 0.16	0.65 ± 0.16	ns			
SBP, mm	122.09 ± 8.85	120.50 ± 11.34	124.27 ± 10.03	ns			
DBP, mm	70.06 ± 6.29	72.00 ± 8.64	74.15 ± 10.94	ns			
CD34$^+$ cell count, cell/μl	2.35 ± 1.14	2.12 ± 0.80	1.58 ± 0.58	<0.001	0.380	0.002	0.024
Clinical features							
DAS28		3.33 ± 0.55	3.61 ± 0.88	ns			
Duration of the symptoms, months		9.37 ± 7.75	6.43 ± 6.00	ns			
Fibrinogen, mg/dl	264.56 ± 50.88	297.26 ± 72.61	321.76 ± 58.91	<0.001	0.068	<0.001	0.343
Vitamin D, ng/ml	31.75 ± 5.05	23.53 ± 4.84	23.68 ± 6.42	<0.001	<0.001	<0.001	0.699
CRP, mg/dl	0.34 ± 0.16	0.50 ± 0.50	0.95 ± 1.18	0.049	1.000	0.011	0.167
ESR, mm		25.06 ± 10.60	27.02 ± 20.40	ns			
HAQ (0–3)		0.52 ± 0.61	1.15 ± 0.64	<0.001			
VAS (0–100)		48.82 ± 15.12	59.42 ± 18.01	0.034			
RF, UI/ml		7.6 ± 2.9	100 ± 100.4	<0.001			
ACPA, n (%)			20 (49.0)				
BASDAI		1.76 ± 2.14					
PASI		0.91 ± 1.31					
Subclinical CVD and myocardial dysfunction parameters							
cIMT, mm	0.79 ± 0.18	0.82 ± 0.19	0.98 ± 0.16	<0.001	1.000	<0.001	<0.001
PWV, m/s	5.11 ± 0.83	6.42 ± 1.39	7.91 ± 1.93	<0.001	<0.001	<0.001	0.009
GLS, %	−23.25 ± 1.80	−21.57 ± 2.59	−18.13 ± 1.36	<0.001	0.020	<0.001	<0.001
GCS, %	−24.50 ± .70	−24.97 ± 2.50	−20.15 ± 1.34	<0.001	1.000	<0.001	<0.001
Echocardiographic assessment							
Septum, mm	10.20 ± 1.00	10.20 ± 1.76	11.20 ± 1.90	ns			
LV mass index	77.40 ± 12.00	77.80 ± 15.50	82.90 ± 10.70	ns			
Posterior wall thickness, mm	9.00 ± 1.20	8.90 ± 1.70	8.70 ± 1.50	ns			
LV DD, mm	50 ± 6.75	52.71 ± 3.5	50.6 ± 2.8	ns			
LV ESD, mm	36.20 ± 2.20	37.00 ± 5.24	35.6 ± 3.90	ns			
E/A	1.10 ± 0.34	1.25 ± 0.10	1.20 ± 0.29	ns			
EF, %	62.88 ± 3.30	61.9 ± 4.79	60.0 ± 4.47	ns			

Variables are summarized as mean ± standard deviation or n (%) unless otherwise stated. Differences were assessed by Kruskal-Wallis tests (with Dunn's Bonferroni correction for multiple comparisons' tests), $\chi 2$ or Mann-Withney U tests, as appropriate.
$^{\#}$*p*-values: *p*-values obtained in Kruskall-Wallis, $\chi 2$ or Mann-Withney tests, depending on the distribution of the variables and the groups included in the analyses. When Kruskal-Wallis tests achieved a *p*-value<0.050, multiple comparisons tests were performed and *p*-values are indicated in the last columns.
BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL: high density lipoprotein-cholesterol; LDL: low density lipoprotein cholesterol; CRP: C-reactive protein.; GLS: global longitudinal strain; GCS: global circumferential strain; PWV: pulse wave velocity; cIMT: carotid intima-media thickness; DAS 28: Disease Activity Score; HAQ: Health assessment questionnaire; VAS: visal analogic scale; PASI: Psoriasis Area Severity Index. LV: left ventricular; EDD: end diastolic diameter; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; ns: non-significant.

in RA patients. Importantly, DAS28 was found to be the only predictor of GLS and GCS in RA, even after adjusting for potential confounders (Table 3). Therefore, in order to avoid any potential collinearity bias among the features analyzed, a PCA was conducted including age, BMI, DAS28, CRP, ESR, fibrinogen, total-, HDL- and LDL-cholesterol, SBP, DBP and duration on the symptoms (Table 4). PCA revealed a good adequacy of the data (KMO = 0.523, Barlett sphericity test $p = 2.03 \cdot 10^{-26}$) and 4 components were obtained, explaining 69.2% of the total variance. Variables included in each component based on their loadings were as follows: component 1 (DAS28, CRP, ESR and fibrinogen), component 2 (age, BMI, total- and LDL-cholesterol), component 3 (SBP and DBP) and component 4 (HDL-cholesterol and duration of the symptoms). Then, a good separation between disease-related and other traditional risk-related factors was achieved. Finally, the association between these components and the myocardial dysfunction was studied by multivariate regression analyses. Interestingly, only disease-related features (component 1) were predictors of GLS and GCS in RA patients, hence confirming our previous findings.

All these results reinforce the relevance of the inflammatory burden in the subclinical impairment of the myocardial functionality in IJD already in the very early stage of these conditions. In addition to the strong association being observed in RA, where GCS and GLS were notably impaired, a clear link was also found in PsA patients with high disease activity. Moreover, GLS was found to be associated with cIMT in these patients. Overall, our findings clearly point to disease activity as the driver of STE impairment in IJD, independently of clinical diagnosis.

Table 2
Characteristics of PsA patients classified according to disease activity.

	DAS28 ≤ 2.9	DAS28 > 2.9	*p*
Age	45.91 ± 7.13	42.71 ± 9.84	0.409
Gender, f/m	8/3	18/6	0.636
CV risk-related parameters			
BMI	24.58 ± 1.68	24.61 ± 2.98	0.875
Total cholesterol	178.00 ± 25.71	180.76 ± 22.35	0.804
HDL-cholesterol	55.14 ± 8.05	59.00 ± 22.63	0.455
LDL-cholesterol	104.00 ± 33.55	93.27 ± 3.95	0.423
Total/HDL-cholesterol ratio	3.32 ± 0.84	3.04 ± 0.92	0.494
Glucose	91.00 ± 12.11	86.00 ± 10.14	0.336
Creatinine	0.68 ± 0.18	0.72 ± 0.16	0.451
SBP	112.00 ± 10.36	123.33 ± 10.46	0.066
DBP	69.00 ± 11.42	73.00 ± 7.74	0.497
Clinical features			
Duration of symptoms	6.90 ± 3.08	9.00 ± 8.9	0.174
Fibrinogen	252.00 ± 43.90	318.00 ± 74.37	**0.008**
CRP	0.21 ± 0.14	0.45 ± 0.56	**0.016**
ESR	17.91 ± 6.48	28.33 ± 10.60	**0.002**
HAQ	0.22 ± 0.37	0.66 ± 0.61	0.038
BASDAI	0.79 ± 1.76	2.19 ± 2.17	0.098
PASI	1.49 ± 1.53	0.72 ± 1.14	0.123
Subclinical CVD parameters			
cIMT	0.80 ± 0.14	0.84 ± 0.34	0.612
PWV	5.50 ± 1.24	6.85 ± 1.27	**0.005**
GLS	−22.35 ± 1.98	−21.04 ± 2.85	0.066
GCS	−27.00 ± 15.74	−24.30 ± 2.37	**0.007**

Differences between PsA patients with low and high disease activity were evaluated by Mann-Withney U tests or $\chi 2$ tests, as appropriate. Variables with significant differences are highlighted in bold.

3.3. Altered CD34$^+$ progenitor cells and vitamin D: associations with subclinical myocardial dysfunction

Finally, we studied whether altered circulating CD34$^+$ progenitor cells or vitamin D levels may underlie the subclinical myocardial dysfunction in IJD.

Vitamin D was negatively associated with cIMT in HC ($r = -0.308$, $p = 0.026$) but not in IJD patients, where decreased levels were found (Table 1), hence pointing to a link between vitamin D and subclinical atherosclerosis. This correlation was also observed in PsA patients with low disease activity (DAS28 < 2.9) ($r = -0.636$, $p = 0.035$), but not in those with higher disease activity ($r = 0.185$, $p = 0.387$).

Moreover, vitamin D levels and DAS28 were independent predictors of CD34$^+$ cells in PsA, whereas vitamin D and duration of the symptoms did in RA (Table 5). Circulating CD34$^+$ cells were decreased in RA (Table 1), negative correlations with STE parameters being disclosed (GCS: $r = -0.291$, $p = 0.068$; GLS: $r = -0.301$, $p = 0.057$).

All these results suggest that vitamin D was independently associated with circulating CD34$^+$ levels in IJD. CD34$^+$ cells paralleled STE parameters in RA, but additional studies are required.

4. Discussion

Chronic rheumatic conditions, such as RA and PsA, are associated with enhanced atherosclerosis and impaired endothelial function [32]. Since these alterations occur shortly after disease onset and traditional CV risk factors cannot solely account for this increased risk, a role for inflammation has been proposed [33]. In the present report, we have demonstrated an association between the disease activity and biomarkers of endothelial function, atherosclerosis and subclinical myocardial function in PsA and RA during the early phase of the disease. These alterations were linked to the inflammatory burden, disease activity being the main predictor of impaired myocardial dysfunction irrespectively of disease diagnosis. Importantly, altered levels of CD34$^+$ cells and vitamin D were found in both conditions. Overall, our results clearly confirm a role for the inflammatory burden in both subclinical endothelial and myocardial dysfunction in these patients, hence providing a rationale for the utilization of STE assessment for the CV risk assessment in IJD.

The most interesting result from our study was the impaired myocardial functionality in both RA and PsA patients in the very early phase of the disease. This finding suggests that patients with IJD exhibit not only an accelerated atherosclerosis development in the peripheral vasculature but also myocardial dysfunction already at disease onset. Although some authors have previously reported a reduced LV myocardial deformation in RA patients [7,34,35], most of these studies have been focused on patients with long-standing disease and increased prevalence of traditional CV risk factors.

Table 3
Multivariate regression analysis of myocardial dysfunction parameters in RA.

		B	95% CI	*p*
GLS	Age	0.033	−0.006, 0.071	0.091
	BMI	0.021	−0.069, 0.112	0.631
	CRP	0.142	−0.095, 0.379	0.229
	ESR	0.005	−0.013, 0.022	0.580
	DAS28	8.075	4.439, 11.710	**<0.0001**
	SBP	0.011	−0.035, 0.057	0.628
	DBP	0.008	−0.031, 0.048	0.672
	Vitamin D	−0.711	−3.150, 1.727	0.554
	CD34$^+$ cells	0.425	−1.298, 2.148	0.617
	Duration of the symptoms	−0.138	−0.965, 0.689	0.735
GCS	Age	0.015	−0.029, 0.060	0.486
	BMI	−0.007	−0.112, 0.097	0.889
	CRP	0.105	−0.169, 0.379	0.440
	ESR	0.015	−0.005, 0.036	0.131
	DAS28	7.214	3.013, 11.415	**0.002**
	SBP	0.030	−0.023, 0.083	0.260
	DBP	−0.019	−0.064, 0.027	0.409
	Vitamin D	−1.860	4.678, 0.959	0.187
	CD34$^+$ cells	0.742	−1.249, 2.733	0.451
	Duration of symptoms	0.072	−0.883, 1.028	0.878

Multiple linear regression analyses of GLS or GCS as dependent variable in RA patients. Variables found to be significant predictors are highlighted in bold.

Table 4
Multivariate regression analysis of PCA components on GLS and GCS in RA.

		B	95% CI	*p*
GLS	Component 1	0.989	0.713, 1.265	**<0.0001**
	Component 2	−0.021	−0.304, 0.261	0.878
	Component 3	−0.262	−0.560, 0.036	0.083
	Component 4	0.118	−0.190, 0.426	0.442
GCS	Component 1	1.067	0.812, 1.323	**<0.0001**
	Component 2	−0.002	−0.263, 0.260	0.988
	Component 3	−0.175	−0.451, 0.100	0.205
	Component 4	0.160	−0.125, 0.445	0.261

Multiple linear regression analyses of GLS or GCS as dependent variable in RA patients. Variables found to be significant predictors are highlighted in bold.

Table 5
Multivariate regression analysis of $CD34^+$ frequency in PsA and RA.

		B	95% CI	*p*
PsA	Age	−0.002	−0.010, 0.006	0.613
	BMI	0.009	−0.017, 0.035	0.491
	CRP	0.154	−0.045, 0.352	0.124
	ESR	−0.001	−0.010, 0.009	0.905
	DAS28	−0.152	−0.307, −0.001	**0.050**
	cIMT	−0.079	−0.674, 0.517	0.788
	PWV	0.002	−0.043, 0.048	0.920
	Vitamin D	0.019	0.005, 0.033	**0.009**
	Duration of symptoms	−0.003	−0.011, 0.006	0.512
RA	Age	0.001	−0.007, 0.008	0.911
	BMI	−0.003	−0.022, 0.016	0.734
	CRP	−0.015	−0.064, 0.033	0.520
	ESR	−0.001	−0.004, 0.003	0.520
	DAS28	0.011	−0.075, 0.097	0.792
	cIMT	−0.258	−0.983, 0.467	0.472
	PWV	−0.029	−0.065, 0.007	0.105
	Vitamin D	0.010	0.001, 0.019	**0.028**
	Duration of the symptoms	0.016	0.004, 0.028	**0.010**

Multiple linear regression analysis including $CD34^+$ frequency as dependent variable. Variables found to be significant predictors are highlighted in bold.

Midtbø and colleagues reported an impaired myocardial function in RA patients with respect to controls, but active RA was related to a higher prevalence of hypertension and diabetes as compared with patients in remission and controls [36]. Therefore, it is likely that the impairment in GLS observed in patients with active RA or PsA in that study may be a consequence of accumulated myocardial damage in the context of these risk factors. Therefore, our results expand the current knowledge of myocardial dysfunction in IJD by confirming its very early onset in these conditions, independently of disease duration, traditional CV risk factors and treatment-related effects. Moreover, we observed for the first time that patients with a more pronounced inflammatory status, assessed by CRP, ESR and fibrinogen, and mainly with a more activity status, had a stronger alteration in myocardial function irrespective of their IJD (RA or PsA), suggesting that inflammation could be the principal driver in impairing myocardial function. Interestingly, other studies have found an association between the exposure to different immunomodulatory drugs and improved myocardial LV strain markers [7,34,35].

Disease activity was found to be associated with GLS and GCS in both RA and PsA in univariate and multivariate analysis, therefore confirming a crucial role of the inflammatory burden in the development of such functional alterations. This idea is in line with the protective effect of the low disease activity to reduce CV risk burden in these conditions [5]. In fact, Solomon and colleagues have revealed that an accumulated high disease activity over time was associated with the development of CV disease in RA [37]. Interestingly, despite exhibiting a comparable duration of the symptoms, a stronger impairment of the endothelial and myocardial function was observed in RA compared to PsA. Moreover, the duration of the symptoms itself was found to be associated with PWV and $CD34^+$ count in RA, but not in PsA. Overall, our findings are in line with an enhanced inflammatory burden in RA compared to PsA. However, the relevance of the inflammatory burden in PsA cannot be underestimated. Although a lower CV risk has been attributed to this condition compared to other IJD [6,38], a substantial increased risk is still found compared to the general population. Actually, PsA patients with high disease activity exhibited impaired PWV and myocardial dysfunction compared to HC in our study. Of note, GLS was found to be a predictor of cIMT in PsA patients, in line with previous studies in psoriasis [39]. Like arterial stiffness, STE parameters are functional surrogate markers of CV risk. As functional measurements, their alteration is likely to be reversible. Taking into account the association between myocardial dysfunction and disease activity, an appropriate control of the inflammatory burden would be advisable in IJD patients. This is especially relevant during the very early stage of the disease, in line with the concept of the therapeutic 'window of opportunity'. Taken together, our results support the need of a prompt and effective control of disease activity for CVD prevention in IJD.

It is noteworthy that among STE parameters, GLS was impaired in both PsA and RA, whereas GCS was only altered in RA. Interestingly, GLS was reported to be a more sensitive marker than circumferential or radial strains [12]. Upon pathological traits, subendocardial myocardial fibers (longitudinally orientated and thus responsible of the longitudinal contraction) are affected earlier than subepicardial fibers (hence accounting for unchanged circumferential and radial strains). Then, a more pronounced

systemic inflammation in RA patients can explain the impairment of both STE parameters compared to their PsA counterparts. Equivalent results were observed when PsA patients were classified by disease activity. These results reinforce our previous findings on inflammatory burden and myocardial dysfunction. The elucidation of the best LV myocardial strain marker according to IJD progression warrant further studies.

Our findings stress the need of an appropriate monitoring of disease activity-mediated myocardial dysfunction in IJD and, presumably, other inflammatory conditions. Recently, other authors have reported that subclinical alterations in the myocardium can be present in other autoimmune rheumatic diseases, such as sarcoidosis [40,41]. Although a number of techniques for CV risk assessment and management have been proposed [32,42,43], most of them are focused on endothelial dysfunction and atherosclerosis, whereas myocardial functionality has not received enough attention. Despite the recent advances in the CV risk management, there is still a considerable room for improvement, hence supporting the need for additional tools. Actually, the research agenda of latest EULAR recommendations for CV risk management in IJD proposes the study of cardiac abnormalities as well as the inclusion of additional CV risk biomarkers to assist in the clinical setting [5]. Taking into account all these ideas, strain imaging by STE can be proposed as a promising tool to address this clinical unmet need. Strain imaging has proved to be a valuable non-invasive opportunity for identifying subclinical CVD [8,44,45], being able to detect subtle LV myocardial dysfunction in an objective and angle-independent fashion. In fact, we have previously reported that STE was able to identify very early mechanical changes in hypertensive patients prior to the occurrence of LV hypertrophy [46], thereby reinforcing its applicability for early assessment and patient stratification.

Finally, the role of $CD34^+$ cells and vitamin D as biomarkers was analyzed. Interestingly, vitamin D was a predictor of circulating $CD34^+$ cells levels in IJD, even after adjusting for disease activity, hence suggesting that vitamin D levels can be a surrogate marker of impaired $CD34^+$ levels. Our findings pose the question as whether vitamin D supplementation could counteract the disease activity-mediated detrimental effects on $CD34^+$ cells and myocardial dysfunction. Chronic inflammation leads to oxidative stress, myocyte dysfunction and increased fibroblast activity causing myocardial collagen deposition and interstitial fibrosis [47–49], hence hampering myocardial contraction [50]. Furthermore, vitamin D deficiency has been related to cardiac tissue remodeling [51] and LV hypertrophy [52]. Since inflammatory pathways and oxidative stress seems to underlie the myocardial dysfunction, and taken into account the effects of vitamin D on tissue remodeling [52] and on anti-inflammatory and anti-oxidative pathways [53,54], the potential beneficial effects of vitamin D on myocardial dysfunction warrants future studies.

In conclusion, the results herein presented expand the current knowledge about the subclinical CV alterations in IJD. To the best of our knowledge, this is the first study where myocardial alterations are analyzed in patients with very early IJD, which represents a major strength of our study. Although a number of previous studies have described an increased prevalence of atherosclerosis and endothelial dysfunction, our results went further by reporting the LV myocardial strain alterations in IJD patients, regardless of disease diagnosis. Additionally, these pathological findings were found in middle-aged patients already at disease onset with preserved LVEF, in the absence of traditional CV risk factors and related to disease activity. Being our patients not exposed to any DMARD at recruitment allowed us to rule out a potential medication-related confounding effect in our findings. A number of limitations of the present study must also be remarked. First, although stringent criteria were used to control for traditional CV risk factors, lifestyle factors such as diet [55] or physical activity were not appraised. However, there is not a strong evidence pointing to these factors as potential bias for STE in the current literature. Second, because of the cross-sectional design of our study, our findings require confirmation in prospective follow-up studies to evaluate the clinical relevance of the subclinical myocardial impairment in IJD patients. Third, although our data support a good reliability and reproducibility of the STE assessments, certain variability may be expected for multi-centric comparisons [56]. Then, standardization of the image processing and analysis algorithms as well as the validation of appropriate cut-off values are required to guide its routine clinical utilization in the future.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

ALG, JRC and GM conceived the study, analyzed and interpreted the data and drafted the manuscript. COA, GD, CZ, SL and MA were in charge of patient recruitment, clinical data collection and clinical data analyses. AS (Ana Suárez) and AS (Antonino Saitta) participated in the conception, design and critical revision of the results. All the authors participated in the discussion of the results and literature search. All authors approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.03.004.

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REVIEW ARTICLE

Cardiovascular Risk in Psoriasis: Current State of the Art

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Abstract: Psoriasis (Pso) is a chronic inflammatory immune-mediated skin disease associated with several comorbidities. Despite the growing number of studies providing evidence for the link between Pso and cardiovascular (CV) disorders, there are still many unsolved questions, dealing with the role of the skin disease as an independent risk factor for CV events, the influence of Pso severity and duration on CV damage, the presence of psoriatic arthritis (PsA) as a predictor of increased CV mortality and morbidity and the detection of reliable clinical, laboratory and/or instrumental parameters to stratify CV risk in psoriatic patients. Moreover, it remains to clarify if the early treatment of the dermatosis may lower CV risk. In this paper we will try to provide answers to these queries in the light of the updated data of the literature.

Keywords: Psoriasis, cardiovascular risk, risk factors, coronary artery disease.

INTRODUCTION

Psoriasis (Pso) is a chronic inflammatory immune-mediated skin disease with an estimated worldwide prevalence of approximately 2-3% [1]. Its impact on quality of life is so dramatic that, in 2013, the World Health Organization (WHO) pointed at Pso as a major global health problem [2]. For a long time considered to be an exclusively cutaneous disorder, Pso is now recognized as a systemic inflammatory disorder sharing pathogenic pathways with many other chronic and progressive health diseases, including psoriatic arthritis, metabolic syndrome (MetS), inflammatory bowel disease, uveitis, obstructive sleep apnoea, non-alcoholic fatty liver disease (NAFLD) and psychiatric disturbances [3]. It is believed that 73% of patients with Pso present at least one comorbidity [4]. Only recently the attention of the researchers has been focused on its link with cardiovascular (CV) disorders. Epidemiologic studies demonstrated high morbidity and mortality in psoriatic patients mainly due to major adverse cardiovascular events (MACEs), including acute myocardial infarction (AMI), stroke and peripheral arterial disease (PAD) [5]. Chronic systemic inflammation has been proposed as a common pathogenic mechanism potentially able to explain the link between skin disease and CV risk via induction and maintenance of atherosclerosis. The inflammatory response in Pso is promoted by T helper (Th)1 and Th17 cells, and pro-inflammatory mediators such as interleukin (IL)-6, IL-12, IL-17, IL-22, IL-23 and tumour necrosis factor (TNF)-α play a crucial role in its pathogenesis [6]. Interestingly, IL-17A-dependent response occurs in parallel with the Th1-dominant immune response during atherogenesis [7]. Both atherosclerotic and psoriatic plaques are foci of cellular immunity, generating a loop in which inflammatory elements within the psoriatic plaque target other tissues, inducing early endothelial dysfunction and maintaining high levels of inflammation, thus leading to a pro-atherosclerotic state [8]. Such link has been well summed-up in the concept of "psoriatic march" [9]. Despite the growing number of studies providing evidence for the link between Pso and CV disorders, there are still many unsolved questions, dealing with the role of the skin disease as an independent risk factor for CV events, the influence of Pso severity and duration on CV damage, the presence of psoriatic arthritis (PsA) as a predictor of increased CV mortality and morbidity and the detection of reliable clinical, laboratory and/or instrumental parameters to stratify CV risk in psoriatic patients [10-14]. Moreover, it remains to clarify if the early treatment of the dermatosis may lower CV risk.

In this narrative review we will try to provide answers to these queries. We systematically searched the MEDLINE

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and EMBASE databases for studies investigating CV morbidity and mortality in adult Pso/PsA patients fulfilling the following criteria: meta-analyses, case-control, cross-sectional, cohort, or nested case-control design; evaluation of MI, stroke, cardiovascular death, or composite cardiovascular end point in conjunction with psoriasis; and analyses that compared psoriasis patients with control groups. Our search was limited to English-language and human-only studies published between January 1980 and June 2017. Secondly, we review the literature with the same methodology searching for clinical, laboratory and/or instrumental parameters of subclinical atherosclerosis to stratify CV risk in Pso patients. Finally, a systematic review of all the studies investigating the potential effects of Pso treatments on CV morbidity and mortality was also done using the same methodology.

QUESTION 1: IS PSORIASIS AN INDEPENDENT RISK FACTOR FOR CV DISORDERS?

Pso patients have a greater prevalence of MetS or its individual components (hypertension, insulin resistance, dyslipidaemia, central obesity) [15]. Armstrong *et al.*, in a systematic review and meta-analysis of the literature, found that the pooled odds ratio (OR) for MetS among patients with Pso was significantly higher compared with unaffected controls, with a dose-response relationship between Pso severity and the prevalence of MetS [16]. On the other hand, it is well-known that MetS significantly contributes to CV morbidity and mortality [17-20]. It is evident that the shared risk factors make the evaluation of the contribution of a single component, cutaneous or metabolic, to CV risk difficult. NAFLD has been related to an increased CV morbidity and mortality [18,21-23]. NAFLD prevalence and severity is higher with a worse prognosis in patients with Pso [24-27]. It has been reported that up to 50% of psoriatic patients may have NAFLD [28]. Furthermore, NAFLD increases Pso severity and is frequently prevalent in patients with PsA [29,30]. Chronic inflammation via both hepatic and skin-derived cytokines represents the underlying pathogenic mechanism that links NAFLD with Pso [31]. It is hard to determine if Pso alone may be considered an CV risk factor or if the skin disease could precipitate, via systemic inflammation, the development of both metabolic and CV damage. Nevertheless, the risk for psoriatic patients to have a CV event in course of life remains high after adjusting for traditional CV risk factors, including smoking and alcohol abuse [5,10,16,32,33].

Pso has been associated with increased risk of AMI in some studies. Meta-analysis of 6 cohort and 4 cross-sectional studies evidenced a combined OR of 1.25 and 1.57, respectively [34]. These data are in conflict with those reported by Brauchli *et al*., with similar overall incidence rate of AMI among patients with or without Pso and, more recently, by Egeberg *et al*., in a Danish Nationwide Cohort Study [35,36]. Psoriatic patients have, however, a worse prognosis after first-time AMI compared with those without Pso [37]. Psoriatic patients have also been found at increased risk to develop coronary artery disease (CAD), with more severe coronary artery involvement [34,38,39]. More debated is the association between Pso and stroke, with contrasting results from 3 large meta-analyses reviewing the risk of increased CV event in psoriatic patients [16,17,34]. Patients with Pso appeared to be exposed to an increased risk of developing atrial fibrillation because the chronic inflammatory state is also increasingly recognized as an independent risk factor [40,41]. Small-scale ECG studies showed that the duration of P-wave dispersion and atrial electromechanical delay were prolonged in patients with Pso compared with control subjects, with increased corrected QT interval dispersion [42]. The link between Pso and dilated cardiomyopathy (DCM) is yet substantially unexplored. The incidence of DCM is reported 10 times higher in patients with Pso, although such association has been described mainly in sporadic case reports, reviewed by Hashim *et al.* [43,44]. Few studies investigated the relationship between PSO and PAD, suggesting a higher PAD prevalence in Pso patients compared with controls [5,34]. Due to the substantial lack of data it is, however, hard to assess the role of Pso as a clear independent risk factor in this field. A higher CV mortality in psoriatic patients compared with healthy subjects was evidenced by several authors [5,16,32,33,45]. Pso remains independently associated to an increased rate of CV death even after adjustment for traditional CV risk factors [46]. Moreover, and similar to other chronic inflammatory diseases, life expectancy of patients is substantially reduced, with CV diseases as a major contributor, especially in patients with a more severe form of Pso [45]. Nevertheless, the uncertainty of this association remains, with some studies reporting a non-significant difference in CV events between psoriatic patients and controls [36,47]. The aforementioned data seem to strongly suggest that Pso may be considered as an independent CV risk factor, but their critical evaluation must involve a series of limitations [16,34,36,48]. First of all, study populations are not necessarily representative of the entire populations of psoriatic patients: the majority of the studies, in fact, employ databases in which patients are identified using billing codes and/or medication prescriptions, thus potentially neglecting a wide number of untreated patients. Other important biases include the lack of a uniform definition of disease severity, the incomplete measurement of confounding factors, the heterogeneity in study designs, outcome definitions and assessment, and the lack of long-term prospective studies. Conversely in a recent study by Dattilo *et al.* [49] showed that patients with mild psoriasis, in the absence of other CV risk factors and without any pharmacological treatment, there were subclinical alterations of both cardiac function and of arterial stiffness. The authors conclude that psoriasis, already in its mild form, may be an independent CV risk factor [49].

Answer: Some studies demonstrated a high prevalence of CV disorders in patients affected by Pso and recent studies showed a possible role for Pso as an independent CV risk factor. However, further evidence is required before definitively stating that Pso is an independent risk factor for CV disease.

QUESTION 2: CAN PSORIASIS SEVERITY AND DURATION INFLUENCE THE RISK OF CV DISEASE?

Several studies and meta-analyses showed a robust association between severe Pso and AMI, stroke and CV death [10,16,34,35,37]. When stratified according to disease severity, the OR is higher in patients affected by more pronounced

skin involvement compared with those with milder involvement. Systemic inflammation may be the clue: the psoriatic plaque is localized to the skin, but its effects are far-reaching. During a cutaneous flare, there are more than 1 billion immune cells activated within the body, contributing to cardiometabolic dysfunction [50]. Currently used clinical algorithms, like Framingham risk score (FRS), may underestimate this risk in severely psoriatic patients, not accounting for the excess risk attributable to severe disease [51]. More intriguing is the relationship between patient age and disease duration and severity. Young patients with severe skin involvement showed a higher incidence of AMI and adjusted relative risk (RR) of CV mortality than older ones [10,35,46]. In a cohort study involving U.S. women, age at diagnosis < 40 years or duration of Pso ≥ 9 years conferred a substantial increase in CV risk [52]. The authors attributed such findings to the often severe phenotype of early onset Pso, accounting for intense systemic inflammation and consequent higher risk of CV disease [53]. The underestimation of CV risk in young Pso patients was indirectly confirmed by echographic findings. In fact, increased aortic stiffness index (ASI), decreased flow-mediated vasodilatation (FMD), and reduction of coronary reserve have been documented in young patients without any standard CV risk factors, evidencing the presence of morphological and physiological alterations yet in a subclinical stage [54-56].

Answer: Patients with severe skin disease are more prone to develop CV events compared with those with mild forms. Early onset and long duration of Pso seem to confer a higher susceptibility for CV damage.

QUESTION 3: ARE PSA PATIENTS MORE EXPOSED TO CV RISK COMPARED WITH THOSE WITH PSO ALONE?

PsA patients have an increased risk of CV disorders when compared with the general population [57]. Morbidity risks for AMI, cerebrovascular diseases and heart failure were increased by 68, 22 and 31%, respectively, with a magnitude of the risk comparable with that observed in patients with severe Pso. About AMI, however, no difference in 10-year risk of fatal CV events was found between PsA patients and healthy subjects; moreover, in a Swedish cohort, the overall risk was only slightly increased, with no association between PsA and the risk of AMI in age-specific strata [37]. Nevertheless, an increased risk of non-fatal AMI among women with PsA was observed in comparison with women with Pso alone, suggesting that PsA may confer a higher CV risk than skin-confined disease [52]. As for severe Pso and rheumatoid arthritis, the FRS underestimates the true CV risk profile in patients newly diagnosed with PsA, with a 10-year cumulative incidence rate for CV disease of 17%, which was about twice as high as the predicted by the FRS [58]. An increased prevalence of subclinical atherosclerosis and endothelial dysfunction in patients with PsA has been highlighted by instrumental assessment. Using coronary CT angiography (CCTA), patients with PsA without known CAD showed a 3 to 4-fold increased prevalence of all types of coronary plaque, suggesting a condition of silent ischemia [59]. Ultrasonographic measurements of carotid total plaque area (TPA) and carotid intima-media thickness (cIMT), has evidenced a more severe subclinical atherosclerosis in PsA compared with Pso alone [60]. Another surrogate marker of subclinical atherosclerosis, FMD, was found significantly lower in PsA patients compared with controls, suggesting an impairment of endothelial function [61,62]. One of the main limitations emerging from the literature is the paucity of studies comparing the CV risk between Pso and PsA patients; another bias is that the retrospective analysis of patient databases does not permit to categorize CV risk according to the 5 different PsA clinical subsets (distal joint disease, oligoarthritis, spondyloarthropathy, polyarthritis and arthritis mutilans).

Answer: PsA is associated with a CV risk profile at least comparable to that observed in severe Pso.

QUESTION 4: WHICH CLINICAL, LABORATORY AND/OR INSTRUMENTAL PARAMETERS MAY BE CONSIDERED USEFUL TO STRATIFY CV RISK IN PSORIATIC PATIENTS?

The early detection of CV disorders and subclinical atherosclerosis is mandatory to reduce the risk of development of MACEs in a Pso population and it may allow to select clusters of patients needing an early therapeutic intervention. An increasing number of circulating biomarkers have been recently evaluated; among these, high sensitivity C-reactive protein (hsCRP) alone may not accurately predict CV risk in Pso patients [63]. An emerging inflammatory biomarker, N-acetylglucosamine/galactosamine (GlycA), appears to be not only a predictor of future CV events, but also a promising tool in the assessment of disease activity and treatment response [64]. Its use in combination with hsCRP might allow early selection of high risk patients, as recently observed in those undergoing coronary angiography [64]. Another promising biological marker is the inflammatory glycoprotein YKL-40 [65]. It regulates the vascular endothelial growth factor and it is correlated with disease activity in the spectrum of CV diseases from endothelial dysfunction to atherosclerosis [66]. Its serum levels are significantly higher both in Pso (independently from the presence of PsA) and in PsA (compared with patients without arthritis) [67].

In a study, homocysteine plasma levels in Pso were significantly higher compared with healthy subjects, with a positive correlation with disease severity [68]. Furthermore, human endothelial cell-specific molecule-1 (endocan) could be used as a marker of CV risk and activity of disease in Pso patients [69]. Its serum levels positively correlated with the Psoriasis Area and Severity Index (PASI), hsCRP and cIMT, suggesting a functional role in endothelium-dependent pathological disorders [70,71]. The neutrophil to lymphocyte ratio (NLR) is recognized as a cardiac inflammatory marker and is considered a predictor of all-cause mortality and CV events. [72]. Minakawa *et al*. demonstrated a significant positive correlation between PASI score and mean NLR level in Japanese Pso patients [73] The elevation of NLR in Pso patients could therefore, be considered as a useful low-cost indicator of increased CV risk. Mean platelet volume (MPV) is a marker of platelet function and activation, which is a determinant feature of atherosclerosis. Elevated MPV is associated with AMI, mortality following myocardial infarction, and restenosis following coronary angioplasty, thus representing a potentially useful prognostic biomarker in

patients with CVD [74]. Conversely, studies on the measurement of MPV in patients with Pso and PsA have shown conflicting results, with no consensus about its role as reliable indicator of disease activity [75,76].

External appearances can be predictive factors of internal abnormalities. Diagonal earlobe creases (ELC), oblique linear hollows between the anterior notch of auricle to the latero-inferior edge of the earlobe, can be a potent predictive factor of CV events [77]. Recently, a strong correlation between bilateral ELC and coronary artery calcification (CAC) was reported in psoriatic patients with high OR compared with negative or hemilateral ELC [78]. This element can be easily checked thus representing a potentially useful clinical marker for CV comorbidity in psoriatic patients.

Several studies demonstrated that echocardiography provided with speckle tracking analysis may be used as a marker for the screening of CV risk [79-81]. In particular a recent study showed a subclinical alteration of cardiac function in patients with mild psoriasis. In this study it was shown that patients with mild psoriasis, in the absence of other CV risk factors and without any pharmacological treatment, there were subclinical alterations of both cardiac function and of arterial stiffness [49].

Recent studies suggested that epicardial fat tissue (EFT) may play a significant role in the development of CV diseases through the secretion of several inflammatory adipocytokines with potential paracrine or endocrine mechanisms [82-84]. EFT, together with cIMT, were significantly increased in Pso patients compared with controls, reflecting subclinical atherosclerosis; moreover, EFT was closely correlated with cIMT in affected subjects. Psoriasis is also positively related to increased EFT volume, assessed by two-dimensional echocardiography on the parasternal long-axis independently of visceral abdominal fat, and to subclinical atherosclerosis [85]. Furthermore, in Pso patients, EFT volume was independently associated with CAC [86].

Elevated serum uric acid (SUA) levels have been associated with an increased CV risk as well as with several metabolic disorders such as MetS, NAFLD and type 2 diabetes [20,87-94]. Hyperuricemia has been also linked to the presence and severity of Pso as well as with PsA [95-98]. However, ethnic differences may exist in the associations between SUA levels and Pso.

Answer: There are certain serum biomarkers potentially enabling early selection of psoriatic patients at risk of future CV disease, whereas only earlobe creases might be useful as a clinical screening tool. Echocardiography provided with speckle tracking analysis is an easily accessible and effective imaging tools to investigate early signs of CV involvement.

QUESTION 5: CAN SYSTEMIC THERAPIES INFLUENCE THE CV RISK PROFILE IN PSO PATIENTS?

Pso patients, especially those with severe skin disease or PsA, often require systemic therapies with traditional and/or biologic drugs [99]. Such treatments may potentially impact on CV health, exerting positive or negative effects and precipitating subclinical CV involvement [100]. Moreover, antipsoriatic drugs may have an indirect effect on CV risk, acting on comorbidities such as MetS or its individual components [101]. On the other hand, early treatment of skin and/or joints could improve CV prognosis by reducing systemic inflammation [102]. A recent review of the literature reported that, among traditional Pso therapeutic options, phototherapy has no major CV effects and it may reduce the levels of proinflammatory cytokines [103]. Acitretin may increase serum lipids and triglycerides, whereas cyclosporine A is potentially more dangerous, increasing blood pressure, serum triglycerides and total cholesterol as well as promoting platelet activation [104-107]; methotrexate is associated with a decreased risk of CVD morbidity and mortality. Biologic therapies for the treatment of moderate-severe Pso include the TNF inhibitors (TNFi) infliximab, etanercept and adalimumab, the inhibitor of the p40 common subunit to IL-12 and IL-23, ustekinumab, and the inhibitors of IL-17A secukinumab and ixekizumab. No significant differences in the risk of MACEs was found in Pso patients exposed to the aforementioned biologic therapies compared with placebo over a short-period [108]. The efficacy of Pso-directed therapies on CV outcomes has been evaluated in a long-term follow-up of a nationwide cohort of patients with severe Pso [109]. At the end of the 5-years period, methotrexate was associated with a lower risk of the composite endpoint of CV death, AMI and stroke compared with patients treated with other therapies. In another study, over a 24-month median follow-up, every 6 months of cumulative exposure to TNFi was associated with an 11% CV event risk reduction ($p = 0.02$) [110]. In contrast, a recent meta-analysis reported a net clinical benefit of TNFi use in terms of adverse CV events in patients with Pso and/or PsA [111]. With regard to IL-12/23 and IL-17A inhibitors, there are limited data about their ability to influence the CV risk profile. The need to treat comorbid diseases determines increased intake of different kind of drugs such as beta-blockers, lithium, antimalarials, and non-steroidal anti-inflammatory agents potentially able to induce or worsen Pso. Long-term hypertensive status, requiring pharmacologic treatment, is associated with an increased risk of Pso [112]. The precise pathogenic mechanism is unknown. Beta-adrenergic receptors are expressed with remarkable densities on keratinocytes, coupling efficiently to the intracellular effector enzyme adenylate cyclase. Their blockage leads to a decrease in cellular levels of cyclic adenosine monophosphate (cAMP), with reduction in intracellular calcium and consequently increased cellular proliferation and epidermal cell turnover [113]. Other widely used medication, including thiazide diuretics, calcium-channel blockers, and ACE inhibitors, were not found to be associated with risk of psoriasis. On the other hand, drugs used for treatment of CV or metabolic diseases may exert positive effects on Pso. About statins, there is insufficient evidence that their use as an adjunctive therapy, even though well tolerated, can reduce the severity of Pso. A systematic review has recently highlighted the paucity of high quality, randomized, double-blind, placebo-controlled trials using clinically objective measures [114]. There is only 1 placebo-controlled, randomized control trial to date that has shown that they may be beneficial in reducing the severity of Pso [115]. A *post-hoc* analysis assessing patients from one primary cardiovascular prevention statin trial and 2 secondary cardiovascular prevention statin trials evidenced comparable lipid-lowering effects of statins in patients with and without Pso, with ex-

pected improvement of CV outcomes in patients with Pso [116].

Answer: Both traditional and biologic therapies show a safety profile with no significant increase of MACEs in Pso patients. Preliminary data seem to indicate that therapies may exert protective CV effects with reduction of long-term risk via the suppression of the inflammatory processes. Future randomized controlled trials will need to evaluate whether biologic therapies result in a significant reduction of CV diseases**.**

CONCLUSIONS

Increasing evidence suggests that cutaneous and CV disease are two faces of a prism, sharing predisposing factor and pathogenic mechanisms with metabolic, gastrointestinal, ocular and psychiatric morbidities linked by a common denominator represented by a systemic inflammatory state. There is a need for a multidisciplinary approach in Pso management. This will stratify the risk profile and predict the development of long-term extracutaneous disorders and tailor the best personalized management strategies. The goal is to take care of patients not only by providing the most effective and safe treatment for the skin disease but also to identify strategies for preventing or delaying CV damage and potentially minimize the disease burden.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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The thromboembolism in COVID-19: the unsolved problem.

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The thromboembolism in COVID-19: the unsolved problem.

Running title: Thromboembolism in COVID-19

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ABSTRACT:

INTRODUCTION: The recent Sars-Cov-2 pandemic (COVID-19) has led to growing research to explain the poor clinical prognosis in some patients.

EVIDENCE ACQUISITION: While early observational studies highlighted the role of the virus in lung failure, in a second moment thrombosis emerged as a possible explanation of the worse clinical course in some patients. Despite initial difficulties in management of such patients, the constant increase of literature in the field is to date clarifying some questions from clinicians. However, several other questions need answer.

EVIDENCE SYNTHESIS: A novel disease (Covid-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was responsible for thousands of hospitalizations for severe acute respiratory syndrome, with several cases of thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. Covid-19 and hospitalizations for Covid-19 may carry several potential risk factors for thrombosis. Severe coagulation abnormalities may occur in almost all of the severe and critical ill COVID-19 cases.

CONCLUSIONS: Despite a strong pathophysiological rationale, the evidences in literature are not enough to recommend an aggressive antithrombotic therapy in COVID-19. However, it is our opinion that an early use, even at home at the beginning of the disease, could improve the clinical course.

Key words: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Thromboembolism; Thrombosis, Low Molecular Weight Heparin.

TEXT

Introduction

Venous thromboembolism (VTE) in hospitalized patients with acute infectious disease is a well know condition which occurs with a moderate to high risk [1, 2, 3].When hospitalization for an infection is required, a VTE occurrence rate of 15.5% is estimated [4] and, in general, even without hospitalization, there is an increased VTE risk [5]. In subjects with pneumonia due to *S. Pneumoniae* or flu virus VTE occurrence was even higher [6,7]. Thromboprophylaxis in critically ill patients with acute infections is currently therefore recommended [8].

Late in December 2019, first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease in humans (COVID-19) were reported from Wuhan, China [9];

late on May 2020, more than 6 million cases and 369,000 deaths have been reported worldwide[10]. A novel disease (Covid-19) was responsible for thousands of hospitalizations for severe acute respiratory syndrome, with several cases of thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.

Cardiovascular and metabolic diseases, including hypertension and diabetes, have been associated with more severe presentations and/or adverse prognosis in Covid-19 *[11]*.

Covid-19 and hospitalizations for Covid-19 may carry several potential risk factors for thrombosis: activation of inflammatory cascade, immobilization, respiratory failure, mechanical ventilation and use of central venous catheters [12,13]. There is some evidence that anticoagulant therapy with low molecular weight heparins (LMWH) appears to be associated with a better prognosis in patients with COVID-19 [14]. When the clinical course of Covid-19 infection shows a sudden clinical deterioration, acute thromboembolism has recently been proposed as a central mechanism accounting for apparently unexpected clinical worsening [15] **(Tab. 1)**.

On the base of such observations, we sought to perform a systematic review on current evidence available on thrombotic and thrombo-embolic complications and anticoagulant therapy in primary and secondary prevention of thrombotic complications in case of Covid-19.

Methods

We performed a systematic research using Embase and PubMed, inserting the keywords and mesh terms relative to the new coronavirus and to VTE: 'COVID-19', 'SARS', 'MERS', 'coronavirus', '2019 n-CoV', venous thromboembolism', 'pulmonary embolism', 'deep vein thrombosis', 'thromboembolism', 'thrombosis'. Boolean operators 'AND', 'OR', 'NOT' were used where appropriate. We found 133 articles of interest but only 20 were selected, providing the most representative information. Inclusion criteria were: a) publication between January and May 2020, b) epidemiological relevance, and c) clinical impact. We excluded publications that: a) were not directly focused on thrombosis, b) were published early during the pandemic, and c) provided information overlap with larger studies or more recent articles. The use of a combination of the inclusion criteria provided the most recent information.

Evidence Acquisition

Thrombotic complications in Covid-19

Despite Covid-19 was initially identified as a predominantly respiratory disease, given the occurrence of severe clinical case of respiratory distress, there is increasing evidence of an association between Covid-19 and thromboembolism. [16, 17, 18]

Patients with cardiovascular disease and COVID-19 have worse clinical course among all other COVID-19 patients and this risk is probably linked to the increased thromboembolic risk [19].

Several cases of arterial [20,26] and venous thrombosis [27,32] on small and large vessels have been reported; Massive coronary thrombosis [33], coronary stent thrombosis [34], acute myocardial infarction with extensive thrombus burden and cardiogenic shock has been reported [35] and failed fibrinolytic therapy [36].

Unfortunately, many patients receiving antithrombotic therapy for thrombotic disease may develop COVID-19, this could influence the choice, dosing, and laboratory monitoring of antithrombotic therapy.

Thromboembolism in Covid-19

Cui et al. found in a retrospective study an incidence of 25% of thromboembolism in a small cohort of 81 patients with pneumonia due to Covid-19, increasing the amount of evidence about the role of thromboembolism [37]. However, severe coagulation abnormalities may occur in almost all of the severe and critical ill COVID-19 cases [38]. SARS-CoV-2 is associated with a high prevalence of coagulopathy with a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism [39].
The etiology of the procoagulant responses seems multifactorial and complex and it might be the result of specific interactions between host defense system and the coagulation system [39].

Giannis D et al highlighted the role of coagulopathy during this infection [40] and Kollias et al. [14…41] showed that in COVID-19 patients the disseminated intravascular coagulation may be linked to a pro-thrombotic state, with a major benefit deriving from anticoagulation.
In a case report by Casey et al. a segmental pulmonary thrombosis was found in a patient without other VTE risk factor, suggesting a major role of the pro-thrombotic state [42]. La Vignera et al. analyzed the possible role of other factors [43]. They started from early observations that the virus' spike protein favors the downregulation of angiotension converting enzyme (ACE2) leading to penetration in epithelial cells and in myocardium. According to the previous evidences of a possible role of Vitamin D in cardiac diseases [44], they hypothesized a possible involvement of the Vitamin D deficiency in the clinical course.

Markedly elevated levels of D-dimer with normal fibrinogen levels are the hallmark laboratory findings and correlate with severity of illness and risk of thrombosis[45]. In particular, in the initial phase of this infection, D-dimer and fibrinogen levels are increased, while activated partial prothrombin time, prothrombin time, and platelet counts are often relatively normal. In case of increased D-dimer levels three times the upper limit of normal may trigger screening for venous thromboembolism [39]. Increased D-dimer concentrations of more than 1.0 μg/ml predict the risk of venous thromboembolism [46].
According to these evidences we had reported a case report characterized by the different clinical course between husband and wife, at the same time diagnosed with COVID-19. Despite previous several cardiovascular diseases and ICD implantation, the wife had an excellent clinical course during hospitalization. Instead, her husband suffering only from arterial hypertension needed intubation. One significant difference has been found; the wife was already in treatment with Edoxaban because of paroxysmal atrial fibrillation. We believe that chronic anticoagulant use had possibly a protective role against the pro-thrombotic state in COVID-19.

The use and the efficacy of either parenteral or oral anticoagulant therapy is still controversial. Tang et al. early during the pandemic described a better clinical course for patients assuming anticoagulants [14]. They found that 28-day mortality of heparin users was lower in patients with sepsis-induced coagulopathy (SIC) score>4 or D-dimer > 3 ug/ml, raising the issue of possible benefit from anticoagulant therapy in Covid-19 patients. A case series by Wang et al. a better clinical course was associated to patients with ARDS by Covid-19 receiving tissue plasminogen activator [47].

In the last months, the use of LMWH has grown, especially for critically ill patients [48] and currently several trials are ongoing to test the best dose. However, should be remembered that even LMWH, as any other drug to date, is not infallible [49-53], so we believe that as many strategies are investigated and available the easier is finding a solution for each patient.
Concomitant VTE management, a potential cause of unexplained deaths, frequently reported in COVID-19 cases, is still challenging due to the complexity between antithrombotic therapy and coagulation disorders. [**38]**

In this way the most recent consensus statement by Zahi et al. provided an important and useful guidance for clinicians before the publication of guidelines [38]. They recommend that in COVID-19 patients "suspected for VTE", in the case that "relevant examinations fail to be conducted due to restricted conditions", LMWH should be started at a full curative dose if no otherwise contraindicated. Another important suggestion by these authors is the use of unfractionated heparin in critically ill patients with severe kidney failure with creatinine clearance rate <30 ml/min.

In all hospitalized patients, thromboprophylaxis using low-molecular-weight heparin is currently recommended. Furthermore, Julie Helms et al [18] demonstrated despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. So, they suggested, that higher anticoagulation targets than in usual critically ill patients should therefore probably be suggested.

The inflammatory host immune response

Severe cases of COVID-19, caused by the SARS-CoV-2, are frequently characterized by increased inflammation, thrombotic state, and intravascular coagulopathy with relevant interactions between the different systems [54]

In acute respiratory distress syndrome (ARDS), the increase in proinflammatory cytokines within the lung leads to recruitment of leukocytes, which may propagate the inflammatory response and so the deposition of fibrin in lung parenchyma is coming. These fibrin deposits are due to the dysregulation of the coagulation and fibrinolytic systems [55]

Tissue factor (TF) exposed on alveolar endothelial cells and on the leukocytes promoting fibrin deposition, while significantly elevated levels of plasminogen activator inhibitor 1 (PAI-1) creating a hypofibrinolytic state. [55]

The virus invades cells through the angiotensin-converting enzyme 2 receptor. However, COVID-19-associated tissue injury is not primarily mediated by viral infection, but rather is a result of the inflammatory host immune response, which may lead cytokine activaction and increased inflammation that affect lung parenchymal cells and endothelial cells, resulting in thrombotic events and intravascular coagulation [56]. The complement system, also known as complement cascade, is a part of the immune system that enhances

the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promoting inflammation, and attacking the pathogen's cell membrane. A crosstalk between complement and the coagulation system exists [57]. Preliminary data providing evidence of complement activation in patients with COVID-19 were reported [58]. It might be the first response of the host immune system to SARS-CoV-2 infection [56]; However, there is growing evidence that excessive activation of complement induced by SARS-CoV-2 in the lungs and other organs may play a pivot role in acute and chronic inflammation, endothelial dysfunction, thrombus formation and intravascular coagulation, and ultimately multiple organ failure and death.

Endothelial dysfunction

In healthy vessels, the endothelium releases the vasodilators and antithrombotic factors, nitric oxide. Whereas in injured vessels, nitric oxide is impaired contributing hypertension and thrombus formation. The "endothelial dysfunction" is a deterioration of endothelium-dependent vasodilatation; it also includes the abnormalities between endothelium and leukocytes, thrombocytes and regulatory molecules resulting in impaired endothelium function [59]. Its correct operation is essential for cardiovascular control. It plays an important role in pathogenesis of many cardiovascular diseases such as atherosclerosis, systemic and pulmonary hypertension, cardiomyopathies and vasculitides.

It is the final common pathway for diabetes/insulin resistance, hypertension, and dyslipidemia. All of these factors are effectively able to promote the original source of heart failure[60]. The inflammatory state, increased oxidative stress, altered nitric oxide bioavailability, and insulin resistance, are key factors of endothelial dysfunction [61,62]. Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. A hallmark of endothelial dysfunction and thrombotic events is suppressed endothelial nitric oxide synthase (eNOS) with concomitant nitric oxide deficiency [63]. The chronic impairment of systemic endothelial function in patients with cardiovascular and metabolic disorders may be aggravated by the adverse effects of SARS-CoV-2. In these patients, other negative influences over the endothelium are due to proinflammatory cytokines, which promote endothelial cellular apoptosis and lead to lung microvascular dysfunction, alveolar edema and hypoxia. Moreover, proinflammatory cytokines increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant and

proadhesive changes, worsening microvascular flow and, consequently, tissue perfusion [64].

Restoring nitric oxide, independent of eNOS, may contribute to pulmonary vasodilatation and may be a potential treatment for SARS-CoV-2. NO interferes with the interaction between coronavirus viral S-protein and its host receptor, ACE-2.

Evidence synthesis

A novel disease (Covid-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was responsible for thousands of hospitalizations for severe acute respiratory syndrome, with several cases of thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. Covid-19 and hospitalizations for Covid-19 may carry several potential risk factors for thrombosis. Severe coagulation abnormalities may occur in almost all of the severe and critical ill COVID-19 cases. According to all these evidences and to the experience of Rotzinger et al. [65] we believe that Chest CT should be performed in all the patients with COVID-19 for at least two reasons: a) subclinical course could be better outlined and b) in patients with severe course and high D-Dimer the CT pulmonary angiography is the most powerful tool to detect pulmonary embolism, providing proper anticoagulation.

There is increasing evidence of an association between Covid-19 and thromboembolism. In the last months, the use of LMWH has grown, especially for critically ill patients and currently several trials are ongoing to test the best dose. In COVID-19 patients “suspected for VTE”, in the case that “relevant examinations fail to be conducted due to restricted conditions”, LMWH should be started at a full curative dose if no otherwise contraindicated. The use of unfractionated heparin in critically ill patients with severe kidney failure with creatinine clearance rate <30 ml/min. In all hospitalized patients, thromboprophylaxis using low-molecular-weight heparin is currently recommended. Prophylaxis treatment of COVID-19 patients with LMWH is important to limit coagulopathy. However, to degrade pre-existing fibrin in the lung it is essential to promote local fibrinolysis.

D-dimer level-guided aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies.

Although angiotensin-converting enzyme 2 serves as the portal for infection [11] (Kevin Clerkin Circ 2020) no increased risk of in-hospital death was found to be associated with the use of ACE inhibitors or the use of ARBs [66]. The relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with Covid-19 admitted between December 20, 2019, and March 15, 2020 was evaluated using an observational database from 169 hospitals in Asia, Europe, and North America[66].

Conclusions

Despite a strong pathophysiological rationale, the evidences in literature are not enough to recommend an aggressive antithrombotic therapy in COVID-19. However, it is our opinion that an early use, even at home at the beginning of the disease, could improve the clinical course. Currently several questions need answer, in particular: a) the proper dose of LMWH for each patient (eg. anticoagulation vs thromboprophilaxis); b) the possible protective role of DOAC; c) how much impact has a massive use of Chest CT instead of Chest X-Ray; d) role of hormonal and metabolic factors. Probably answers to these questions will be soon available.

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Conflicts of interest.

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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TABLES

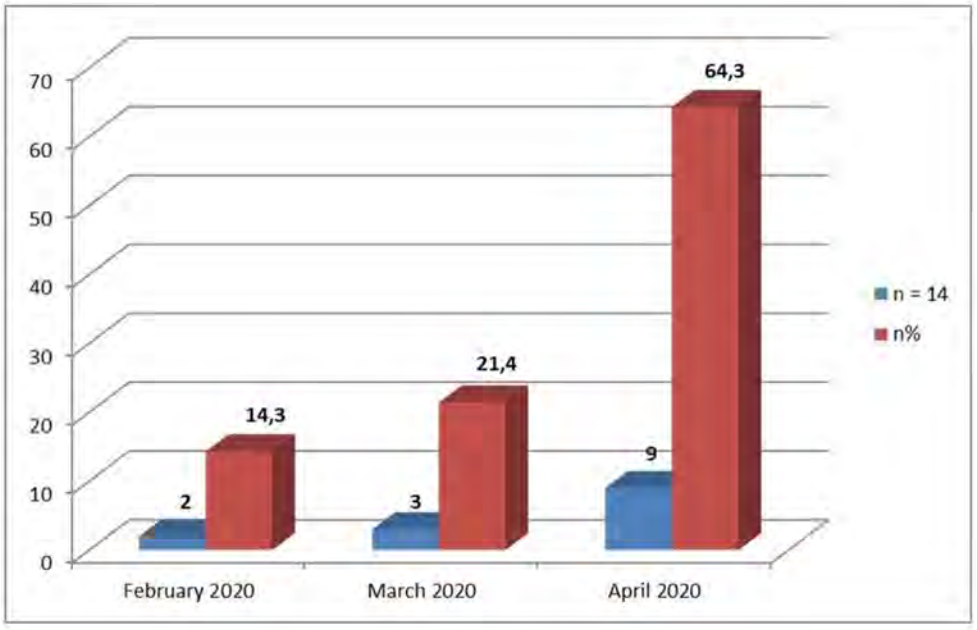
Table I.— **Tab.1. COVID-19 and thromboembolism: new insights**

POTENTIAL RISK FACTORS FOR THROMBOSIS	EVIDENCE OF PRO-THROMBOTIC STATE	THE INFLAMMATORY HOST IMMUNE RESPONSE	Endothelial dysfunction (ED)
Activation of inflammatory cascade	Concomitant pulmonary embolism	Cytokine activaction and increased inflammation affect lung parenchymal cells and endothelial cells	Covid-19 accelerates ED and nitric oxide deficiency
Immobilization	Anticoagulant therapy associated with a better prognosis	Proinflammatory cytokines increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant and proadhesive changes	A hallmark of ED and thrombotic events is suppressed endothelial nitric oxide synthase (eNOS) with concomitant nitric oxide (NO) deficiency
Respiratory failure	Better clinical course in patients receiving tissue plasminogen activator	Recruitment of leukocytes propagate the inflammatory response	NO is impaired contributing hypertension and thrombus formation
Mechanical ventilation	Presence of a segmental pulmonary thrombosis without other VTE risk factors	Proinflammatory cytokines promote endothelial apoptosis and lung microvascular dysfunction, alveolar edema and hypoxia	NO interferes with the interaction between coronavirus viral S-protein and its host receptor, ACE-2
Use of central venous catheters		Deposition of fibrin in lung parenchyma	SARS-CoV-2 Cell entry is blocked by a clinically proven protease inhibitor
		Complement activation in Covid-19	
		Excessive activation of complement may play a pivot role in inflammation, endothelial dysfunction, thrombus formation and intravascular coagulation.	

Table note: *VTE: Venous thromboembolism; ED:* Endothelial dysfunction; NO: nitric oxide eNOS: endothelial nitric oxide synthase**.**

TITLES OF FIGURES

Figure 1. Absolute and percentage literature contribution sorted by month. The major contribution was provided by articles published in April 2020.



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REVIEW

Infection, atherothrombosis and thromboembolism beyond the COVID-19 disease: what similar in physiopathology and researches

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Abstract

The recent Sars-Cov-2 pandemic (COVID-19) has led to growing research on the relationship between thromboembolism and Sars-Cov-2 infection. Nowadays, endothelial dysfunction, platelet activation, coagulation, and inflammatory host immune response are the subject of extensive researches in patients with COVID-19 disease. However, studies on the link between microorganisms or infections and thrombotic or thromboembolic events met fluctuating interest in the past. We, therefore, aimed to briefly summarize previous evidence on this topic, highlighting common points between previous data and what experienced today with SARS-COV2 infections.

Keywords Coronavirus disease 2019 (COVID-19) · Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Thromboembolism · Thrombosis

Introduction

Infections may increase the risk of cardiovascular events. Respiratory infections are associated with an increased risk of thrombotic vascular disease such as myocardial infarction, ischemic stroke and venous thrombosis [1]. Up to one-third of patients hospitalized with pneumococcal pneumonia may be affected by major adverse cardiac events during or after pneumonia [2]. An increased risk of cardiovascular mortality has been observed after pneumonia [3]. Apparently, for every infection type, an increased likelihood of venous thromboembolism (VTE) may be observed. In subjects with pneumonia, either due to *S. Pneumoniae* or influenza virus, VTE occurrence was even higher [4, 5]. Furthermore, lung infection is complicated by platelet aggregation [6] and clotting system activation (up-regulation of tissue factor and down-regulation of activated protein C) [3]. Thromboprophylaxis in critically ill patients with acute infections is recommended [7], mainly in the case of pulmonary infections.

The recent severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) pandemic, characterized in many cases by severe acute respiratory syndrome and thrombotic complications, has boosted research on the relationship between thromboembolism and Sars-CoV-2 infection.

We have already reported on thrombotic complications and thromboembolism in coronavirus disease-19 (COVID-19) [8], emphasizing the fundamental role of the endothelial dysfunction, platelet activation, clotting system and inflammatory host immune response. However, studies on the link between microorganisms or infections and thrombotic or thromboembolic events met fluctuating interest in the past (Table 1). We, therefore, aimed to briefly summarize previous evidence on this topic, highlighting common points between previous data and what experienced today with SARS-COV2 infections.

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Methods

We performed a systematic research using Embase and PubMed, using the keywords and mesh terms relative to the infection and thromboembolism or thrombotic complications. Boolean operators 'AND', 'OR', 'NOT' were used where appropriate. Inclusion criteria were: (a) publication between January 2000 and June 2020, (b) epidemiological relevance, and (c) clinical impact. We excluded publications that: (a) were not directly focused on thrombosis or thrombotic complications, (b) provided information overlap with larger studies or more recent articles. The use of a combination of the inclusion criteria provided the most recent information.

Infection and thromboembolism

Generally, infection and immobilization had an addictive effect on the thromboembolic risk, and this effect is present in COVID-19 patients, too. However, hospitalization with infection is a strong thromboembolic stimulus also in non-immobilized patients [9].

SARS-CoV-2 is frequently associated with coagulopathy with possible large vessel thrombosis and major thromboembolic complications, including pulmonary embolism [10]. Beyond the association between thromboembolism and COVID-19 disease [11–13], several etiologic agents have been correlated with thromboembolism. A higher incidence of venous thromboembolism (VTE) in patients with HIV infection has been described [14]. Interestingly, HIV patients may develop VTE and precapillary pulmonary hypertension (PH) [15]. HIV-PH is included in group 1 PH group classification and need a multidisciplinary approach [16]. Thrombotic complications in COVID-19 patients may also need a similar multidisciplinary approach (pneumologists, cardiologists, infectious disease specialists, intensivists). The physiopathology of PH is characterized by endothelial dysfunction. The endothelial function in patients with cardiovascular diseases may be hampered by the SARS-CoV-2 infection: inflammatory cytokines may increase the expression of adhesion molecules and further inflammation activation, resulting in procoagulant changes, endothelial activation and, finally, in worsening microvascular perfusion [17].

Restoring nitric oxide may contribute to pulmonary vasodilatation and may be a potential treatment for SARS-CoV-2. In patients with pulmonary arterial hypertension (PAH) (group 1 of the PH classification), progressive disease with thrombotic findings, characterized by increased pulmonary vascular pressure and right heart failure, specific pulmonary vasodilators are strongly recommended [18].

A special condition occurs in patients with HCV and cirrhosis of various etiologies, being at increased risk of several types of thromboembolic events. Porto-pulmonary hypertension (PoPH), a relatively common pulmonary vascular complication of advanced liver disease [19], is also included in the group 1 of the PH classification and need specific pulmonary vasodilators and a multidisciplinary approach.

Infection in atherothrombosis

Infection and products of the endogenous microbiome might modulate atherosclerosis and its complications, either directly or indirectly, by eliciting local and systemic

Table 1 Infections with thrombotic and throemboembolic complications and possible similarities to those of infection SARS-CoV-2

Infectious agent	Thrombotic or thromboembolic complications	Therapeutic possibilities
HIV infection	VTE Pulmonary hypertension Endothelial dysfunction Inflammation	Anticoagulants Pulm. vasodilatator Anti-inflammatory drugs
HCV infection	VTE Pulmonary hypertension	Anticoagulants Pulm. vasodilatator
Respiratory infections	Myocardial Infarction Ischemic stroke Venous thrombosis	Anticoagulants Thrombolysis Antiaggregants
Pneumococcal pneumonia	Major adverse cardiac events (total death, Myocardial infarction, ischemic stroke, HF hospitalization)	Antiaggregants
S. pneumoniae or flu pneumonia	VTE Atherosclerotic events	Anticoagulants Antiaggregants
Chlamydia pneumoniae	Coronary artery disease	Antibiotic therapy
Helicobacter pylori	Coronary artery disease	Antibiotic therapy
Mycoplasma pneumoniae	Coronary artery disease	Antibiotic therapy

HIV human immunodeficiency virus, *VTE* venous thromboembolism, *HCV* hepatitis C virus, *HF* heart failure, *Pulm* pulmonary, *S* streptococcus

responses. [20] Previous studies have identified markers of nucleic acid and antigens of viral and bacterial pathogens within atherosclerotic plaques, allowing to speculate that infection could play a role in precipitating atherosclerotic events. Furthermore, bacterial products can stimulate vascular inflammation [21, 22] and Gram-negative bacterial endotoxin may strongly elicit inflammatory responses from endothelial cells. Chronic infections, not in the vascular district, could provide a stimulus that contributes to inflammatory burden [23]. The body responses induced by the infection may precipitate complications of atherosclerosis or enhance their consequences because acute consequences of bacterial infections can increase myocardial oxygen requirements, decrease oxygen availability, promote clot formation, and impair the endogenous fibrinolytic system. In particular, during sepsis, tachycardia and fever can lead to a hyperkinetic state that increase oxygen demands and may predispose to acute coronary syndromes; in case of patients with coronary heart disease, the decreased oxygen supply due to hypoxemia can worsen myocardial ischemia.

Increased rates of cardiovascular events and thrombosis in patients with pneumonia have shown how respiratory infections can affect clinical outcomes [3]; previous observational and pathophysiologic evidence supports the association between recent respiratory infections [24–27] or influenza [28] and atherosclerotic events. It was also demonstrated that pneumonia may accelerate the progression of atherosclerosis [25]. A randomized open-label study showed that acetyl-salicylic acid may be beneficial in the reduction of acute coronary syndrome complications and cardiovascular mortality in patients with pneumonia [29]. Different viruses and bacteria may be associated with atherosclerotic diseases. Previous data support the hypothesis that a previous influenza virus infection may be associated with acute myocardial infarction [30, 31]. Chlamydia pneumoniae infection was considered a risk factor for atherosclerosis and coronary heart disease (CAD) [32] The level of Chlamydia pneumoniae and Helicobacter pylori-specific IgG antibodies have been found elevated in CAD patients; their presence has been associated with the development of the CAD and correlated to cholesterol levels. Chlamydia pneumoniae-specific IgG were significantly correlated with hsCRP, suggesting an important role of these organisms in the development of CAD by altering lipid profile and induction of inflammation [33]. Previous studies showed the presence of Chlamydia pneumoniae, chlamydial antigens or nucleic acid in atherosclerotic plaques [34]. None of the known risk factors for cardiovascular disease was significantly associated with Chlamydia pneumoniae seropositivity IgG [35]. Mycoplasma pneumonia patients exhibited a 37% increase in the risk of subsequently developing ACS [36].

However, trials with antibiotics did not reduce the recurrence of cardiovascular events. Treatment with macrolides such as azithromycin, or fluoroquinolones or gatifloxacin showed no reduction of cardiovascular events in the tested patients [37]. Vaccination also has not yet achieved the desired results in reducing cardiovascular events in [20].

Coronary thrombosis [38], coronary stent thrombosis [39], acute myocardial infarction [40] and failed fibrinolytic therapy [41] have been reported in COVID-19 patients. However, SARS-CoV-2 has not been identified in coronary plaque so far. Mechanisms linking SARS-CoV-2 to plaque instability can be hypothesized. Immune-mediated inflammation may play a key role in the pathogenesis of COVID-19 and persistent anti-viral immune response may elicit an important hyperinflammatory response (like a cytokine storm) causing cells damage. Other suspected factors are the hypercoagulability and the development of coronary microvascular thrombosis [42], the diffuse endothelial injury and 'endothelitis' as a direct consequence of SARS-CoV-2 viral involvement and/or resulting from host inflammatory response [43], and, the same inflammation causing coronary plaque rupture.

Despite a widespread use of broad-spectrum antibacterials in COVID-19 patients [44], in the absence of documented cases of bacterial coinfections, preliminary data show that early administered antibiotics in COVID-19 patients do not seem to significantly affect mortality or delay hospital-acquired infections in critically ill patients [45]. Instead, anti-inflammatory interventions such as anticytokine therapy and colchicine have shown some efficacy in CAD. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that reducing inflammation by administering an anti-IL-1 beta antibody in men and women who had a prior heart attack and residual inflammation despite standard-of-care therapy can reduce recurrent events [46, 47]. The anti-inflammatory therapy yielded a significant 15% reduction in the primary endpoint of "hard" major adverse cardiovascular events. Anticytokine therapy (IL-6 inhibitors, IL-1 inhibitors, anti-TNF-α agents, corticosteroids) and colchicine have been tested also for SARS-CoV-2 [48]. Further studies are needed to establish the efficacy of these drugs in COVID-19 patients.

According to Libby et al. [20], inflammation, immunity, and infection can contribute to atherogenesis or trigger atherosclerotic events without diminishing the role of classic risk factors; such factors should be rather considered as adjunctive to classic pathobiological processes than alternative (Fig. 1). COVID-19 patients are frequently characterized by increased inflammation, pro-thrombotic state, and coagulopathy with important interactions between these systems [49]. Also in COVID-19 infection, inflammation response and immunity can contribute to atherogenesis or trigger atherosclerotic events, making the pathobiological process very complex and perhaps causing variability in antithrombotic or anticoagulant therapy effect. Recently, growing interest in intestinal microflora in

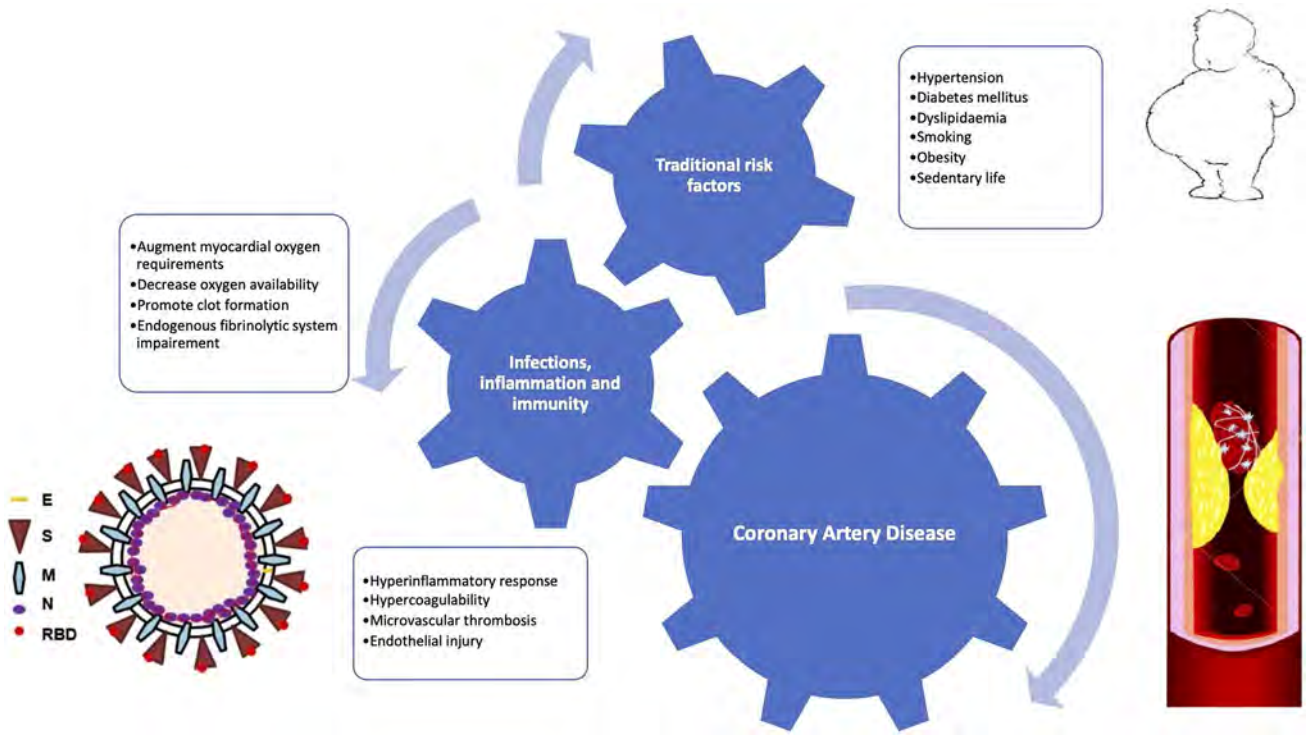

Fig. 1 Infection, inflammation and immunity contribute to atherogenesis without replacement of traditional risk factors. Infection, inflammation and immunity contribute to atherogenesis or trigger atherosclerotic events without diminishing the role of classic risk factors but they are an addition to the classic pathobiological process than a replacement of the specific agents

the cardiometabolic disease was reported [50, 51]. Bacteria in the gastrointestinal tract provides a rich source of bacterial products such as endotoxins. In cases of the impaired epithelial barrier, these bacterial products might convey into the circulation and provide another source of inflammatory stimuli. Gut microbiota is considered as an endocrine organ with metabolic capacity to produce multiple messengers that through circulation can reach distant districts. Recently, Carnevale et al. [52] hypothesized that, in particular, conditions (as in leaky gut), a penetration of LPS produced by Escherichia coli through the bloodstream into the coronary bed, where it may exert a thrombogenic effect, leading to the acute coronary syndrome.

Evidence synthesis

Infections are independent risk factors for venous thromboembolism and should be considered as potential indications for venous thromboembolism prophylaxis [53]. Microbial products, increased inflammation and pro-thrombotic state can promote the thromboembolism in several infections. While direct infection may not be a common driver of atherogenesis, remote infections and bacterial products from extra-vascular infections may promote atherosclerosis. Acute bacterial infections such as Gram-negative sepsis can precipitate type 2 acute coronary syndromes. Thrombotic complications due to increased inflammation, pro-thrombotic state, and endothelial dysfunction were detected in the novel disease (Covid-19) due to SARS-CoV-2 infection, responsible for the recent pandemic. Serious coagulation abnormalities may occur in several critically ill COVID-19 patients.

Conclusions

Infections may influence several diseases, either directly or indirectly, acutely or chronically. Pneumonia may accelerate the progression of atherosclerosis. In patients with pneumonia, increased rates in cardiovascular events and thrombosis have been demonstrated. A novel disease COVID-19 due to SARS-CoV-2 infection is characterized by coagulation abnormalities and inflammation with thrombotic and thromboembolism complications. Studies on the link between microorganisms or infections and thrombotic or thromboembolic events met fluctuating interest in the past. Looking back to what is known and what is currently discovered in SARS-CoV-2 infection, could be of help in the development of new therapies for the prevention of thrombotic complication in COVID-19.

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Compliance with ethical standards

Conflict of interest Authors have no potential conflict of interest to disclose.

Ethical standards The paper was written according to ethical standards principles.

Statement of human and animal rights This is a review paper. No human or animal experiments have been conducted.

Informed consent Not applicable.

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Letter to the Editor

Time-based clinical and functional achievements in real-life HF patients on ARNI treatment

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Six-min walk test

To the Editor

The prevalence of chronic heart failure (CHF) in the general population is gradually increasing mainly due to prolonged life expectancy of the general population and effective interventional and medical treatment of acute cardiac syndromes. Even though in-hospital survival has improved, the evolution towards CHF is documented approximately in 5% of patients with recent acute syndromes, rising up to 10% when considering elderly people [1–3].

Overall, 5-year survival has increased from 29% before to 59% after the year 2000, but the occurrence of CHF still carries a poor prognosis. After the era of Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), β-blockers and diuretics, recent therapeutic innovations were demonstrated to lead to excellent outcomes in HF patients. A new compound, initially named LCZ 696 (Sacubitril-Valsartan), was demonstrated to significantly ameliorate quality of life and symptoms in most patients [4,5]. Neprilysin is known as the enzyme responsible for inactivating atrial (A-type), brain (B-type) and cardiac (C-type) natriuretic peptides (NPs), all of them crucial pathophysiological frameworks in HF settings [4]. Neprilysin-inactivation by Sacubitril is an innovative treatment of NYHA class II-III patients with impaired systolic function, as from large multicenter trials and real-world studies [5–7]. However, inhibition is accompanied by persistent levels of Angiotensin II and the combination with Valsartan in the same drug is required in order to mitigate that drawback.

Therapeutic use of the ARNI improves daily routine activities, exertion tolerance and clinical prognosis in a high proportion of CHF patients, with trivial side-effects as titration is accurate. Also, left ventricular (LV) remodeling, systolic function and arrhythmic burden have been shown to ameliorate with therapy. As a consequence, clinical interest on the remarkable properties of NPs and Neprilysin-modulation has increasingly perceived in the last five years, at least in patients with reduced LV ejection fraction (rEF) [6–8].

Conversely, only little evidence is available on time-based achievements in clinical and functional markers after ARNI treatment or whether such effects continue indefinitely over time. In this regard, we studied 42 patients with HFrEF, fulfilling the same inclusion criteria as in the PARADIGM trial [5]. They were followed up to 14 months in a single-centre outpatient HF unit at University Hospital of Messina. In accordance with the nationwide healthcare system, patients had to be in treatment with an ACE-inhibitor or ARB for at least 12 weeks prior the start of ARNI therapy. Our study aimed at evaluating the time elapsed from optimal medical therapy plus ARNI implementation to clinical and functional improvements. Therapy was delivered on the basis of current European guidelines on CHF, and to avoid outcome interferences, device-assisted patients (implantable cardioverter defibrillator or cardiac resynchronization therapy plus defibrillator) were given Sacubitril-Valsartan at least 6 months after implantation. Clinical and functional check-up was scheduled at 3, 6 and 12 months. Quality of life by Kansas City Cardiomyopathy Questionnaire (KCCQ), 12-lead ECG, echocardiography, 6-minute walk distance (6MWD), and laboratory samples were performed in everyone. ACE–inhibitors or ARBs were stopped before starting with Sacubitril-Valsartan. Up-titration was established as the higher dosage was not contraindicated for symptoms, blood pressure values, hypopotassemia or impaired renal function. Laboratory testing included dosage of B-type NP (BNP) and N-Terminal proBNP (NT-proBNP), renal function and glomerular filtrate. Conventional echocardiography was regularly performed with particular care to left ventricular (LV) end-diastolic, end-systolic volumes, LVEF and myocardial global longitudinal strain (GLS) [9].

The patient population was 61.5 ± 11.0 (range 42–82) years of age, 32 were males (76%), with CHF from an ischemic etiology in 67%, 62% NYHA class II and 38% class III, and 22 (52%) had received an implantable defibrillator, in combination with cardiac resynchronization therapy in 3 cases. The median (IQR) follow-up length was 394 (245–429) days. The study confirmed important clinical and functional improvements in most patients, especially during the first 6 months of treatment. Ten patients moved from NYHA class III to class II, and 6 from class III to class I at 6-month follow-up. At the end of study, nobody was class III, 31 were class I (74%) and 11 class II (26%) ($p < 0.001$ vs baseline).

Cumulative changes in the main clinical and morphofunctional markers are displayed in Fig. 1. Step-by-step changes are also reported (oval-shaped boxes refer to Δ% changes from the last examination), as follows: NT-proBNP (Δ − 35%), KCCQ (Δ + 27%), GLS (Δ + 19%), NYHA class (Δ − 17%), and 6MWD (Δ + 11%) were the earliest (0 to 3

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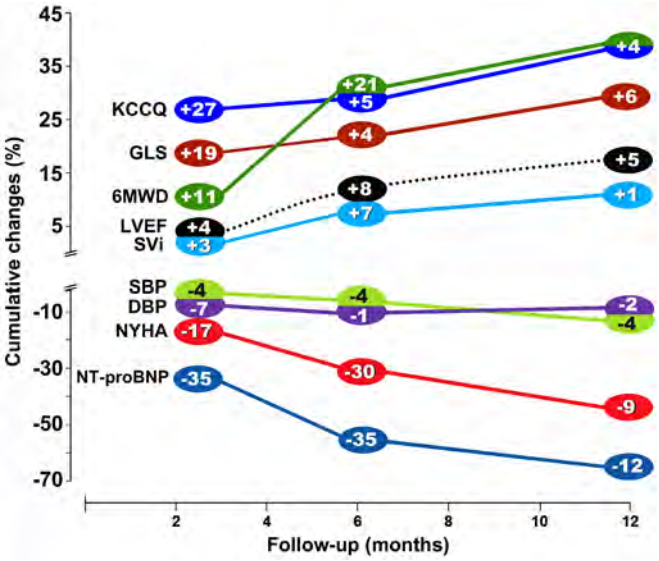

Fig. 1. Legend Cumulative changes in the main clinical, biochemical and morphofunctional markers on Sacubitril-Valsartan treatment in 42 patients with HFrEF. Oval-shaped boxes depict step-by-step percent changes during the follow-up.
Abbreviations: DBP, diastolic blood pressure; GLS, global longitudinal strain; KCCQ, Kansas City cardiomyopathy questionnaire; LVEF, left ventricular ejection fraction; 6MWD, 6-minute walk distance; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-BNP; SBP, systolic blood pressure; SVi, stroke volume index.

months) markers to improve, whereas only mild, though statistically significant, changes in LV volumes, EF, stroke volume and blood pressure were recognized all through the follow-up. NYHA class and 6MWD further improved afterwards (3–6 months), in accordance with a decrease in circulating NT-proBNP levels.

Over the second half of the study, additional advantages were smaller than those achieved in the first 6 months of therapy. Clinical condition stabilized and just a little amelioration was noticed on exercise tolerance and cardiac functional indices thereafter.

An averaged 10% decrease in blood pressure levels was encountered in the whole study population, and office systolic blood pressure <100 mmHg was the most important warning factor to go on a higher dosage of the ARNI. Renal function did not change significantly (e-GFR from 85.7 $\pm$ 25.2 at baseline to 81.9 $\pm$ 23.1 ml/min^{-1} at 12 months). BNP trend was unpredictable with no statistical differences at 12 months vs baseline.

Important findings indicate symptoms and exercise performance as the earliest markers to improve on treatment (<6 months), according to a decrease in NT-proBNP serum levels. On the contrary, LV reverse remodeling and function mildly and more gradually improved, with the exception of GLS, the sole clinical-linked ultrasound marker.

Our results are in agreement with recent studies demonstrating a very fast (30 days) enhancement in 6MWD [10] and peak oxygen consumption at 6-month cardiopulmonary exercise [8]. On the contrary, present findings did not confirm such a rapid LV reverse remodeling described elsewhere, being this effect more gradual over time. In our opinion, the risk for misinterpreting changes in LV volumes and EF as true treatment-related improvements, at least when <8 points %, should be broken out of the "physiological" inter- or intra-observer variability on quantitative assessment by ultrasound.

On the other hand, evidence for multi-tasking beneficial actions of Sacubitril/Valsartan in real-world CHF settings is relevant. Peripheral arteriolar compliance, cardiovascular stiffness, myocardial tissue relaxation, renal function and/or natriuretic effect and tissue fibrosis were proven to be inherent targets of ARNI treatment [5–8].

Among the largely used ultrasound markers in our and other studies, the GLS seems to be the most sensitive in the short-term period, reflecting an improved myocardial deformation as expression of the aforementioned mechanistic outcomes.

However, the precise timing of ARNI effects on the bio-humoral-endocrine imbalance still remains worthy to be elucidated. Present findings likely remark the lowering trend in NT-proBNP as a mirror of the clinical status and exercise tolerance, especially in the short and mid-term periods, in accordance with the important results of the PIONEER-HF trial. Safety and efficacy of Sacubitril–Valsartan was there demonstrated in patients with acute decompensated HF, and the NT-proBNP was one out the most useful biomarkers to check for clinical benefits [7].

In conclusion, in our single-centre experience, Sacubitril–Valsartan led to valuable short-term clinical and functional effects in HErEF patients, with quality of life upgraded after 6 months of continued therapy.

Long-term studies will surely improve current knowledge on such surprising ARNI effects on the neurohormonal system, which remains a primary target of cardiovascular research in CHF.

Declarations of Competing Interest

None.

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ORIGINAL RESEARCH ARTICLE

Effects of Sacubitril/Valsartan in Patients with High Arrhythmic Risk and an ICD: A Longitudinal Study

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Abstract

Purpose Patients affected by heart failure with reduced ejection fraction (HFrEF) receive clinical and functional beneficial effects from treatment with sacubitril/valsartan. However previous studies have shown that patients with an implantable cardioverter defibrillator (ICD) could obtain even greater benefit, but only make up a only a small proportion of patients. In the current study we evaluated the effect of sacubitril/valsartan in patients with an ICD.

Methods Thirty-five outpatients with HFrEF (aged 60 ± 11 years, 28 were males), on optimal medical therapy were studied. All patients received an ICD at least 6 months before enrollment or were non-responders to ICD plus resynchronization (CRT-D). An open-label sacubitril/valsartan treatment was established at the maximum tolerated dose. Clinical assessment, 6-min walk test (6MWT) and echocardiography, were performed during follow-up at 90, 180, and 360 days. Quality of life score and perceived fatigue on exercise were assessed.

Results Clinical conditions dramatically improved in most patients, especially within the first 6 months of therapy (76 % were in NYHA-I and 24 % in NYHA-II at the end of study vs 71 % NYHA-II and 29 % NYHA III at enrollment, $p < 0.001$). Quality of life and exercise performance significantly improved according to N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels lowering. Walking distance at 6MWT increased from 274 ± 97 to 389 ± 53 m and walking speed from 0.74 ± 0.27 to 1.07 ± 0.15 m/s ($p < 0.001$), while oxygen saturation did not differ significantly (from 90 ± 1 % to 91 ± 2 %). More gradual was left ventricular reverse remodeling. Ejection fraction improved mildly (+ 5 points %, $p < 0.001$). Global longitudinal strain and diastolic function were also assessed over time.

Conclusion Sacubitril/valsartan therapy for HFrEF may lead to significant clinical and functional improvements even in patients with ICD at greater arrhythmic risk. Clinical improvement is obtained within the first 6 months of treatment while reverse remodeling needs more time.

Key Points

This study investigated the effectiveness of sacubitril/valsartan treatment in HFrEF patients with an ICD or CRT-D.

The study results show clinical and functional improvements in selected patients with HFrEF and ICD or CRT-D, especially within the first 6 months of treatment.

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1 Introduction

Prevalence of heart failure (HF) is about 2% in adults and rises to 10% in elderly patients aged over 70 years. HF, in particular with reduced ejection fraction (HFrEF), leads to reduced functional capability, increased risk of comorbidity and sudden cardiac death [1–4]. Despite use of appropriate evidence-based therapy, risk of clinical worsening remains high in most patients [1, 3, 4]. Availability of novel drugs might affect the modern interplay between pharmacological and device therapy in HFrEF [5]. Multicenter studies on sacubitril/valsartan therapy demonstrated significant clinical improvements in patients with HFrEF in NYHA class II and III. However, patients with an implantable cardioverter defibrillator (ICD), which could obtain the greater benefit made up only a small proportion [6–8]. In this study we evaluated the effects of 1-year sacubitril/valsartan treatment on clinical status, exercise tolerance, left ventricular (LV) remodeling and function, in HFrEF patients with high arrhythmic risk and ICD.

2 Methods

2.1 Study Design

From December 2017 to October 2018 we enrolled patients affected by HF from any etiology, fulfilling the PARADIGM criteria [6]. In particular, they were in New York Heart Association (NYHA) functional class II or III, with left-ventricular ejection fraction (LVEF) $\leq$ 35 %. All patients received an ICD at least 6 months before admission [1 year before patients with a biventricular ICD (CRT-D)]. Ineligibility was established for patients in NYHA class IV, refractory HF, glomerular filtration rate < 30 mL/min/1.73 m^2, severe hepatic dysfunction, hypotension, permanent atrial fibrillation, history of angioedema, hospitalization within the last 3 months due to hemodynamic decompensation, acute coronary syndrome, or surgery.

An open-label sacubitril/valsartan treatment was established at the maximum tolerated dose (starting from 24/26 mg up to 97/103 mg twice a day, the up-titration occurred after a 4-week time interval). Optimal medical therapy, including beta-blockers, diuretics and mineralocorticoid receptor antagonists were administered with proper adjustments during the sacubitril/valsartan up-titration and every 3 months on follow-up. Clinical assessment and quality of life (QOL) evaluation, 12-lead ECG, transthoracic echocardiography, 6-min walk test (6MWT), ICD check and laboratory samples were performed for each patient. The study protocol was approved by the local advisory board (AOU Policlinico G Martino, Messina, Italy). All patients gave written informed consent, according to the Declaration of Helsinki.

2.2 Clinical Evaluation and KCCQ Score Quality of Life

Symptoms and signs of chronic HF (dyspnea, asthenia, chest pain, pulmonary rales, and peripheral edema) were regularly evaluated in each patient during follow-up. Because the Kansas City Cardiomyopathy Questionnaire (KCCQ) is considered the most reliable self-administered and disease-specific instrument for QOL estimation in HF patients, especially in presence of cardiac device, we administered a 23-item questionnaire to each patient every 3 months. As in the PARADIGM trial, patients were requested to give answers on physical function, symptoms, social function and QOL domains. Answers were transformed to a 0–100 points score, in which higher values reflect a better status [6, 9].

2.3 Echocardiography

An ultrasound system was used for echocardiography studies. Experienced operators were asked to measure M-mode, two-dimensional Doppler, and strain-derived parameters, blinded to previous findings from the same patient. Studies were stored in a Digital Imaging and Communications in Medicine (DICOM) format and then analyzed offline. The investigators performing echocardiographic measurements were also blinded for treatment. Conventional measurements were performed for each patient, in particular LV end-diastolic volumes, end-systolic volumes and LVEF that were calculated by the modified biplane Simpson method. Global longitudinal strain (GLS) was also assessed by automated multipoint speckle mapping, manually adjusted to achieve the best curve from the 4-, 3- and 2-chamber apical views [10–14]. Longitudinal strain values are negative numbers. To avoid misinterpretation, GLS measures are showed as positive numbers (−%) in tables and graphics.

2.4 Six-min Walking Test (6MWT)

All patients were assessed by a 6MWT on enrollment and every 3 months during the follow-up. Testing was performed indoors, along a flat straight corridor. The walking course was 30 m in length, with turnaround points clearly marked with safe markers. Patients were asked to walk as fast as possible, resting if necessary. Heart rate, oxygen saturation and symptoms were monitored during the walk [15, 16]. The category-ratio (CR) 100-point scaling (in which 0 % represented no symptoms, 50 % heavy/strong and 100 % extremely strong exercise) was used in order to assess changes over time in effort capability during the test [17]. Absolute (6MWD) and predicted walking distance (p6MWD), as well as walking speed were calculated. Predicted 6MWD was computed considering the

most important limiting individual characteristics (weight, height, and age), as follows [18]:

[(7.57×height in cm) − (5.02×age) − (1.76×weight in kg) − 309 m] for men.

[(2.11×height in cm) − (2.29×weight in kg) − (5.78×age) + 667 m] for women.

2.5 Laboratory Testing

Blood sample tests were collected from each patient on a regular basis. B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured with Elisa method. The values < 35 pg/mL for BNP and < 125 pg/mL for NT-proBNP were considered as the normal limit [19]. Renal function with the estimated glomerular filtration rate (e-GFR, mL/min/1.73) and electrolytes were all monitored.

3 Statistical Analyses

Statistical analyses were performed by SPSS for Windows (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as numbers and percentages (%). Continuous variables were compared with the Student paired *T*-test or Mann–Whitney *U*-test when appropriate. Categorical data were analyzed with Pearson's or Fisher's exact test when appropriate, according to the normality of the clinical variables. Clinical and instrumental indices as well as laboratory samples were compared from baseline to 3-, 6-, and 12-month values from the angiotensin receptor-neprilysin inhibitor (ARNI) starting dose. The null hypothesis was rejected at two-tails for $p < 0.05$ [95 % confidence interval (CI)].

Table 1 Demographic and clinical characteristics of study population ($n = 35$)

Mean age, years	60.2 ± 11.0
Males, *n* (%)	28 (80)
Body surface area, m^2	1.92 ± 0.17
BMI, kg/m^2	26.1 ± 2.8
Systolic BP, mm Hg	129.5 ± 12.5
Diastolic BP, mm Hg	70.2 ± 8.4
Etiology and risk factors	
Ischemic heart disease, *n* (%)	25 (71.4)
Non-ischemic etiology, *n* (%)	10 (28.6)
Primary dilated cardiomyopathy, *n* (%)	5 (14.3)
Hypertensive heart disease, *n* (%)	2 (5.7)
Previous myocarditis, *n* (%)	3 (8.6)
Hypercholesterolemia, *n* (%)	17 (48.6)
Overweight (BMI > 28 g/m^2), *n* (%)	8 (22.8)
Smoking attitude, *n* (%)	8 (22.8)
Average NYHA functional class	2.3 ± 0.5
ICD/CRT-D, *n* (%)	28 / 7
Laboratory samples	
Serum creatinine, mg/dL	1.00 ± 0.13
e-GFR, mL/min/1.73 m^2	87.3 ± 17.7
B-type BNP, pg/mL	140.1 ± 72.62
NT-proBNP, pg/mL	1442.4 ± 1262.3
Therapy	
Diuretics, *n* (%)	35 (100)
Beta-blockers, *n* (%)	30 (85.7)
Antiplatelet drugs, *n* (%)	27 (77.1)
Mineralocorticoid antagonist, *n* (%)	32 (91.4)
Statins, *n* (%)	28 (80)
Other drugs, *n* (%)	10 (28.6)

BMI body mass index, *BNP* B-type natriuretic peptide, *BP* blood pressure, *CRT-D* biventricular ICD, *dL* deciliters, *e-GFR* estimated glomerular filtration rate, *ICD* implantable cardioverter defibrillator, *mL* milliliters, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association functional class

4 Results

4.1 Baseline Characteristics

The initial study cohort consisted of 41 patients, but 3 patients (7.3 %) were excluded because of starting-dose drug intolerance and 3 were lost to follow-up. The final study cohort included 35 patients (mean age 60.2 ± 11.0—range 42–83 years; 28 were males—80 %). Demographic and clinical characteristics are reported in Table 1.

An ischemic etiology was established in 25 cases (71 %). Twenty-eight patients (80 %) received an ICD and 7 (20 %) a biventricular ICD (CRT-D). At the beginning of the study 25 patients (71 %) were NYHA class II and 10 (29 %) were class III. Optimal medical treatment included angiotensin-converting enzyme (ACE) inhibitors or ARB in all patients within the 3–6 months prior to enrollment. At the end of study, 27 patients were taking the intermediate ARNI dose (49/51 mg) and 8 the highest dose (93/103 mg) twice a day.

4.2 Clinical Outcomes, Natriuretic Peptides and KCCQ

The median follow-up time was 356 (IQR 285–367) days. Improvement in clinical status was observed in almost all patients (Fig. 1, Table 2), with an average increase of at least one NYHA functional class. At the end of follow-up no patient was in NYHA class III. No acute decompensation or critical events occurred during the study, except for one case

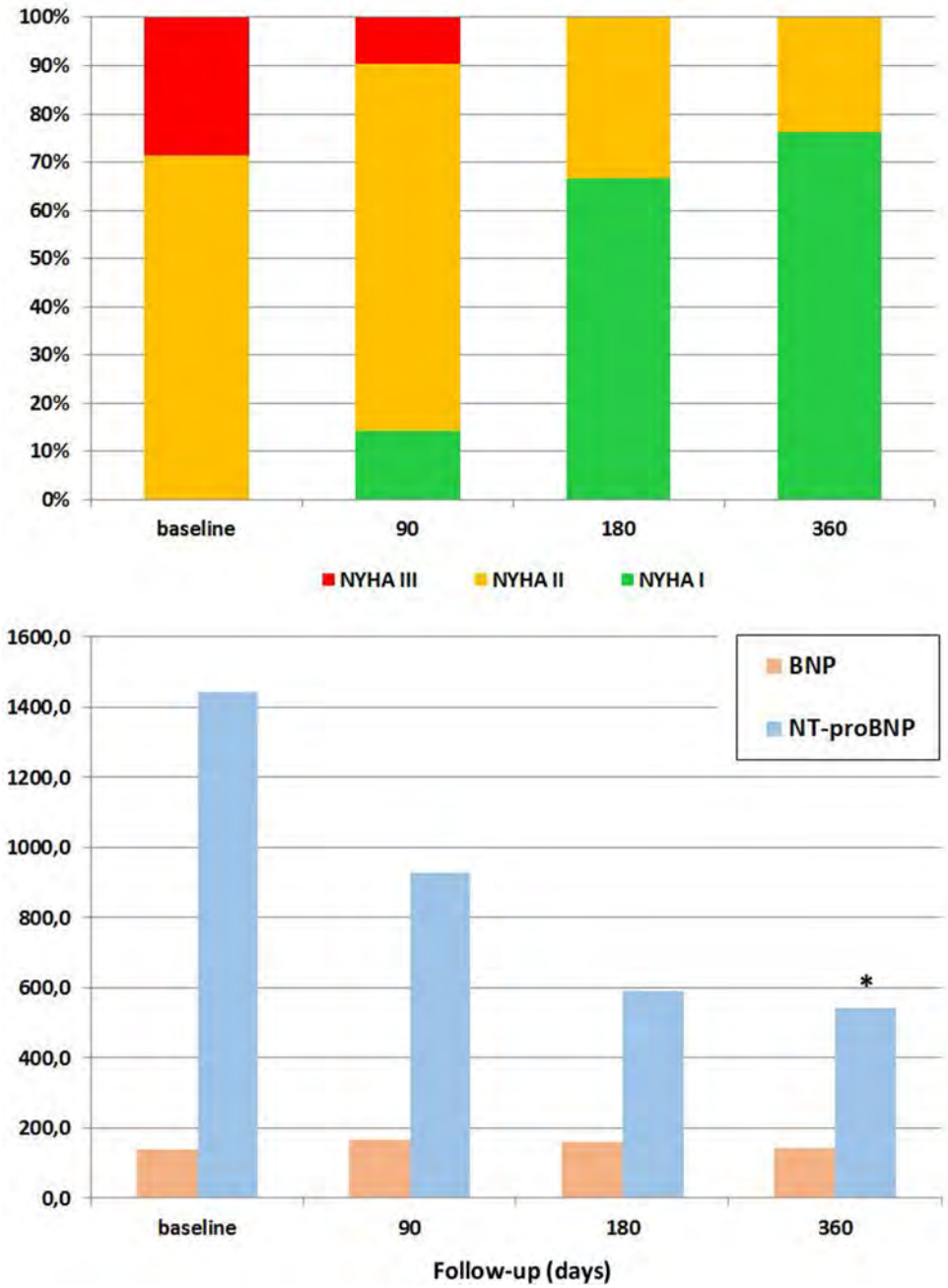

Fig. 1 An improvement in clinical symptoms was observed in almost all the patients with an average improvement of at least one NYHA functional class. At the end of follow-up nobody was in NYHA class III (upper panel). NT-proBNP rapidly decreased within the first 180 days of treatment, whereas BNP mildly increased (bottom panel)

of paroxysmal atrial fibrillation, treated with amiodarone. No relevant ventricular arrhythmias were recorded. A quick clinical amelioration was claimed by all patients, with substantial stability after 6 months and in particular no patient remained in NYHA class III. Sixteen patients, initially in NYHA class II, were reclassified in class I at between 6 and 12 months ($p < 0.001$). Subjective wellness perception and QOL gradually ameliorated with therapy in approximately 85 % of cases. No relevant drug-related side effects or ECG changes were recorded during the study. As expected, a decrease in both systolic and diastolic blood pressure was observed in most patients. This was the most relevant restriction for up-titration of sacubitril/valsartan, and patients with systolic blood pressure < 100 mmHg could not receive a higher dose. No relevant changes to other drug dosages were necessary, except for diuretics, which required a dose reduction in 85 % of patients. Renal function and the e-GFR were stable over time. NT-proBNP rapidly decreased within the first 180 days of treatment, whereas BNP mildly increased (Table 2, Fig. 1).

4.3 Exercise Tolerance

Both absolute and predicted 6MWD, as well as walking speed, improved in most patients from baseline to 180 days

Table 2 Changes in clinical and functional indices on treatment

Timeline (days)	Baseline	90	180	360
Clinical findings and quality of life				
Average NYHA class	2.29 ± 0.27	1.95 ± 0.27	1.33 ± 0.27*	1.24 ± 0.27*
NYHA class I, *n* (%)	–	5 (14.3%)	23 (65.7%)†	27 (74.1%)†
NYHA class II, *n* (%)	25 (71.4%)	26 (74.3%)	12 (34.3%)†	8 (25.9%)†
NYHA class III, *n* (%)	10 (28.6%)	4 (11.4%)$^{\#}$	–	–
Heart rate, bpm	60 ± 5	62 ± 8	62 ± 6	60 ± 6
Systolic BP, mm Hg	129.5 ± 12.5	120.7 ± 12.7$^{\#}$	117.1 ± 12.2†	110.7 ± 7.8†
Diastolic BP, mm Hg	70.2 ± 8.4	66.4 ± 7.4*	68.1 ± 6.6	65.2 ± 5.6
KCCQ score	49.2	64.8†	68.6†	72.0†
Laboratory samples				
e-GFR, mL/min/1.73 m^2	87.3 ± 17.74	84.9 ± 27.6	86.4 ± 18.3	86.1 ± 15.8
NT-proBNP, pg/mL	1442.4 ± 1262.3	927.0 ± 783.6†	589.1 ± 394.5†	541.3 ± 325.0†
BNP, pg/mL	137.2 ± 72.0	161.3 ± 68.5†	156.3 ± 55.8$^{\#}$	139.0 ± 58.7
Exercise changes				
6MW distance, m	274.1 ± 97.0	312.8 ± 97.8$^{\#}$	371.5 ± 57.5†	389.0 ± 52.6†
Predicted 6MW distance, %	49.4 ± 18.3	56.7 ± 19.4$^{\#}$	67.4 ± 14.0†	70.7 ± 13.9†
6MW speed, m/s	0.74 ± 0.27	0.85 ± 0.27$^{\#}$	1.02 ± 0.16†	1.07 ± 0.15†
6MW > 350 m, %	23.8%	38.1%	71.4%†	71.4%†
Category-ratio 100, %	80 ± 12	54 ± 13$^{\#}$	33 ± 18$^{\#}$	32 ± 21$^{\#}$
Left ventricular remodeling and function by echocardiography				
End-diastolic volume, mL	181.8 ± 23.1	177.9 ± 22.3	174.9 ± 18.3*	163.3 ± 19.6†
End-systolic volume, mL	132.3 ± 19.7	127.1 ± 18.9$^{\#}$	120.8 ± 16.5†	110.0 ± 15.4†
Ejection fraction	0.27 ± 0.04	0.29 ± 0.04*	0.31 ± 0.05$^{\#}$	0.33 ± 0.04†
Stroke volume, mL	49.5 ± 9.2	50.8 ± 8.5	54.0 ± 8.1$^{\#}$	53.3 ± 8.7$^{\#}$
E/E' ratio	13.8 ± 1.57	13.0 ± 1.56$^{\#}$	12.3 ±1.71†	12.0 ± 1.45†
GLS, %	9.5 ± 1.5	11.4 ± 2.3$^{\#}$	11.7 ± 1.7†	12.4 ± 1.7†

6MW 6-minute walk, *BNP* B-type natriuretic peptide, *BP* blood pressure, *bpm*, beats per minute, *CR* category-ratio point scaling, *E/E'* mitral inflow *E*/tissue *E* velocity ratio, *e-GFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *KCCQ* Kansas City cardiomyopathy questionnaire, *m* meters, *mL* milliliters, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association

p values vs baseline *< 0.05; $^{\#}\leq$ 0.01; $^{\dagger}\leq$ 0.001

but further advantage was less pronounced in the second half of follow-up. Figure 2 depicts all relevant clinical and functional changes in the study population, according to NT-proBNP serum levels. Twenty-five patients (71 %) were able to walk >350 m after 180 days, compared to 8 (24 %) at baseline, and 13 (38 %) at 90 days ($p < 0.001$). Blood pressure did not significantly change during the walking test. The CR100 point scaling significantly ameliorated within the first 6 months and stabilized thereafter. There were no significant changes in oxygen saturation (from 90 ± 1 % to 91 ± 2 %).

4.4 Cardiac Remodeling and Function

A trend towards a reduction in LV volumes was observed in all study population and this implied a weak, but statistically significant, improvement in LVEF and stroke volumes (Table 2, Fig. 3). Cardiac positive remodeling was gradually achieved over time, with better global diastolic function (E/E' ratio) and with GLS, which improved by 2.9 %.

5 Discussion

The current study shows that 1-year sacubitril/valsartan implementation yielded noteworthy advantages in patients with ICD. Clinical benefit was recognized in terms of daily routine activities as well as subjective perception. These findings are consistent with improved exercise tolerance in most patients, mainly during the first 6 months of therapy. LV remodeling and function improved more gradually over time. Overall current findings are in agreement with the demonstrated effectiveness of sacubitril/valsartan by important studies such as PARADIGM-HF and its post hoc analyses, PARALLEL-HF and the PIONEER trials [6–8, 20, 21]. However, in these studies the prevalence

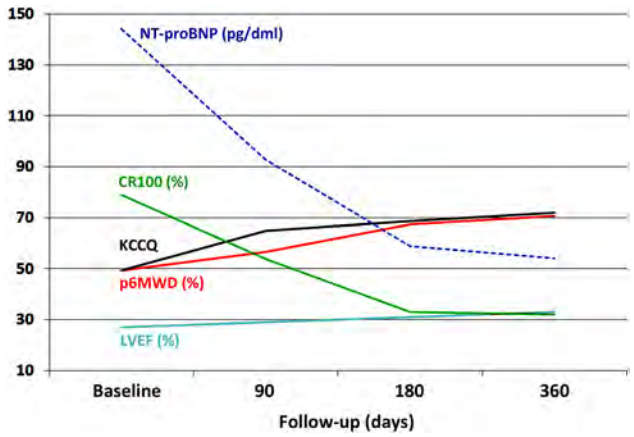

Fig. 2 (Blue line) NT-proBNP rapidly decreased within the first 180 days of treatment; (green line) the CR100 point scaling significantly ameliorated within the first 6 months, and stabilized thereafter; (Black line) Subjective wellness perception and QOL gradually ameliorated with therapy approximately in 85 % of cases; (red line) Predicted 6MWD markedly improved in most patients from baseline to 180 days, but further improvement was less pronounced in the second half of follow-up. (Light blue line) A weak, but statistically significant improvement in LVEF, was observed during follow-up

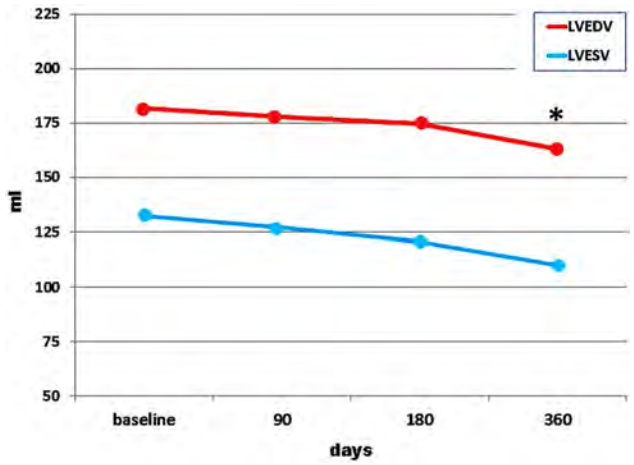

Fig. 3 A trend towards a reduction in LV volumes (LVEDV and LVESV) was observed in the entire study population

of ICD patients was rather low, despite that these patients had severely impaired LVEF and were likely to obtain the best benefit. Only 14.8 % patients in the PARADIGM-HF trial [6] received an ICD and ≤ 7 % received a CRT-D, which is in contrast to approximately 12 % in the Japanese PARALLEL-HF population [6]. Furthermore, recent ICD implantation was an exclusion criterion in the PIONEER trial [21]; whereas only Moliner-Abós at al [22] included > 50 % ICD/CRT-D patients. To the best of our knowledge this is the first study evaluating specifically ICD patients in optimal medical therapy, and the first study to assess the subjective status by KCCQ. While the majority of our patients received an ICD at least six months before, 7 patients received a CRT-D 1 year before, being classified as non-responders. All subjects were assuming an individually up-titrated therapy from at least three months. Between three patients not assuming MRA, two had hyperkalemia and one refused to receive the drug because of gynecomastia. According to our data, a mechanistic action of sacubitril-valsartan as assumed by other authors [23, 24], could also apply in ICD patients.

LV remodeling, stroke volume, ejection fraction and longitudinal deformation gradually improved in our study population, but less quickly than clinical advantage. Furthermore, a propensity to a functional steady state after 180 days of treatment was observed, suggesting a maintenance of achieved outcomes. However, such a trend could indicate a pleiotropic impact of the ARNI treatment on the endocrine asset with potential counter-modulation after the initial period. Our patients experienced a noteworthy relief of symptoms during treatment, as confirmed by exercise tolerance, CR100 and KCCQ. Our subjects showed a functional stability in the second half of the follow-up, as in other real-world studies [22] and in a secondary analysis of the PARADIGM trial [25].

Clinical effect of ARNI treatment could also be linked to reverse LV remodeling and improved systolic and diastolic function [8, 14, 22, 26–29]. LVEF increased from 5 to 6 % in our sample, as in previous studies [29]. Improvements in GLS may be less operator-dependent and suggestive of true myocardial functional reverse remodeling during treatment [10–14, 30, 31]. Myocardial deformation could be directly influenced by neprilysin inhibition or just as consequence of hemodynamic changes in this clinical setting. Januzzi et al. [28] demonstrated an inverse relationship between LV volume changes and NT-proBNP serum levels, as in our population. On the other hand, beta-endorphin increase could also be a novel potential mechanism of ARNI-related early improvements in exercise and clinical tolerance, irrespective of LV function, at least in experimental models [32]. Of note, the best effectiveness of ARNI was observed within the first 180 days, in agreement with other real-life studies [22, 24, 29, 30]. Blood pressure values were the most important restriction for up-titrating drug dosages, and this may limit further clinical improvement in these patients. Of note, 2 patients (9 %) only were excluded due to drug intolerance, which is a good marker of tolerability. Accordingly, 24 % of our patients tolerated the highest sacubitril-valsartan dosage. Hyposthenia, dizziness, and fatigue were the most frequently reported side effects. While treatment of high-risk arrhythmic conditions is evolving by new technologies [33], there is increasing evidence that ARNI may play a role in this subset of patients [34].

5.1 Study Limitations

Numerical consistency, lack of randomization and case-control comparison are the most important limitations in the current study. Randomized case-control trials remain the gold standard to determine incremental effect of innovative versus standard therapy. However, longitudinal paired analyses are also accepted to assess relevant changes in the functional status and cardiac performance, especially in observational studies [35].

6 Conclusions

Sacubitril/valsartan therapy for HFrEF may lead to significant clinical and functional improvements, even in patients with ICD at greater arrhythmic risk. One-year treatment dramatically improved clinical symptoms, subjective wellness perception and exercise tolerance, according to decreased NT-proBNP serum levels, especially within the first 6 months of treatment. While clinical improvement is obtained within the first 6 months, a true reverse remodeling and an increase in systolic performance are gradually observed over time. We believe that treatment of high-risk arrhythmic conditions is rapidly evolving: the interplay between technology and drug therapy may allow the most effective results.

Compliance with Ethical Standards

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Conflict of interest The authors declare no conflict of interest.

Author contributions Conceptualization, GD and CG; methodology, GD and CG; formal analysis, MC and GD; investigation, GL, VV, CM; data curation, MC and MC; writing—original draft preparation, MC and MC; writing—review and editing, MC and MC; visualization, SSS, FL and NK; supervision, FL; project administration, GD and CG. All authors have read and agreed to the published version of the manuscript.

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Trend of perceived quality of life and functional capacity in outpatients with chronic heart failure and in treatment with sacubitril/valsartan: a real-life experience.

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Trend of perceived quality of life and functional capacity in outpatients with chronic heart failure and in treatment with sacubitril/valsartan: a real-life experience.

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BACKGROUND: Despite the use of optimal medical therapy, HFrEF remains a leading cause of morbidity, mortality and health care costs. The introduction of angiotensin receptor/neprilysin inhibitors (ARNIs) had a revolutionary impact on the treatment of patients with heart failure and reduced left ventricular ejection fraction (HFrEF).

METHODS: The aim of the study was to monitor over time the perceived quality of life, the physical performance, the trend of BNP and NT-ProBNP and the NYHA functional class in patients with HFrEF during treatment with sacubitril/valsartan. We enrolled 37 patients (63 ± 10 years old, 76% men) who underwent a total of one year follow-up. All patients underwent clinical evaluation, 6MWT, blood analysis (in particular NT-pro-BNP and BNP, renal function test); Kansas City Cardiomyopathy Questionnaire (KCCQ) and the NYHA functional class assessment were also performed, at the beginning of the study and after 3, 6 and 12 months of therapy.

RESULTS: We observed at each follow-up a significant improvement of KCCQ score, 6MWT, NT-ProBNP, BNP and ~~of~~ NYHA class. However, analyzing the Δ % of variation of each single parameter, the improvement was not uniform in time. We also observed that only 37% of patients tolerated the full recommended dose of sacubitril/valsartan (97/103 mg b.i.d.); of the remaining, 40% tolerated the intermediate dose (49/51 mg b.i.d.) and 23% the minimum (24/26 md b.i.d.).

CONCLUSIONS: Sacubitril/valsartan therapy improves significantly quality of life, physical effort resistance, BNP and NT-ProBNP and NYHA functional class in patients with HFrEF. Although not all the patients tolerated the maximum recommended dose, the beneficial effects were significant even at lower doses.

Keywords: Heart failure with reduced ejection fraction; Sacubitril/Valsartan, Kansas City Cardiomyopathy Questionnaire, 6-minutes walking test, Natriuretic Peptides.

1 Introduction

Heart failure (HF) is the final common pathway of many cardiovascular diseases. Despite the use of optimal medical therapy, heart failure whit reduced ejection fraction (HFrEF) is one of the most impacting disease to health care costs **[1,2].** Among all chronic diseases, HF had the major therapeutic innovations in the last decades. However, since the introduction of cardiac resynchronization therapy there were limited pharmacological changes **[3].** Recently, advances in understanding of the renin–angiotensin–aldosterone (RAAS) pathway and natriuretic peptides system led to the validation of the combination of sacubitril/valsartan for the treatment of HFrEF **[4-10].** The angiotensin receptor blocker-neprilysin inhibitor (ARNi) LCZ696 provided a new approach, blocking simultaneously the renin–angiotensin–aldosterone system (RAAS) and augmenting endogenous natriuretic peptides, with limited increase in bradykinin **[11,12].** The Prospective comparison of angiotensin Receptor-Neprilysin inhibitor with Angiotensin-Converting Enzyme inhibitor to determine impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial provided evidence of benefits in terms of cardiovascular (CV) morbidity and mortality of sacubitril/valsartan when compared to enalapril in patients with HFrEF **[13].** Following the trial, the drug has been approved for treatment of HF and international HF guidelines now endorse sacubitril/valsartan as a class I recommendation for the management of HFrEF **[14,15].**

The aim of this study was to monitor over time the perceived quality of life, the physical performance improvements, the trend of BNP and NT-ProBNP and the NYHA functional class in patients with HFrEF during treatment with sacubitril/valsartan.

2 Materials and Methods

2.1 Study Population

During eighteen months a total of 37 patients (63 ± 10 years old, 76% men) with CHF in NYHA functional class II-III were enrolled after undergoing a cardiac examination to evaluate the eligibility for treatment with sacubitril/valsartan, according to international recommendations **[14,15].**

Enrollment criteria included left ventricular (LV) EF ≤35%, systolic blood pressure ≥100 mmHg, eGFR ≥30 ml/min/1.73m², potassium levels ≤5.4 mmol/l. All patients were treated with ACE-inhibitor and angiotensin receptor antagonist for at least 6 months and then started treatment with sacubitril/valsartan therapy as recommended by the 2016 ESC guidelines on HF diagnosis and treatment. All patients underwent a clinical evaluation, 6MWT, blood analysis (in particular NT-pro-BNP and BNP, renal function test), Kansas City Cardiomyopathy Questionnaire (KCCQ) for the self-assessment of quality of life and the NYHA functional class assessment **(Fig.1)** at the beginning and after 3, 6 and 12 months of therapy. All patients read and signed an informed consent and the protocol was approved by the local ethics committee, in accordance with the principles of the Declaration of Helsinki and national regulations.

2.2 Kansas City Cardiomyopathy Questionnaire

KCCQ is a valid, sensitive, and prognostically relevant tool for quantifying health status and quality of life in patients with HF **[16].** The test is a 23-item self-administered instrument to assess specific health domains pertaining to HF: physical limitation, symptoms, quality of life, social limitation, symptoms stability, and self-efficacy **[17].** An overall summary score can be derived from the physical function, symptoms (frequency and severity), social function and quality of life domains. Values range from 0 to 100 with higher scores indicating better health status. The self-efficacy domain is designed to assess whether or not a patient feels having knowledge and skills to manage their disease as an outpatient **[18].** Since the validity of each individual domain was independently established, all components of the summary score are considered valid representations of their intended domains **[19].** A mean difference over time of 5 points on the KCCQ Summary score reflects a clinically significant change in heart failure status **[20].**

2.3 Six minutes walking test (6MWT)

The 6-min walk test (6MWT) is a submaximal exercise test, widely approved for assessing functional capacity in HF and/or respiratory patients **[21,22].** The 6-MWT is very efficient to evaluate HF

patients' status and clinical improvements in response to therapies. A 6MWT was performed according to guidelines provided by the American Thoracic Society.

Testing was performed indoors, along a flat straight corridor with a hard surface. The walking course was 25 m in length, with turnaround points clearly marked with 2 safe signals. Patients were asked to walk as fast as possible with no restriction in resting for a while, if necessary. The 6MW distance was calculated at baseline, 3, 6 and 12 months.

Statistical analysis

The SPSS (SPSS Inc., Chicago, Illinois) release 24 was used for statistics. Continuous variables are expressed as mean ± SD and categorical variables as numbers and percentages (%). Paired data analysis of clinical (NYHA and KCCQ score) and functional (6MWT distance, BNP, NT-proBNP) markers was performed at 3-, 6- and 12-month time follow-up vs the previous timeline step by using the Pearson model with an alpha level of 0.016 for statistical consistency. Moreover, analysis of variance by ANOVA with Leneve and Tukey correction was performed in order to establish between-group homogeneity in patients taking ARNI at a daily dose of 100mg vs 200mg. The null hypothesis was rejected at two-tail $p<0.01$.

Results

We initially enrolled 37 patients. After few months 2 were excluded (one did not tolerate the drug because of hypotension and the second had two hospitalizations). The remaining 35 patients had a mean age of 63 ± 10 (75% males); they were revaluated during follow up at 3, 6 e 12 months. Clinical characteristics are summarized in **Table 1.**

We observed an increase of about 5 points in the KCCQ in 29 patients at 3 months from the start of therapy and, comparing the time zero with the values at 6 and 12 months, other 4 patients had a significant increase for a total of 33 subjects. Only 2 did not reach a significant increase of KCCQ during follow-up. A further clinical improvement was observed in 7 patients between 3 and 6 months

and in 8 patients between 6 and 12 months. NT-ProBNP was reduced at each follow-up, starting from 1812 ± 1404 at baseline to 1177 ± 789 at 3 months ($p<0.0001$). A further reduction was observed from 3 to 6 months (698 ± 496), which was again statistically significant ($p<0.0001$). Even in the period between 6 and 12 months there was a significant further reduction (614 ± 352; $p= 0.03$) **Table 2**.

The trend of BNP showed a significant increase in the first weeks, starting from 169 ± 91 at the enrollment to 206 ± 92 at 3 months ($p<0.0001$) and after a small decrease at 6 months (191 ± 74) ($p= 0.04$). A further decrease was observed at 12 months (154 ± 66, $p<0.0001$ 6 months vs 12 months) (Tab.2). The 6-MWT showed a progressive increase at each follow-up, starting from 270 ± 93 at the enrollment to 307 ± 76 at 3 months ($p<0.0001$). A further increase from 3 to 6 months (367 ± 58) was statistically significant ($p<0.0001$). Also, between 6 and 12 months there was a significant increase (381 ± 47) ($p<0.0001$) **(Tab 2).** NYHA class showed a progressive improvement (starting from 67% of NYHA class II and 37% in NYHA class III at the enrollment, to 74% of patients in NYHA class I and 26% in NYHA class II after 12 months of therapy) **(Tab 2).** There were no significant variations about arterial blood pressure and kidney function evaluated by serum creatinine. Analyzing, in percentage (%), the Delta (Δ) difference of variation of each single parameter, we observed that the KCCQ score was the one that reached the maximum positive variation at 3 months, with a reduced increase - still significant and constant - in the successive follow-up. The 6-MWT reached the maximum Δ % of increase at 6 months with a successive positive and significant trend but with a slower growth. NT-ProBNP reduced progressively, with a maximum Δ % of reduction at 6 months, maintaining a significant trend in reduction until 12 months, even if with a minor Δ %. BNP showed a biphasic trend **(Fig.2).**

The starting dose of 50 mg (24/26 mg BID) sacubitril/valsartan was well tolerated by each patient during the first 3 months. In 24 out of these (69%), the ARNI dose was up-titrated at 100 mg (49/51 mg BID) from 3 to 6 months. At the end of follow-up, 16 patients (46%) were on 200 mg and 19 on 100 mg daily dosage. Study population heterogeneity was tested by ANOVA with Leneve correction

with respect of the drug dosage (100 mg vs 200 mg) (Table 3). Clinical and functional benefit was confirmed in both groups.

Discussion

PARADIGM-HF trial provided evidence of benefits in terms of morbidity and mortality in patients with HFrEF **[13]** and, to date, all international guidelines **[14,15]** recommend sacubitril/valsartan for the treatment of HFrEF. The use of sacubitril/valsartan in real-life can also reduce the costs of HF, ~~by~~ reducing the number of HF hospitalizations **[23]**.

To the best of our knowledge, this is the first prospective study to assess the temporal trend of perceived quality of life, physical effort resistance, BNP and NT-ProBNP and NYHA functional class in patients with HFrEF treated with sacubitril/valsartan.

In fact, the main peculiarity of our study is the monitoring of the temporal trend of objective parameters which identify perceived quality of life and functional capacity. According with recent literature we also obtained an improvement of EF. In particular we observed an improvement of the perceived quality of life, assessed by a significant increase of the KCCQ score, an improvement of effort resistance documented by a significant increase of the distance walked in the 6MWT, a significant reduction of NT-ProBNP and of BNP (perhaps due to the reduction of the myocardial wall stress) and an improvement of NYHA functional class. The improvement of each parameter, even if significant at each follow-up, was not uniform in time. Moreover, analyzing the Δ % of variation of each single parameter, the major subjective perception of improvement of the quality of life (KCCQ) was obtained at 3 months despite the major increase of effort resistance (6MWT), as well as the major reduction of myocardial wall stress, were obtained at 6 months. This could be explained by the fact that already at the starting of sacubitril/valsartan therapy there is an inversion of the temporal progression of the disease, which is strongly perceived by the patient.

Therefore, the clinical benefit at the beginning suggests hemodynamic effects rather than myocardial remodeling **[24].** Most part of the beneficial effect of sacubitril/valsartan was attributed to the increase

of natriuretic peptides by neprilisin (NEP) inhibition **[25].** However, some further mechanisms could be considered. In fact, NEP is needed for degradation of other vasoactive peptides such as adrenomedullin, bradykinin, angiotensin II and endothelin **[26].** Moreover, endorphins are substrates of NEP and modifications of this metabolic pathway could be linked to the initial perceived positive effects **[26,27].**

In a recent study, Maslov et al. **[28],** found that therapy with sacubitril/valsartan increase beta-endorphins concentrations already in the first weeks and, in literature, several studies correlated the mood with serum beta-endorphins concentrations **[29] [30] [31].** So, we can speculate that an early increase of serum endorphins in the first weeks of sacubitril/valsartan can determine an improvement of mood and this is the rationale for a rapid increase of KCCQ score. As in a previous study **[15]** our data show an improvement of physical effort resistance but the major %Δ of variation is between 3 and 6 months, later than improvement of KCCQ score but at the same time of NT-proBNP and at the time in which BNP trend, begins to reduce.

NEP doesn't directly affect degradation of natriuretic peptides precursors such as proBNP and its N-terminal fragment (NT); the consequence is that their plasma levels are not directly affected by NEP inhibition **[13].** Therefore, ProBNP and NT-proBNP remain useful biomarkers during sacubitril/valsartan therapy, being NT-pro-BNP indirectly reduced as a consequence of myocardial wall stress reduction in HF **[32].**

We can suppose that the initial beneficial effects of the drug are due to hemodynamic effects and that the increase of physical endurance is at least in part due to endorphins but the major %Δ of endurance is reached at the moment of initial reverse myocardial remodeling. These hypotheses are supported from several studies **[24-31, 32-35]** but other trials are needed to confirm them in the future. Another finding of interest is not all patients achieved the maximum recommended dose of sacubitril / valsartan, despite adequate reduction of diuretic therapy to avoid hypotension**.** However, all the patients had significant improvement in all the tested parameters at each follow-up. These data suggest that, in real life data set, all of the patients with HFrEF that do not tolerate the maximal

recommended dose, obtain durable benefits even after low dose of Sacubitril/valsartan in accordance with previous works **[34, 36].**

Limitations

Our study had some limitations, the most important given from the small dimension of the study population, that did not allow us to evaluate the dose-dependent effect. Another limitation was the lack of echocardiographic evaluation at each follow-up, that would have been useful to evaluate the inversion of myocardial remodeling and the EF trend over time, even in comparison with other parameters. However, this element was not considered in the study design, being in particular focused on the temporal trend of clinical parameters rather than instrumental measures. These considerations in fact were made only *a posteriori* after the evaluation of the temporal trend of the tested parameters. Nevertheless we believe that these limitations could be a starting point for other studies.

Conclusions:

In a real world scenario, sacubitril/valsartan therapy improves significantly quality of life, physical effort resistance, BNP and NT-ProBNP and NYHA functional class in patients with HFrEF. The improvement of perceived quality of life shows up earlier than the improvement of all the other parameters. Even if not all the patients tolerated the maximum recommended dose, the beneficial effects were significant also at lower doses of Sacubitril/valsartan. However, further and multicentric studies are need to demonstrate this.

Author contribution

All authors contributed to: (1) substantial conception, design, acquisition of data, analysis and interpretation of data, (2) drafting of the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

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Table 1: Baseline clinical characteristics of the population.

Clinical characteristics		Drug Therapy	
Patients. number	37	**Class of drugs in treatment**	**Patients %**
Age (mean ± SD) years	63 ± 10	ACEi	46
Sex (mean ± SD) %	76 men	ARB	54
SBP (mean ± SD) mmHg	125 ± 13	βeta-blocker	81
DBP (mean ± SD) mmHg	73 ± 9	MRA	59
Heart Rate (mean ± SD) b/m	65 ± 6	Loop diuretics	76
EF (mean ± SD) %	27 ± 4	Thiazide diuretics	30
Etiology of HFrEF %	76 ICM	Digoxin	24
	11 HCM	Ivabradine	5
	13 PCM	Amiodarone	27
NYHA functional class %	62 NYHA II	(#) Anticoagulant	22
	38 NYHA III	(*) Antiplatelet	70
Creatinine (mean ± SD) mg/dl	1.05 ± 0.18	Statin	68
NT-proBNP (mean ± SD) pg/mL	1812 ± 1404		
BNP (mean ± SD) pg/mL	169 ± 91	Type 2 diabetes	32
ICD %	81	Hypertension	86
CRT-D %	5	Chronic pulmonic disease	21
		OSAS	13

SD: standard deviation; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure; **EF**: left ventricular ejection fraction; **HFrEF**: heart failure whit reduced ejection fraction; **ICM**: ischemic cardiomyopathy; **HCM**: hypertensive cardiomyopathy; **PCM**: primary cardiomypathy; **NYHA**: New York Heart Association; **NT-proBNP**: N-terminal prohormone of brain natriuretic peptide; **BNP**: brain natriuretic peptide; **ACEi**: angiotensin-converting enzyme inhibitor; **ARB**: angiotensin receptor blocker; **MRA**: mineralocorticoid receptor antagonist; **(#):** includes vitamin K antagonists, rivaroxiban, dabigatran, apixaban and edoxaban; (*): includes aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, and their combinations; **ICD**: implantable cardioverter defibrillator; **CRT-D**: cardiac resynchronization therapy defibrillator.

Tab.2 Comparison of evaluated parameters.

Variable	Time zero (Enrollment)		Follow-up (3 months)		Follow-up (6 months)		Follow-up (12 months)
NT-proBNP (mean ± SD) pg/mL	1812 ± 1404	p<0.0001	1177 ± 789	p<0.0001	698 ± 496	p<0.03	614 ± 352
BNP (mean ± SD) pg/mL	169 ± 91	p<0.0001	206 ± 92	p=0.04	191 ± 74	p<0.0001	154 ± 66
KCCQ	52 ± 11	p<0.0001	66 ± 9	p<0.0001	70 ± 9	p<0.0001	73 ± 7
6-MWT meters	270 ± 93	p<0.0001	307 ± 76	p<0.0001	367 ± 58	p<0.0001	381 ± 47
Creatinine (mean ± SD) mg/dl	1,05 ± 0,18	NS	1,04 ± 0,17	NS	1,02 ± 0,19	NS	1,02 ± 0,13
SBP (mmHg)	126 ± 13	NS	119 ± 11	NS	114 ± 11	NS	111 ± 7
DBP (mmHg)	73 ± 9	NS	67 ± 8	NS	66 ± 6	NS	65 ± 6
NYHA I class. %	0	p=0.04	17	p<0.0001	66	N.S	74
NYHA II class. %	63	N.S	71	p=0.004	34	N.S	26
NYHA III class. %	37	p=0.03	12	N.S	0		0

Table 3. Between-group homogeneity related to ARNI dosage

		n	Mean	SD	SE	F	p-value
NYHA class	100mg	19	-1.11	.567	.130	.183	.671
	200mg	16	-1.12	.619	.155		
6MWD (m)	100mg	19	110.1	70.47	16.17	.042	.838
	200mg	16	106.6	70.23	17.56		
6MWT changes	100mg	19	.546	.571	.131	.070	.793
	200mg	16	.568	.661	.165		
KCCQ changes	100mg	19	.417	.314	.0735	.105	.748
	200mg	16	.487	.269	.0674		
NT-proBNP changes	100mg	19	-.629	.161	.0373	.916	.345
	200mg	16	-.538	.206	.0516		
BNP changes	100mg	19	.040	.561	.1288	.474	.486
	200mg	16	.082	.455	.1139		

*ANOVA testing for between-group heterogeneity (Leneve correction). BNP, Brain Natriuretic Peptide; KCCQ, Kansas City Cardiomyopathy Questionnaire; 6MWD, six-minute walk distance; 6MWT, six-minute walk test; NYHA, New York Heart Association functional class; NT-proBNP, N-terminal pro-BNP;

Figure 1: Study Design

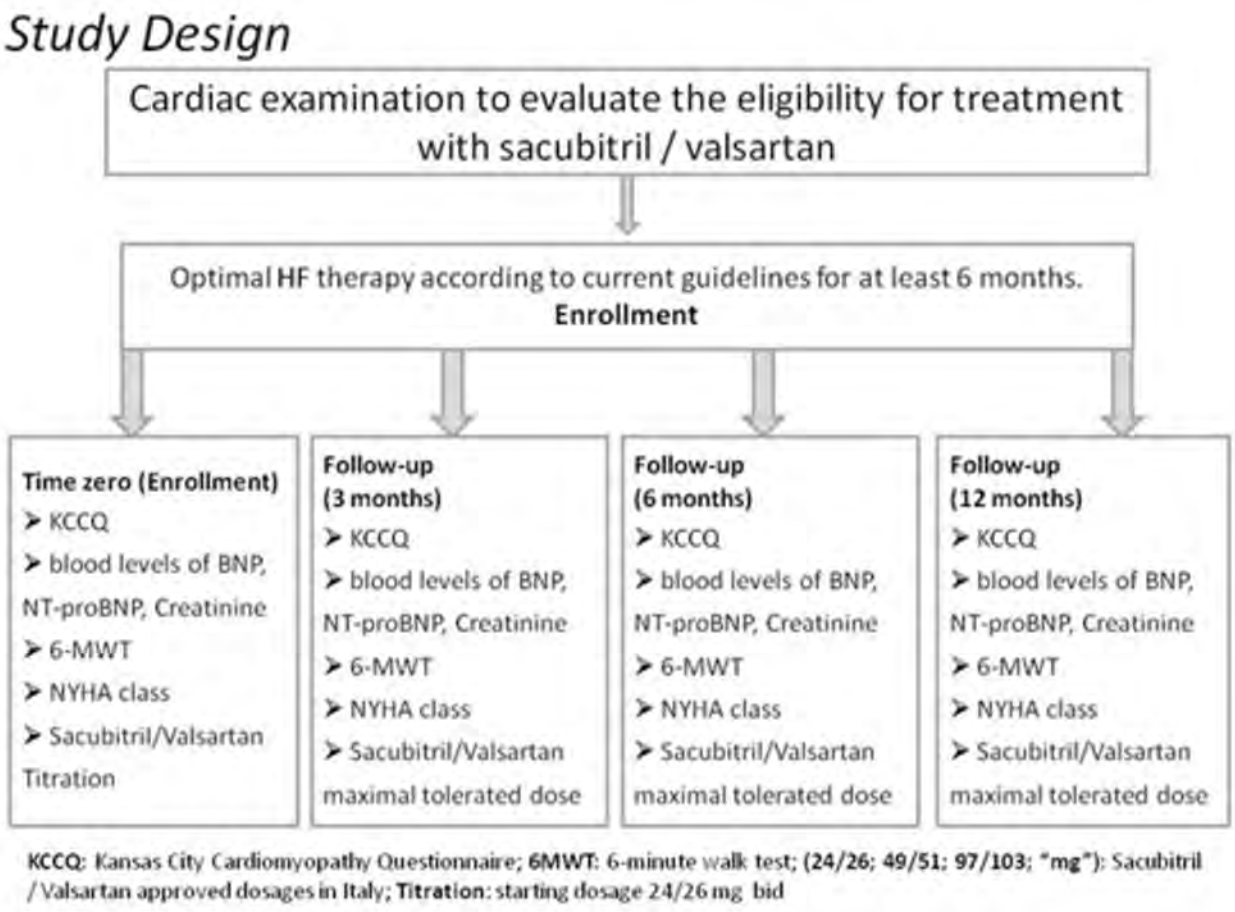
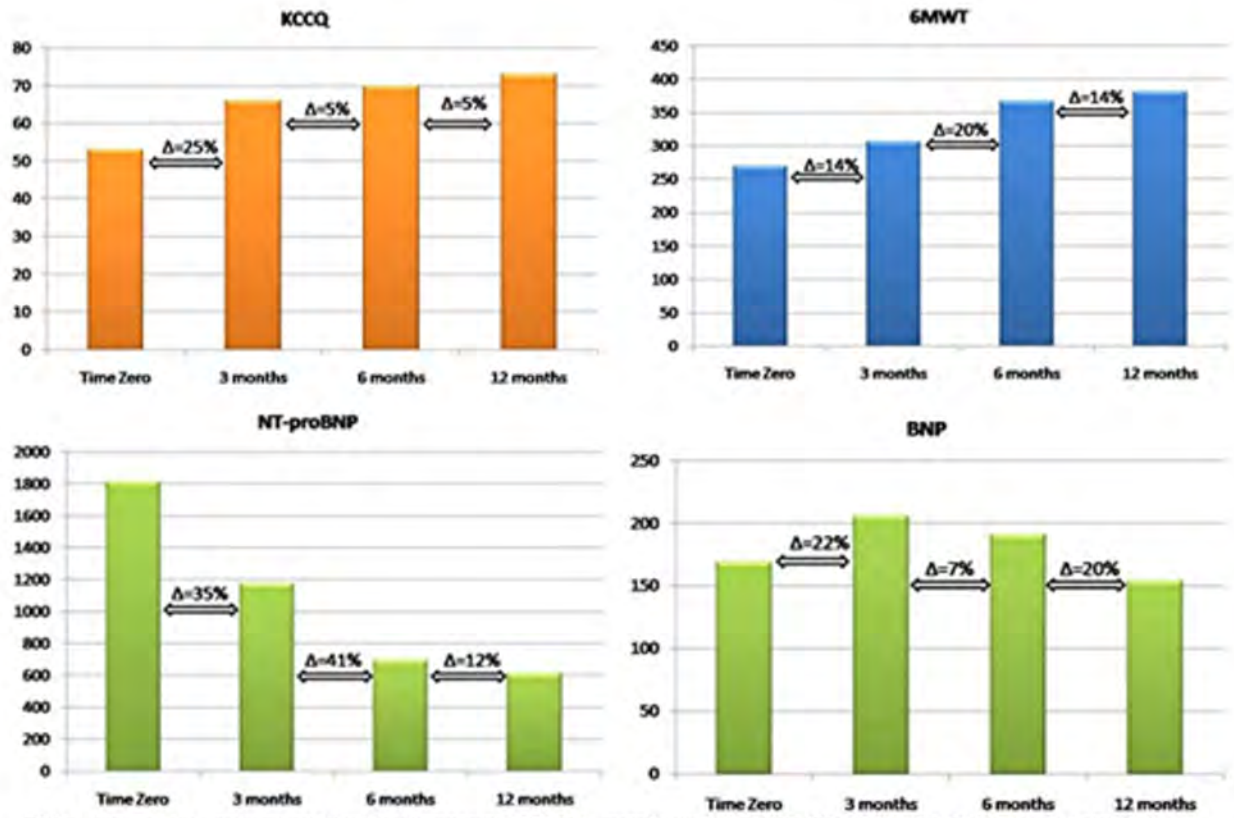


Figure 2: the percentage (%) of the difference Delta (Δ) of variation of each single parameter, at time zero (enrollment) and at 3, 6 and 12 months



KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWT: 6-minute walk test; (24/26; 49/51; 97/103; "mg"): Sacubitril /Valsartan approved dosages in Italy; **Titration**: starting dosage 24/26 mg bid

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Low- vs high-dose ARNI effects on clinical status, exercise performance and cardiac function in real-life HFrEF patients

--Manuscript Draft--

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Abstract:	Purpose. Only a few studies are available on dose-related effects of Sacubitril/Valsartan (ARNI) in real-life patients with heart failure and refuced ejection fraction (HFrEF). We sought to investigate clinical and functional changes in patients treated by different ARNI dose. Methods. This was an observational study in consecutive outpatients admitted for HFrEF from October 2017 to June 2019. The PARADIGM criteria were needed for enrollment. ARNI was uptitrated according to blood pressure, drug tolerability, renal function and kaliemia. At least 10-month follow-up was required in each patient. Clinical assessment, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, 6-minute walk test and strain-echocardiography were performed in each patient on a reguar basis during the observational period. At the end of study patients were divided in two groups based on the median yearly dose of the ARNI medication. Results. 90 patients, 64±11 years, 82% males were enrolled. The cut-off dose was established 75mg BID, and the study population divided into group A (≤75mg), 52 patients (58%) and a group B (>75mg), 38 patients (42%). Follow-up duration was 12 moths (range 11-13). NYHA class, KCCQ score and 6MWT performance ameliorated in both groups, with a quicker time-to-benefit in group B. The proportion of patients walking >350m increased from 21% to 58% in group A ($p<0.001$), and from 29% to 82% in group B ($p<0.001$). Poisitive effect was also disclosed in the left ventricular remodelling, strain deformation and diastolic function. Conclusion. One-year ARNI treatment was effective in our real-life HFrEF patient population, leading to clinical and functional improvements in both study groups, weakly greater and with a shorter time-to-benefit in group B.
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Low- vs high-dose ARNI effects on clinical status, exercise performance and cardiac function in real-life HFrEF patients

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ABSTRACT

Purpose. Only a few studies are available on dose-related effects of Sacubitril/Valsartan (ARNI) in real-life patients with heart failure and refuced ejection fraction (HFrEF). We sought to investigate clinical and functional changes in patients treated by different ARNI dose.

Methods. This was an observational study in consecutive outpatients admitted for HFrEF from October 2017 to June 2019. The PARADIGM criteria were needed for enrollment. ARNI was uptitrated according to blood pressure, drug tolerability, renal function and kaliemia. At least 10-month follow-up was required in each patient. Clinical assessment, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, 6-minute walk test and strain-echocardiography were performed in each patient on a reguar basis during the observational period. At the end of study patients were divided in two groups based on the median yearly dose of the ARNI medication.

Results. 90 patients, 64±11 years, 82% males were enrolled. The cut-off dose was established 75mg BID, and the study population divided into group A (≤75mg), 52 patients (58%) and a group B (>75mg), 38 patients (42%). Follow-up duration was 12 moths (range 11-13). NYHA class, KCCQ score and 6MWT performance ameliorated in both groups, with a quicker time-to-benefit in group B. The proportion of patients walking >350m increased from 21% to 58% in group A ($p<0.001$), and from 29% to 82% in group B ($p<0.001$). Positive effect was also disclosed in the left ventricular remodeling, strain deformation and diastolic function.

Conclusion. One-year ARNI treatment was effective in our real-life HFrEF patient population, leading to clinical and functional improvements in both study groups, weakly greater and with a shorter time-to-benefit in group B.

Keywords: ARNI, heart failure, left ventricular function, 6-minutes walking test, Sacubitril/valsartan.

Introduction

Heart failure (HF) is the final stage of many cardiovascular diseases. Despite optimal medical therapy (OMT), HF with reduced ejection fraction (HFrEF) remains a central issue, due to its high social and economic impact, worldwide [1-3]. Among the latest technological and pharmacological innovations, Sacubitril/Valsartan drug combination, also known as Angiotensin Receptor Neprilysin Inhibition (ARNI), has been demonstrated to get relevant benefit in this clinical setting [4-8]. Although neurohormonal modulation by ARNI has gradually become a landmark of HF treatment, questions on its dose-dependent effectiveness are open yet [7-9].

We sought to evaluate clinical and functional effects in low- vs high-dose medication treated real-life HFrEF patients.

Methods

This was a prospective observational study conducted at Messina and Palermo University Hospitals (Italy). Among all outpatients admitted from October 2017 to June 2019 due to HFrEF from any aetiology, we enrolled those fulfilling the same inclusion criteria as in the PARADIGM-HF study [5]. Hence, patients should have been New York Heart Association (NYHA) functional class II or III, stabilized since the last hospitalization, with left ventricular ejection fraction (LVEF) ≤ 0.35. Patients who had received an implanted cardioverter defibrillator (ICD) at least 3 months prior admission to study, whether in combination with cardiac resynchronization therapy (CRT-D), were also included.

Conversely, refractory HF, impaired glomerular filtration rate (<60 mL/min), severe hepatic dysfunction, sustained hypotension, permanent atrial fibrillation, aortic or mitral stenosis, history of angioedema, hospitalization within the last 3 months due to destabilization, acute coronary syndrome, and recent surgery were exclusion criteria.

According to the Italian Heath Care Regulatory System, the ARNI administration was authorized after 6-month treatment with ACE-inhibitor or Angiotensin-receptor blocker (ARB). Medication was given on top of optimal medical therapy (OMT) at the starting dose of 50 (24/26) mg twice a day (bis in die, BID), in an open-label fashion. According to 2017 guidelines [10], up-titration to 100 (49/51) mg and 200 (97/103) mg BID, was established within the first two-month period, upon clinical condition, drug tolerance, home-reported BP, renal function, and the kaliemia. Patient had to accomplish at least 10-month follow-up treatment. The observation period ended July 2020. The median medication dose was calculated on the annual dose taken by each patient and served for clustering the low-mid (group A) and mid-high dose (group B) recipients.

Physical examination, quality of life (QoL) assessment by Kansas City Cardiomyopathy Questionnaire (KCCQ) [11], 12-lead ECG, transthoracic echocardiography, 6-minute walk test (6MWT), ICD check and laboratory samples were planned every 3 months. Changes in NT-proBNP levels and estimated glomerular filtration rate (eGFR) from serum creatinine (Cockroft-Gault equation) were monitored all through the study length. The protocol was conducted according to international guidelines, so it was just approved by the local Advisory Boards, with no trial number registration required.

All patients gave informed consent to the study.

Six-minute walk test

An indoor 6MWT was performed along a flat straight corridor with hard surface. The walking course was 30 meters in length, with turnaround points safely marked. Patients were asked to walk as fast as possible with no restriction in resting for a while, if necessary. Heart rate (HR) and symptoms were monitored during the walk. Absolute and predicted walk distance (WD), and walk

speed, were calculated in everyone. Predicted WD was calculated according to individual characteristics (weight, height and age), as follows [12,13]:

Men: [(7.57×height in cm) − (5.02×age) − (1.76×weight in kg) − 309 meters]

Women: [(2.11×height in cm) − (2.29×weight in kg) − (5.78×age) + 667 meters]

Echocardiography

Color-Doppler ultrasound examination with standard measurements was performed in each participant. Examiners were blinded to previous achievements by the patient. Studies were stored in a Digital Imaging and Communications in Medicine format and then analysed offline. Left ventricular end-diastolic/-systolic volumes and LVEF were calculated using the modified biplane (4- and 2-chamber apical views) Simpson rule method [14].

In 77/90 patients (85.5%) LV diastolic function was assessed by mitral valve early Doppler velocity (E) / early tissue velocity (E') ratio (normal value <12). Also, global longitudinal strain (GLS) deformation (normal value -18%) was evaluated in the same subgroup, as average value from the 4-, 3- and 2-chamber apical views.

Statistical methods

Continuous variables are expressed as mean ± SD and categorical variables as numbers and percent (%). Paired data analysis of clinical (NYHA and KCCQ score) and functional (6MWT distance, BNP, NT-proBNP) markers was performed at 3-, 6- and 12-month time follow-up vs the previous timeline step by using the Pearson model with an alpha level of 0.01 for statistical consistency. Moreover, analysis of variance by ANOVA with Leneve's and Tukey correction was performed to establish the between-group homogeneity. Interobserver variability for

echocardiographic measurements was calculated in each laboratory as by 0.052 (95% CI 0.034-0.063). The null hypothesis was rejected at two-tail p<0.01.

Results

A total of 90 HFrEF patients, mean aged 64.5 ± 10.9 years, 74% males, predominantly of an ischemic aetiology (72%), were enrolled from an initial study population of 96 patients. Six more were excluded due to ARNI intolerance in 3 cases, allergic reaction in one, and non-cardiac hospitalization (COVID-19) in another 2. Demographic and clinical characteristics are summarized in **Table 1.** Forty-six patients (51%) had received an ICD, and 17 (19%) CRT-D.

The study duration was 12 months (range 11-13) in length, and nobody was lost to follow-up. According to the median annual dose of the ARNI (75 mg BID), 52 patients (58%) entered the group A (≤75 mg) and 38 (42%) the group B (>75 mg).

Most patients gradually required a less amount of loop diuretics on follow-up (online **Table 2**). Systolic BP was mildly higher in patients from group B, both on admission and follow-up, and this allowed keeping a greater dose of medication.

A clinical improvement was observed in most patients from both groups, according to QoL. No relevant side effects or adverse events were observed. Renal function (eGFR) showed just a trivial decline in both medication arms.

Regarding exercise tolerance, mildly greater WD and walk speed were observed in group B, especially after the first 6-month treatment (**Figure 1**). This difference, however, become trivial as normalized for sex and weight. The proportion of patients walking >350m increased from 21% to 58% in group A (p<0.001), and from 29% to 82% in group B (p<0.001).

Clinical condition improved according to a lessening in NT-proBNP levels, quicker in group B. Left ventricular volumes decreased in all patients, with a mild improvement in the stroke volume and

LVEF (3 points % in group A, 5 points % in group B, p=NS). Positive effect was also seen in the E/E' ratio and GLS (online **Table 3; Figure 2**).

Discussion

Twelve-month ARNI therapy was clinically advantageous in our real-life HFrEF patient population. We analysed the impact of different ARNI dosage on clinical status, physical performance, QoL and echocardiographic parameters in outpatients, previously treated with conventional medical therapy. After switching to ARNI, both groups moved into a better clinical condition. Exercise performance, LV reverse remodelling and systo-diastolic function ameliorated according to a gradual decrease in circulating NT-proBNP levels, and this could have a positive impact on the progression and prognosis of HFrEF patients. Overall, patients from group B attained weakly greater and quicker functional achievements, which were satisfactory in both groups at the end of follow-up.

Despite the proportion of high-dose ARNI recipients in large pivotal trials, the adherence to multidrug therapy remains challenging in clinical practice, even if adults with cardiovascular diseases are prone to polypharmacy due to comorbidities and complexity of medication regimens [15,16]. Though we have already observed drug-related benefits even in patients at a high risk of arrhythmic disorders, high-dose ARNI therapy showed some practical limitations, especially in respect to BP values [17,18]. In facts, despite suitable clinical characteristics, Martens et al. demonstrated that top doses were administered only to 32% of HFrEF patients [19].

Unfortunately, the PARADIGM-HF study showed that patients scheduled to a dose reduction were at a higher risk of major cardiovascular events [5,9]. Nevertheless, Vardeny et al. reported a reduced risk of death and HF hospitalization even by taking lower doses, compared to ACE-inhibitors [20]. A more recent meta-analysis confirmed the dose of 200 mg BID to be possible in

35% of European patients, with discontinuation in 12.8% [21]. These findings likely indicate that real-life patients are different from pivotal studies, encouraging clinicians to the search for OMT without extremes.

In our study, exercise performance improved in both groups, and this is an important therapeutic target. The proportion of patients walking >350m at the end of study was greater in group B (82%) than in group A (58%), but we also demonstrated that confounders like weigh, body mass, sex, and physical inactivity can affect WD.

The interplay between clinical and functional achievements and NT-proBNP levels confirmed previously published data by Pandey et al. who found that even lower than standard doses of ARNI were able to reduce the NT-proBNP and diuretic requirement, without any relevant change in potassium or serum creatinine [22]. Although the dose of 50 mg BID has been considered the lowest ARNI dose for HFrEF patients, clinical advantages have also been shown with very-low doses (12/23 mg BID) [23].

Regarding LV function by echocardiography, drug-related reverse remodelling likely remains a controversial issue. In previous studies, ARNI was effective when initiated early after diagnosis, and at least for 3 months [24-26]. Though most patients in our series have got a decrease in cardiac chamber volumes, chiefly related to a reduced end-systolic volume, case-by-case and interobserver variability represent important shortcomings for a correct interpretation of these findings. The weak improvement in LVEF (4 points %) in our patients, a bit more relevant in group B, confirmed a study by Almufleh et al. who reported +5% LVEF in high-dose vs +4% in low-dose recipients [26]. Conversely, we cannot confirm the complete functional recovery found in 17% of non-ischemic HF patients by Chang et al. [27].

Tissue Doppler and strain imaging could be the way to overcome the limitation of LVEF variability. Improved GLS and LV diastolic function was recognized in our subset of patients,

though their absolute values remained quite low. Strain echocardiography likely represents an interesting imaging modality to explore myocardial impairment in HF patients as consequence of tissue oedema, inflammation, and fibrosis [28], which can be counterbalanced by Sacubitril/Valsartan [29,30].

Limitations

The small sample size is the main limitation of the present study. Our patients, however, were strongly asked to follow the whole scheduled observational period, and this allowed the study completion at one-year follow-up. Findings from the study population were not compared to controls, and this may have affected the true assessment of clinical responses. However, the aim of the study was not at establishing the ARNI effectiveness vs conventional therapy, but the dose-related discrepancies. Though no serious outcomes occurred in our study population, no information is available on subclinical events, like intercurrent atrial fibrillation or ventricular arrhythmias, except for ICD-monitored patients. Echocardiography examination was only partially blinded, and the examiner could retain therapeutic information. Prospective longitudinal studies with a central echo data reading should be encouraged to avoid interference in data analysis. Further functional information might have been achieved by cardiopulmonary exercise testing, which remains the gold standard for functional assessment of HF patients.

Though the prevalence of type-2 diabetes was not so high in our study population, metabolic parameters interact to the cardiomyocyte function and lead to increased inflammation, apoptosis, reactive oxygen species, altered calcium signalling [31]. Diabetes cardiomyopathy likely impairs prognosis and deserves more awareness in HF populations, also in view of the most recent studies on SGLT2 inhibitors in both diabetic and nondiabetic patients [32].

Current literature also suggests early initiation of the ARNI (50 mg BID) as an effective, risk-free, therapeutic approach, that increases quality-adjusted life expectancy and cost savings compared with no initiation or initiation late after hospitalization [33,34].

Conclusion

One-year Sacubitril/Valsartan treatment on top of OMT was advantageous in our real-like HFrEF patient population. Beneficial effects on clinical condition, QoL, exercise performance, LV remodelling and function were observed in both study groups, weakly greater and with a shorter time-to-benefit in patients from group B.

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Author' contribution

EC, GD, GC, CM, EB, LZ, GN, CDG were involved in the clinical management, ultrasound imaging, and treatment of the patients. EC revised the manuscript. CDG drafted, revised and upgraded the manuscript; interpreted the patient data and performed statistical analysis; LZ was also involved in the literature search. All authors have read and approved the manuscript.

Declarations

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Conflicts of interest and competing interests

None to declare

Availability of data and material

Upon request

Compliance with Ethical Standards

Research involved human participants, following current international criteria for treating HF

Informed consent was given by each participant for clinical management and ultrasound imaging

FIGURE LEGEND/CAPTION

Figure 1. Functional achievements at 6-min walk test in both study groups. NT-proBNP serum levels are also displayed on thebottorm right panel. In-group differences and detalilled measuments are reported in Table 3. *NT-proBNP*, N-terminal pro B type natriuretic peptide; *P<0.05

Figure 2. Overtime changes in left ventricular (LV) volumes, ejection fraction (LVEF), and global longitudinal strain (GLS) at transthoracic echocardiography. *LVEDVi*, left ventricular end-diastolic volume index; *LVESVi*, left ventricular end-systolic volume index; *NT-proBNP*, N-terminal pro B type natriuretic peptide. LVEF is reported in %. *P<0.001.

Table 1. Demographic and clinical characteristics of the study population

	All (n=90)	Group A (n=52)	Group B (n=38)	p-value
Mean age, years	**64.5 ± 10.9**	65.7 ± 9.8	62.9 ± 10.4	0.201
Males, *n (%)*	**74 (82.2)**	44 (84.6)	30 (78.9)	0.675
Body surface area, m^2	**1.91 ± 0.18**	1.92 ± 0.19	1.91 ± 0.16	0.849
Body mass Index, g/m^2	**27.7 ± 4.1**	28.2 ± 4.6	27.0 ± 3.2	0.147
NYHA class II, *n (%)*	**57 (63.3)**	33 (63.5)	24 (62.2)	0.924
NYHA class III, *n (%)*	**33 (36.7)**	19 (36.5)	14 (36.8)	0.848
Systolic BP, mm Hg	**123.2 ± 14.8**	118.1 ± 11.0	130.1 ± 16.6	<0.001
Diastolic BP, mm Hg	**72.8 ± 9.9**	73.1 ± 10.3	72.5 ± 9.5	0.785
Ischemic heart disease, *n (%)*	**65 (72.2)**	40 (76.9)	25 (59.4)	0.121
Non-ischemic etiology, *n (%)*	**35 (38.9)**	12 (23.1)	13 (40.6)	0.122
• Primary dilated cardiomyopathy, *n (%)*	**27 (30.0)**	15 (28.8)	12 (31.6)	0.957
• Hypertensive heart disease, *n (%)*	**2 (2.2)**	1 (1.9)	1 (2.6)	0.614
• Previous myocarditis, *n (%)*	**6 (6.7)**	4 (7.7)	2 (5.3)	0.982
Overweight /obesity (BMI>28 g/m^2), *n (%)*	**39 (43.3)**	23 (44.2)	16 (42.1)	0.987
Smoking attitude, *n (%)*	**10 (11.1)**	6 (11.5)	4 (10.5)	0.945
Type-2 Diabetes, *n (%)*	**30 (33.3)**	18 (34.6)	12 (31.6)	0.867
ICD, *n (%)*	**46 (51.1)**	29 (55.8)	17 (44.7)	0.408
CRT-D, *n (%)*	**17 (18.9)**	14 (26.9)	3 (9.4)	0.072
NT-pro BNP, *pg/mL*	**1650 ± 1301**	1680 ± 1401	1613 ± 1180	0.811
LV ejection fraction	**0.30 ± 0.09**	0.31 ± 0.11	0.28 ± 0.05	0.096
Therapy (baseline)				
Prior ACE-inhibitors, *n (%)*	**68 (75.5)**	38 (73.1)	30 (78.9)	0.654
Prior AR-blockers, *n (%)*	**22 (24.5)**	14 (26.9)	8 (21.1)	0.567
Loop diuretics, *n (%)*	**82 (91.1)**	48 (92.3)	34 (84.2)	0.944
Beta-blockers, *n (%)*	**80 (88.9)**	50 (96.1)	31 (81.6)	0.385
Anti-platelet drugs, *n (%)*	**54 (60.0)**	34 (65.4)	20 (52.6)	0.314
Mineralocorticoid antagonists, *n (%)*	**61 (67.7)**	33 (63.5)	28 (73.7)	0.343
Others, *n (%)*	**10 (11.1)**	6 (11.5)	4 (10.5)	0.865

ACE, Angiotensin-Converting Enzyme; AR, Angiotensin II Receptor; BP, blood pressure; dL, deciliters; ICD, implantable cardioverter defibrillator; CRT-D, resynchronization therapy; mL, milliliters; LV, left ventricular; NYHA

New York Heart Association functional class.

Table 2. Sacubitril/Valsartan and loop-diuretic use in the study population

	Group A (n=52)	**Group B (n=38)**	
50 mg (BID), *n (%)*	33 (63.5)	-	-
100 mg (BID), *n (%)*	19 (36.5)	28 (73.7)	<0.01
200 mg (BID), *n (%)*	-	10 (26.3)	-
Average yearly-based dose, *mg*	59.1 ± 12.1	102.0 ± 24.6	<0.001
Loops diuretics (baseline), *mg*	63.3 ± 56.2	50.0 ± 28.2	0.208
Loops diuretics (12 months), *mg*	49.2 ± 34.6*	36.0 ± 67.4*	0.019

*P<0.01, vs baseline

Table 3. 12-month effects of the ARNI treatment in the study population

	Baseline			*12 months*			*vs baseline*	
	Group A	**Group B**	**p-value**	**Group A**	**Group B**	**p-value**	**Group A**	**Group B**
NYHA class	2.37 ± 0.49	2.37 ± 0.49	0.977	1.92 + 0.55	1.39 + 0.49	<0.001	0.049	0.009
NYHA class 2, n (%)	33 (62)	24 (63)	0.976	28 (54)	15 (39)	0.078	0.234	0.020
NYHA class 3, n (%)	19 (36)	14 (37)	0.965	6 (11)	0 (0)	0.020	0.040	0.005
KCCQ score, %	64.7 ± 19.0	57.2 ± 15.7	0.060	72.8 ± 16.8	75.4 ± 10.2	0.508	<0.001	
NT-proBNP, pg/ml	1680 ± 1401	1613 ± 1180	0.814	748 ± 988	643 ± 425	0.334	<0.001	
eGFR, ml/min	82.5 ± 31.6	84.8 ± 21.9	0.705	78.9 ± 28.9	81.4 ± 19.6	0.643	0.008	
Systolic BP, mm Hg	118.1 ± 11.0	130.1 ± 16.6	0.001	113.2 ± 14.5	114.7 ± 12.8	0.614	0.011	0.001
Diastolic BP, mm Hg	73.1 ± 10.3	72.5 ± 9.5	0.536	69.3 ± 8.3	68.0 ± 7.1	0.133	0.166	0.251
Walk distance, m	269.8 ± 94.5	292.1 ± 91.9	0.267	346.8 ± 110.7	389.4 ± 67.0	0.038	<0.001	
Predicted WD, %	54.0 ± 18.1	55.3 ± 19.5	0.741	69.9 ± 22.2	73.9 ± 16.1	0.355	<0.001	
Walk speed, m/min	45.0 ± 15.7	48.7 ± 15.3	0.267	57.8 ± 18.4	62.6 ± 12.5	0.039	<0.001	
WD < 350 m, n (%)	41 (78.8)	27 (71.1)	0.554	22 (42.3)	7 (18.4)	0.030	<0.001	
LVEDVi, ml/m2	93.3 ± 25.6	96.3 ± 18.2	0.364	86.5 ± 22.2	88.8 ± 17.6	0.038	0.003	
LVESVi, ml/m2	65.4 ± 20.4	68.9 ± 13.8	0.825	58.7 ± 17.4	59.4 ± 12.5	0.825	<0.001	
LVSVi, ml/m2	27.6 ± 8.5	27.0 ± 6.9	0.703	27.8 ± 7.9	29.4 ± 20.4	0.350	0.900	0.149
E/E' ratio	13.9 ± 5.5	14.5 ± 3.2	0.554	11.7 ± 4.3	12.6 ± 3.5	0.320	0.040	0.020
LV ejection fraction	0.30 ± 0.10	0.28 ± 0.05	0.218	0.33 ± 0.07	0.33 ± 0.04	0.687	0.340	0.078
GLS, -%	8.9 ± 2.0	9.3 ± 1.7	0.421	11.3 ± 2.4	12.2 ± 2.1	0.112	0.020	0.016

Main changes in laboratory, diuretic use and morphofunctional indices after 12-month ARNI treatment.; BP, blood pressure; E/E', early diastolic velocity diastolic through the mitral valve inflow / early mean tissue velocity; GLS, global longitudinal strain; KCCQ, Kansas City cardiomyopathy questionnaire; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; m, meters; ml, milliliters; NYHA, New York Heart Association; NT-proBNP, N terminal pro brain natriuretic peptide; WD, absolute walk distance.

Figure 1

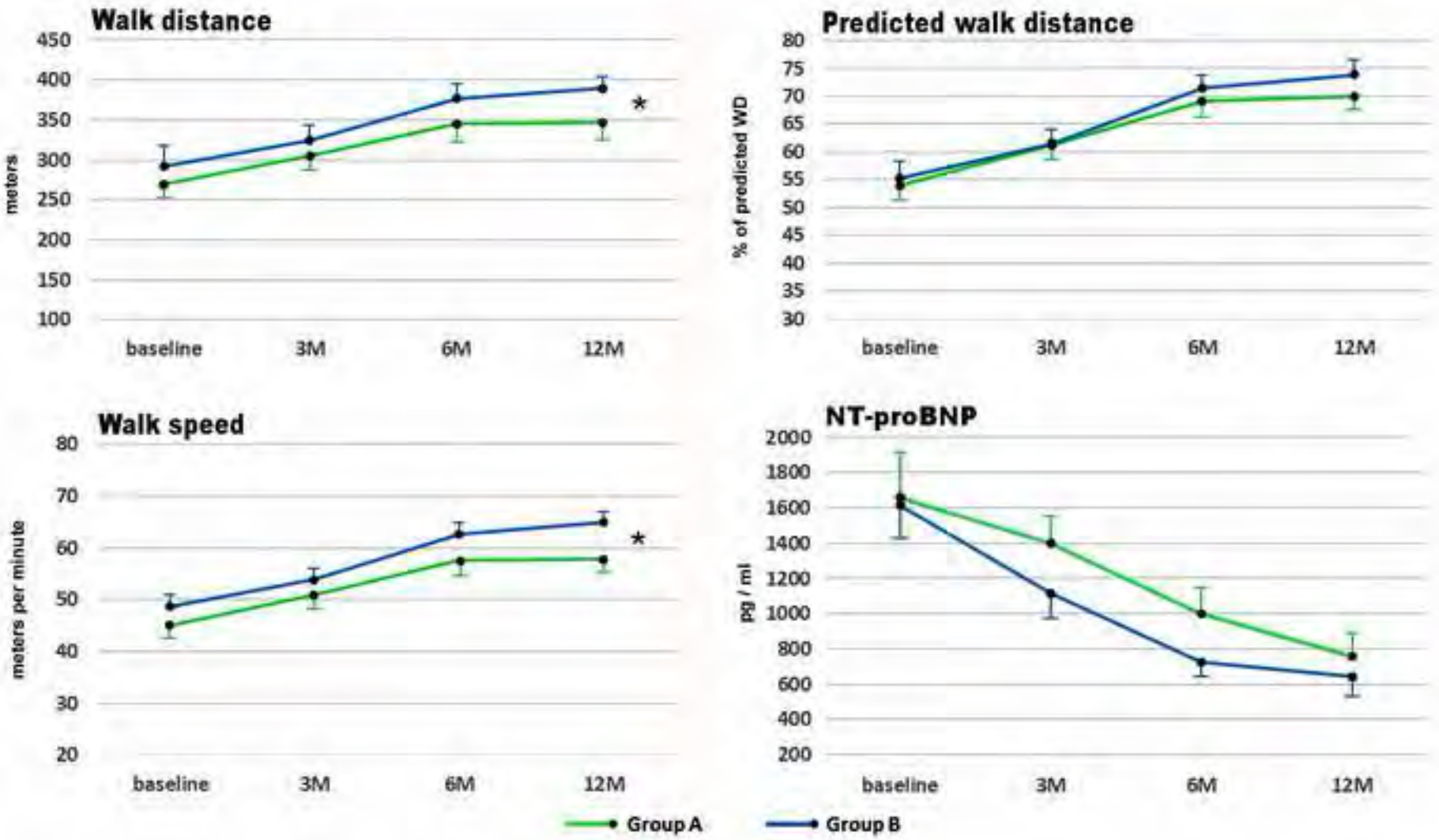
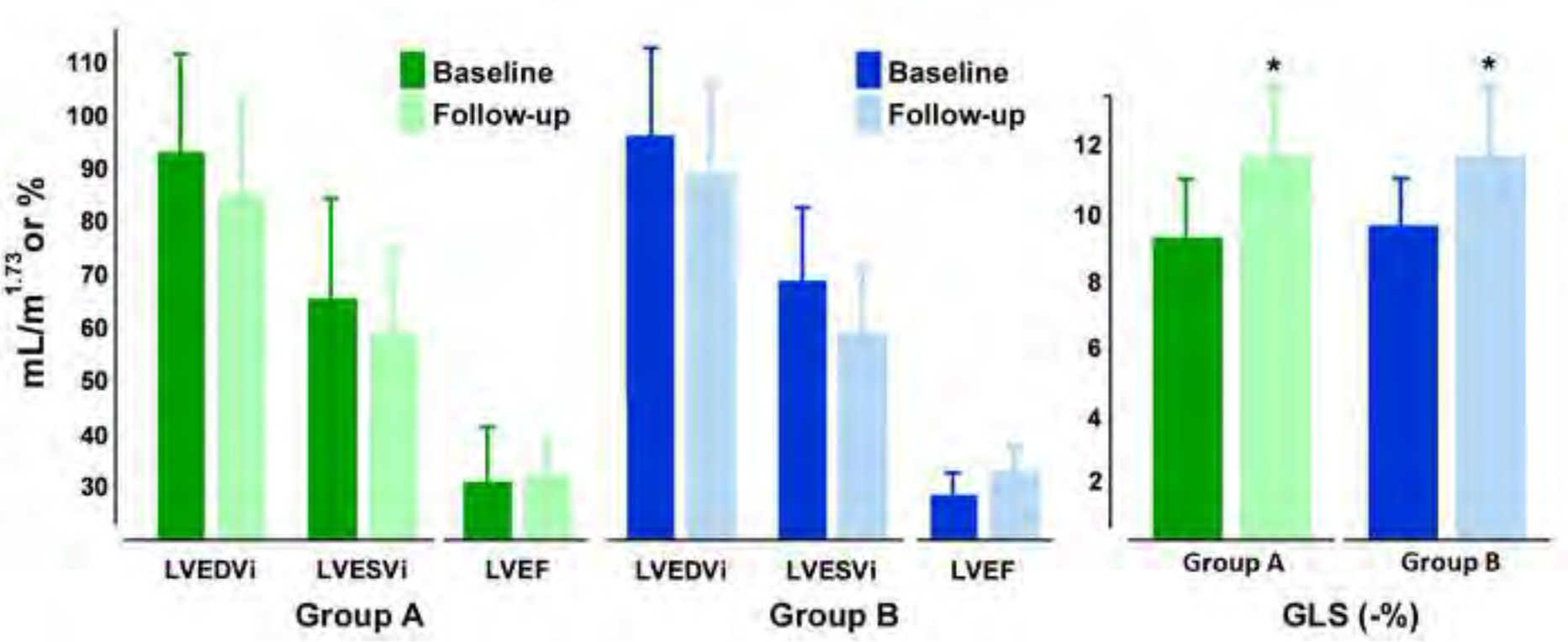


Figure 2



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POSITION PAPE

Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology

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Heart failure (HF) is common and associated with a poor prognosis, despite advances in treatment. Over the last decade cardiovascular outcome trials with sodium–glucose co-transporter 2 (SGLT2) inhibitors in patients with type 2 diabetes mellitus have demonstrated beneficial effects for three SGLT2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) in reducing hospitalisations for HF. More recently, dapagliflozin reduced the risk of worsening HF or death from cardiovascular causes in patients with chronic HF with reduced left ventricular ejection fraction, with or without type 2 diabetes mellitus. A number of additional trials in HF patients with reduced and/or preserved left ventricular ejection fraction are ongoing and/or about to be reported. The present position paper summarises recent clinical trial evidence and discusses the role of SGLT2 inhibitors in the treatment of HF, pending the results of ongoing trials in different populations of patients with HF.

Keywords Heart failure • Sodium–glucose co-transporter 2 inhibitors • Type 2 diabetes mellitus • Cardiovascular outcomes • Quality of life

Introduction

Heart failure (HF) and type 2 diabetes mellitus (T2DM) often occur together with an associated increased risk of adverse outcomes. HF is one of the most common cardiovascular conditions and one of the major causes of mortality in patients with T2DM.[1,2] Furthermore, T2DM is frequent in patients with HF, occurring in almost 40% of patients hospitalised for HF and up to 30% of those with chronic HF.[3] Despite numerous available treatments for HF, the prognosis remains poor, with a small increase in survival over the last decade.[4] Concomitant T2DM confers a worse prognosis in HF, as the risks of cardiovascular and all-cause mortality are significantly increased, independent of other factors.[5,6]

Over the last decade, cardiovascular outcome trials have investigated several classes of new glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium–glucose co-transporter 2 (SGLT2) inhibitors, and all have demonstrated cardiovascular safety in patients with T2DM. Furthermore, some of these agents have been proven to have beneficial effects in reducing both major adverse cardiovascular events (MACE), as well as hospitalisation for HF, and a few of these drugs have also reduced cardiovascular mortality (i.e. empagliflozin in EMPA-REG OUTCOME[7] and liraglutide in LEADER[8]). Of particular importance has been the consistent finding of a reduction in HF hospitalisations in trials with SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) in patients with T2DM.[9] Also, there was a consistent finding of renal protection in T2DM with these drugs.[10–12] The safety profile and position of the new glucose-lowering agents in T2DM in general has been described in the 2019 European Society of Cardiology guidelines on diabetes, pre-diabetes, and cardiovascular diseases,[13] the 2019 Heart Failure Association (HFA) position paper on the role and safety of new glucose-lowering medications,[14] and the HFA clinical practice update on HF.[15] These documents suggest that SGLT2 inhibitors, empagliflozin, canagliflozin and dapagliflozin, can be used to prevent HF hospitalisation in patients with T2DM.

Recently, the DAPA-HF trial reported that dapagliflozin reduced the risk of worsening HF or death from cardiovascular causes in patients with HF, with and without T2DM.[16] The results of this trial put forward the need to further update the role of SGLT2 inhibitors in the treatment of HF. Hence, the present position paper extends the 2019 documents by providing a summary of evidence from the recent trials and discusses the role of SGLT2 inhibitors in the treatment of HF.

New clinical trials with sodium–glucose co-transporter 2 inhibitors

In patients with T2DM, SGLT2 inhibitors have been shown to reduce the risk of hospitalisation for HF as demonstrated for the first time for empagliflozin, and then for canagliflozin and dapagliflozin.[9] Of note, soon after the results of EMPA-REG OUTCOME became known, the executive committee of DECLARE-TIMI 58 changed the trial endpoint from initially having a primary safety outcome of MACE.[17] This was changed to having two primary efficacy outcomes – MACE and cardiovascular death or hospitalisation for HF (with a split of alpha level equally), and no change in the primary safety outcome or the sample size. In the final results, the MACE co-primary outcome was not significantly reduced, but the second co-primary outcome was reduced, being entirely driven by HF hospitalisation, with no effect on cardiovascular mortality.[17] Recently, DAPA-HF has been the first trial to investigate efficacy of dapagliflozin in patients with HF and reduced ejection fraction (HFrEF) regardless of the presence of T2DM. This trial explored whether dapagliflozin 10 mg once daily, compared to placebo, improves morbidity, mortality and quality of life in symptomatic patients with HF and a left ventricular (LV) ejection fraction ≤40%, largely receiving guideline-directed medical therapy (GDMT) for HF.[16]

In 4744 patients enrolled in DAPA-HF, the primary endpoint of cardiovascular death or worsening HF (defined as a HF hospitalisation or urgent outpatient visit for the treatment of HF) was significantly reduced [hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.65–0.85, $P < 0.001$].[16] The number needed to treat in order to prevent one event was 21 over the median follow-up of 18.2 months. Reductions in the risk of other outcomes were also observed, including cardiovascular mortality (HR 0.82; 95% CI 0.69–0.98). Beneficial effects were evident in patients mostly receiving optimal GDMT; namely, 94% were treated with

an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or sacubitril/valsartan (of note, 11% received the latter at baseline), 96% with a beta-blocker and 71% with a mineralocorticoid receptor antagonist (MRA). Furthermore, patients who received dapagliflozin were more likely to have a clinically relevant improvement in their quality of life after 8 months of treatment as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). Importantly, there was no difference in pre-specified serious adverse events between the dapagliflozin and placebo groups. There was no evidence of heterogeneity in the efficacy of dapagliflozin in any of the pre-specified subgroups, except possibly for the New York Heart Association (NYHA) functional class, given that patients with NYHA class III–IV appeared to derive less benefit compared to patients with NYHA class II. However, there were no heterogeneities in other subgroups of patients, including those with lower LV ejection fraction or higher N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, or in patients with more advanced renal insufficiency, which suggests that dapagliflozin may be similarly effective in patients with more severe HF.[16] Most importantly, there was no difference in the efficacy of dapagliflozin in patients with and without T2DM. An exploratory analysis of DAPA-HF demonstrated that the efficacy of dapagliflozin was similar over the entire spectrum of glycosylated haemoglobin values.[18] These findings suggest that the SGLT2 inhibitor dapagliflozin exerts beneficial effects in HFrEF irrespective of T2DM status, and it appears that the mechanism of action of dapagliflozin in HFrEF extends beyond a simple glucose-lowering effect.

In addition to the DAPA-HF trial, another trial of interest to learn lessons as to how to prevent HF development was the CREDENCE trial.[12] In this trial, 4401 patients with T2DM and an estimated glomerular filtration rate of 30 to <90 mL/min/1.73 m^2 and albuminuria [ratio of albumin (mg) to creatinine (g), >300–5000] were randomised to canagliflozin or placebo.[12] Of the included patients, 15% had a history of HF at baseline, but these patients are not well characterised. Canagliflozin substantially reduced the risk of the primary composite endpoint of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death (HR 0.70; 95% CI 0.59–0.82; $P < 0.001$).[12] There was also a significant reduction in the secondary outcome of HF hospitalisations (HR 0.61; 95% CI 0.47–0.80; $P < 0.001$),[12] indicating that HF prevention is possible also in the setting of high-risk patients with T2DM and concomitant chronic kidney disease (CKD). The preventive role of SGLT2 inhibitors for HF also pertains to other high-risk patients such as those with T2DM and established atherosclerotic cardiovascular disease, in whom cardiovascular outcome trials have consistently shown lower risk for HF hospitalisation with SGLT2 inhibitors.[9]

In addition to clinical outcomes, a potential for an improvement in functional status has been recently explored with SGLT2 inhibitors. The effect of SGLT2 inhibitors on exercise tolerance in patients with HFrEF with and without T2DM is still under debate as the DEFINE-HF trial has not shown a significant effect of dapagliflozin on mean NT-proBNP levels, but increased the proportion of patients achieving a combined endpoint of improved functional status (as measured by the KCCQ), or ≥20% reduction in NT-proBNP.[19] The results of DEFINE-HF trial could be considered as hypothesis generating. In contrast to these results, according to the recent press release, the EMPERIAL Reduced and Preserved trials failed to demonstrate an effect of empagliflozin on functional status in patients with HFrEF and HF with preserved ejection fraction (HFpEF), with and without T2DM over a period of 3 months.[20] After these disappointing head-line results became known, the DETERMINE Reduced and Preserved trials (testing the impact of dapagliflozin vs. placebo on quality of life and functional capacity over 3 months) changed their primary endpoint to be quality of life-focused (rather than relying on 6-min walking test distance as originally planned) and they were somewhat increased in size to improve power. Quality of life improvement may, however, need longer periods of time to become apparent (i.e. 8 months in DAPA-HF), but if achieved, would lend support to a possibility of decreasing the burden of HF symptoms with SGLT2 inhibitor treatment.

Biological mechanisms and effects of sodium–glucose co-transporter 2 inhibitors in heart failure

At present, the mechanisms underlying protective cardiovascular and renal effects of SGLT2 inhibitors in patients with and without T2DM are not completely understood, and several, not mutually exclusive, mechanisms have been proposed,[21,22] as summarised in *Figure 1*.

Sodium–glucose co-transporter 2 inhibitors lower the threshold for glycosuria (60–90 g/day) by lowering the maximum renal transport capacity for glucose reabsorption.[23] This effect attenuates at low glucose levels, explaining the low risk of hypoglycaemia with SGLT2 inhibitors. In addition to glycosuria, SGLT2 inhibitors promote natriuresis and uricosuria.[7,17,24–26] Their favourable metabolic effects include increased insulin sensitivity and glucose uptake in the muscle cells,[27] decreased gluconeogenesis and increased ketogenesis.[28,29] These drugs also stimulate weight loss due to the renal caloric loss in glycosuria,[7,17,24] and have a favourable impact on body fat distribution.[30,31] Recent findings also suggest a reduction in liver steatosis and the accompanying hepatocellular injury.[32–35] Of note, SGLT2 inhibitors provide nephron protection, most likely through a tubulo-glomerular feedback-mediated vasoconstriction of the afferent arteriole and the reduction in intra-glomerular pressure.[11,36–38] This effect is important to reduce glomerular hyperfiltration in T2DM, which may decrease the risk of subsequent nephropathy.[11,12] These favourable metabolic and reno-protective effects may provide long-term benefits for outcomes; however, a relatively early separation of treatment curves for worsening HF or cardiovascular mortality seen in DAPA-HF suggests that more rapid mechanisms may be involved (e.g. improvement in haemodynamic status, direct metabolic or vascular effects).[39]

The favourable haemodynamic effects are mediated by a number of mechanisms including osmotic diuresis, natriuresis and plasma and interstitial fluid volume reduction, leading to a reduction in ventricular preload and afterload.[23,40,41] Furthermore, a

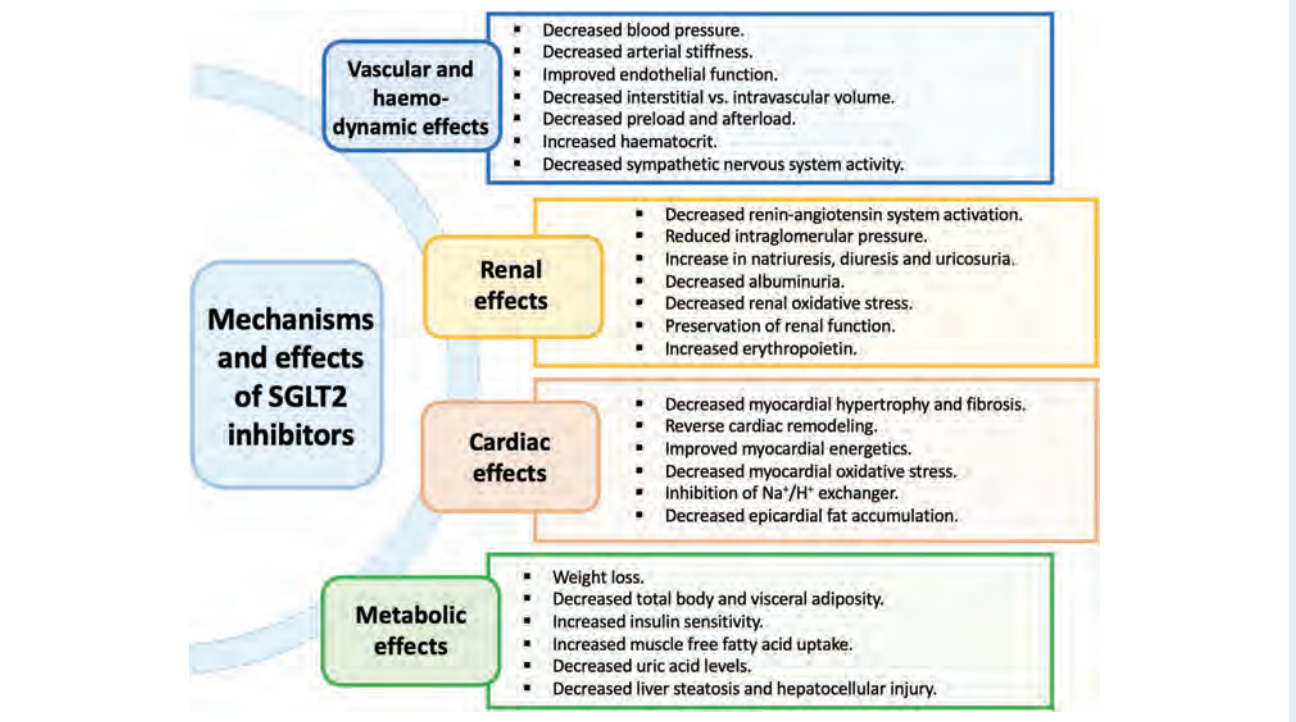

Figure 1 Proposed biological mechanisms and effects of sodium–glucose co-transporter 2 (SGLT2) inhibitors.

mathematical model has been used, coupled with clinical data on water an electrolyte excretion, to illustrate that, unlike diuretics, SGLT2 inhibitors seem to exert a greater reduction in interstitial fluid compared with plasma volume (mediated by peripheral sequestration of osmotically inactive sodium), which may prevent plasma volume depletion and subsequent hypoperfusion occasionally observed with diuretics.[42] An increasing body of evidence suggests that SGLT2 inhibitors may less likely induce electrolyte disturbances, neurohormonal activation and a decline in renal function that can occur with diuretics.[43,44] Indeed, they prevent a decline in kidney function, which may have a favourable impact on HF prevention.[12,44]

Interestingly, a mediation analysis exploring the contribution of different factors to the cardiovascular mortality reduction seen with empagliflozin in the EMPA-REG OUTCOME trial, identified an increase in haemoglobin and haematocrit (i.e. likely due to a decrease in plasma volume) as the largest contributors, supporting the above described haemodynamic hypothesis.[45,46] This is consistent with further observations from the EMPA-REG OUTCOME trial demonstrating that the cardiovascular effects of empagliflozin were independent of glycaemic control.[47]

In addition to haemodynamic effects, other mechanisms may be involved in the increase in haematocrit. Given that an increase in haematocrit lasts longer compared with the increase in urine output after an SGLT2 inhibitor initiation, it has been suggested that an increase in renal erythropoietin production could be a potential mechanism for the change in haemoglobin and haematocrit levels.[48,49]

Another proposed mechanism for the beneficial effect of SGLT2 inhibitors is inhibition of the sodium–hydrogen exchanger (NHE1) activity, which is up-regulated both in T2DM and HF.[50] By inhibiting the NHE1 receptors, SGLT2 inhibitors may protect the heart from toxic intracellular Ca^{2+} overload.[51,52] SGLT2 inhibitors may also exert direct effects on myocardial metabolism[40,53] and decrease myocardial oxidative stress.[54] Similar to T2DM, HF is characterised by a state of insulin resistance.[55] In the insulin-resistant heart, free fatty acids (FFA) are favoured as an energy source over glucose.[56] This metabolic shift results in decreased cardiac metabolic efficiency (i.e. insufficient ATP production). In an experimental model, empagliflozin prevented a decrease in cardiac function and increased cardiac ATP production without changing overall metabolic efficiency.[57] This increase in cardiac energy production was the result of increased glucose oxidation, lower FFA oxidation, without changes in ketone body oxidation. Additionally, overall rates of ketone body oxidation were decreased and remained unchanged with empagliflozin treatment, although ketone body supply to the heart was increased. This suggests that the ability of SGLT2 inhibitors to increase circulating ketone body levels may provide an additional source of energy to sustain cardiac contractile function. This was supported by another experimental study showing that empagliflozin ameliorated LV remodelling in pigs, an effect mediated by a greater uptake of ketone bodies, FFA and branched-chain amino acids.[53]

A benefit on ventricular remodelling was also demonstrated in patients with T2DM and coronary artery disease in the EMPA-HEART CardioLink-6 study, which showed a reduction

Table 1 Ongoing clinical trials with sodium–glucose co-transporter 2 inhibitors

Cardiovascular outcomes in patients with HFrEF or HFpEF

EMPEROR-Reduced (NCT03057977)
- Empagliflozin in patients with HFrEF with/without T2DM
- Primary outcome: cardiovascular death or HF hospitalisation

EMPEROR-Preserved (NCT03057951)
- Empagliflozin in patients with HFpEF with/without T2DM
- Primary outcome: cardiovascular death or HF hospitalisation

DELIVER (NCT03619213)
- Dapagliflozin in patients with HFpEF with/without T2DM
- Primary outcome: composite of cardiovascular death, hospitalisation for HF or urgent HF visit

SOLOIST-WHF (NCT03521934)
- Sotagliflozin in patients with T2DM and HF (following hospitalisation for worsening HF)
- Primary outcome: cardiovascular death or hospitalisation for HF in patients with LVEF <50%, as well as in the total patient population (regardless of LVEF)
- Prematurely discontinued

Symptoms and functional status

DETERMINE-Reduced (NCT03877237)
- Dapagliflozin in patients with HFrEF with/without T2DM
- Primary outcome: change from baseline in KCCQ and 6-min walk distance at week16

DETERMINE-Preserved (NCT03877224)
- Dapagliflozin in patients with HFpEF with/without T2DM
- Primary outcome: change from baseline in KCCQ and 6-min walk distance at week16

Outcomes in patients with chronic kidney disease

EMPA-KIDNEY (NCT03594110)
- Empagliflozin in patients with chronic kidney disease with/without T2DM
- Primary outcome: kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomisation) or cardiovascular death

DAPA-CKD (NCT03036150)
- Dapagliflozin in patients with chronic kidney disease with/without T2DM
- Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESKD or cardiovascular death or renal death
- Prematurely discontinued for efficacy

Cardiac physiology and metabolism

EMPA-VISION (NCT03332212)
- Empagliflozin in patients with HFrEF or HFpEF with/without T2DM
- Primary outcome: effect on cardiac physiology and metabolism as assessed by cardiac magnetic resonance spectroscopy

EMPA-TROPISM (NCT03485222)
- Empagliflozin in patients with HFrEF (LVEF <50%) without T2DM
- Primary outcome: effect on left ventricular systolic and diastolic volumes as assessed by cardiac magnetic resonance imaging

EmDia (NCT02932436)
- Empagliflozin in patients with T2DM
- Primary outcome: effect on left ventricular diastolic function as assessed by echocardiography

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; T2DM, type 2 diabetes mellitus.

in LV mass index (as measured by cardiac magnetic resonance) and an improvement in diastolic function without changes in LV systolic function after 6 months of treatment with empagliflozin.[58] Furthermore, a significant reduction in LV mass in patients with T2DM was observed with dapagliflozin in the DAPA-LVH trial, suggesting a possibility of reverse LV remodelling.[59] However, this was not corroborated by the recent REFORM trial, in which dapagliflozin had no impact on any of the parameters of LV remodelling over 12 months of treatment.[60] These issues might be resolved by ongoing clinical studies utilizing advanced

echocardiographic techniques (e.g. speckle tracking and real-time three-dimensional echocardiography) and cardiac magnetic resonance imaging to assess the effects of SGLT2 inhibition on cardiac structure and function (*Table 1*).

Another currently unproven hypothesis about the cardiovascular effect of SGLT2 inhibitors includes possible cardiac anti-fibrotic effects[40,61] and an improved balance in adipokine secretion.[62] Beneficial effects on endothelial function,[63] blood pressure, central pulse pressure,[7,17,24] and parameters of arterial stiffness and vascular resistance,[64] as well as a reduction in sympathetic nervous system activity,[65] may also play an important role in the prevention of HF. Furthermore, it has been hypothesised that a favourable change in the trajectory of cellular responses to environmental stressors may be yet another mechanism of cardiorenal protection with SGLT2 inhibitors that needs to be explored.[66]

The role of sodium–glucose co-transporter 2 inhibitors in the prevention and treatment of heart failure

Currently, DAPA-HF is the only published trial demonstrating a reduction in clinical endpoints with an SGLT2 inhibitor, dapagliflozin, in patients with HFrEF, with and without T2DM.[16] Hence, a role of SGLT2 inhibitors in the treatment of HFrEF can only be documented for dapagliflozin, pending the results of ongoing trials with other SGLT2 inhibitors.

Two points need to be noted when discussing the place of dapagliflozin in the treatment of HFrEF. First of all, the benefit of dapagliflozin on reducing important clinical events was seen within weeks of its initiation.[16] Given that HF is associated with severely impaired survival, a timely initiation of an agent with a proven benefit on outcomes is of crucial clinical importance.

Secondly, a sub-analysis of the DAPA-HF trial demonstrated that dapagliflozin can produce a significant improvement in quality of life as assessed by the KCCQ in patients with HFrEF,[67] which is of high clinical value.[19] Furthermore, dapagliflozin appears safe and effective in vulnerable elderly patients, as well as in those with impaired renal function (excluding patients with estimated glomerular filtration rate <30 mL/min/1.73 m^2), in whom up-titration of GDMT may be challenging.[68,69] A post-hoc analysis of the DAPA-HF trial demonstrated similar risk reductions in HF hospitalisation and mortality with dapagliflozin, irrespective of background HF therapy, including ACEi/ARB, beta-blockers, MRAs, ivabradine, sacubitril/valsartan, cardiac resynchronisation therapy and implantable cardioverter-defibrillators.[70] Furthermore, the results were consistent regardless of whether patients received ≥50% or <50% of guideline-directed target doses of ACEi/ARBs, beta-blockers, or MRAs.[70] These observations indicate a complementary value of dapagliflozin in addition to the established GDMT for HF, and further support its use in ambulatory patients with symptomatic HFrEF in order to improve clinical outcomes.

Besides, significant renal protection observed with canagliflozin in the CREDENCE trial of T2DM patients with CKD and albuminuria (also noted in outcome trials with other SGLT2 inhibitors in the general population of T2DM patients) needs to be taken into account when discussing the role of SGLT2 inhibitors in HF.[12] Recently, a press release reported that the DAPA-CKD trial, enrolling 4245 patients with CKD, with and without T2DM, was prematurely stopped because of efficacy.[71] Since CKD is prevalent and associated with high mortality in HF,[72,73] prevention of the progression and/or worsening of CKD needs to be considered as an important goal that may translate into improved outcomes in HF.

Emerging data from EMPA-RESPONSE-AHF suggest potential safety of an early introduction of an SGLT2 inhibitor, empagliflozin, in acute HF patients, with and without T2DM.[74] Pending confirmation from a larger trial, these results could be promising in advancing the treatment of acute HF.

Ongoing trials will further elucidate the role of SGLT2 inhibitors in the treatment of HF, as well as the underlying mechanisms by which SGLT2 inhibitors impact on cardiac structure, physiology and metabolism (*Table 1*).

Conclusions

Based on the available evidence, SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) could be recommended to reduce the risk of HF hospitalisation in T2DM patients with either established cardiovascular disease or at high cardiovascular risk. Currently available data suggest that dapagliflozin could be considered in the treatment of HFrEF patients, with and without T2DM. Further mechanistic studies and ongoing large-scale clinical trials will provide a more comprehensive overview of the role in the treatment of HF with other SGLT2 inhibitors and will also extend our knowledge on their potential for the treatment of acute HF and HFpEF.

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POSITION PAPER

Heart Failure Association of the European Society of Cardiology update on sodium–glucose co-transporter 2 inhibitors in heart failure

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The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has recently issued a position paper on the role of sodium–glucose co-transporter 2 (SGLT2) inhibitors in heart failure (HF). The present document provides an update of the position paper, based of new clinical trial evidence. Accordingly, the following recommendations are given:

- Canagliflozin, dapagliflozin empagliflozin, or ertugliflozin are recommended for the prevention of HF hospitalization in patients with type 2 diabetes mellitus and established cardiovascular disease or at high cardiovascular risk.
- Dapagliflozin or empagliflozin are recommended to reduce the combined risk of HF hospitalization and cardiovascular death in symptomatic patients with HF and reduced ejection fraction already receiving guideline-directed medical therapy regardless of the presence of type 2diabetes mellitus.

Keywords Heart failure • Sodium–glucose co-transporter 2 inhibitors • Type 2 diabetes mellitus • Cardiovascular outcomes • Renal function

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has recently issued a position paper on the role of sodium–glucose co-transporter 2 (SGLT2) inhibitors in heart failure (HF).[1] This document was published awaiting the results of ongoing clinical trials that have since become available. Hence, the present document provides an HFA update of the position paper on the role of SGTL2 inhibitors in the prevention and treatment of HF[1] in light of new evidence from clinical trials.

Recently, the VERTIS-CV (Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes) trial demonstrated that ertugliflozin vs. placebo reduces the risk of HF hospitalization in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular (CV) disease (23.7% with a history of HF), with a hazard ratio (HR) of 0.70 [95% confidence interval (CI) 0.54–0.90, *P*-value not provided in accordance with the pre-specified hierarchical statistical testing plan].[2] The benefit was similar in patients with or without a history of HF. These findings are consistent with those of empagliflozin, canagliflozin and dapagliflozin, described in the previous document,[1] and solidify the evidence that SGLT2 inhibitors have a beneficial effect in reducing the risk of hospitalizations for HF in patients with T2DM and CV risk factors or established CV disease.

Furthermore, in 3730 patients with symptomatic HF and reduced ejection fraction (HFrEF), with or without T2DM, the EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) demonstrated a significant risk reduction with empagliflozin 10 mg daily vs. placebo in the primary combined endpoint of CV death or hospitalization for HF (HR 0.75, 95% CI 0.65–0.86; $P < 0.001$) during a median follow-up of 16 months.[3] The trial included ~50% of patients without T2DM, 73% had left ventricular ejection fraction <30%, 79% had N-terminal B-type natriuretic peptide level ≥1000 pg/mL and almost a half of patients had significant renal dysfunction at baseline [estimated glomerular filtration rate (eGFR) ≥20 to 60 mL/min/1.73 m^2]. The benefit was observed regardless of the presence of T2DM, baseline renal function, or the use of medications for HFrEF treatment, including sacubitril/valsartan (~20% of the trial patients). Risk reduction was primarily driven by a substantial decrease in HF hospitalizations (HR 0.69, 95% CI 0.59–0.81; $P < 0.001$). The trial has also shown a significant reduction in the two pre-specified secondary outcomes, namely, the total number of HF hospitalizations (first and recurrent events: HR 0.70, 95% CI 0.58–0.85; $P < 0.001$) and a decline in renal function (defined as a mean slope of change in eGFR, mL/min/1.73 m^2 per year).

A meta-analysis which used study-level data from DAPA-HF (A Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and patient-level data from EMPEROR-Reduced further explored the effect of SGLT2 inhibition with dapagliflozin or empagliflozin in a broader spectrum of HF patients from both trials.[4] The meta-analysis demonstrated a reduction in both CV (HR 0.86, 95% CI 0.76–0.98; $P = 0.027$) and all-cause mortality (HR 0.87, 95% CI 0.77–0.98; $P = 0.018$) with SGLT2 inhibition, without any evidence of a statistical heterogeneity between dapagliflozin and empagliflozin. Similarly, SGLT2 inhibition reduced the risk of the combined endpoint of HF hospitalization or CV death (HR 0.74, 95% CI 0.68–0.82; $P < 0.0001$), as well as the first HF hospitalization (HR 0.69, 95% CI 0.62–0.78; $P < 0.0001$), the total number of HF hospitalizations or CV mortality (HR 0.75, 95% CI 0.68–0.84; $P < 0.0001$) and worsening renal function (HR 0.62, 95% CI 0.43–0.90; $P = 0.013$). The results were consistent in patients with or without T2DM. Data on the safety profile of both agents were reassuring given that no excess risk in adverse events was noted compared with placebo, including renal adverse events, volume depletion, severe hypoglycaemia, bone fractures, amputations or Fournier's gangrene.[4] In particular, ketoacidosis was uncommon with only three cases in DAPA-HF (all in patients with T2DM) and no cases observed in EMPEROR-Reduced.[4]

In addition, a secondary analysis of the DAPA-CKD trial (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) in patients with chronic kidney disease (eGFR 25–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio 200–5000 mg/g) with or without T2DM, revealed a significant risk reduction in hospitalizations for HF or CV death (HR 0.71, 95% CI 0.55–0.92; $P = 0.0089$) with dapagliflozin vs. placebo.[5]

[†]These authors contributed equally to the position paper.

Assessing the landscape for the use of SGLT2 inhibitors in the prevention and treatment of HF, it can be concluded:

- **Canagliflozin, dapagliflozin empagliflozin, or ertugliflozin are recommended for the prevention of HF hospitalization in patients with T2DM and established CV disease or at high CV risk.**
- **Dapagliflozin or empagliflozin are recommended to reduce the combined risk of HF hospitalization and CV death in symptomatic patients with HFrEF already receiving guideline-directed medical therapy regardless of the presence of T2DM.**

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Vascular and metabolic effects of SGLT2i and GLP-1 in heart failure patients

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Abstract

Alterations of endothelial function, inflammatory activation, and nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway are involved in the pathophysiology of heart failure. Metabolic alterations have been studied in the myocardium of heart failure (HF) patients; alterations in ketone body and amino acid/protein metabolism have been described in patients affected by HF, as well as mitochondrial dysfunction and other modified metabolic signaling. However, their possible contributions toward cardiac function impairment in HF patients are not completely known. Recently, sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have emerged as a new class of drugs designed to treat patients with type 2 diabetes (T2D), but have also been shown to be protective against HF-related events and CV mortality. To date, the protective cardiovascular effects of these drugs in patients with and without T2D are not completely understood and several mechanisms have been proposed. In this review, we discuss on vascular and metabolic effects of SGLT2i and GLP-1 in HF patients.

Keywords Gliflozin · SGLT2i · GLP-1 RA · Heart failure · Endothelial function · Metabolic effect

Introduction

Alterations of endothelial function, inflammatory activation [1], and nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway are involved in the pathophysiology of heart failure (HF) [2]. In patients affected by HF, eNOS expression is downregulated, less NO is produced, and consequently, flow-mediated vasodilation (FMD) is reduced, leading to vasoconstriction effect [3]. Moreover, production of vasoconstrictors increases vascular resistance, resulting in vascular remodeling and endothelial dysfunction. Furthermore, HF is related to an altered redox state and production of reactive oxygen species [4]. These molecules, interacting with NO, determine a further oxidant, the peroxynitrite anion. The resulting reduction of NO bioavailability contributes to the progression of HF [3].

Metabolic alterations have been studied in the myocardium of HF patients, underlying a reversion to a more fetal-like metabolic profile (depressed fatty acid oxidation and concomitant increased dependence on use of glucose) [5]. Currently, alterations in ketone body and amino acid/protein metabolism have been described in

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patients affected by HF, as well as mitochondrial dysfunction and others modified metabolic signaling [6]. However, their possible contributions toward cardiac function impairment in HF patients are not completely known.

Type 2 diabetes (T2D) and HF are major public health issues and their prevalence continues to increase. They are common and often coexisting conditions, with a detrimental relationship [7]. Despite the success of many antihyperglycemic therapies to lower hyperglycemia in T2D, the high prevalence of HF persists, suggesting the possibility that additional factors beyond glycemia might contribute to the increased HF risk in diabetes. Recently, sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have emerged as a new class of drugs designed to treat patients with T2D, but have also been shown to be protective against HF-related events and CV mortality. SGLT2i block renal glucose reabsorption in the proximal tubule, leading to increased urinary sodium and glucose excretion. Long-term CV safety trials of SGLT2 inhibitors have shown significant cardiovascular benefits across various subgroups [8] (Table 1). In all these trials, the effect of SGLT-2i on the risk of HF remained significant regardless of the presence of a history of HF or established atherosclerotic cardiovascular disease at baseline. These trials confirmed the reduction in HF hospitalizations as a likely class effect of SGLT2 inhibitors. All three randomized controlled trials (RCTs), specifically designed to assess the effects of SGLT2 inhibitors in the HF population (Table 2), found a significant reduction in the composite endpoint of first HF hospitalization or cardiovascular death.

GLP-1 RAs are a new glucose-lowering medication with mimicking incretins' actions [16] usually secreted by L-cells of the gastrointestinal tract in response to food ingestion. Their activity is due to the binding with Gs protein-coupled receptors, increasing intracellular cyclic adenosine monophosphate and calcium release and leading to specific responses according to the targeting organ and system [17, 18]. The class of GLP-1 RAs is broad; there are several completed CVOTs [19–28]with GLP-1 Ras (Table 3). These trials with GLP-1 RAs did not reveal a significant effect on HF risk in patients with T2D. Even though the results of these dedicated studies were not positive, a recent meta-analysis reported a 9% reduction in hospitalization rate for HF in patients treated with GLP-1RAs [29].

To date, the protective cardiovascular effects of these drugs in patients with and without T2D are not completely understood and several mechanisms have been proposed [30, 31]. In this review, we discuss on vascular and metabolic effects of SGLT2i and GLP-1 in HF patients.

Table 1 SGLT2i: long-term CV safety trials

Trial	Characteristics of the population	Main results	References
EMPA-REG OUTCOMES (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes)	Patients with T2D and established cardiovascular disease	35% decrease in HF hospitalizations at a median of 3.1 years	Zinnman et al. [9]
CANVAS (Canagliflozin Cardiovascular Assessment Study and Canagliflozin Cardiovascular Assessment Study-Renal) program	Patients with T2D and cardiovascular disease (65.6%) or high cardiovascular risk (34.4%)	Lower risk of HF hospitalization (− 33%) compared with placebo	Neal et al. [10]
DECLARE TIMI-58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction trial)	T2D patients with, or at risk for, atherosclerotic cardiovascular disease	Significant reduction (− 17%) in the primary composite efficacy endpoint of CV death or hospitalization for HF with dapagliflozin compared to placebo, mainly driven by a significant reduction in HF hospitalizations (− 27%)	Wiviott et al. [11]
VERTIS-CV trial (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial)	Patients with T2D and established atherosclerotic cardiovascular disease (23.7% HF)	Decrease in hospitalization for HF compared to placebo	Cannon et al. [12]

Table 2 SGLT2i: heart failure trials

Trial	Characteristics of the population	Main results	Ref
DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)	Patients with HFrEF [(EF ≤ 40%, NYHA stages II–IV, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels] with or without diabetes in optimal medical therapy for HF	Reduction of 26% of the primary endpoint of worsening HF or CV mortality, as well as the individual endpoints of worsening HF event (reduction of 30%) and CV mortality (reduction of 18%), compared to placebo This effect was independent of diabetes status	McMurray et al. [13]
EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction)	Patients with HF (LVEF ≤ 40%), with or without T2D, on top of recommended HF treatment	Empagliflozin reduced the risk of the primary outcome variables as well as total hospitalizations for HF by 25% to 30%. The benefits were seen in patients with or without diabetes	Packer et al. [14]
SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure)	T2D patients, recently hospitalized for worsening HF	Sotagliflozin resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations for HF than placebo	Bhatt et al. [15]

Vascular effects of SGLTi2 in heart failure patients

In several experimental models of T2D, almost all gliflozins improved endothelial function [32], arterial stiffness and vascular smooth muscle dysfunction [33], and decreased oxidative stress and showed anti-inflammatory effects [34], so we are led to consider their class effects. In fact, these vascular improvements were accompanied by reductions in circulating markers of inflammation. In cultured human endothelial cells, canagliflozin directly inhibits endothelial pro-inflammatory chemokine/cytokine secretion by AMPK-dependent and -independent mechanisms [35]. Vascular function improvement was also related to empagliflozin-mediated non-glycemic actions, such as weight loss and volume contraction [36], and via anti-inflammatory mechanisms [37]. Cardioprotective properties for empagliflozin may in part be linked to the ability of empagliflozin to preserve and restore the structural integrity of the endothelial glycocalyx (GCX), which helps to maintain vascular health by promoting an anti-inflammatory endothelium. Empagliflozin restored heparinase III–mediated GCX disruption and the normal mechanotransduction responses in GCX-compromised HAAECs [38].

Empagliflozin as an add-on treatment of metformin therapy significantly improved arterial stiffness compared to metformin in T1DM patients [39]. Empagliflozin may decrease arterial stiffness in patients with T2DM [40]. Through osmotic diuresis, empagliflozin may increase blood viscosity and, consequently, shear stress, promoting the synthesis of vasoactive substances [41].

Dapagliflozin induces vasodilation via the activation of Kv channels and protein kinase G and is independent of other K + channels, Ca2 + channels, intracellular Ca2 +, and the endothelium [42]. In subjects with T2D, dapagliflozin produces a decrease in arterial stiffness, expressed as a decrease of the velocity of the carotid-femoral pulse (VPc-f) by tonometry, [43] and it improves endothelial function measured by flow-mediated vasodilation compared with that associated with an increased dose of metformin [44]. Two days of treatment with dapagliflozin acutely improved endothelial function and reduced aortic stiffness in T2D patients [45]. Dapagliflozin and empagliflozin rather restore NO bioavailability by inhibiting ROS generation than by affecting eNOS expression or signaling [46].

Empagliflozin restored beneficial effects of cardiac microvascular endothelial cells by reducing mitochondrial ROS production and cytoplasmic ROS accumulation, which led to restoration of endothelial NO bioavailability and preservation of CM contraction and relaxation [47].

Tofogliflozin treatment significantly increased FMD in patients with T2DM and heart diseases (ischemic heart

Table 3 Completed CVOTs with the GLP-1 RAs

Trial	Characteristics of the population	Main results	Ref
ELIXA	T2D patients with myocardial infarction or hospitalization for unstable angina (within previous 180 days)	The addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular events or other serious adverse events	Pfeffer et al. [19]
LEADER trial	T2D and high cardiovascular risk	Liraglutide treatment significant results in reducing MACE, all-cause mortality, and CV mortality	Marso et al. [20]
SUSTAIN-6	T2D at high cardiovascular risk	The rate of CV death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo	Holman et al. [21]
HARMONY Outcomes	T2D and cardiovascular disease	Albiglutide significantly reduced MACE	Hernandez et al. [22]
Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND)	T2D patients with either a previous CV event or CV risk factors	Dulaglutide reduced MACE (CV death, nonfatal myocardial infarction) and stroke in comparison with control	Gerstein et al. [23]
PIONEER-6 (Semaglutide)	T2D patients at high cardiovascular risk (age of $\geq$ 50 years with established CV or chronic kidney disease, or age of $\geq$ 60 years with CV risk factors only)	The cardiovascular risk profile of oral semaglutide was not inferior to that of placebo	Husain et al. [24]
Exenatide Study of Cardiovascular Event Lowering (EXSCEL)	T2D with or without previous CV disease,	The incidence of MACE did not differ significantly between patients who received exenatide and those who received placebo	Fudim et al. [25]
Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial	HFrEF patients (NYHA F.C III–IV) with and without T2D	No significant effect of liraglutide on mortality or HF hospitalizations in comparison with placebo	Sharma et al. [26]
Multi-center, Placebo-controlled Study to Evaluate the Safety of GSK716155 and Its Effects on Myocardial Metabolism, Myocardial Function, and Exercise Capacity in Patients With NYHA Class II/III Congestive Heart Failure	HFrEF < 40% in NYHA II or III	There was no detectable effect of albiglutide on cardiac function	Lepore et al. [27]
LIVE Study	HFrEF patients (LVEF $\leq$ 45%) clinically stable with or without T2D and on optimal HF treatment	Liraglutide did not affect left ventricular systolic function compared with placebo and increased heart rate and number of serious cardiac adverse events in comparison with control	Jorsal et al. [28]

Table 4 Trials on vascular effects in patients in treatment with SGLT2i

Trial	Characteristics of the population	Main results	Ref
ADDENDA-BHS2	Diabetic participants randomized to dapagliflozin 10 mg/day or glibenclamide 5 mg/day on top of metformin	No resulted posted	Cintra et al. [52]
EMBLEM trial	T2D and established CVDs, including HF or coronary artery disease or stroke or peripheral artery disease or the presence of coronary artery stenosis (≥ 50%)	24 weeks of treatment did not affect endothelial function compared with placebo	Tanaka et al. [53] (second analysis [54])
Randomized, Placebo-Controlled, Crossover Clinical Study to Analyse the Effect of Dapagliflozin on Microvascular and Macrovascular Circulation and Total Body Sodium Content	T2D patients	A vascular remodeling improvement after six weeks of dapagliflozin treatment	Ott et al. [55]

disease, arrhythmia, valvular heart disease, cardiomyopathy, and congenital heart disease) [48].

In a meta-analysis about the effects of DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors on endothelial function and arterial stiffness, assessed by FMD and pulse wave velocity (PWV), only SGLT2 inhibitors significantly improved FMD, but not DPP-4 inhibitors or GLP-1 RA. Both GLP-1 RA and DPP-4 inhibitors significantly decreased PWV [49].

After 12-month treatment with gliflozins, SGLT2i or GLP-1RA and SGLT2i showed a greater decrease of PWV (10.1% and 13%) than insulin or GLP-1RA (3.6% and 8.6%) [50]. The GLP-1RA and SGLT2i therapy showed the greatest effect in patients with left ventricular EF < 55%.

The direct effects of SGLT2 inhibition on vascular function, combined with the natriuresis effects of SGLT2 inhibition, may contribute to hemodynamic effects [51].

A few results from trials [52–55] on vascular effects in patients in treatment with SGLT2i were reported (Table 4). Further trials are needed in order to understand the real effect of gliflozin on endothelial function in HF patients regardless of T2DM. Vascular effects of SGLT2i are reported in Fig. 1.

Vascular effects of GLP-1 in heart failure patients

Recently, GLP-1 demonstrated beneficial effects on a variety of tissues such as the cardiovascular and neurological systems and this has high clinical relevance given the multiple and common post-diagnosis complications associated with T2D [56].

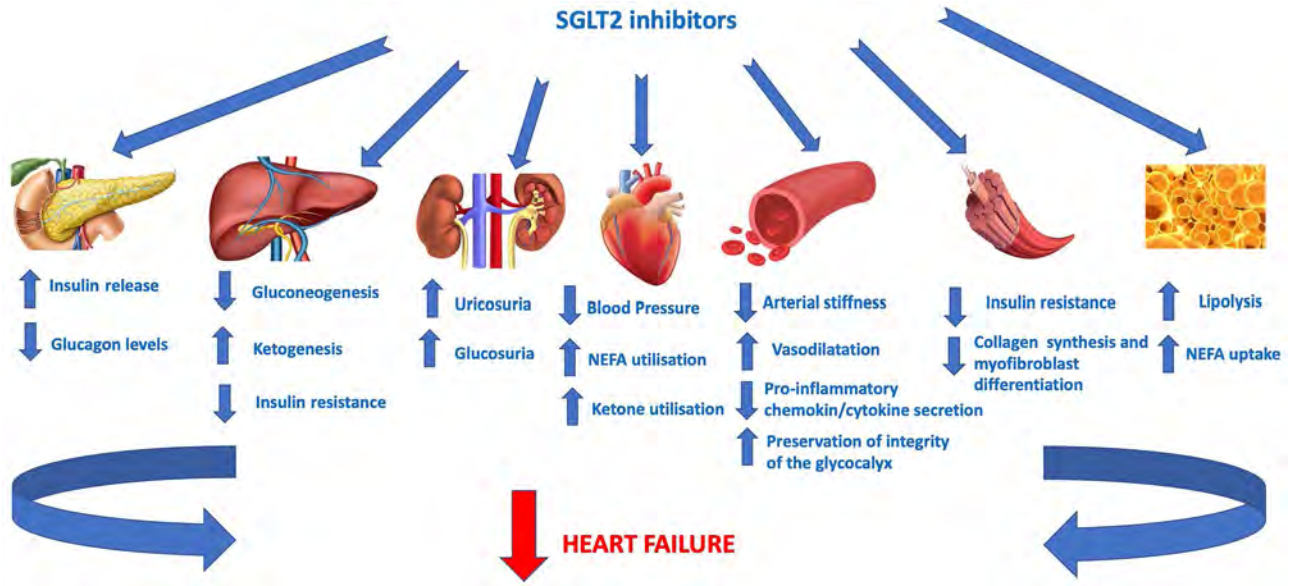

Fig. 1 Effects of SGLT2i on different organs: different mechanisms and pathways secondary to SGLT2i

Cytoprotection is among the pleiotropic actions described for GLP-1 in different cell types, including cardiomyocytes[57]. Particularly relevant is the role of GLP-1 on the oxidative pathways. The interaction of GLP-1 with its receptors induces antioxidative effects by augmentation of cAMP, PI3K, and PKC pathways. The final result is an enhanced expression of antioxidant enzymes and increased activation of the nuclear factor erythroid-related factor 2–antioxidant response elements (Nrf2-AREs) pathway [58, 59]. Nrf2 increases the activation of antioxidants such as NAD(P)H dehydrogenase, superoxide dismutases, and glutathione peroxidases [58] with a consequent decrease of reactive oxygen species [60]. The enhanced expression of Nrf2 due to GLP-1 has a cardioprotective effect counteracting cardiac oxidative stress.

Moreover, GLP-1 reduces oxidative stress–induced apoptosis in cardiac progenitor cells. This mechanism is mediated by the activation of its receptor and the consequent augmentation of PKA activity, with resulting inhibition of the signaling of the MKK4/MKK7/JNK cascade that mediates apoptosis [61]. GLP-1 and the GLP-1RAs exenatide and liraglutide improved NO synthase activity in human endothelial cells [62, 63].

GLP-1RAs may also have long-term benefits on the progression of underlying atherosclerosis. Liraglutide significantly decreases carotid intima media thickness, indicating involvement with the progression of atherosclerosis [64]. An additional role can be played by the reduction of inflammatory cytokines and ROS production made by GLP-1 that can contribute to the reduction of atherosclerosis progression [65].

Additionally, liraglutide increased acetylcholine-induced vasodilation. These effects may provide some benefits during the acute phase of cardiac ischemia.

GLP-1 also contributes to a significant reduction of systolic blood pressure due to their suppression of the renin-angiotensin system [66].

More studies addressing the possible vascular effects are needed. Vascular effects of GLP-1 are reported in Fig. 2.

Metabolic effects of SGLT2i in heart failure patients

Several studies showed that SGLT2i has the capacity to reduce arterial stiffness and in preventing endothelial dysfunction [67]. This latter effect may be associated with the increased uricosuria, a possible cardioprotective factor, observed in response to SGLT2 inhibition. The uric acid is secreted from the tubular cells by glucose activation of the glucose–uric acid transporter (GLUT9b). An increase in glucose leads to an increase in uric acid excretion with a consequent decrease in uricemia [30].

There is also a group of favorable metabolic mechanisms related to SGLT2, including increased insulin sensitivity with glucose uptake in muscle cells, decreased gluconeogenesis, and increased ketogenesis [68, 69]. Particularly, they can improve cardiac energetic metabolism and decrease myocardial oxidative stress in patients with T2D or HF, in which there is a state of insulin resistance with free fatty acids (FFAs) as a principal energy source. In patients with T2D, whole-body and myocardial insulin-mediated glucose utilization are impaired (i.e., insulin resistance), and a larger (80%) than normal (50–70%)

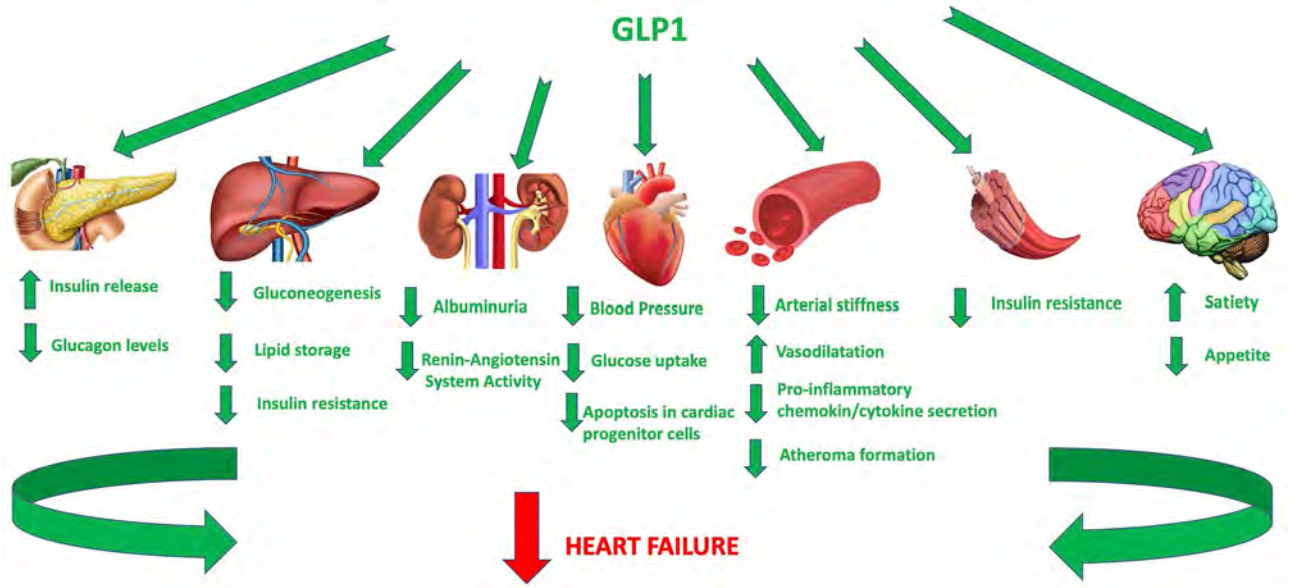

Fig. 2 Effects of GLP-1 on different organs: different mechanisms and pathways secondary to SGLT2i

proportion of energy is derived from the oxidation of fatty substrates. FFAs require 8% more oxygen than glucose to produce the same number of calories. This metabolic condition results in decreased cardiac metabolic efficiency and insufficient ATP production.

Instead, SGLT2i enhance the production of the ketone β-hydroxybutyrate (βOHB) and this could be an alternative and less expensive myocardial energy source in these patients.

Under conditions of mild, persistent hyperketonemia, b-hydroxybutyrate is freely taken up by the heart (among other organs) and oxidized in preference to fatty acids. This fuel selection improves the transduction of oxygen consumption into work efficiency at the mitochondrial level in the endangered myocardium (and may also improve metabolic status and function of other organs, mainly the kidney).

The increased ketogenesis improves cardiac function and mechanical efficiency [70]. Empagliflozin improves adverse cardiac remodeling in HF by stimulating the switches of myocardial fuel utilization away from glucose toward ketone bodies, improving myocardial energetics, improving systolic function, and getting better cardiac reverse remodeling [71].

In patients with T2D, SGLT2i, but not GLP1 RAs, induce glycosuria and thus lower plasma glucose and insulin levels and raise fasting and postmeal glucagon concentrations. The subtraction of large amounts of glucose from the glucose pool, coupled with the dual hormonal changes, results in a restriction of glucose utilization, and a concomitant increase in lipid mobilization and usage for energy production. Under conditions of reduced portal insulin-to-glucagon ratio, the increased delivery of FFAs to the liver stimulates ketogenesis, resulting in a metabolic condition resembling a prolonged fast. In addition, SGLT2i is believed to decrease ketone elimination by the kidneys.

Furthermore, the increase of βOHB levels may prevent the pro-hypertrophy pathway. In fact, recent experimental data showed that these drugs have antifibrotic effects, including suppression of collagen synthesis and inhibition of myofibroblast differentiation.

SGLT2i effectively reduce the liver fat [71] and visceral fat mass [72], and recently, Yanai et al. [73] demonstrated that SGLT2i reduced the degree of hepatic fibrosis in patients at high risk of hepatic fibrosis.

Dapagliflozin treatment for 5 weeks in patients with T2D increased fat oxidation improved hepatic and adipose insulin sensitivity and improved 24-h energy metabolism [74].

Empagliflozin exhibited superior effects on cardiometabolic biomarkers, such as uric acid, high-density lipoprotein cholesterol, ketone bodies, and insulin sensitivity than sitagliptin [75].

Empagliflozin might decrease mitochondrial DNA damage and oxidative stress, leading to mitochondrial biogenesis and raising ATP levels [77].

The EMPA-VISION trial [76] is a double-blind, randomized, placebo-controlled, mechanistic study assessing the effects of empagliflozin treatment on cardiac energy metabolism in human subjects.

Moreover, there are unproven hypotheses about a possible improved balance in adipokine secretion [31]. Most of metabolic effects of SGLT2i can be considered as a class effect and are reported in Fig. 1.

Metabolic effects of GLP-1 in heart failure patients

GLP-1 and its analogs bind their receptors on pancreatic β and α cells, increasing insulin release and reducing the glucagon circulating levels, respectively. Inversely, they inhibit hepatic glucose production, with the net effect of improved glycemic homeostasis.

Systemic glycemic balance is the primary function of GLP-1. Incretins, indeed, emerge as a direct modulator of cardiovascular physiology due to their metabolic effects. In chronic HF, the GLP-1 pathway is frequently downregulated, so the use of positive modulators represents an attractive therapeutic prospect [77].

The improvement of glycemia and glycated hemoglobin levels has a favorable impact on HF due to the reduction of macrovascular and microvascular damage [78, 79]; nonetheless, the protective effects of GLP-1 RA on cardiovascular functions can be accomplished through different mechanisms.

The patients affected by chronic HF frequently have elevated levels of leptin which is involved in adipose-mediated inflammation, and hepatic steatosis and fibrosis. Liraglutide demonstrated in clinical trials a reduction of GOT and GPT levels and reduced lipid storage in the liver, with a possibly beneficial effect on non-alcoholic fatty liver disease commonly associated with heart dysfunction [80]. In contrast, plasma levels of natriuretic peptides were not meaningfully changed [81].

GLP-1 RAs reduced the sense of hunger, and the increased importance of satiety, mediated by receptors expressed on the central nervous system, causes moderate weight loss [82, 83]. Collectively, weight loss, in addition to the slowing of the atheroma formation and the improvement of endothelial and platelet function, can exert a protective effect on thromboembolic events in HF patients.

GLP-1 RAs also have a protective effect on the kidney from oxidative injury due to reduced ROS production [84, 85]. Moreover, the activation of GLP-1 receptors reduces the reabsorption of sodium from the proximal renal tubules and improves glomerular filtration. This tends to reduce albuminuria and also microvascular damage [86, 87]. The slowing of the progression of renal failure, in contrast

with other diabetes therapies, makes GLP-1 RAs a good candidate for glycemic control in patients with chronic HF and advanced CKD [88].

In conclusion, GLP-1 and its analogs represent a class of drugs that own relevant and interesting implications that counteract pivotal pathophysiological mechanisms of chronic HF, such as oxidative stress. Further studies would probably evidence their impact on the quality of life by reducing comorbidities and events. Most of metabolic effects of GLP-1 can be considered a class effect and are reported in Fig. 2.

Future prospects

In DAPA-HF[13] and EMPEROR-reduced[14], dapagliflozin and empagliflozin were added to recommended heart failure with reduced ejection fraction (HFrEF) therapy demonstrating the incremental efficacy and safety in HFrEF patients with and without diabetes. This incremental efficacy might be justified by mechanisms of action that go beyond the RAAS inhibition, in accordance with the one already proposed for the search for new pharmacological targets in HF patients and new biomarkers for HF [89].

Furthermore, the benefits from drugs based on neurohumoral and hemodynamic modulation may early achieve a plateau [90], with hardly likely additional benefits from incremental doses or additional drugs with the same mechanism.

We consider essential that the development of new drugs for HF must be necessarily focused on additional targets and metabolic and vascular effects might be the most promising effects of the new drugs.

Recently, some trials have been designed in patients affected by T2D to demonstrate the gliflozin effects on vascular function. The PROCEED trial has been designed to assess the effect of ipragliflozin on endothelial dysfunction in T2D and chronic kidney disease [91]. EXCEED-BHS3 trial will be the first study to evaluate the add-on effect of PCSK9i on endothelial function of T2D patients under regular use of empagliflozin [92].

Pharmacological targeting of the energy metabolic pathways may be a new therapeutic approach to improving cardiac efficiency, decreasing the energy deficit and increasing cardiac function in HF. The EMPA-VISION trial [76] will be the first clinical trial assessing the effects of empagliflozin treatment on cardiac energy metabolism in human subjects in vivo by cardiovascular magnetic resonance.

In the future, possible beneficial effects on endothelial function deriving from the simultaneous administration of drugs for HF, such as ARNI together with gliflozins, should be increasingly investigated.

Furthermore, given the rapid reduction in HF hospitalization, it is conceivable that the benefits of SGLT2 inhibitors are due to favorable hemodynamic and metabolic effects on LV. In a network meta-analysis, [93] SGLT2 inhibitors were more significantly associated with improved LVEDD and LVMI significantly decreased 6 months after the administration of dapagliflozin [94]. Empagliflozin improves adverse cardiac remodeling in HF improving myocardial energetics and systolic function [95]. Future research will be aimed at evaluating the possible effect of these drugs on LV ventricular remodeling. Furthermore, it would be interesting to know whether SGLT-2 inhibitors exert beneficial effects on right ventricular remodeling, also additive to their effects on the left ventricle.

Conclusions

To the best of our knowledge, SGLT2i are the best choice in patients with HFrEF to improve CV prognosis and HF-related outcomes and also to prevent kidney-related outcomes. Actually, GLP1-receptor agonists could be an alternative in patients who are intolerant or have some contraindications to SGLT2i. Metabolic and vascular effects might be the most promising pleiotropic effects of these new drug classes. An intense collaboration between diabetologists and cardiologists should be encouraged for a holistic and effective strategy to reduce the burden of cardio-renal-metabolic interaction.

The paper is not under consideration elsewhere. None of the paper's contents has been previously published.

Author contribution All authors have read and approved the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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Patent Foramen Ovale: Comparison among Diagnostic Strategies in Cryptogenic Stroke and Migraine

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Objective: The aim of this study was to compare transthoracic echocardiography (TTE) and transcranial Doppler ultrasonography (TCD) with transesophageal echocardiography (TEE) in order to define the best clinical approach to patent foramen ovale (PFO) detection. Methods: In total, 72 consecutive patients (33 men) with a mean age of 49 ± 13 years were prospectively enrolled. The TEE indication was cryptogenic stroke (36 patients) or migraine (36 patients, 22 with aura). All patients underwent standard TTE, TCD, and TEE examination. For any study, a contrast test was carried on using an agitated saline solution mixed with urea-linked gelatine (Haemaccel), injected as a rapid bolus via a right antecubital vein. A prolonged Valsalva maneuver was performed to improve test sensitivity. Results: TEE identified a PFO in 65% of the whole population: 56.5% in the migraine cohort and 43.5% in the cryptogenic stroke cohort. TTE was able to detect a PFO in 55% of patients positive at TEE (54% negative predictive value, 100% positive predictive value, 55% sensitivity, and 100% specificity). TCD was able to identify a PFO in 97% of patients positive at TEE (89% negative predictive value, 98% positive predictive value, 94% sensitivity, and 96% specificity). Conclusions: In patients with cryptogenic stroke and migraine, there is a fair concordance ($k = 0.89$) between TCD and TEE in PFO recognition. Accordingly, TCD should be recommended as a simple, noninvasive, and reliable technique, whereas TEE indication should be restricted to selected patients. TTE is a very specific technique, whose major advantage is the ability to detect a large right-to-left shunt, particularly if associated with an atrial septal aneurysm. (ECHOCARDIOGRAPHY, Volume 26, May 2009)

patent foramen ovale, *transesophageal echocardiography*, *transthoracic echocardiography*

Patent foramen ovale (PFO) is a hemodynamically trivial interatrial communication that is present in about 25% of the adult population.[1] It is associated with increased risk of cerebrovascular events (CE),[2–9] particularly in young patients with previous cryptogenic stroke (CS).[4,5,8,10]

Both the PFO incidence and the clinical significance of the associated right-to-left shunt (RLS) are variable in different studies,[4–6,8,10–11] according to the technique used for PFO detection, patient population, comorbidity, and age.[9,11–15]

Although the clinical significance of PFO in relation to CE is still controversial, identification and assessment of this abnormality are nowadays a routine diagnostic procedure. In the last few years, a change in the clinical features of patients undergoing ultrasound investigation to detect an RLS has been observed. The search for PFO is becoming more and more common in young subjects suffering from migraine, especially migraine with aura,[16,17] and those with atrial septal aneurysm (ASA).[1,5,8,10,17]

Several contrast echographic techniques are currently available for PFO detection, including transesophageal echocardiography (TEE),[18,19] transthoracic echocardiography (TTE),[20,21] and transcranial Doppler ultrasonography (TCD).[22,23] Because of its optimal resolution, TEE is defined as the "gold standard,"[24–28] but it is a semiinvasive procedure. TCD is an attractive alternative to TEE in the recognition of RLS and has been used in

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many studies of patients with CE; it is unable, however, to identify the shunt site.[29–32] TTE with second harmonic imaging (HI) has also been proposed in this clinical setting since it has been reported that its sensitivity is similar to that of TEE.[20,21,33–40]

The aim of the present research was to compare TTE and TCD with TEE in order to define the best clinical approach to PFO detection.

Methods

Patient Population

From October 2006 to December 2007, 72 consecutive patients (33 men) with a mean age of 49 ± 13 years were prospectively enrolled. TEE indication was CS (36 patients) or migraine (36 patients, 22 with aura). The diagnosis of CS and migraine had been previously performed according to the Trial of ORG 10172 (danaparoid) in Acute Stroke Therapy [TOAST] criteria[41] and the guidelines of the International Headache Society,[42] respectively.

The major demographic and clinical characteristics of patients are summarized in Table I.

TTE and TCD studies were performed on the same day by two different experienced cardiologists, unaware with respect to the result of the other study. Within the subsequent week, each patient underwent TEE study performed by a third cardiologist, not aware of data from the previous studies. The patients were examined in the fasting state and received local pharyngeal anesthesia with 10% topical lidocaine; since the endoscope was well tolerated by almost all subjects, no patient was sedated with intravenous midazolam, in contrast to what has been reported by the great majority of studies.[20,21,33,35,38,40] Written informed consent was obtained from all patients.

TABLE I

Demographic and Clinical Characteristics of Patients

	Patients (n = 72)
Age (years)	49 ± 13
Male (%)	45.8
BMI >30 (%)	14
Hypertension (%)	38
Diabetes (%)	11
Hypercholesterolemia (%)	20
Cigarette smokers (%)	41
Migraine (%)	50
Migraine with aura (%)	61
Cryptogenic stroke (%)	50

Echocardiographic and Transcranial Doppler Examinations

A baseline TTE examination was performed with a Prosound α-10, ALOKA echo-machine (Aloka Science & Humanity, Tokyo, Japan), using a 3-MHz probe, according to standard practice guidelines,[43] with the patient in left lateral position. An apical four-chamber view with optimal visualization of both the atria, ventricles, and atrial septum was selected and the gain setting was adjusted to analyze the fossa ovalis area.

A baseline TCD examination was carried on with the same equipment as for the TTE study, using a different echo-machine setting. The patients were lying comfortably on a stretcher in supine position. The side of the cranium with the superior temporal window was chosen. The middle cerebral artery (MCA) was identified with color Doppler and insonated bilaterally. An 8-mm pulsed-wave (PW) Doppler sample volume and a low gain provided the optimal setting for discriminating microembolic signals (MES) from the background spectrum (Fig. 1).[44,45]

A TEE study was performed using a Vivid Seven machine (GE, Horten, Norway) with a 5.0-MHz multiplane probe, according to a standard protocol including color flow Doppler data. The atrial septum was analyzed from the transverse mid-esophageal four-chamber view to the longitudinal biatrial-bicaval view. Since PFO is, at times, not clearly recognized by a bicaval view at 90° rotation, additional image planes (60°–90° and/or 110°–130°[20,21,33]) were used to better analyze the atrial septum.

The baseline two-dimensional (2D) loops, color Doppler data, and contrast test results, triggered by the QRS complex, were digitally stored and evaluated offline.

For any examination (TTE, TCD, or TEE), a contrast test was performed using an agitated saline solution mixed with urea-linked gelatine (Haemaccel, Aventis Pharma, AG, Frankfurt, Germany). The contents of two syringes (one with 2 ml of saline solution and one with 2 ml of Haemaccel) were rapidly mixed until a homogenous solution was obtained (contrast solution [CSL]). This was injected as a rapid bolus (5 seconds), via a 21-gauge intravenous catheter inserted in the right antecubital vein. CSL was prepared by the same nurse using the same method in all studies.

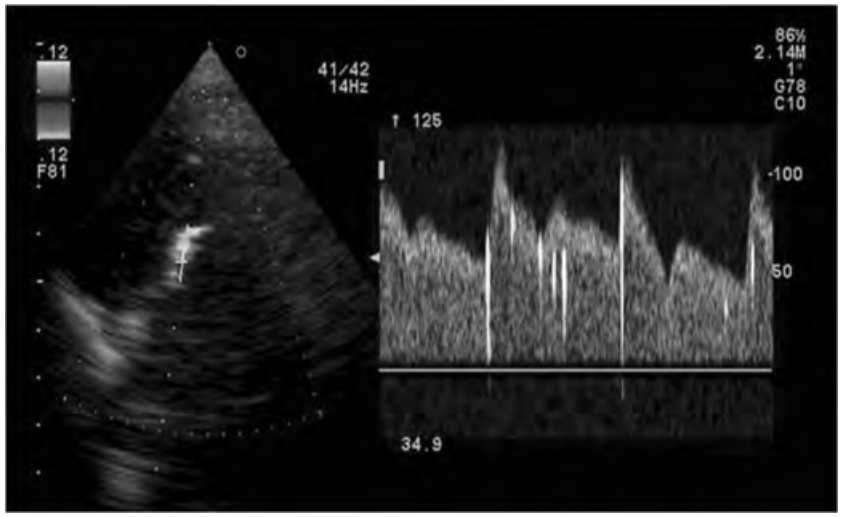

Figure 1. *Contrast-enhanced transcranial Doppler study. After contrast injection, less than 10 microembolic signals can be clearly distinguished from the middle cerebral artery background spectrum, revealing a small right-to-left shunt.*

Since the majority of RLS cannot be seen during a conventional study, the Valsalva maneuver (VM) has been used to disclose transient RLS. It has been demonstrated that the sensitivity of contrast echocardiography in PFO detection increased from 5% to 18% using VM;[46] accordingly, before every procedure, the patients were meticulously trained to perform VM. The patients started the maneuver about 5 seconds after CSL injection, pressing against the closed glottis for at least 10 seconds. They then performed a deep expiration and inspiration, followed by a deep expiration. On TTE and TEE studies, the effectiveness of VM was verified by a reduction in right ventricular and atrial size and by bulging of the atrial septum into the left atrium (LA). This so-called "septal shifting" was a prerequisite of TEE and TTE studies, because in its absence, the chance of MBs passage through a PFO is significantly decreased, as recently discussed.[47,48] On TCD, the effectiveness of VM was verified by a reduction of the MCA flow velocity, in comparison with the basal spectrum. This phenomenon may depend on a temporary stroke volume decrease due to transient preload reduction. VM, thus,

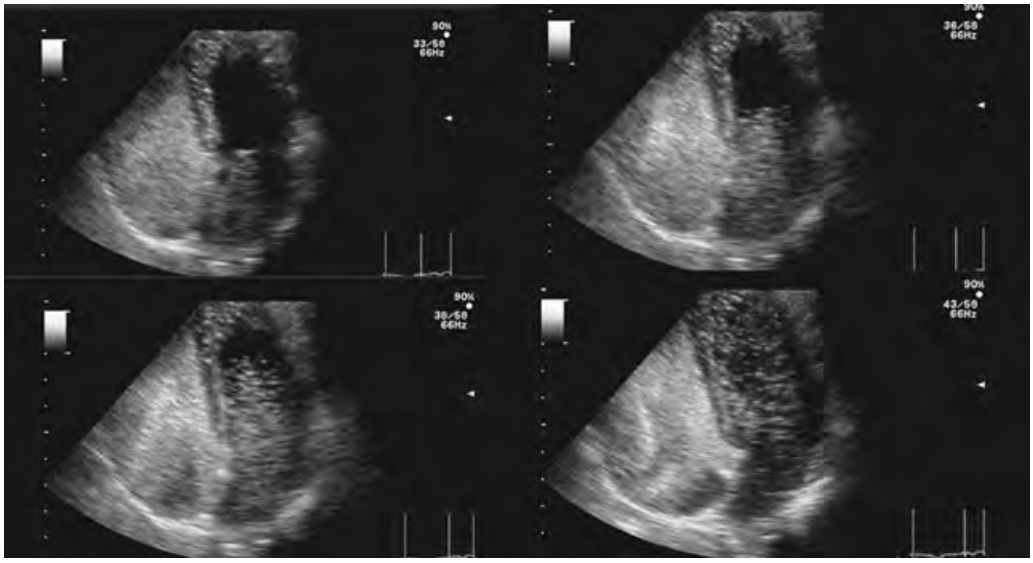

Figure 2. *Contrast-enhanced transthoracic echocardiogram. Upper panel: early after Valsalva maneuver, several microbubbles (MB) pass through the atrial septum, revealing a large right-to-left shunt. Lower panel: in the ensuing cardiac cycles, MB opacify all of the left atrium.*

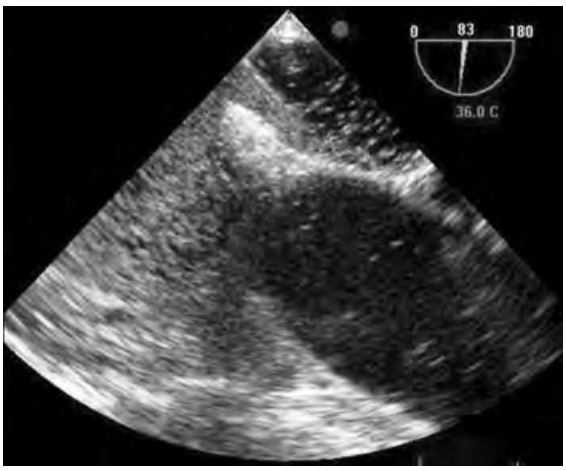

Figure 3. *Multiplane transesophageal echocardiogram, biatrial-bicaval view (83°): after contrast solution injection and Valsalva maneuver, a lot of microbubbles pass from the right to the left atrium through a PFO, demonstrating a large right-to-left shunt.*

raises the right atrial pressure, resulting in an obstacle to the venous return. Another possible explanation of flow velocity reduction in MCA during VM is intracranial pressure increase.

For any examination, if the first contrast injection was negative, the test was repeated. For optimal PFO detection, patients must be well trained in performing VM and, as pointed out by Attaran et al.,[47] several consecutive VM attempts are necessary prior to excluding an RLS. Our study protocol was based on a training phase including up to five VM attempts, with at least two resulting in unequivocal septal shifting or MCA flow velocity reduction. CSL was then injected and VM solicited; this was repeated at least twice until two effective attempts resulted in the same response (either presence or absence of RLS).

Since TCD studies were performed bilaterally, the overall number of attempts was higher with this technique than with TTE and TEE studies. This could represent a minor limitation of our study, since theoretically TCD sensitivity could have been increased by the larger amount of injections.

Criteria for RLS Diagnosis

To assess PFO, a semiquantification of the RLS was used. On TTE and TEE, the evaluation was based on counting the number of microbubbles (MBs) moving from the right atrium (RA) to the LA through the PFO after VM, within the first three cardiac cycles[6,35] (Figs. 2 and 3). A PFO was diagnosed if at least one MB

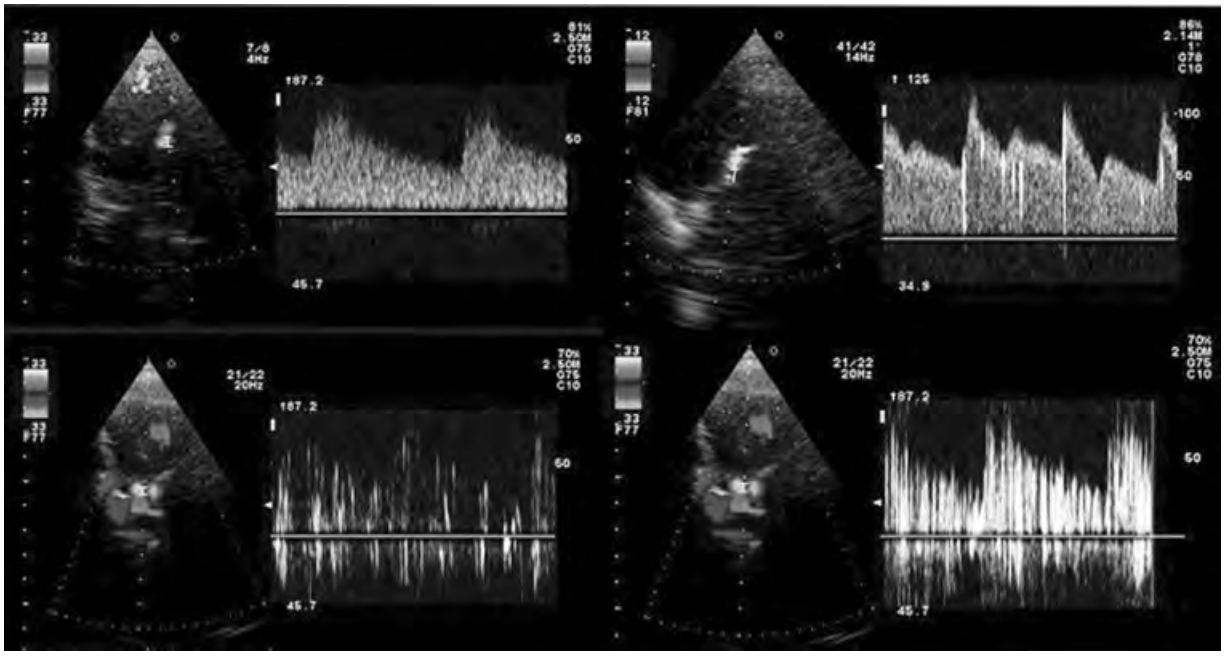

Figure 4. *Classification of right-to-left shunt with transcranial Doppler study. Upper panel: left, no microembolic signals (MES); right, 1–10 MES (small shunt). Lower panel: left, more than 10 MES (medium shunt); right, more than 10 MES with "curtain" effect (large shunt).*

was detected in the LA. MBs appearing after the first three cardiac cycles were classified as pulmonary shunt.[33–35] This three-cardiac cycle cutoff is described in several studies,[15,20,33–35,49] although some authors[38,40,47] prefer to take into account five cardiac cycles, defining early RLS as a shunt occurring within the third cardiac cycle, and late RLS as a shunt manifesting at the fourth or fifth cardiac cycle. Woods and Patel[48] reported that the so-called three-beat rule, derived from two isolated descriptions of cardiac catheterization (with indocyanine green dye dilution curves) and M-mode echocardiographic studies, has survived unaltered, despite technical advancement; in the authors' opinion, a strict adherence to this paradigm could result in false conclusions. Attaran et al.[47] suggest that a PFO may be diagnosed whenever MBs appear in the LA within 3–5 cardiac cycles, but, on the other hand, underlines that only a few data support this viewpoint. As recommended, we excluded transpulmonary shunting not only on the basis of the temporal cutoff but also by carefully following bubble movements with a frame-by-frame analysis or, when possible, independently assessing each pulmonary vein origin for bubble entry during each TEE/TTE contrast study. Finally, we accepted this cutoff as the best one since a further delay increases the risk of finding, in the LA, MBs from the pulmonary flow, especially in young patients with hyperdynamic circulation.

The shunt was defined as small (<10 MBs), medium (>10 MBs), or large if all of the LA was opacified. If the quantitative results were variable between the first and second study, both for TTE and TEE, the largest number of MBs decided the shunt size.

TCD was deemed positive if at least one MES was recorded on TCD spectrum within the first three cardiac cycles from CSL injection. As recommended,[44,45] the Doppler spectrum was continuously recorded for 40 seconds after VM was completed. The results were classified as follows: 0 MES: test negative, 1–10 MES: small shunt, >10 MES: medium shunt, and >10 MES with "curtain" effect: large shunt (Fig. 4). As for TTE and TEE studies, in case of doubt, the whole procedure was repeated.

According to previous studies,[6,50] ASA was defined as a >10-mm protrusion beyond the plane of the septum into the left or right atrium.

A statistical analysis was performed by means of JMP statistical software, version 4.0.0 (SAS Institute, Inc., Cary, NC, USA). Quantitative data were expressed as the mean ± standard deviation, qualitative data as the percentage. The performance indexes used were sensitivity, specificity, predictive positive value (PPV), negative predictive value (NPV), and k concordance index, which expresses the agreement proportion beyond chance. A P-value <0.05 was considered statistically significant. All tests were 2-tailed.

Results

TEE identified an RLS due to a PFO in 65% (46 patients) of the whole population: 56.5% (26 patients) in the migraine cohort and 43.5% (20 patients) in the CS cohort. Considering TEE as the gold standard technique, TTE was able to detect a PFO in 26 (55%) of the 46 PFO patients, with NPV 54%, PPV 100%, sensitivity 55%, and specificity 100% (Table II). In patients positive on TTE, 92% had an RLS classified as medium or large on TEE.

TCD was able to identify 45 (97%) of the 46 patients with PFO, 1 patient being TCD positive and TEE negative, and 1 patient being TCD negative and TEE positive. Table II shows that TCD has 89% NPV, 98% PPV, 94% sensitivity, and 96% specificity. TCD showed a high concordance (k = 0.89) with TEE in PFO recognition; concerning RLS quantification, the agreement between TCD and TEE was relatively good

TABLE II

Sensitivity, Specificity, Negative Predictive Value (NPV), and Positive Predictive Value (PPV) of Transcranial Doppler Ultrasonography (TCD) and Transthoracic Echocardiography (TTE) in Comparison with Transesophageal Echocardiography (TEE) in Patent Foramen Ovale (PFO) Detection

Technique	PFO (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Contrast-enhanced TTE	55	100	54	55	100
Contrast-enhanced TCD	97	98	89	94	96

because RLS grading was classified with the same score in 71% of cases.

TEE detected an ASA in 17 patients (24%); all of them were also correctly identified by TTE. When considering TEE contrast test results in patients with ASA, 88% (15/17) showed a PFO with at least a medium RLS.

Discussion

PFO has been reported in 40–54% of patients with ischemic stroke[1,2,8] but its prevalence is 77% if only patients with CS are considered.[3,4,10,51] PFO, in addition, is very common in migraine patients (48–62%).[16,52–55] In our study, PFO prevalence was 65%, being higher ($P < 0.001$) in patients with migraine (56.5%) than in patients with CS (43.5%).

Although the exact relationship between PFO and CE is not completely understood, a correct diagnosis of PFO is of paramount clinical importance, since technical advances have led to new therapeutic options, including transcatheter PFO closure. Contrast echocardiography has been a cornerstone in recognizing PFO with RLS over four decades. An improvement of methods used for shunt detection has led to an accurate identification of even a small RLS, whose clinical implication is still debated.

Although being a relatively invasive procedure, TEE (Fig. 5) has been considered by some authors as the gold standard for PFO detection.[25–28] TTE and TCD are less reliable, when compared with TEE; in addition, their sensitivity and specificity for RLS detection are variable in different studies.[20,21,29,33–36] Recent advances in TTE, including the development of HI, have improved image quality and decreased artifacts. Several studies have pointed out that TTE with HI, in combination with agitated saline injection, can detect RLS with an accuracy that is similar to that provided by TEE.[20,21,33,35,37–40] In contrast with our results, a TTE sensitivity identical to, or even higher than, that of TEE has been reported by the above atricles, apart from the study by Ha et al.,[34] who found a TTE sensitivity of 62.5% and a specificity of 100%. The relatively low PFO detection rate with TEE in these studies,[20,21,33,35,37–40] however, could be dependent on the deep sedation of patients, resulting in impairment of effective VM. Performing a satisfactory VM during TEE, thus, is inversely related to the level of sedation.[47] It should be pointed out that our patients did not receive any intravenous anesthesia; our relatively high TEE sensitivity, moreover, may also depend on the use of multiple sections, in contrast to studies in which atrial septum analysis was based on a more limited approach (90° in the article by Thanigaraj et al.,[40] and 110–130° in that by Trevelyan and Steeds[38]).

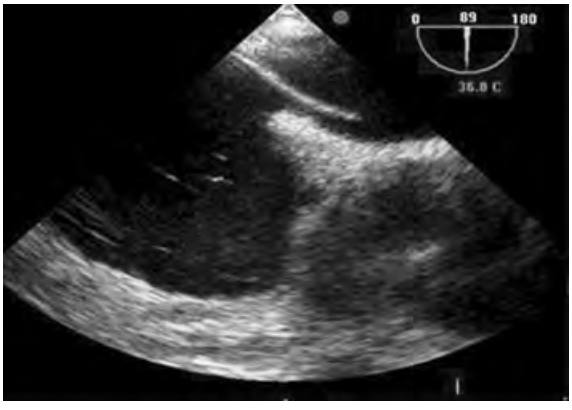

Figure 5. *Multiplane transesophageal examination, biatrial-bicaval view (89°), showing a channel-like patent foramen ovale.*

In our study, contrast-enhanced TTE was shown to have excellent PPV and specificity but relatively low NPV and sensitivity. TTE becomes more and more sensitive as RLS severity increases, but is less sensitive when RLS is mild: 92% of our PFO patients identified on TTE had a medium or large RLS. On the other hand, several studies reported that the clinical significance of PFO is related to the defect size and the amount of RLS.[56,57] In our study, 20 (43.4%) patients with PFO were not recognized with the contrast-enhanced TTE examination. This could depend on the following: (1) TTE with HI cannot be compared with TEE for image quality; it should be pointed out that 14% of our patients had a body mass index (BMI) >30 (Table I), and that the fatter the patient, the tougher is the TTE study; (2) for its spatial location within the heart, the atrial septum is, in some patients, very difficult to be analyzed by 2DTTE; (3) a deep expiration and inspiration followed by a deep expiration can hamper atrial septum visualization, especially in patients with poor acoustic window; (4) intravenous CSL during VM is often not helpful because of the difficult fossa ovalis visualization resulting from movement artifacts; (5) analysis of RLS is, to a certain extent, dependent on the type of CSL; polygelatin CSL rather than agitated saline, as in the study of Kuhl et al.,[21] increases TTE sensitivity; and (6) PFO has

often a channel-like shape, with dynamic opening and closure movements that are difficult to be recognized at 2DTTE examination.

Contrast-enhanced TCD is able to detect both cardiac and pulmonary shunts. The specificity for a RLS at the atrial level may be increased by a defined time of MBs appearance. A general agreement for a cutoff interval does not exist, and a different range from 6 seconds[30] to 25 seconds for Echovist (Berlin, Germany)[58] and up to 22 seconds for agitated saline solution[59] has been applied. The passage time from the antecubital vein injection site to the MCA through an intracardiac shunt is about 11 seconds, whereas it is about 14 seconds in case of pulmonary passage. An overlap interval between intrapulmonary passage and passage at the atrial level must be, therefore, assumed. Moreover, an exact definition of the critical time window is difficult, since the VM introduces an additional variability into hemodynamic parameters. A direct comparison of TCD versus TEE using different cutoff limits was given by Droste et al.,[44,45] and it further supports the conclusion that a rigid diagnostic time window is meaningless.

In comparison with TEE, TCD is: (1) easy to be performed and repeated, if necessary, (2) less expensive, and (3) noninvasive. The literature data show a good concordance between contrast-enhanced TCD and contrast-enhanced TEE, with sensitivity ranging from 70% to 100% and specificity >95%. Consequently, this technique has achieved a position in class IIA for RLS identification.[60] TCD sensitivity and specificity in detecting cardiac RLS, however, are variable according to both protocol and diagnostic criteria.[32,44,45,61] Comparison of contrast TCD and TEE is difficult, since some studies used unilateral recordings and others used bilateral recordings, diagnostic time windows were nonstandardized, and only some protocols included test repetition following a negative first result.[44,45] In addition, shunt quantification is even more difficult, and comparison among different imaging techniques is hard, according to the variability in the amount of injected bubbles, injection speed, and blood flow. It has recently been reported that Echovist increases TCD sensitivity from 94% to 100%.[62] It should be pointed out that we did not use Echovist, and that the injected CSL did not contain air. Agitated saline solution is an easily available contrast agent for PFO screening and has several advantages, including safety and low cost: saline solution rather than Echovist has been recommended by a consensus statement for TCD study of RLS.[62] Finally, repeating VM, a time window of 40 seconds, and no threshold in MES number improve TCD sensitivity.

The clinical significance of a shunt demonstrated only during TCD is unknown; this phenomenon is commonly attributed to intrapulmonary shunt,[35,45,61,62] although a very small intracardiac shunt, not detected by TEE, cannot be excluded. It should be pointed out that, despite training, VM may occasionally be less effective during TEE than during TCD, owing to the presence of the esophageal tube as well as sedation. This could explain some false-negative cases at TEE.

Finally, the clinical importance of ASA recognition should be pointed out: in 88% of patients with ASA, a medium or large RLS was discovered on TEE examination. The association of ASA and PFO, thus, reveals the likelihood of a clinically significant RLS;[63] moreover, it is also well known that ASA may increase the risk for stroke in the presence of PFO with RLS.[5,10] A severe limitation of TCD is just its inability to diagnose an atrial septal defect or an ASA. This limitation remarks that TTE should be performed together with TCD for a more complete evaluation.

Clinical Implications

In diagnosing paradoxical brain embolism, the demonstration of an RLS is a keystone. Contrast echocardiography (TTE and TEE) has become the method of choice to discover a PFO, since it permits direct shunt visualization. TEE appears superior to other ultrasonographic techniques because it provides high-quality images, but is semi-invasive, time-consuming, and expensive. An easier, cheaper, and less invasive technique that is able to recognize PFO would be preferable, particularly in some patients such as those with migraine.

Our findings show that contrast-enhanced TCD has a very high sensitivity (94%) and specificity (96%) in PFO detection and RLS quantification. Although the diagnostic power of this technique has been demonstrated several years ago,[30] to the best of our knowledge, only a single study comparing all the three techniques (TCD, TEE, and TTE) has been published.[35] Different from the present research, however, in that study, TEE was performed under deep sedation.

Contrast-enhanced TTE is very accurate in detecting ASA, which seems to be an

independent risk factor for CS and is frequently associated with a largely shunting PFO. An integration of TTE and TCD could be considered as the first-line diagnostic approach for PFO, whereas TEE should be limited to the following selected categories of subjects: (1) patients scheduled for transcatheter PFO closure, (2) patients in whom either the PFO diagnosis is uncertain or an alternative embolic cardiac source must be considered, (3) patients with high-risk PFO, particularly those experiencing recurrent CE, and (4) patients with ASA and/or large RLS or curtain effect on TCD.

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REVIEW ARTICLE

Therapy of Cardiac Arrhythmias in Children: An Emerging Role of Electroanatomical Mapping Systems

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Abstract: ***Introduction:*** Cardiac arrhythmias are challenging diseases in childhood. Most of them in pediatric subjects (90.2%) are atrioventricular reentrant tachycardias and atrioventricular nodal reentrant tachycardias. The standard 12-lead ECG is a highly accurate diagnostic tool but an invasive electrophysiological study is often required. The main concern about this kind of procedures is their invasive nature and the need of radiations, so antiarrhythmic agents are currently the first line therapy. However, they often show side effects and can be insufficient for the rate control.

Materials and Methods: We performed a systematic research on Embase and PubMed. We found 563 articles and selected the most representative 50.

Discussion: Management of cardiac arrhythmias could be very difficult in several scenarios, especially in children with body weight <15 kg and age <4 years. In general, pediatric subjects show a cumulative risk of malignancy greater than adults, having greater life expectancy. On this basis the guiding principle during radiation delivery in electrophysiological procedures is "as low as reasonably achievable" (acronym: ALARA). The development of 3-dimensional (3D) electroanatomical mapping systems allowed significant reduction of exposure. The most recently reported experiences demonstrate safety and feasibility of fluoroless ablation in the most common arrhythmias in children, even in challenging conditions.

Conclusions: The first reasonable approach in cardiac arrhythmias involving younger patients seems to be pharmacological. However antiarrhythmic drugs pose problems both in terms of side effects and often have poor efficacy. Expertise in electrophysiological techniques is constantly increasing and the development of new technologies allow us to encourage the use of electroanatomical mapping systems in order to reduce the radiation exposure in children undergoing to catheter ablation, especially for accessory pathways.

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INTRODUCTION

Cardiac arrhythmias are considered as challenging conditions, especially in children [1]. Their incidence was estimated to amount to 19% in patients admitted in pediatric intensive care unit and, between them, tachyarrhythmias occur more rarely, with an incidence of 2% [2]. Incidence is even greater in children older than 1 year and in patients with grown-up congenital heart diseases [3].

Among all arrhythmias in newborns, the most common are supraventricular tachycardias [4]. The most recent researches demonstrate a key role of the electrophysiological properties of pluripotent stem cell-derived cardiomyocytes in the creation of a pathophysiological substrate [5]. All aspects of the myocardium are involved in arrythmogenesis: molecular, functional and morphological [6-9].

In children the less frequent arrhythmias seem to be atrial fibrillation and atrial flutter, being often associated with reversible conditions, to Fontan's surgical correction of univentricular heart or to congenital heart diseases involving atrial dilatation [10-11]. The most common are instead the atrioventricular reentrant tachycardias (AVRT) and atrioventricu-

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lar nodal reentrant tachycardias (AVNRT), which amount to 90.24% of the cases [3]. In both the forms there is involved an anatomically determined circuit. AVRT is caused by an accessory pathway (most often a muscular bypass tract) in the atrioventricular groove placed anywhere along the mitral and tricuspid annulus (except for the region between the right and left fibrous trigones). The accessory pathway creates a connection between atrium and ventricle such that the impulse arising from sinus node reaches the ventricle and depolarizes part of it (pre-excitation), bypassing the normal pathway of the atrioventricular node (AVN). If an impulse reaches the bypass tract during its refractory period it is conducted to the ventricle only by the AVN and, from here, it returns back to the atrium by the accessory pathway, originating an AVRT (known also as Wolff-Parkinson White syndrome) [1-3, 12]. AVNRT is due to a longitudinal separation in two pathways of the AVN: a fast pathway and a slow pathway. In this setting an impulse can find one of the two pathways refractory and be conducted down only by one, returning up by the second one: the main characteristic is that the circuit is totally in the AVN and that activation of atria and ventricles is in parallel [1-12].

1.1. Drug Therapy

To date the main approach in the acute setting in haemodynamically stable patients is represented by vagal maneuvers and, in case of failure, by intravenous administration of propranolol [3-12]. The chronic management, made in order to prevent recurrences, is represented by Class I and Class IV antiarrhythmic drugs. In fact it was recently reported that 37.8% of the centers use flecainide and 32.4% use atenolol as first option for the prevention of the recurrences of supraventricular tachycardias [3]. Antiarrhythmic drugs are in general the first line therapy in infants under 5 years and catheter ablation is most often performed only in case of failure of 2 or more agents and/or in case of tachycardiomyopathy [3]. It was reported that propranolol is effective in 73.5% of cases in infant supraventricular tachycardia [13] and that, in several cases of incessant supraventricular tachycardias, only a combination of beta-blocker, flecainide and amiodarone is necessary to avoid recurrences [14]. Between these drugs flecainide is not suitable in case of structural heart disease [15]. It has already been widely observed that most of the antiarrhythmic agents can show modest efficacy and significant side effects [15].

1.2. Electrophysiological Study and Ablative Therapy

The 12-lead ECG is the first line tool and maintains a high diagnostic value especially for well-trained cardiologists [16]. However, several circumstances require an invasive approach to definitively solve both the diagnostic process and recurrences [17]. In these cases an electrophysiological study is performed with the objective of mapping and ablating the arrhythmia circuit [18]. Their efficacy and safety were both studied in children and in adults with congenital heart diseases [19-20], also in complex procedures involving trans-septal puncture of the interatrial septum [21]. The main concerns about catheter ablation of cardiac arrhythmias is represented by the use of radiations. In a study it was estimated that a single ablation procedure increased the risk of fatal malignancy during a lifetime of 0.02% with a mean fluoroscopy time of 14.4 min [22]. Some authors suggested that being supraventricular tachycardias most often nonfatal conditions, it seems difficult to justify even a small risk [23]. This could be true especially in children where the degree of the cellular turnover is higher. Furthermore, radiations are associated with a risk of dermatitis, cataracts, thyroid disease and birth defects in the patients' offspring [23]. Based on these assumptions, several studies investigated feasibility and safety in children of non-fluoroscopic mapping systems, already used in adults [24].

2. MATERIALS AND METHODS

We performed a systematic research using Embase and PubMed and the keywords ‘electroanatomical mapping’, ‘electrophysiological study’, ‘catheter ablation’, ‘antiarrhythmic drugs’, ‘arrhythmias in children’, ‘radiation exposure’, ‘non-fluoroscopic cardiac ablation’, and ‘congenital heart diseases’. We found 563 articles of interest but only 50 were selected, providing the most representative information. Inclusion criteria were: a) publication in 2016-2017 or, at least, between 2013 and 2015, b) epidemiological relevance, and c) clinical impact.

We excluded publications that: a) complied with less than two key words, b) were published before 2013, and c) provided information overlap with larger trials or more recent articles. The use of a combination of the inclusion criteria provided the most recent information in this field. In particular most part of the included literature (24 articles) represents the “state of art” available from the last year (Table **1**; Fig. **1**). Exceptions to this general rule are represented by the

Table 1. Table showing the relative contribute of the articles selected, sorted by year of publication. The table is provided with an absolute (n) and percentage (%) number.

Year of Publication (Total 50)	Articles (n)	%
2016-2017	24	48
2015	7	14
2014	2	4
2013	2	4
Before 2013	15	30

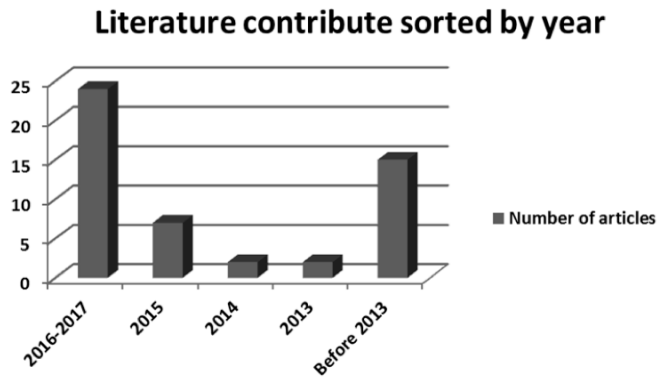

Fig. (1). Chart showing the literature contribute sort by year.

large epidemiological and clinical studies with high relevance. Furthermore, all the selected studies with a publication year previous to 2013 provided consolidated information that, to date, did not change.

3. DISCUSSION

Catheter ablation of supraventricular tachycardias in children became available in 1990. One of the first big registries in this field is represented by the "Pediatric Radiofrequency Catheter Ablation Registry", which demonstrated efficacy and safety of radiofrequency ablation (RFA) in children. It is currently considered one of the milestones in electrophysiology because it clarified that critical factors in RFA are body weight and age [25]. In fact a body weight <15 kg proved to be associated with a higher complication rate and age <4 years predicted the occurrence of complications. It also demonstrated that ablations of AVNRT are burdened by a major risk of atrioventricular block in comparison to AVRT.

In 2004, the safety and efficacy of RFA in children were validated further by the Prospective Assessment after Pediatric Cardiac Ablation (PAPCA) database [26]. From the year 2000 cryoablation became available as a new tool for supraventricular tachycardias ablation [27]. This tool is based on the cold injury made by the nitrous oxide circulating through the tip of the catheter. The advantage is that tissue cooling can be checked and eventually stopped if an undesirable effect is seen (e.g. atrioventricular block), allowing the tissue to rewarm before creating a permanent effect. This advancement called 'cryomapping' allows greater safety during AVNRT ablation, eliminating the risk of atrioventricular block [28]. This was the starting point for better management also of extremely young patients [29]. However, all these procedures need fluoroscopy and radiation exposure. It is well recognized that it is associated with a risk of malignancy, cataracts, dermatitis, dysthyroidism and birth defects in patients' offspring and that children, having a greater life expectancy, show a cumulative risk greater than adults [23]. For this reason the guiding principle in electrophysiological procedures involving radiations is "as low as reasonably achievable" (acronym: ALARA) [30]. In 2008 some authors estimated that a single ablation procedure with a mean fluoroscopy time of 14.4 min carried out an increase of fatal malignancy risk of the 0.02% and observed that the greatest absorbed dose were directed to the lung, followed by bone marrow and breast [22]. Their conclusion was that the increase in risk of malignancy after a single RFA procedure in children is low. Recently, it was underlined that a proper balance between risks and benefits is crucial and that radiation exposure during radiological exams should be minimal, with a very small risk [31].

Gianicolo *et al*. showed that so far there are methodological limits in the available studies and that the risk of radiation exposure in adolescents and children is not well estimated [32]. Minimization of the negative effects of ionizing radiation was recently investigated by Kutanzi *et al*. [33]. They concluded that in children it seems appropriate to take actions in order to reduce exposure. Some authors suggested that because supraventricular tachycardias (the most frequent arrhythmias in a pediatric population [3]) are most often not fatal conditions, it seems reasonable to aim for a further reduction of radiation use [24].

A significant reduction of the absorbed dose during catheter ablations was made possible by the development of 3-dimensional (3-D) electroanatomical mapping systems [24, 25, 34]. To date there are two tools available in children: the EnSite Navix system (St. Jude Medical, Inc., Little Canada, Minnesota, USA) and the CARTO system (Biosense Webster, Inc., One Johnson & Johnson Plaza, New Brunswick, New Jersey, U.S.). The EnSite Navix measures electrical impedance and the CARTO the magnetic fields deriving from the heart (Fig. **2**). After the selection of the heart chamber of interest these systems allow a reconstruction of its spatial geometry, allowing the visualization of the ablation catheter in relation to the reconstructed model (Fig. **3**) [23,24,34]. Recently, a hybrid magnetic/impedance mapping system called Rhythmia (Boston Scientific Corporation, Marlborough, Massachusetts, United States) was introduced; this provides highly accurate reconstructions by continuous mapping. Although it was tested for mapping scar-related atrial tachycardias [35], its role in a pediatric population still needs investigation. However, it seems an attractive option in postoperative arrhythmias after congenital heart disease surgery.

Scaglione *et al.* demonstrated in 21 children symptomatic for AVNRT the feasibility of a fluoroless cryoablation [36]. The advantages of cryomapping and cryoablation were combined with those ones deriving from the electroanatomical mapping systems. Fluoroless cryoablation was feasible in 19 patients and only two cases needed 45 and 50 sec of fluoroscopy, respectively, because of difficult catheter progression in the venous system. Another study by the same group was conducted in 2015 on 44 children and adolescents with AVRT. This study demonstrated that an ablation of an accessory pathways determining AVRT was feasible both by cryoenergy and radiofrequency under electroanatomical guidance [37].

Akdeniz *et al.* in 2016 conducted a study on 35 children affected by idiopathic right ventricular arrhythmias [38]. The authors demonstrated that electroanatomical mapping systems are effective also in guiding ablations of challenging arrhythmias such as the ventricular ones. Also, in this experience, a limited fluoroscopy time was reported. Although some interesting experiences with newborns were described in the literature the most recent report was published by Bigelow *et al*. [39]. Non-fluoroscopic cardiac ablation was

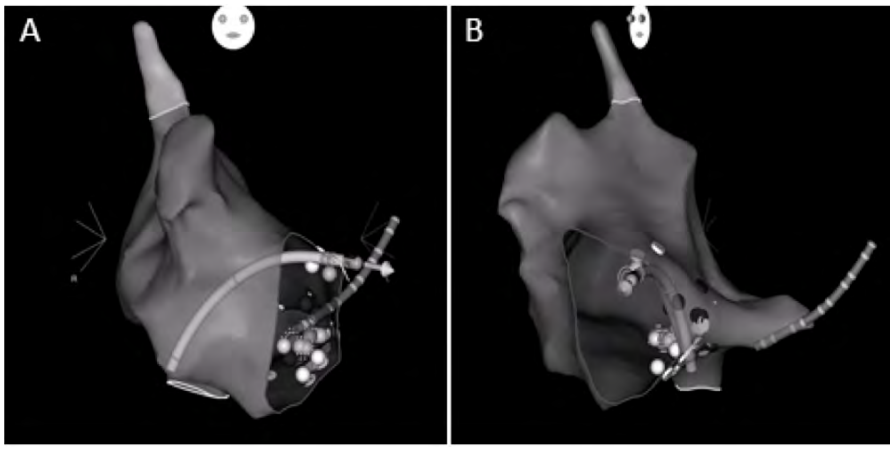

Fig. (2). Example of AVNRT ablation under guidance of an electroanatomical mapping system. A tridimensional reconstruction of the right atrium was performed by direct contact of the catheter on the endocardium. Right atrium is showed in anteroposterior view (panel A) and left anterior oblique (LAO) view (panel B). The system allow a rotation of the reconstructed model of the chamber of interest, making the physician aware of the spatial position of the catheters. In the figure are shown also the ablation catheter (in white) in the region of the triangle of Koch and a decapolar catheter positioned in the coronary sinus (in the right of both panels). The slow pathway was tagged by white discs and the other ones instead show the points in which radiofrequency ablation was performed. In fact the system allows, before each procedure, to define the disc colors according to several criteria. In this case were defined the criteria of location stability, force over time, impedance drop and temperature. The final color of the disc will result from the achievement of these set criteria. By this way it is possible to mark areas of interest to avoid or areas in which it was already performed a radiofrequency application. The color density of the red discs in this case visually display the quality of the radiofrequency application. AVNRT= atrioventricular nodal reentrant tachycardia; LAO left anterior oblique.

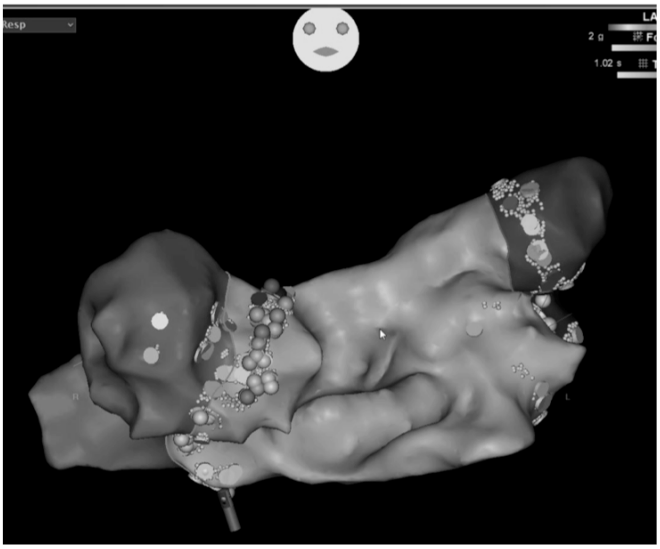

Fig. (3). Insulation of pulmonary veins in a patient affected by paroxysmal atrial fibrillation. In this image an antero-posterior view of the left atrium is shown with the exploring catheter close to the inferior right pulmonary vein. The face on the top gives an idea of the perspective from which is seen the chamber of interest. The inflow tracts of the pulmonary veins were highlighted with different colors, making the physician aware of the zones in which perform the radiofrequency application. Normally these applications are guided by the vein potentials recorded close to the ostia, often arising from muscular branches of myocardium. In these procedures the tridimensional model is crucial in giving anatomical information. The discs show, as in figure 2, the points in which ablation was performed, according to the predetermined settings, guiding towards an effective result.

performed safely in two newborns with congenital heart diseases (pulmonary atresia and Ebstein's anomaly, respectively). Minimization of the fluoroscopy times was feasible in both infants. The most recent study involved 30 children affected by manifest and concealed left accessory pathways [40]. Its importance is based on the fact that this kind of procedures involve a trans-septal approach, with longer fluoroscopy times. They demonstrated that radiation exposure and number of catheters can be reduced also in these challenging patients by the way of new technologies applied to electroanatomical mapping systems. These systems already proved in adults to significantly reduce fluoroscopy times, by creating an overlay on preregister classical fluoroscopic views of the reconstructed tridimensional models both of the cardiac chambers and of the catheters [41]. Catheter manipulation is so allowed without further use of radiation. The value of the experience of Drago *et al*. [40] is that the same procedure also demonstrated efficacy and safety in children.

The evidence described above, suggest that electroanatomical mapping systems should be routinely used in ablation procedures in pediatric patients, especially in the case of accessory pathways conditioning atrioventricular reentrant tachycardias. In AVNRT, these systems, due to their high costs, seem to be avoidable, especially in case of availability of a cryomapping system, which allow very limited fluoroscopy time. In fact the target of an AVNRT is the slow pathway, which is located in most of the cases in the postero-inferior aspect of the triangle of Koch [42-44]. This allows the physician to target it directly, minimizing the absorbed dose. Cryoablation in these circumstances is effective and safer than RFA; so its systematic use seems advisable, especially in pediatric patients.

Other tachyarrhythmias, such as atrial fibrillation and atrial flutter, having different and heterogeneous causes seem to be more responsive to prevention as first line therapy [10-12]. These arrhythmias are often related to heart failure but an effective prevention of this condition is not always easy, especially in extremely young patients. However recent interesting researches in this direction highlighted new possible clinical and therapeutic tools [44, 45].

The evaluation of epicardial fat as a novel marker of subclinical atherosclerosis seems a very interesting option [46]. In fact, obesity is one of the most important problems both in pediatric and adult population, being associated with an increased incidence of cardiovascular and other systemic diseases predisposing to arrhythmogenesis [46]. To date it is clear that prevention is the real first line therapy for atrial fibrillation and atrial flutter. Our group in fact demonstrated that proper echocardiographic screening, especially when used in combination with other clinical and biochemical parameters, can avoid the worsening of several congenital conditions which often are manifest in adult age [47, 48]. By this way in certain circumstances the use of recently introduced tools seems helpful [49]. It was also demonstrated that proper evaluation of myocardial deformation seems to add useful information and, in this scenario, a further reduction of radiation exposure also in the diagnosis phase seems possible [50].

CONCLUSION

Cardiac arrhythmias are challenging conditions, especially in childhood. The main demonstrated predictors of complications are body weight <15 kg and age <4 years. Therefore, newborns are the most difficult patients. In this setting it seems reasonable to treat cardiac arrhythmias by antiarrhythmic drugs as a first line approach in younger patients. However, antiarrhythmic drugs are not always the best choice because of their side effects. Moreover they often fail in rate and rhythm control. Expertise in electrophysiological techniques is constantly increasing. All the experiences encourage the use of electroanatomical mapping systems, in order to reduce radiation exposure in children but, more in general, in all patients undergoing catheter ablation. This is true especially for atrioventricular reentrant tachycardias. Current limitations in the diagnosis and cure of cardiac arrhythmias may soon be overcome by the progress in tools and technologies.

AUTHOR CONTRIBUTION

All authors contributed to: (1) substantial conception, design, acquisition of data, analysis and interpretation of data, (2) drafting of the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Editorial

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Takotsubo Cardiomyopathy: A Benign Condition or a Bad Omen?

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Keywords
Takotsubo cardiomyopathy, pathogenesis, comorbidity, prognosis

Takotsubo cardiomyopathy (TC), also known as "stress cardiomyopathy" or "broken heart syndrome," is a transient disorder, typically following an acute emotional or physical stress, mimicking an acute coronary syndrome (ACS). Patients with TC complain of chest pain and show electrocardiogram dynamic changes such as ST-segment elevation or negative T waves with a mild increase in cardiac biomarkers and absence of significant coronary artery involvement. Left ventricular (LV) wall motion abnormalities in TC are typically akinesia or hypokinesia of apical segments (apical balloon-like dilation pattern) associated with hyperkinesia of the basal segments.[1-3] Echocardiography plays a key role in the diagnosis, allowing direct visualization of the typical apical ballooning pattern, and it is considered specific. New technologies, such as speckle tracking echocardiography, are useful.[4-7] Despite the fact that these findings are unlikely in ACS, coronary angiography is needed to rule out myocardial infarction.[1-3]

Do We Know the Exact Pathogenesis of TC?

Several pathophysiological mechanisms have been proposed: (1) artery vasospasm and microvascular dysfunction may to lead to the typical apical ballooning pattern, which can cause acute heart failure and (2) abnormal response to catecholamines; this seems to be the most accredited hypothesis. Activation of α- and β-adrenoceptors is widely recognized as a key element in TC abnormalities; Wittstein et al[8] found 2- to 3-fold higher concentrations of the serum catecholamine in patients with TC compared with myocardial infarction. They have suggested that serious emotional stress could play a role as precipitating factor. This hypothesis is supported by the demonstration that pheochromocytoma and catecholamines administration can cause the typical pattern.[9,10] Interestingly, stressful conditions may cause intracellular calcium overload and subsequent cardiac dysfunction through the β_1-adrenoceptor signal transduction pathway.[11] Lyon et al[12] theorized a mechanism, the so-called "stimulus trafficking," to explain the decline in myocyte contractile capability in TC. Raised levels of catecholamines that induce β_2-coupling from Gs to Gi causes a negative inotropic effect, particularly on the apical myocardium where β-adrenoceptors density is highest. The rationale of "stimulus trafficking" is that a switch to Gi plays a protective activity on the myocytes against stimulation of Gs, which causes the apoptosis. Slow but significant increases in serum troponin level may explain early minimal necrosis of myocardial tissue. Mori et al noticed an increased β_2-adrenoreceptors concentration gradient from apex to base commonly found in TC.[13] All these results validated that physical and emotional stressors by inducing the release of large amounts of epinephrine could be effective in determining the local apical response of myocardial tissue that is closely related to different distribution of β_2-receptors.[14] In this context, myocardial biopsy showed regions characterized by contraction band necrosis, inflammatory cells with macrophage infiltration, and localized fibrosis.[15] All these changes were caused by direct catecholamine toxicity on myocytes[16] and oxidative stress, leading to necrosis and wall motion abnormalities. The univalent reduction of oxygen generates reactive intermediates, also known as reactive oxygen species (ROS), responsible for oxygen-mediated toxicity. There is evidence that ROS affect the function of calcium channels.[17-19] The cardioprotective properties of estrogen are known and this mechanism has been related to the high morbidity associated with TC in postmenopausal women; about 90% of patients presenting with TC are postmenopausal women.[20,21] The authors noted a correlation between Myocardial Infarction and genetic variants of estrogen receptors ESR1 and ESR2, questioning a genetic substrate for ACS in women with specific polymorphisms.[22,23] Estrogens play a relevant role in reducing the release of epinephrine in the presynaptic cardiac sympathetic nerve fibers and in calcium-dependent myocardial contraction, and based on the prevalence of TC in postmenopausal women, we can assume a

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role played by estrogens in this nonischemic disease. In this context, ovariectomized rats exposed to stress, without estradiol supplementation, showed significantly greater increases in the heart rate and LV dysfunction compared with rats on estradiol supplementation.[24] This strengthens the idea that postmenopausal women have a lack in protective effect of estrogens, resulting in a dangerous response to serum catecholamines.

Comorbidity and Prognosis

Patients with TC frequently have a good prognosis. The consequences of TC are potentially reversible with a benign prognosis. However, concomitant acute hemodynamic decompensation and comorbidities are associated with worse prognosis.[25,26] El-Battrawy et al demonstrated that different variants of TC are closely related to different clinical presentations, complications, and prognoses. Patients with the apical form of TC show a trend for consequences and are older but less likely to smoke; patients with hypertension had a higher predilection to present with the apical form.[27] Furthermore, in a 2-year follow-up, concomitant coronary artery disease (CAD) complicated their outcome leading to raised mortality compared with TC without CAD.[28] In a recent study, El-Battrawy et al showed higher rates of in-hospital events and mortality in the patients with TC having atrial fibrillation (AF) compared with patients with TC without AF.[29] Bill et al,[30] in this issue of *Angiology*, observed that patients with TC and kidney failure (KF), compared with patients with TC without KF, have a worse prognosis. Patients ($n = 108$) with TC were divided in 2 groups, depending on the absence ($n = 76$) or presence ($n = 32$) of KF. No differences were found for gender distribution, age, cardiovascular risk factors, and clinical presentation between the 2 groups. The mean follow-up was 5 years. The authors observed that KF may affect the outcome in patients with TC due to high serum catecholamine levels. In turn, these increased levels of catecholamines may originate from lower serum renalase (which degrades catecholamines) activity, potentially leading to a worse outcome when both TC and KF coexist.[31,32] The study by Bill et al did not show differences in major adverse events during hospital stay; inhospital all-cause mortality rate was higher in patients with KF, but did not reach significance (5.2% vs 15.6%, $P = .12$), but event-free survival after a follow-up of 5 years was lower in patients with KF ($P < .01$) at any time after discharge. Although this is a single-center study with a small number of patients, the results are interesting and could encourage planning larger multicenter studies.

This interesting field is constantly in evolution and establishing the role of KF will clarify its relation with TC. The medical community should consider these findings as suggestive of a potentially worse outcome in patients with TC affected by certain comorbidities. The picture of TC, as a benign condition, could change substantially in different scenarios.

Declaration of Conflicting Interests

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Venous thromboembolism in hospital emergency room. A retrospective study on climatic effect

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ABSTRACT

Several cardiovascular conditions exhibit seasonality in frequency and mortality, but little is known about the seasonality of Venous ThromboEmbolism (VTE), a very relevant medical condition, and seasonal influences are still conflicting. Patients having co-morbidities, individual suffered from dyspnea, swelling, edema of lower limb, pain (chest, lower limbs) are admitted frequently to the hospital emergency room (HER), particularly. Both mark a potential risk for VTE, that can be increased also by seasonality. A four years retrospective analysis (2016–2019) was carried out in individuals and patients admitted to the HER of the Hospital of Catania (a Mediterranean city of Sicily, Italy) to evaluate the VTE frequency and its seasonal differences, common symptoms, potential usage of some common laboratory tests. Dyspnea, swelling, edema of lower limb and pain (chest, lower limbs) were considered to suspect pulmonary embolism (PE) or for deep vein thrombosis of lower limb (DVT). Platelet count, platelet volume, fibrinogen, C-reactive protein, and D-dimer were considered. VTE frequency per year was 2.9/10,000 (2016), 4.9/10,000 (2017) 3.6/10,000 (2018), and 5.1/10,000 (2019) respectively. Dyspnea was highly frequent for PE, edema and lower limb pain were frequent in DVT patients. Fibrinogen, C reactive protein, and D-dimer values were found raised in all the VTE patients. Platelet volume was found higher in DVT than PE VTE events that occurred in warm periods were modestly greater (57 VTE: 38 DVT, 19 PE) compared to cold months (52 VTE: 34 DVT, 18 PE). Our results could be explained by the increased sweating due to the high temperatures, which in turn, can affect both on plasma concentration and on hematocrit value coupled to the reduction in atmospheric pressure determining both a hyper-coagulative condition. Climate seasonal characteristics, and environmental conditions in Catania city (Sicily) may be as reasonable items in expecting on different VTE rates in warm period compared to cold. This study highlights no specific symptoms, and confirms the common lab tests for individuals and patients admitted to HER as simple and helpful tools in initiating none or mini-invasive diagnostic strategy for the VTE. Finally, the climate/seasonality coupled with latitude can have a direct influence on the incidence of DVT.

1. Introduction

Venous thromboembolism (VTE) is a very relevant medical question particularly in more advanced societies (Europe, USA) (Silverstein et al., 1998; Oger, 2000). Older individuals, and patients affected from co-morbidities have high risk for VTE, both are quoted as favorable conditions in provoking the VTE (Heit, 2005, 2015; Rothwell et al., 2004; Heit et al., 2002; Tagalakis et al., 2013; Lopez-Jimenez et al., 2006). Nevertheless, the VTE clinical presentation often have a poor clinical presentation. Although a number of pre-clinical scores have been established, there is still a failure in the early diagnosis of VTE (Tzoran et al., 2012). Moreover, the precocious also minimal no invasive

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diagnostic strategy, and early pharmacological prophylaxis are crucial in counteracting poor prognosis both for progression and consequence of VTE (Mean et al., 2013; Jakobsson et al., 2010; Faller et al., 2017; Attia et al., 2001; Hirsch et al., 1995; Cook et al., 2000). A large number of individuals or patients daily admitted to the Hospital Emergency Room (HER) has been considered, often they are suffering of symptoms such as dyspnea, chest pain, edema or swelling or pain of lower limb. Although studies have elucidated on real burden of VTE in general population, however the results on VTE, generally, are reported on single individuals and the patients admitted to the HER are not many.

Several studies also highlighted environmental risk factors for VTE such as air pollution exposure, especially to a $PM_{2.5}$ and PM_{10} (Signorelli et al., 2019), and to climatic conditions as reported by White study (2003). White reports that seasonality may affect the occurrence of VTE, with a higher incidence in the winter than in summer (White, 2003). However, Bounameaux et al. observed no such seasonal variation in the incidence of DVT (Bounameaux et al., 1996). Also, using a large French data set (n = 127,318), Boulay et al. found 10%–15% more admissions during winter months and 10%–15% fewer admission during the summer (Boulay et al., 2001). Berentsen et al. (2020) for the first time, demonstrated differences between cold and warmer climates regarding prevalence (20 vs 5 cases/million) and incidence (1.9 vs 0.48 cases/million per year) in cold agglutinin disease patients with an increased risk of venous thrombosis patients in cold periods.

Best of our knowledge our study is the first particularly focused on VTE in HER carried out on south of Italy.

A retrospective analysis on individuals admitted to the HER of the Catania university hospital was carry out (University Hospital G. Rodolico, Catania, Sicily, Italy).

The aims of our study were the follows:

- to assess the frequency of VTE (PE, DVT) in individuals admitted to HER,
- evaluation of significance (frequency) both of the common symptoms affecting individuals or patients admitted to HER subsequently diagnosed for the VTE, of common lab tests as helpful items to suspect the VTE in individuals or in patients admitted to HER.
- Finally, we focused also on the seasonality of VTE occurrence.

2. Materials and methods

The study was performed according to the Declaration of Helsinki and was approved by the Local Ethics Research Committee (Local Ethic Committee Catania 2).

We considered data of individuals admitted to HER of University Hospital G. Rodolico (Catania, Italy) from January 2016 to December 2019. For analysis, we checked on code ICD9-CM of International Statistical Classification of Diseases considering the follow codes: ICD 451.11 ICD 451.19, and ICD 451.81. We checked on individual were admitted to the HER because they showed dyspnea, lower limb edema and pain of lower limbs. We searched on procedures as angio-CT scan (CT scan) and lower limb ultrasound (US) addressed to diagnose the PE, and the DVT. Age, gender, weight (normal, overweight, obesity), recent immobilized position, co-morbidities (type-2 diabetes, chronic renal failure, obstructive lung disease, congestive heart failure) were considered, as well as smoking habit. Furthermore, from patients diagnosed as VTE patients we registered lab data about red cells count, white cells count, platelet count, platelet volume (PLV), fibrinogen (F), C reactive protein (CRP), D-dimer (D-d)).

2.1. VTE diagnosis

Angio CT-scan (CT) showing large or minor defects in one or more pulmonary artery branches was considered for the PE diagnosis.

Ultrasound Doppler examination (US), showing non-compressibility of one or more veins in the lower limbs using the US probe (CUS test), and evident echogenicity in vein lumen were considered in DVT diagnosis.

2.2. Statistical analysis

Data were evaluated using appropriate statistics: medians (interquartile ranges) and frequencies (percentages) for quantitative and categorical variables. The $\chi -$ squared test of independence (Fisher's exact test) and the Mann-Whitney U test evaluated the differences between the VTE, PE and DVT groups in lab test data. SPSS 21.0 software was used for the statistical analysis (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Frequency of VTE events

65,030 in 2016, 64,813 in 2017, 66,509 in 2018, 67,210 in 2019 individuals were admitted to the university hospital HER. A total of 109 events of VTE were diagnosed, of which 52 (47.7%) were PE, 57 (52.3%) were DVT of the lower limbs. Table 1 shows the demographics of the individuals diagnosed with VTE. The annual frequency of total VTEs was 2.9/10,000 (19 VTE events), 4.9/10,000 (32 VTE events) 3.6/10,000 (24 VTE events), and 5.1/10,000 (34 VTE events) ranging by 2016–2019, respectively (Fig. 1). In gender terms, males accounted for 56 out of 109 (61.04%) VTE events, of which 27 out of 55 (49.9%) were PE while 29 out of 56 (47.3%) were DVT. In females, there were 53 out of 109 (49.1%) VTE events, of which 23 out of 53 (43.4%) were PE while 30 out of 53 (53.6%) were DVT. Table 2 shows the frequency of VTE events in patients admitted to the HER, classified for various chronic or transient diseases and condition as a risk condition for VTE.

3.2. Laboratory tests

In 109 VTE patients, we detected raised level of white blood cell (WBC) count in plasma, whereas the red blood cell (RBC) and platelet

Table 1
Demographics of the patients with VTE.

Variables	Total n (%)	PE n (%)	DVT n (%)	p-value
Gender				
Female	53 (49.1)	23 (44.2)	30 (53.6)	0.332
Male	55 (50.9)	29 (55.8)	26 (46.4)	
Median age (years) (IQR[a])	64 (54–73)	61 (49–76)	63 (50–75)	0.993
Median Weight (kg) (IQR)	79 (69–85)	75 (67–90)	80 (75–85)	0.627
Median High (cm) (IQR)	170 (163–179)	170 (165–178)	164 (155–180)	0.503
Median BMI (kg/m^2) (IQR)	26 (24–30)	26 (24–30)	28 (24–34)	0.703
Smoking status				
Former smokers	12 (11.2)	12 (23,1)	0	**
Current smokers	56 (52.3)	25 (48,1)	31 (56.4)	
Never smokers	39 (36.4)	15 (28.8)	24 (43.6)	
Cigarette cigarette/day median (IQR)		20 (9–20)	20 (15–40)	0.201
Alcohol consumption				
Yes	5 (17.2)	5 (27.8)	0	**
No	24 (82.8)	13 (72.2)	11 (100)	
Use of drugs/illegal substance				
Yes	1 (12.5)	1 (33.3)	0	**
No	7 (87.5)	2 (66.7)	5 (100)	
Orthopedic prostheses				

**p-values were not furnished because the assumption of the chi-square test was not satisfied.

[a] IQR: interquartile range.

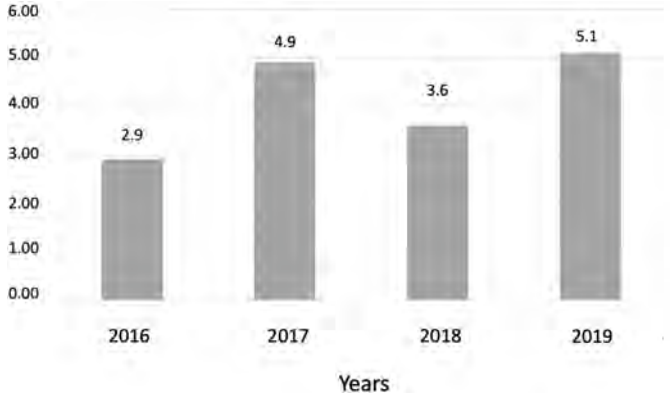

Fig. 1. Frequency (%) of VTE events per year in individuals admitted to hospital emergency room.

Table 2
Prevalence of total VTE, both pulmonary and deep vein thrombosis events in individuals affected from chronic medical diseases. Such of the diseases (cancer, chronic obstructive lung disease, heart failure, chronic renal failure) are listed as risk condition for VTE.

Favouring conditions	VTE (n.109)	PE (n.53)	DVT (n.56)	PE Vs DVT p-value
Cancer (n./%)	23 (21.5)	12 (23,1)	11 (20)	0.815
Type 2 diabetes (n./%)	15 (14.2)	7 (13.7)	8 (14.5)	n.s.
Arterial hypertension (n./%)	51 (51.37)	26 (51.0)	15 (27,3)	0.017
Chronic renal failure (n./%)	23 (21.9)	8 (15.7)	15 (27.8)	0.16
Chronic obstructive lung disease (n./%)	14 (13.2)	8 (15.7)	6 (10.9)	0.57
Heart failure (n./%)	19 (17.9)	11 (21.6)	8 (14.5)	0.44
Immobilization[(1)] (n./%)	10 (9.5)	6 (12.20)	4 (7.1)	0.59

counts were within the acceptable range (Table 3). The PLV for DVT was found higher than for PE (medians 10.106 ± 0.35 f/L and 9.767 ± 0.27 f/L respectively), the difference not being statistically significant ($p < 0.394$).

The median values of F (overall VTE 430 mg/dl, PE 453 mg/dl, and DVT 478 mg/dl), of CRP of both types of VTE patients (DVT 63,21 ± 10, and PE 49,71 ± 7,90 mg/dl), raised normal values released from the general clinic laboratory of hospital (F ≤ 400 mg/dl, CRP ≤ 10 mg/dl). The D-d median values found in both types of VTE patients (707.85 ± 232.9 μg/L in PE and 688.47 ± 192.2 μg/L in DVT patients) were higher compared to control values from hospital general laboratory.

Table 3
Laboratory essays carried out on VTE patients.

	Pulmunary embolism (PE) (N.53)	Deep vein thrombosis (DVT) (N.56)	PE Vs DVT
Red cell (mm^3)	4.4550,96 ± 94.74	4.187,68 ± 101.39	0,019
White cell (mm^3)	13,918,46 ± 3158,7	13,653,35 ± 2772,4	0,889
Platelet (mm^3)	219,332 ± 13,69	214,698 ± 11,42	0,982
Platelet volume	9767 ± 0,27	10,106 ± 0,35	0,394
Fibrinogen (mg/dl)	434,718 ± 20.97	428,05 ± 26.06	0,229
D-dimer (U/L)	707,85 ± 23,29	688,47 ± 19,22	0,507
CRP (mg/dl)	49,71 ± 7,90	63,21 ± 10,26	0,343

3.3. Symptoms

As shown in Table 4 patients experienced different symptoms such as dyspnea, lower limb edema and leg pain: 37 out of 109 (40.33%) VTE patients experienced dyspnea, of which 24 (26.16%) were diagnosed for the PE, 13 (14.17%) were diagnosed for the DVT. Lower limb edema was found in 20 out of 109 (21.80%) VTE patients, of which 5 were PE patients (5.45%) and 15 (16.35%) were DVT patients. Leg pain occurred in 46 out 109 (50.14%) VTE patients, 17 were PE patients (18.53%) 29 DVT patients (31.61%).

3.4. Seasonality

We checked on the number of VTE events occurring in different seasons (Fig. 2). We found that VTE events occurred in warm periods (summer/spring) were modestly greater (57 VTE: 38 DVT, 19 PE) compared to cold months (autumn-winter) (52 VTE: 34 DVT, 18 PE).

4. Discussion

A relevant number of individuals are admitted daily to the hospital HER, particularly those suffered from acute or exacerbated chronic diseases. It is known that patients admitted or hospitalized to emergency departments for acute or worsening chronic diseases have a risk for the VTE (Signorelli et al., 2020).

Lawaal (Lawall et al., 2007) found 7.8% of VTEs in daily patient surveys concluding that there was a high mortality risk for VTE patients hospitalized in acute emergency units compared to patients hospitalized in general care units. A low rate of VTE diagnosis was found in studies planned for shorter observational times (i.e. daily, 48 h from admission or weekly). The rate of VTE diagnosis ranged between 1.7% (Hirsch et al., 1995) to 5.5% (Moser et al., 1994). Cook et al. (2005) found the 9.6% of thrombotic venous diagnoses but study concerned DVT alone in patients admitted to intensive units (Cook et al., 2005). Interesting data from Li et al. (2011) showed 7.3% of PE events in acutely ill patients during follow-ups. Interestingly results sourced from an autopsy study showing 14.3% incidence of PE in patients admitted to emergency department who died from mixed medical and surgical diseases (Berlot et al., 2011). We want to draw attention on early diagnosis and management in individuals admitted to the HER at the time of the VTE occurrence are crucial for their good outcome and also in reducing the mortality risk (Llojd et al., 2008; Kakkar et al., 2011). There is a large body of evidence on the efficacy of anti-thrombotic drugs to lower VTE mortality and counter its progression (Lilly et al., 2014; Bustos et al., 2017; Conti et al., 2018; Gussoni et al., 2013; Monreal et al., 2009).

Coagulation factors are known to be crucial in causing the venous thromboembolism and some genes that code for hemostatic factors such as the FVII, FVII, and FVII. In addition, tissue-type plasminogen activator can respond to the environment changes as reported by Feinberg (2018). As previously demonstrated, the epigenetic leads to gene activation and gene repression, respectively thus influencing the expression levels of genes encoding hemostatic proteins, such as the FVII (Friso et al., 2012), the FVIII (El-Maarri et al., 2007), and the tissue-type plasminogen activator (Zwingerman et al., 2015).

However, results from a study performed by using the whole-genome

Table 4
Frequency of symptoms showed by individuals diagnosed as VTE patients.

Symptom	Overall VTE	PE	DVT
Dyspnea	N° 37/109 % (40.33)	N°24/109 % (26.16)	N°13/109 % (14.17)
Lower limb edema	N°20/109 % (21.80)	N° 5/109 % (5.45)	N° 15/109 % (16.35)
Pain	N° 46/109 % (50.14)	N° 17/109 % (18.53)	N° 29/109 % (31.61)

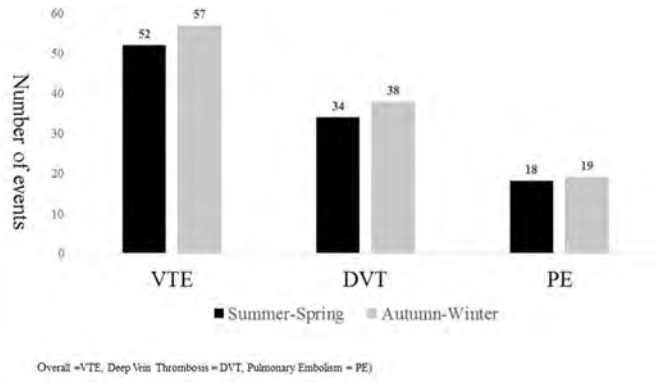

Fig. 2. Number of VTE events in different climatic periods of the year. Comparison of VTE events in warm period (summer–spring) Vs cold period (autumn-winter).

DNA methylation analysis method (MWAS) to identify a potential correlation between methylation marks and quantitative traits of coagulation cascade did not showed effect of DNA on the FV Leiden polymorphism and neither it contributed to explain the incomplete penetrance (Aïssi et al., 2014).

Concerning the balance between activated or reduction of gene expression it is noteworthy potential capability of the so called citrullination in modulating the risk of VTE related to different stimuli (i.e., infectious agents, sterile inflammation, autoimmunity, cancer, neutrophils undergo to apoptosis and expulsion of neutrophil extra-cellular traps NETs) (Fritz, 2013; Schulz et al., 2013; van Montfort et al., 2013).

In our retrospective study, we included individuals admitted to the HER of the University Hospital 'Policlinico G. Rodolico (Catania, Sicily, Italy) because suffered from such no diagnostic, specific symptoms (dyspnea, edema and edema or pain of the lower limb) however these are most frequently showed from individuals admitted to the HER. It is to note that these symptoms are mandatory in forwarding patients to the HER particularly for having chronic disease. We focused on these common, although non-diagnostic and no-specific symptoms for VTE as being possible indicators to start diagnostic procedure for VTE occurrence (PE, DVT). We estimated that the high total of individuals forwarded to the HER during the period might be representative of general population VTE, which highlights a strength of the study. Our results confirm that cancer is concomitant in patients diagnosed for the VTE both PE and DVT. We found that arterial hypertension is concomitant in VTE patients. As expected, we found dyspnea to be more frequent in patients with PE compared to DVT, the difference being significant ($p < 0.004$). Edema of the lower limbs was most frequent in patients with DVT alone than in PE patients ($p < 0.005$). Lower limb pain is more frequently in DVT patients than in PE patients. In lab tests, we noted the raised PLV value in VTE patients overall, a direct relationship between RBC count with VTE events ($p < 0.019$). It is worth remarking that platelet contributes to clotting thus it play a role in initiating and progressing thrombosis. On the high PLV value, we would like to discuss on platelet in venous thrombosis. Raised PL counts characterize a number of acute diseases (i.e., infections, acute, chronic heart disease, and lung disease). Furthermore, it is known that increased platelet count is closely related to the relapse of tissue factor (TF) which is efficient player in explaining the high risk or frequency of VTE events particularly in cancer patients (Gussoni et al., 2013; Monreal et al., 2009; Trujillo-Santos et al., 2008).

Finally, about the environmental effects, we found a modest difference of VTE events occurred in warm period compared to cold time. Our findings are different to results of some previous studies focusing on this issue (Dentali et al., 2009; Baccarelli et al., 2008; White et al., 2003; Bounameaux et al., 1996; Boyle et al., 2001; Berentsen et al., 2020; Hong et al., 2020). On this concern, we suggest to take into account the climate characteristics in Sicily in those periods.

Sicily is a Mediterranean region located directly in the middle of the Mediterranean climate zone and it is situated in an area with dry summer subtropical climate. The Mediterranean climate is generally characterized by moderate temperatures, wet winters and dry and hot summers.

The island is subject also to the Scirocco, the hot wind from Africa, which often increase the temperature to around 20 °C (68 °F) or above in winter and from June to August, the temperature reached as high as 44/45 °C (111/113 °F) in Catania city (Sicily, Southern Italy).

Aiming to explain the difference with northern Italy major frequency of VTEs in winter, we take into account the increase of sweating during Sicilian summers that in turn can affect both on plasma concentration and on hematocrit value. Both factors could lead in determining hypercoagulative conditions. The meteorological variables registered in Catania (Table 5), typical of southern Italy, may help explain difference between our findings with data occurred in northern countries of Italy and Europe. Climate seasonal characteristics, depending also by the latitude, and environmental conditions in our city may be as reasonable items in expecting on different VTE rates in warm period compared to cold. In this regard, we want to take in account the interesting relationship already demonstrated between climate, temperature with thrombotic venous diseases. Brown et al. (2009) reported that DVT is particularly associated with reduction in atmospheric pressure that more often occur in spring and summer. Similarly, to our results, Salehi et al. (2016), Mahmoud et al. (2011) and, Górriz et al. (2007) report a higher DVT occurrences in summer months (Hong et al., 2020; Brown et al., 2009; Mahmoud et al., 2011; Górriz et al., 2007; Signorelli et al., 2019).

Regarding the seasonal variations also the location of the thrombus is influenced as reported by Fink et al. (2002). Fink reports that distal DVT was more frequent during the winter half while proximal DVT was diagnosed more often during the summer half of the year. There is reliable evidence that acute thrombosis including DVT follow a typical seasonal pattern and particularly display a characteristic spike during holiday periods (Lippi et al., 2011).

In addition, for cerebral venous thrombosis (CVT), Aaron et al. (2020) showed an incidence significantly higher in summer (42.3%) compared with autumn (32.7%) and winter 242 (25%); ($P = 0.038$) and reports that higher ambient temperatures were consistently associated with higher incidence of CVT (Aaron et al., 2020).

Instead, in Northern Italy and Europe the lowest temperature in winter than in south Italy can increase the DVT risk due the decreased physical activity in people as reported by White (1998). In fact, also the Gallerani's study (Gallerani et al., 2004) reports a significant seasonal pattern with a winter peak in the occurrence of DVT studied on patients of Ferrara (1998–2002), a city of the Northern Italy (that features severe winters and humid summers with heavy rains in spring and autumn).

Frappè and colleagues (2015) studied the seasonal variation in the superficial vein thrombosis frequency in France. Data of three French prospective multicenter studies were evaluated. Frappè reports that superficial vein thrombosis relative risks were 0.80, 1.40 and 1.20, for summer, winter and spring, respectively (Frappè et al., 2015).

Concerning the close relationship between the influences of environment with the venous thrombotic diseases, we found several findings.

Several studies reported an increased transitional metal plasma levels (Ferrante et al., 2017; Signorelli et al., 2017), and high levels of surrogate oxidative stress markers in patients suffering from DVT (Baccarelli et al., 2007, 2008, 2009; Dales et al., 2010; Kan et al., 2010; Shih et al., 2011; Bonzini et al., 2010; Cozzi et al., 2007; Emmericht et al., 2011; Signorelli et al., 2019; Signorelli and Ferrante 2017; Santo et al., 2006).

We would postulate in our country also the relationship between characteristics of the environment leading to hypercoagulative conditions as favorable in provoking venous thromboembolic disorders.

Table 5
Climatic characteristics registered in the four seasons.

	Autumn median (IQR)	Winter median (IQR)	Spring median (IQR)	Summer median (IQR)
Average Temperature, °C	20.0 (15,8–22.3)	9.0 (8.0–11.0)	14.0 (13.0–16.0)	24.5 (23.0–25.8)
Min. Temperature, °C	14.5 (10.0–17.0)	4.0 (3.0–6.0)	9.0 (7.3–11.0)	19.0 (17.0–19.8)
Max. Temperature, °C	25.0 (21.0–26.0)	16.0 (14.0–17.0)	20.0 (18.0–22.0)	29.0 (27.3–31.0)
Relative humidity, %	72.5 (62.8–79.0)	77.0 (71.0–80.0)	68.5 (59.0–74.0)	57.5 (50.3–63.0)
Atmospheric pressure, hPa	1015 (1012–1019)	1017 (1013–1026)	1014 (1010–1017)	1015 (1012–1016)
Average wind speed, km/h	13 (12.0–16.3)	11 (9.0–13.00)	13 (11.0–18.8)	13 (12.0–14.0)
Max wind speed	27.0 (19.8–32.0)	20.0 (15.0–24.0)	26.0 (20.5–32.8)	26.0 (22.0–33.0)

5. Conclusions

Our findings want to draw attention to suspecting VTE in individuals admitted to the HER presenting common symptoms but no diagnostic for VTE. Furthermore, we want to draw attention also to significant number of individuals admitted to the HER were suffering from chronic co-morbidities which may promote the VTE risk or onset. Furthermore, a large number of individuals or patients admitted to HER because showed they suffered from non-specific and/or non-diagnostic symptoms such as dyspnea, lower leg edema and leg pain. We want to emphasize the common practice of inducing these individuals to be forwarded to the HER. However, because none of the above-mentioned symptoms are effective in diagnosing either PE or DVT (Dentali et al., 2010) we confirm that in individuals showing one or more symptoms and having comorbidities must be carefully considered (Dentali et al., 2010; Piazza et al., 2009) as potential VTE diagnosed patients. It is important to check on individual risk profile for VTE to provide adequate clinical process. Physicians alerted on potential risk for venous thrombosis diseases in hospitalized, and suspected patients, early prophylaxis or therapy VTE (Kearon et al., 2012). This option improves outcome and prognosis of patients (Piazza et al., 2009). Risk profile check consists both on pretest scores, on measurement of D-dimer about, and in performing the US examination with the CUS test. In conclusion, we want to promote a greater awareness of suspected VTE in individuals forwarded to HER despite showing one or more common symptoms. We suggest that environment can have a direct influence (Shi et al., 2015) on the incidence of DVT as a very intriguing issue to evaluate in the future studies the seasonality of VTE in different climate (Signorelli et al., 2019; Signorelli and Ferrante, 2017; Ferrante et al., 2017). Studies carried out for assessing the seasonal variation influence on venous thrombosis (CVT) are few and often with conflicting conclusions. Data, also if limited, of the present study suggest that seasonality and climate (linked to latitude) can increase the DVT frequency in human, encouraging researchers for further studies to elucidate on role played by climate, temperature, and environment on VTE occurrence.

Further researches could test the correlation between both climatic and thrombotic factors and the pathogenesis of DVT. Clarify and better understand the pathophysiological mechanism of the DVT can permit to contribute to a better prevention and treatment of risk groups of patients in certain periods of the year, through easy and cheap indications.

Authors' contributions

SS Signorelli. Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication, G Oliveri Conti. Substantial contribution to drafting and reviewing the article, final approval of the article for publication.

G Carpinteri, Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication. G Lumera. Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication, M Fiore. Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication, G Dattilo. Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication, A Gaudio. Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication, M Ferrante. Substantial contribution to conception and design, drafting the article, analysis and interpretation data, final approval of the article for publication.

All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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DICHIARAZIONE DI CONFORMITA'

Il sottoscritto Prof. Alfredo Antonio CHETTA dichiara di avere partecipato, in via telematica, alla riunione tenutasi il 11/01/2021 alle ore 12.30 per lo svolgimento dei lavori della procedura di valutazione comparativa per la stipula di n. 1 contratto di diritto privato per ricercatore, a tempo determinato, per il Settore Concorsuale 06/D1 e per il Settore Scientifico Disciplinare Med 11 bandita dall'Università degli Studi di Messina, ai sensi dell'art. 24, comma 3, lettera B) della legge 30 dicembre 2010, n. 240 e di avere preso parte alla stesura del relativo verbale, aderendo al contenuto dello stesso.

Parma, 11 gennaio 2022

Prof. Alfredo Antonio CHETTA

DICHIARAZIONE DI CONFORMITA'

Il sottoscritto Prof. C. Vancheri dichiara di avere partecipato, in via telematica, alla riunione tenutasi il 11/01/2022 alle ore 12.30 per lo svolgimento dei lavori della procedura di valutazione comparativa per la stipula di n. 1 contratto di diritto privato per ricercatore, a tempo determinato, per il Settore Concorsuale 06/D1 e per il Settore Scientifico Disciplinare Med 11 bandita dall'Università degli Studi di Messina, ai sensi dell'art. 24, comma 3, lettera B) della legge 30 dicembre 2010, n. 240 e di avere preso parte alla stesura del relativo verbale, aderendo al contenuto dello stesso.

data
11/01/2022

Prof. C. Vancheri

PROCEDURA DI VALUTAZIONE COMPARATIVA PER LA STIPULA DI N. 1 CONTRATTO DI DIRITTO PRIVATO PER RICERCATORE A TEMPO DETERMINATO, AI SENSI DELL'ART. 24, COMMA 3, LETT. B) DELLA LEGGE 30 DICEMBRE 2010, N. 240, - SC 06/D1 - SSD MED/11 (Malattie Dell'apparato Cardiovascolare) Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali PRESSO L'UNIVERSITA' DEGLI STUDI DI MESSINA

VERBALE N. 3

(Discussione pubblica e punteggi)

L'anno 2022 il giorno 24 del mese di Gennaio alle ore 12.30 si riunisce al completo, per via telematica, ognuno nella propria sede universitaria, la Commissione giudicatrice, della procedura di valutazione comparativa in epigrafe, nominata con D.R. prot. prot. n. 2698 del **05/11/2021** pubblicato sul sito internet dell'Università di Messina, per procedere con la discussione pubblica dei titoli e delle pubblicazioni dei candidati precedentemente ammessi.
Sono presenti i sotto elencati commissari:
Prof. Carlo Vancheri Università degli Studi di Catania
Prof. Alfredo Antonio Chetta Università degli Studi di Parma
Prof. Antonio Micari Università degli Studi di Messina

In videoconferenza, la Commissione dà atto che i canali telematici in utilizzo (Microsoft TEAMS) sono idonei al riconoscimento dei soggetti coinvolti e che è attraverso il link pubblico è garantita la partecipazione dei docenti invitati alla discussione.

La Commissione procede, quindi, all'appello dei candidati ammessi nella riunione precedente.
Sono presenti i seguenti candidati dei quali è accertata l'identità personale.
1) Francesco Costa
2) Giuseppe Dattilo

I candidati sono chiamati a sostenere la discussione in ordine alfabetico.

Al termine della discussione pubblica, la Commissione procede ad attribuire un punteggio **ai titoli e a ciascuna delle pubblicazioni**, tenendo conto dei criteri stabiliti nella prima riunione (All. A). Riesaminati i motivati giudizi analitici espressi nella valutazione preliminare, sulla base dei punteggi attribuiti ai titoli e alle pubblicazioni in esito alla discussione pubblica, la Commissione dichiara vincitore il dott. **Francesco Costa** con la seguente motivazione: il candidato ha ottima attività di ricerca e ottima attività di progettazione nell'ambito della ricerca . Ha inoltre partecipato in qualità di faculty a numerosi congressi internazionali. La sua attività e' stata riconosciuta con l'assegnazione di premi alla ricerca internazionali e nazionali.

La Commissione individua, inoltre, gli idonei alla stipula del contratto, predisponendo, altresì, sulla base dei punteggi conseguiti, una graduatoria.

I candidati sono collocati in graduatoria se raggiungono, all'esito della valutazione, un punteggio di almeno **65 punti**.

CANDIDATO	TOTALE PUNTEGGIO VALUTAZIONE TITOLI	TOTALE PUNTEGGIO VALUTAZIONE PUBBLICAZIONI	TOTALE PUNTEGGIO ASSEGNATO AL CANDIDATO
Francesco Costa	33.5	60	93.5
Giuseppe Dattilo	29	60	89

Il presente verbale viene redatto, letto, sottoscritto seduta stante.

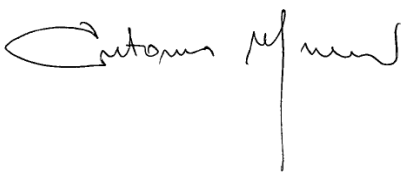
La seduta è tolta alle ore 13.20.

LA COMMISSIONE

Prof. C Vancheri(Presidente)

Prof. A.A. Chetta (Componente)

Prof. A.Micari (Segretario)



ALLEGATO A)

PUNTEGGIO TITOLI E PUBBLICAZIONI

CANDIDATO: Francesco Costa

VALUTAZIONE TITOLI

	Titoli	*Punti assegnati*	*Punteggio max (come stabilito nel I verbale dei criteri)*	*Punteggio totale*
A	***Dottorato***	***8***	***8***	***8/8***
B	***Attività Didattica***	***1***	***5***	***1/5***
C	***Formazione e Ricerca all'estero***	***4***	***4***	***4/4***
D	***Attività Clinica***	***4***	***4***	***4/4***
E	***Realizzazione attività progettuale, o partecipazione***	***1.5***	***3***	***1.5/3***
F	***Organizzazione, direzione, coordinamento gruppi di ricerca nazionali e internazionali o partecipazione agli stessi***	***5***	***5***	***5/5***
G	***Brevetti***	***0***	***4***	***0/4***
H	***Relatore a Congressi e convegni nazionali e internazionali***	***5***	***5***	***5/5***
I	***Premi e riconoscimenti***	***2***	***2***	***2/2***
L	***Attività Editoriale***	***3***	***3***	***3/3***
	TOTALE	***33.5***		***33.5***

VALUTAZIONE PUBBLICAZIONI

Originalità, innovatività, rigore metodologico e rilevanza	*Congruenza con SSD*	*Rilevanza scientifica collocazione editoriale e diffusione*	*Apporto individuale candidato*
15/15	***15/15***	***15/15***	***15/15***
			60/60

CANDIDATO: Giuseppe Dattilo

VALUTAZIONE TITOLI

	Titoli	*Punti assegnati*	*Punteggio max (come stabilito nel I verbale dei criteri)*	*Punteggio totale*
A	***Dottorato***	***8***	***8***	***8/8***
B	***Attività Didattica***	***5***	***5***	***5/5***
C	***Formazione e Ricerca all'estero***	***0***	***4***	***0/4***
D	***Attività Clinica***	***4***	***4***	***4/4***
E	***Realizzazione attività progettuale, o partecipazione***	***1***	***3***	***1/3***
F	***Organizzazione, direzione, coordinamento gruppi di ricerca nazionali e internazionali o partecipazione agli stessi***	***5***	***5***	***5/5***
G	***Brevetti***	***0***	***4***	***0/4***
H	***Relatore a Congressi e convegni nazionali e internazionali***	***2***	***5***	***2/5***
I	***Premi e riconoscimenti***	***1***	***2***	***1/2***
L	***Attività Editoriale***	***3***	***3***	***3/3***
	TOTALE	***29***		***29***

VALUTAZIONE PUBBLICAZIONI

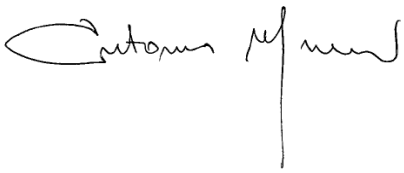
Originalità, innovatività, rigore metodologico e rilevanza	*Congruenza con SSD*	*Rilevanza scientifica collocazione editoriale e diffusione*	*Apporto individuale candidato*
15/15	***15/15***	***15/15***	***15/15***
			60/60

LA COMMISSIONE

Prof. C. Vancheri (Presidente)

Prof. A.A. Chetta (Componente)

Prof. A. Micari (Segretario)



PROCEDURA DI VALUTAZIONE COMPARATIVA PER LA STIPULA DI N. 1 CONTRATTO DI DIRITTO PRIVATO PER RICERCATORE A TEMPO DETERMINATO, AI SENSI DELL'ART. 24, COMMA 3, LETT. B) DELLA LEGGE 30 DICEMBRE 2010, N. 240, **- SC 06/D1 - SSD MED/11 (Malattie Dell'apparato Cardiovascolare) Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali**

PRESSO L'UNIVERSITA' DEGLI STUDI DI MESSINA

RELAZIONE CONCLUSIVA

L'anno 2022 il giorno 24 del mese di Gennaio alle ore 12.30 si riunisce al completo, per via telematica, ognuno nella propria sede universitaria, la Commissione giudicatrice, della procedura di valutazione comparativa in epigrafe, nominata con D.R. prot. prot. n. 2698 del **05/11/2021** pubblicato sul sito internet dell'Università di Messina, per procedere con la discussione pubblica dei titoli e delle pubblicazioni dei candidati precedentemente ammessi.

Sono presenti i sotto elencati commissari:

Prof. Carlo Vancheri Università degli Studi di Catania

Prof. Alfredo Antonio Chetta Università degli Studi di Parma

Prof. Antonio Micari Università degli Studi di Messina

La Commissione ha svolto i sui lavori nei giorni:

I riunione: giorno 2 dicembre dalle ore 12 alle ore 13

II riunione: giorno 22 Dicembre dalle ore ore 18.30 alle ore 19.30;

III riunione: giorno 11 Gennaio dalle ore 12.30 alle ore 13.30;

IV riunione: giorno 24 Gennaio dalle 12.30 alle ore 13.30.

La Commissione ha tenuto complessivamente n. 4 riunioni iniziando i lavori il 2 Dicembre e concludendoli il 24 Gennaio 2022;

Nella prima riunione la commissione ha deciso i criteri di valutazione dei candidati.

Nella seconda riunione si è proceduto alla valutazione dei titoli e delle pubblicazioni dei candidati. Essendo molte le pubblicazioni presentate dai due candidati si è deciso di aggiornarsi a successiva riunione per completare la valutazione. Nella terza riunione si è completato quindi la valutazione di titoli e pubblicazioni e ammessi entrambi i candidati alla discussione pubblica.

Nella quarta riunione si è proceduto alla discussione dei titoli e delle pubblicazioni per entrambi i candidati in ordine alfabetico e alla prova di inglese. Si è redatto quindi il verbale conclusivo che sancisce il Dott. Costa quale vincitore del concorso.

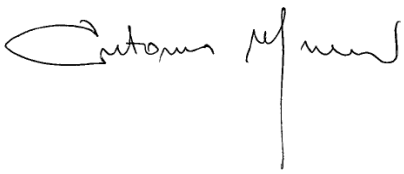
La Commissione tenuto conto della somma dei punteggi attribuiti ha proceduto collegialmente all'espressione di un motivato giudizio in relazione alla quantità e alla qualità delle pubblicazioni valutando la produttività complessiva anche in relazione al periodo di attività.
La Commissione dichiara vincitore il dott. Francesco Costa avendo ottenuto l'unanimità dei voti dei componenti della commissione giudicatrice.

La Commissione predispone inoltre, sulla base dei punteggi conseguiti, una graduatoria degli idonei o dei partecipanti più meritevoli:

1. Francesco Costa
2. Giuseppe Dattilo

I verbali della presente procedura, già inseriti nella piattaforma informatica, saranno resi pubblici sul sito web dell'Ateneo a seguito dell'approvazione degli atti della procedura da parte del Rettore.
La Commissione termina i lavori alle ore 13.30 del giorno 24 Gennaio 2022
Letto approvato e sottoscritto.

LA COMMISSIONE
Prof. C. Vancheri (Presidente)
Prof. A.A. Chetta (Componente)
Prof. A. Micari (Segretario)

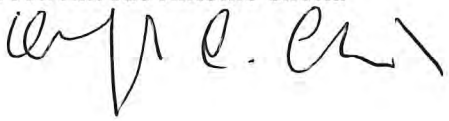


DICHIARAZIONE DI CONFORMITA'

Il sottoscritto Prof. Alfredo Antonio Chetta dichiara di avere partecipato, in via telematica, alla riunione tenutasi il 24/01/2022 alle ore 12.30 per lo svolgimento dei lavori della procedura di valutazione comparativa per la stipula di n. 1 contratto di diritto privato per ricercatore, a tempo determinato, per il Settore Concorsuale 06/D1 e per il Settore Scientifico Disciplinare Med 11 bandita dall'Università degli Studi di Messina, ai sensi dell'art. 24, comma 3, lettera B) della legge 30 dicembre 2010, n. 240 e di avere preso parte alla stesura del relativo verbale, aderendo al contenuto dello stesso.

data 24/01/2022

Prof. Alfredo Antonio Chetta



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data
24/01/2022

Prof. C. Vancheri