Aus dem Deutschen Herzzentrum der Charité
Klinik für Kardiologie, Angiologie und Intensivmedizin
am Campus Virchow-Klinikum
Kommissarischer Klinikdirektor: Prof. Dr. med. Leif-Hendrik Boldt

Habilitationsschrift

Diagnostik und Früherkennung von Herzinsuffizienz mit erhaltener Auswurffraktion (HFpEF): Von der Validierung der Diagnose zur Entwicklung innovativer Deformitätsanalysen mittels Kardio-MRT

zur Erlangung der Lehrbefähigung
für das Fach Innere Medizin und Kardiologie

vorgelegt dem Fakultätsrat der Medizinischen Fakultät
Charité-Universitätsmedizin Berlin

von

Dr. med. Djawid Hashemi, MSc
geboren in Andernach

Eingereicht: 05/2023

Dekan: Prof. Dr. med. Joachim Spranger

1. Gutachterin: Prof. Dr. Birgit Aßmus, Gießen

2. Gutachter: Prof. Dr. Peter Lüdike, Essen

1. Inhaltsverzeichnis

2. Abkürzungen

ACE-Hemmer	-	Angiotensin-Converting-Enzyme-Hemmer
AHA	-	American Heart Association
ARB	-	Angiotensin-Rezeptor-Blocker
CMR	-	cardiovascular magnetic resonance imaging
ESC	-	European Society of Cardiology
EF	-	ejection fraction
GLS	-	global longitudinal strain
GCS	-	global circumferential strain
HF	-	heart failure
HFimpEF	-	heart failure with improved ejection fraction
HFrEF	-	heart failure with reduced ejection fraction
HFmrEF	-	heart failure with mildly reduced ejection fraction
HFpEF	-	heart failure with preserved ejection fraction
HI	-	Herzinsuffizienz
INTERMACS	-	Interagency Registry for Mechanically Assisted Circulatory Support
LAVI	-	linksatrialer Volumenindex
LV	-	linker Ventrikel
LVAD	-	left ventricular assist device
LVEDP	-	left ventricular enddiastolic pressure
LVEF	-	left ventricular ejection fraction
MRA	-	Mineralokortikoid-Rezeptor-Antagonist
MRT	-	Magnetresonanztomographie
NYHA	-	New York Heart Association functional class
RAAS	-	Renin-Angiotensin-Aldosteron-System
RV	-	rechter Ventrikel
SGLT2	-	Sodium glucose linked transporter 2
SNS	-	sympathisches Nervensystem

3. Einleitung

3.1. Definition und Klassifikation der Herzinsuffizienz

Die Herzinsuffizienz (HI) ist ein klinisches Syndrom, das durch diverse Ätiologien und charakteristische Symptome wie myokardiale Dysfunktion, Dyspnoe und Hypervolämie verursacht wird.[1,2]

Die 2021 publizierte universelle Definition der HI definiert sie als ein klinisches Syndrom bestehend aus der (vormaligen) Präsenz (Fig. 1) von

- Zeichen (auffälliger Untersuchungsbefund) und/ oder Symptomen der Herzinsuffizienz durch eine strukturelle und/ oder funktionelle kardiale Dysfunktion

und

a. erhöhte natriuretische Peptide oder
b. eine objektivierbare pulmonale/ systemische Stauung (via Bildgebung oder invasiver Messung) in Ruhe oder bei Belastung.

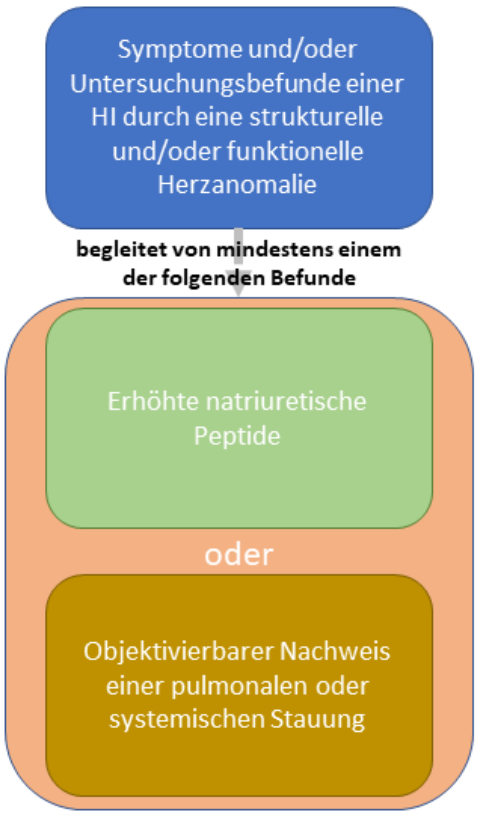


Fig. 1 – Universale Definition der Herzinsuffizienz adaptiert aus: Bozkurt et al., Universal Definition and Classification of Heart Failure, 2021.[3]

Im Einklang mit dieser Definition sind die HI-Definitionen der ESC und die der amerikanischen kardiologischen Gesellschaft (American Heart Association, AHA), die eine klassischere Kombination vorsehen: HI ist definiert als Kombination aus Symptomen und einem auffälligen Untersuchungsbefund hinsichtlich einer HI mit entweder einem inadäquaten Herzzeitvolumen und/ oder erhöhten intrakardialen Füllungsdrücken aufgrund struktureller/ funktioneller Herzanomalien in Ruhe oder bei Belastung.[1,4,5]

Die Klassifikation von HI hat therapeutische und prognostische Bedeutung und kann phänomenologisch (NYHA-Klassifikation, INTERMACS-System) oder pathophysiologisch (akute und chronische HI, Rechts- und Linksherzinsuffizienz, Einteilung anhand der linksventrikulären Auswurffraktion, LVEF) erfolgen.

Der subjektive Schweregrad gliedert die Patient*innen anhand der New York Heart Association (NYHA) von NYHA-Klasse I (momentaner Beschwerdefreiheit über HI-Beschwerden bei Belastung) bis NYHA-Klasse IV (momentane Beschwerden in Ruhe).[1,3] Erkrankte Personen mit hoher Beschwerdelast (NYHA III und IV) werden zusätzlich anhand des Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) klassifiziert. Das INTERMACS-System bindet weitere Therapiekontexte (wie kreislaufunterstützende Medikation) in die Klassifikation ein und teilt Patient*innen in sieben Stufen (INTERMACS 7: Patient*in mit abzusehender Verschlechterung bis INTERMACS 1: Patient*in im kardiogenen Schock) ein.[6]

Die amerikanische Klassifikation schließt vier Stadien (Stadien A, B, C und D) ein. Den Stadien A und B werden asymptomatische Betroffene mit Risikofaktoren und möglichen morphologischen kardialen Veränderungen zugeordnet.[3,7]

Die Klassifikation der HI ist die traditionelle Einteilung anhand der linksventrikulären Auswurffraktion (LVEF), die als Parameter der systolischen Funktion das Verhältnis des vom linken Ventrikel ausgestoßenen Blutvolumens zum enddiastolischen Volumen beschreibt (Tab. 1).

Entsprechend wird anhand der LVEF unterschieden zwischen

- HI mit reduzierter Auswurffraktion (*HF with reduced ejection fraction, HFrEF*),
- HI mit mäßig reduzierter Auswurffraktion (*HF with mildly reduced EF, HFmrEF*) und
- HI mit erhaltener Auswurffraktion (*HF with preserved EF, HFpEF*).[1]

Die universelle Definition der Herzinsuffizienz führte 2021 eine vierte Kategorie ein: HI-Erkrankte mit vormals reduzierter und im Verlauf verbesserter LVEF (*HF with improved EF, HFimpEF*).[3] Aufgrund der noch fehlenden therapeutischen Konsequenz ist dieser Terminus noch nicht in den klinischen Alltag eingezogen, er illustriert allerdings die Dynamik des Parameters LVEF, der sich im Krankheitsverlauf verändern kann – auch positiv.

HI Entität		**HFrEF**	**HFmrEF**	**HFpEF**
Kriterien	**1**	Symptome ± Krankheitszeichen*	Symptome ± Krankheitszeichen*	Symptome ± Krankheitszeichen*
	2	LVEF ≤ 40 %	LVEF 41–49 %	LVEF ≥ 50 %
	3	–	–	Objektive Hinweise auf strukturelle und/oder funktionelle Herzanomalien, die auf eine diastolische LV-Dysfunktion/ erhöhte LV-Füllungsdrücke hindeuten, einschließlich erhöhter natriuretischer Peptide.

Tab. 1 – Definition der Herzinsuffizienz nach McDonagh et al. und der deutschen Version der Leitlinie.[1,8]

*Krankheitszeichen: HI zuzurechnende pathologische Untersuchungsbefunde. HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HI: Herzinsuffizienz: LV: linker Ventrikel; LVEF: left ventricular ejection fraction.

Liegt der Wert einer physiologischen LVEF bei > 50 %, so ist bei Patient*innen mit HFrEF oder HFmrEF der definitionsgemäß notwendige Nachweis einer kardialen Dysfunktion bereits durch die LVEF erbracht.[1,9]

Bei Erkrankten mit HFpEF und einer LVEF ≥ 50 % ist eine kardiale Dysfunktion nicht anhand der LVEF per se ersichtlich, sodass weitere Parameter notwendig sind. Bei erhaltener LVEF ist eine HI durch das Vorhandensein einer diastolischen Funktionsstörung bzw. eines erhöhten LV-Füllungsdrucks definiert.

Die HFrEF ist primär als *kategorische Erkrankung* zu verstehen. Sie wird dadurch charakterisiert, ob sie präsent ist oder nicht. Ihr Vorhandensein wird durch den Nachweis

einer reduzierten LVEF festgestellt. Dies ist vergleichbar mit einer malignen Tumorerkrankung, bei der der Nachweis maligner Zellen per definitionem zeigt, ob eine Erkrankung (hier Krebs) vorhanden ist oder nicht.[2]

Bei HFpEF ist diese Fassbarkeit nicht gegeben, ihr Krankheitswert ist charakterisiert durch das Kompositum verschiedener klinischer und laborchemischer Parameter vor dem Hintergrund ihrer prognostischen Bedeutung – es handelt sich um eine *numerische Erkrankung*.[2] Ein unterkomplexer Vergleich kann die Pathologie-Schwelle der arteriellen Hypertonie dienen: Der Grenzwert, ab dem ein erhöhter Blutdruck als behandlungsbedürftig bzw. pathologisch angesehen werden kann, ist durch die prognostische Bedeutung durch eine Assoziation mit fatalen Ereignissen und der Mortalität im Verlauf definiert.[2] Ähnlich sind Charakteristika bei HFpEF zu werten, deren Klassifizierung als *pathologische Kombination* davon geprägt ist, ob sie eine prognostische Bedeutung haben.

3.2. Epidemiologie der Herzinsuffizienz

Mit einer hohen Morbidität, Mortalität und ökonomischen Belastung stellt HI eine Herausforderung für die öffentliche Gesundheit dar.[10] Sie ist eine der Hauptursachen für Krankenhausaufenthalte im Allgemeinen. Bei älteren Erwachsenen stellt sie sogar die Hauptursache für wiederholte Aufenthalte im Krankenhaus dar.[1]

<u>Prävalenz</u>

Die Prävalenz von Herzinsuffizienz ist weltweit hoch, mit fortbestehend steigender Tendenz.[1,10] In Europa beträgt sie etwa 1-2 %, in Deutschland primär aufgrund des höheren durchschnittlichen Lebensalters der Bevölkerung approximativ 4 %.[11,12]

Die HI-Prävalenz steigt mit dem Alter, wobei etwa 10 % der Menschen über 60 Jahre und 20 % über 70 Jahre betroffen sind.[13] Die Prävalenz von Herzinsuffizienz ist in der Gesellschaft heterogen verteilt, ihr Vorkommen ist bedeutend vom Alter, vom Geschlecht und von der Ethnie geprägt.[14] Männer haben ein höheres Risiko an HI zu erkranken als Frauen und ethnische Unterschiede mit höherem Risiko bei afrikanischem Ursprung wurden ebenfalls festgestellt.[6,15]

Die Prävalenz von HI mit erhaltener Ejektionsfraktion (HFpEF) hat zugenommen und macht mehr als 50 % der HI-Fälle aus.[16] Auch dieser Umstand ist in dem Kontext der

demographischen Umstrukturierung industrieller Gesellschaften zu verstehen. Das Alter ist nicht nur selbst Risikofaktor, es ist auch einhergehend mit der Präsenz und der Dauer von Komorbiditäten wie Bluthochdruck und Diabetes, die mit HFpEF assoziiert sind.[17] Im Vergleich dazu hat die Prävalenz von HFrEF abgenommen, möglicherweise aufgrund von Verbesserungen in der Prävention und Behandlung von ischämischen Herzerkrankungen, die häufig zu HFrEF führen.[18]

Inzidenz

Die Inzidenzen von HFpEF und HFrEF unterscheiden sich ebenfalls abhängig von den Charakteristika der jeweiligen Population. In Fig. 2 werden die führenden Einflussfaktoren auf alle drei HI-Entitäten illustriert.[19] Die Inzidenz von HI in Europa wird auf 3,9 bis 6,7 Fälle, in Deutschland auf 3,5 Fälle pro 1000 Personenjahre geschätzt.[12,20] HFrEF tritt häufiger in jüngeren Populationen auf, während HFpEF bei älteren Menschen und Frauen stärker vertreten ist.[15,19,21] Risikofaktoren für die Entwicklung von HFpEF sind unter anderem arterielle Hypertonie, Diabetes mellitus und Adipositas.[1,17] Insgesamt ist die Inzidenz von HFpEF in den letzten Jahren gestiegen, während die von HFrEF tendenziell abgenommen hat.[11,19,22]

Risikofaktoren

Risikofaktoren für HI umfassen demographische, klinische, genetische und umweltbedingte Faktoren sowie Bedingungen des Lebensstils. Nikotinkonsum, unausgewogene Ernährung und Bewegungsmangel stellen modifizierbare Lebensstilfaktoren dar, die eine HI begünstigen.[23] Alkoholmissbrauch und Drogenkonsum können ebenfalls das Risiko für HI erhöhen – ihre Überwindung ist jedoch häufig von weiteren Hürden begleitet.[24] Klinische Risikofaktoren sind arterielle Hypertonie, Diabetes mellitus, Adipositas, koronare Herzerkrankung, chronische Nierenerkrankungen und Schlafapnoe.[17,25] Genetisch bedingte Herzerkrankungen und Umweltfaktoren wie Luftverschmutzung oder Lärmbelästigung sind weitere Risikofaktoren.[26-31]

Prognose

Die Prognose von Patient*innen mit HI bleibt trotz der Fortschritte in der Diagnose und Behandlung ungünstig. Die Mortalitätsraten bei Herzinsuffizienz sind hoch, wobei etwa 50 % der Erkrankten innerhalb von fünf Jahren nach der Diagnose versterben.[32] Die Ein-Jahres-

Mortalität für HI-Patient*innen beträgt etwa 20-30 %, abhängig von der Schwere der Erkrankung und von den Begleiterkrankungen.[33,34] Die Morbidität ist ebenfalls erheblich und Betroffene leiden unter wiederkehrenden Krankenhausaufenthalten und einer eingeschränkten körperlichen Leistungsfähigkeit.[1] Etwa 24 % der HI-Patient*innen werden innerhalb von 30 Tagen nach der Entlassung erneut aufgrund einer HI hospitalisiert.[35]

Die Prognose bei Herzinsuffizienz variiert je nach HI-Entität. Die Mortalität bei HFrEF-Patient*innen ist trotz etablierter Pharmakotherapiestrategien weiterhin hoch.[1,5] Die Erkrankten leiden häufig auch an Arrhythmien und plötzlichem Herztod – etwa die Hälfte der Todesfälle von HFrEF-Patient*innen sind Arrhythmien zuzurechnen.[1,7] Bei HFpEF sind die therapeutischen Möglichkeiten limitiert. Die Mortalitätsraten bei HFpEF sind ähnlich hoch wie bei HFrEF.[1,19] Die Heterogenität der HFpEF-Population und das unzureichende Verständnis der Pathophysiologie erschweren die Identifikation geeigneter Therapieansätze, um die Prognose bei HFpEF zu verbessern.[22]

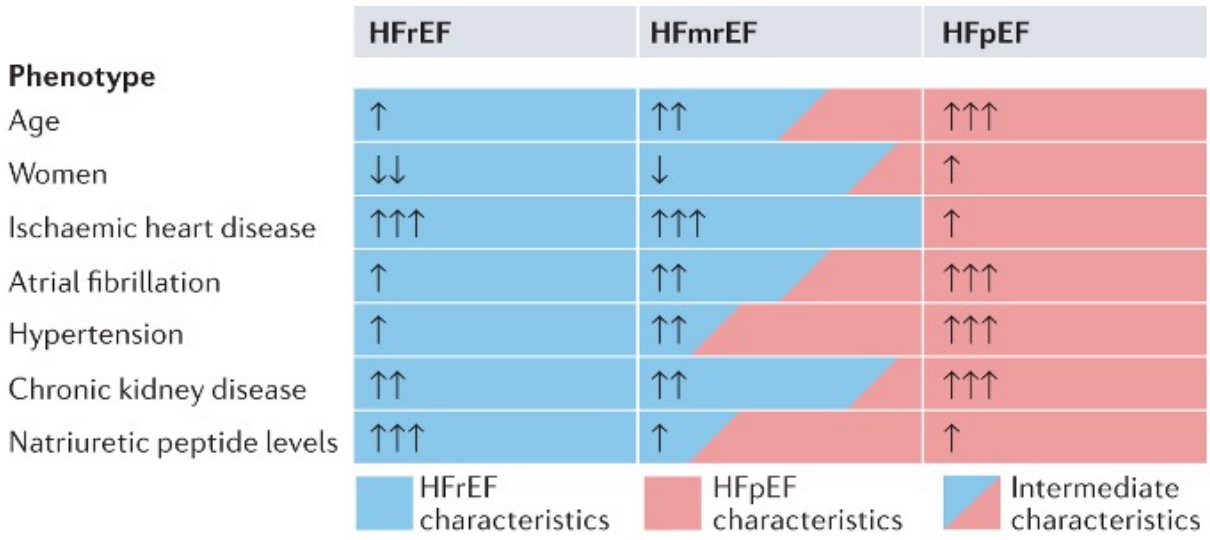


Fig. 2 – Vergleich der Phänotypen der drei HI-Kategorien, entnommen aus Saverese et al.[19] und modifiziert.

Age: Alter; Atrial Fibrillation: Anteil an Vorhofflimmern; chronic kidney disease: Anteil derer mit chronischer Niereninsuffizienz; HFmrEF: Herzinsuffizienz mit mäßig reduzierter Auswurffraktion; HFpEF: Herzinsuffizienz mit erhaltener Auswurffraktion; HFrEF: Herzinsuffizienz mit reduzierter Auswurffraktion; HI: Herzinsuffizienz; Hypertension: Anteil derer mit arterieller Hypertonie; Ischaemic heart disease: Anteil der ischämischen Herzerkrankungen; Natriuretic peptide levels: Spiegel der natriuretischen Peptide; Women: Anteil der Frauen. ↑ and ↓ zeigen höhere Niveaus oder häufigeres Vorkommen bzw. geringere Niveaus oder selteneres Vorkommen gegenüber einer altersadaptierten Vergleichsgruppe (Ausnahme: Alter, hier verweist ↑ auf eine Häufung gegenüber dem durchschnittlichen Erwachsenen).

Epidemiologische Trends

Die Prävalenz und Inzidenz der HI werden voraussichtlich weiter zunehmen, was auf die Alterung der Bevölkerung und erhöhte Überlebensraten bei kardiovaskulären Erkrankungen zurückzuführen ist.[36,37] Um die Belastung durch HI zu reduzieren, ist es daher entscheidend, wirksame Präventions- und Therapiestrategien zu entwickeln.

Ein optimales Management der Risiko- und Einflussfaktoren ist maßgebend, um den Anstieg der HI-Prävalenz zu verlangsamen oder umzukehren.[10] Neben den unmittelbar medizinischen Einflussgrößen stellt die Veränderung sozioökonomischer Faktoren, die eine HI begünstigen und die geographische wie soziokulturelle Heterogenität beeinflussen, eine gesellschaftliche Herausforderung dar.[38] Für die Entwicklung und Implementierung zielgerichteter politischer und gesellschaftlicher Maßnahmen ist eine vollständigere Erfassung sozioökonomischer Parameter notwendig.[39] Dass Public-Health-Interventionen effektiv in der Verbesserung der Prävention, Diagnose und Behandlung von Herzinsuffizienz sind, um den Anstieg der Prävalenz und Inzidenz der Erkrankung einzudämmen, konnte bereits gezeigt werden.[40]

3.3. Pathophysiologie der Herzinsuffizienz

Die Pathophysiologie der HI ist komplex und unterscheidet sich bei HFrEF, HFmrEF und HFpEF. Diese Arbeit konzentriert sich auf die HFpEF, deren Prävalenz und damit Relevanz in den letzten Jahren an Bedeutung gewonnen hat.

Allgemeine Aspekte der Pathophysiologie der HI

Die Hauptmechanismen der HI sind das Versagen der *kardialen Kompensationsmechanismen* und die *neurohumorale Aktivierung*. Zuletzt ist das *ventrikuläre Remodeling* ein zentraler Prozess in der Pathophysiologie der HI.

Die *kardialen Kompensationsmechanismen* schließen den Frank-Starling-Mechanismus, die Herzfrequenz-Regulation und die myokardiale Kontraktilität ein.[41]

Die *neurohumorale Aktivierung* spielt eine zentrale Rolle beim Erkrankungsprogress. Sie umfasst in erster Linie die Aktivierung des Renin-Angiotensin-Aldosteron-Systems (RAAS), des sympathischen Nervensystems (SNS) und des Arginin-Vasopressin-Systems.[42]

Das *ventrikuläre Remodeling*, ein weiterer zentraler Prozess in der Pathophysiologie der HI, bezieht sich auf die strukturellen und funktionellen Veränderungen des Herzmuskels, die als

Reaktion auf chronische Belastung auftreten.[43,44] Dies kann sich in Hypertrophie, Dilatation oder Fibrose des Myokards niederschlagen.[44]

Pathophysiologie der HFrEF

Die Pathophysiologie der HFrEF ist gekennzeichnet durch eine systolische Dysfunktion, bei der die Kontraktilität des Myokards und die Inotropie beeinträchtigt sind.[1] Eine Verminderung der Kontraktilität kann durch zelluläre und molekulare Veränderungen wie gestörtes Calcium-Handling und mitochondriale Dysfunktion verursacht werden.[45]

Neurohumorale Aktivierung, insbesondere die Aktivierung des RAAS und des SNS, trägt ebenfalls zur Pathophysiologie der HFrEF bei.[46] Zusätzlich zu den allgemeinen HI-Mechanismen kommt hier ein gestörtes Calcium-Handling zum Tragen. Dieses beeinträchtigt die myokardiale Kontraktilität bedeutsam.[47] Ebenso trägt die mitochondriale Dysfunktion, die durch oxidative Schäden, einen veränderten Energiemetabolismus und Veränderungen in der mitochondrialen Dynamik verursacht wird, zur eingeschränkten Herzfunktion bei HFrEF bei.[48]

Pathophysiologie der HFmrEF

HFmrEF teilt gemeinsame Pathomechanismen sowohl mit HFrEF (z. B. systolische Dysfunktion und kardiales Remodeling) als auch mit HFpEF (z. B. diastolische Dysfunktion und erhöhte Füllungsdrücke). Es verbleibt noch offen, mögliche spezifische Mechanismen der HFmrEF zu identifizieren.

Pathophysiologie der HFpEF

Die HFpEF ist geprägt von Pathomechanismen wie diastolischer Dysfunktion, endothelialer Dysfunktion und vaskulärer Steifigkeit sowie Entzündung und Fibrose.[49] Die resultierende Erhöhung der linksventrikulären Füllungsdrücke führt zur Erhöhung des hydrostatischen Drucks im Pulmonalbett und sekundär zu Atemnot und Flüssigkeitsretention.[1] Die Entkopplung des linken Ventrikels und des arteriellen Gefäßsystems (ventricular-arterial uncoupling) ist ebenso ein relevanter Mechanismus im Rahmen der Pathogenese der HFpEF, der mit erhöhter vaskulärer Steifigkeit und endothelialer Dysfunktion einhergeht.[50] All diese Mechanismen haben einen sich gegenseitig verstärkenden Effekt mit Erhöhung der Nach- und der Vorlast.[50,51]

Unterschiede und Gemeinsamkeiten zwischen HFrEF, HFmrEF und HFpEF

HFrEF, HFmrEF und HFpEF teilen einige klinische Merkmale, unterscheiden sich aber hinsichtlich der zugrunde liegenden Pathophysiologie und der Therapieansätze. HFrEF ist vorrangig durch systolische Dysfunktion gekennzeichnet, bei HFpEF liegt diastolische Dysfunktion im Vordergrund und HFmrEF zeigt sich als Mischbild der beiden klassischen Entitäten.[1,19]

Bei HFrEF ist eine medikamentöse Basistherapie mit prognostischer Bedeutung mittels Betablocker, ACE-Hemmer, Angiotensin-Rezeptor-Blocker (ARBs), Mineralokortikoid-Rezeptor-Antagonisten (MRAs) sowie SGLT-2-Hemmer (Sodium glucose linked transporter 2) gut etabliert – sie zeigt eine eindeutige Mortalitätsreduktion.[1] Für HFpEF gibt es seit der EMPEROR-preserved-Studie eine wirksame medikamentöse Therapie mittels SGLT-2-Hemmer, die prognostisch hinsichtlich einer HI-Hospitalisierung und kardiovaskulären Mortalität relevant ist.[22] HFmrEF-Patient*innen könnten von einigen Therapieansätzen profitieren, die bei HFrEF wirksam sind, jedoch ist die Evidenzlage dazu nicht eindeutig.[1]

3.4. Diagnose und Therapie der Herzinsuffizienz

Die Diagnose und Therapie der Herzinsuffizienz umfasst eine Kombination aus Methoden, die sowohl die Erkennung der Erkrankung als auch die Behandlung von Komorbiditäten und das Selbstmanagement des Erkrankten abdecken.

Diagnostik

Die Herzinsuffizienz wird auf Basis einer Stufendiagnostik festgestellt, bei der zunächst eine klinische Untersuchung durchgeführt wird. Die Echokardiographie mit Bestimmung der Herzdimensionen und der LVEF ist dabei das bedeutendste Instrument zur Diagnose von HFrEF und HFmrEF. Für die Diagnose von HFpEF spielen zusätzliche Parameter wie das E/e'-Verhältnis, der LAVI (linksatrialer Volumenindex) und das Regurgitationsvolumen über der Trikuspidalklappe eine Rolle.[1]

Die Stufendiagnostik kann eine Bildgebung mittels kardiovaskulärer Magnetresonanztomographie (Kardio-MRT oder *cardiovascular magnetic resonance imaging, CMR*) oder eine Computertomographie der Koronararterien oder des Perikards umfassen. Eine erweiterte invasive Diagnostik (z. B. eine Herzkatheteruntersuchung oder eine

Endmyokardbiopsie) oder eine erweiterte laborchemische oder humangenetische Diagnostik können auch Teil der Stufendiagnostik sein.[1,52] Vor allem bietet das CMR eine nicht-invasive Möglichkeit einer Abklärung der Ätiologie und auch einer Gewebecharakterisierung der Herzinsuffizienz.

Die komplexere Konstellation zum Nachweis einer diastolischen Dysfunktion zur Diagnosestellung der HFpEF hat zwei Score-Systeme hervorgebracht, die die bei HFpEF häufig veränderten Parameter in ihrem Zusammenwirken abbilden sollen:

(1) Der HFA-PEFF-Score bewertet Parameter, um eine HFpEF-Diagnose zu unterstützen, darunter natriuretische Peptide, linksventrikuläre Hypertrophie, diastolische Dysfunktion, Füllungsdrücke, Rechtsherzbeteiligung und linksatriale Dilatation.[53] Wenn sich nach einer basalen Diagnostik die Verdachtdiagnose einer HFpEF erhärtet, empfehlen die Autor*innen eine erweiterte Diagnostik, die unter Berücksichtigung des Score-Wertes eine HFpEF bestätigen oder ausschließen kann. Bleibt der Score-Wert inkonklusiv, ist eine Stress-Bildgebung notwendig, um zu überprüfen, ob eine relevante diastolische Dysfunktion unter Belastung auftritt (Fig.3).[53]

(2) Der H2FPEF-Score beurteilt die Prävalenz und das Ausmaß von Komorbiditäten wie Alter, Body-Mass-Index, Vorhofflimmern, pulmonaler Hypertonie und Nierenfunktion, um das Vorliegen einer HFpEF zu identifizieren.[54]

Insgesamt unterstützen sowohl der HFA-PEFF-Score als auch der H2FPEF-Score die Diagnose von HFpEF, wobei der H2FPEF-Score stärker auf die Rolle von Komorbiditäten abzielt.[53,54] Die Identifizierung der zugrunde liegenden Ätiologie und die Durchführung einer Differentialdiagnostik sind für alle Entitätstypen von Herzinsuffizienz bedeutsam, um eine gezielte Therapie zu ermöglichen.[1]

Die Strainbildgebung in Echokardiographie und CMR ermöglicht eine genauere Bewertung der Myokardfunktion – sie hat u. a. aufgezeigt, dass bei HFpEF trotz erhaltener LVEF die systolische Funktion reduziert ist, die sich in der eingeschränkten myokardialen Deformation im Strain, jedoch nicht in der LVEF zeigt.[55] Ebenso hat sie ihren besonderen Stellenwert in der Differentialdiagnostik der HFpEF gegenüber Amyloidosen, hypertrophen Kardiomyopathien oder dem Cor hypertonicum.[56]

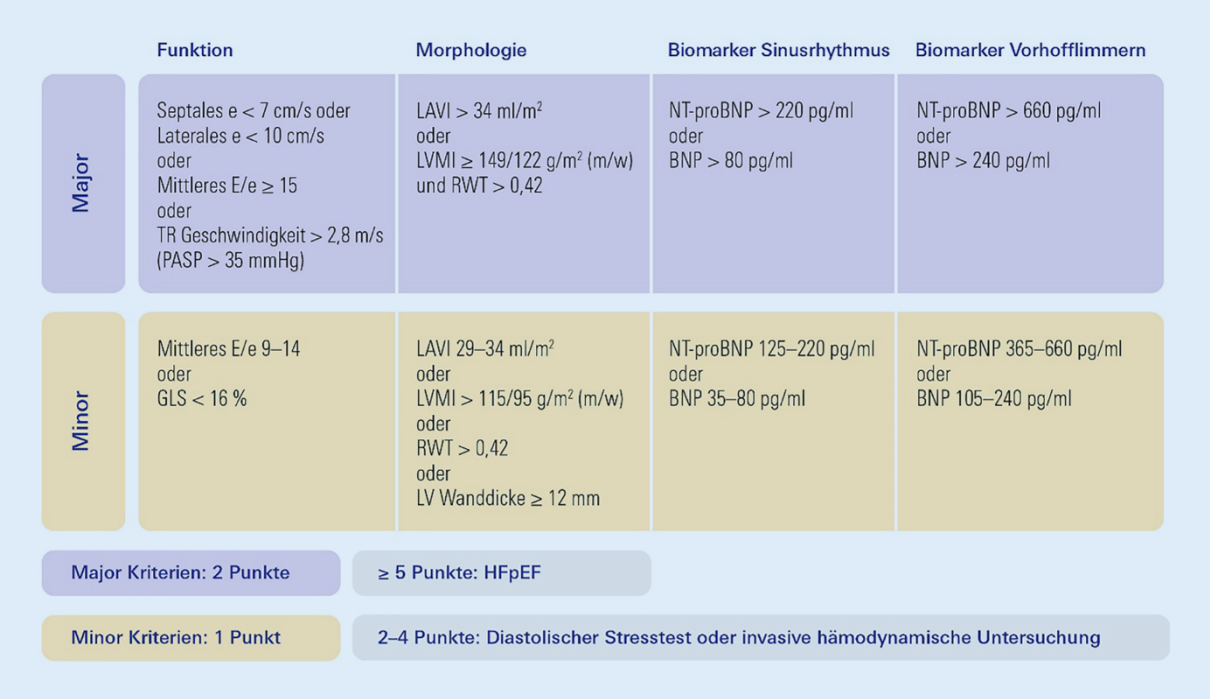


Fig. 3 – Diagnostische Punktevergabe zur HFpEF-Diagnose nach Pieske et al.[53], entnommen aus Güder et al.[57]
BNP: brain natriuretic peptide; LAVI: linksatrialer Volumenindex; LV: linker Ventrikel; LVMI: linksventrikulärer Massenindex; NT-proBNP: N-terminal pro-brain natriuretic peptide; PASP: pulmonary artery systolic pressure / pulmonalarterieller systolischer Druck; RWT: relative wall thickness; SR: Sinusrhythmus; TR: trikuspidale Regurgitation.

Therapie

Die Therapie der chronischen Herzinsuffizienz umfasst medikamentöse und nicht-medikamentöse Ansätze, die individuell an den Betroffenen angepasst werden sollten.[1] Die Behandlungsstrategien unterscheiden sich je nach Entität der Herzinsuffizienz. Gemein ist allerdings allen Typen der Herzinsuffizienz bei Flüssigkeitsretention und Stauungssymptomen, dass die volumenreduzierende Wirkung durch Diuretika (vorrangig Schleifendiuretika) erzielt wird. Dies erfolgt vor allem unter symptomatischen Gesichtspunkten.[58]

Bei HFrEF besteht die prognostische Standardtherapie aus einer als *Fantastic Four* beschriebenen Kombination von Substanzen, die primär in die beschriebenen derangierten Kompensationsmechanismen eingreifen:

1. auf das SNS wirkende Betablocker,
2. auf das RAAS wirkende Angiotensin-Converting-Enzyme-Hemmer (ACE-Hemmer) bzw. Angiotensin-Rezeptor-Blocker (ARB) – in den neuesten Leitlinien weitestgehend abgelöst

von Angiotensin-Rezeptopr-Neprilysin-Inhibitoren (ARNI), die zusätzlich auch auf das System der natriuretischen Peptide wirken,

3. ebenso das RAAS inhibierende Mineralokortikoidrezeptor-Antagonisten (MRA) und schließlich
4. in ihrer Wirkung noch nicht restlos verstandene Inhibition des renalen Natrium-Glukose-Kotransporters 2 (SGLT2, *entsprechend SGLT2i; i für inhibition*).[1,59]

In der medikamentösen Therapie der HFrEF mittels der *Fantastic Four* wird nicht zwischen den Ätiologien der HI differenziert.[1]

Eine Ergänzung zur medikamentösen Behandlung sind gerätebasierte Therapien wie die kardiale Resynchronisationstherapie (CRT) und implantierbare Kardioverter-Defibrillatoren (ICD). Während die kardiale Resynchronisation eine sekundär-prophylaktische Therapie bei bestimmten Patient*innen mit HFrEF und elektrokardiographischem Blockbild darstellt, ist die ICD-Therapie bzw. Defibrillationstherapie im Rahmen eines CRT-Systems eine primär-prophylaktische Therapie bei HFrEF-Patient*innen mit einer LVEF < 35 %.

Die Therapie bei HFmrEF ähnelt der HFrEF-Therapie, wobei Betablocker, ACE-Hemmer/ARBs und MRA häufig verwendet werden, obgleich die Evidenzlage bei HFmrEF deutlich schwächer ist.[1,19] Die Behandlung leitet sich in erster Linie aus der Erfahrung von HFrEF-Patient*innen, deren LVEF sich unter der Pharmakotherapie in den HFmrEF-Bereich gebessert hat (als HFimpEF bezeichnet), ab.[1,19] Evidenzbasiert lässt sich aktuell nur eine Therapie mittels SGLT2i empfehlen, die einen prognostischen Vorteil hinsichtlich HI-bedingter Hospitalisierung und Mortalität aufgezeigt hat.[1] Die Therapie sollte an die individuelle klinische Situation angepasst werden und die Trajektorie aus einer möglicherweise vormals bestehenden HFrEF berücksichtigen.

Die Therapie bei HFpEF stellt eine besondere Herausforderung dar, da bisherige Interventionsstudien (mit Ausnahme der SGLT2i) überwiegend negative Ergebnisse lieferten.[1] Die Behandlung konzentriert sich primär auf die symptomatische Linderung und die Kontrolle von Komorbiditäten, einschließlich des Einsatzes von Diuretika zur Volumenkontrolle und zur Blutdruckeinstellung.[1] Erstmals konnte eine prognostische Besserung durch eine Therapie mittels SGLT2i erzielt werden.[60,61]

Auch Interventionen bei Patient*innen mit Herzinsuffizienz und Herzklappenerkrankungen, insbesondere bei Mitralinsuffizienz, spielen eine bedeutsame Rolle bei der Reduktion der

Symptome der Herzinsuffizienz.[62] Der MitraClip ist ein minimalinvasives Verfahren, das die Mitralklappeninsuffizienz modifiziert und den Rückfluss des Blutes verringert. Bei fortgeschrittener Herzinsuffizienz stehen auch Herztransplantationen und linksventrikuläre Unterstützungssysteme (LVAD) als Optionen zur Verfügung.

Neben der Therapie sind die Identifikation und die Behandlung von Komorbiditäten ausschlaggebend. Dazu gehören Vorhofflimmern, Diabetes, Niereninsuffizienz und Anämie. Die optimale Behandlung dieser Erkrankungen ist entscheidend für den langfristigen Behandlungserfolg der Herzinsuffizienz-Patient*innen.[63]

In jedem Fall ist die optimale Therapie der Komorbiditäten Teil des Behandlungsmanagements, zumal jede Akutsituation (z. B. eine Infektexazerbation oder ein akuter Schub einer systemischen Erkrankung) das zeitnahe Auftreten einer akuten Herzinsuffizienz wahrscheinlicher macht und damit prognostisch ungünstig ist.

Die Bereitschaft Erkrankter zum Selbstmanagement (Compliance) ist mit der Medikamenteneinnahme entscheidend für den Behandlungserfolg.[1] Hierzu zählen Lebensstiländerungen wie regelmäßige körperliche Aktivität, eine ausgewogene Ernährung und die Reduzierung von Übergewicht. Flüssigkeits- und Natriumbeschränkungen können ebenfalls helfen, Symptome zu lindern.[1]

Eine kontinuierliche Überwachung von HI-Patient*innen ist erforderlich, um frühzeitig auf auffällige Werte zu reagieren. Regelmäßige Kontrolluntersuchungen und Laborwertüberwachungen sind dabei essenziell. Telemedizin ist eine sinnvolle Ergänzung zur Überwachung und Betreuung der Erkrankten. Sie hilft, kardiale Dekompensationen frühzeitig zu erkennen, Krankenhausaufenthalte zu reduzieren und das Selbstmanagement der Patient*innen zu unterstützen.[64]

Multidisziplinäre Herzinsuffizienz-Teams, bestehend aus Kardiolog*innen, Hausärzt*innen, Physiotherapeut*innen, Pflegepersonal, Rehabilitationszentren und Apotheken sowie regelmäßige Beratungsmöglichkeiten zur Ernährung und Psychotherapie tragen zur optimalen Versorgung der Betroffenen bei.[65-67]

Insgesamt erfordert die Betreuung von HI-Patient*innen eine umfassende Herangehensweise, die alle Aspekte der Erkrankung berücksichtigt, um die Prognose und damit die Lebensqualität zu optimieren.

3.5. Risikostratifizierung bei Herzinsuffizienz

Die Relevanz der Risikostratifizierung bei HI ergibt sich aus der abzuleitenden differenzierten Einschätzung der Prognose und des individuellen Krankheitsverlaufs. Diese Dimensionen tragen dazu bei, gezielte und effektive therapeutische Interventionen in Studien zu entwickeln und in der Klinik anzuwenden sowie die Versorgungsqualität und das klinische Outcome der betroffenen Patient*innen zu verbessern. Eine ungenaue Risikostratifizierung kann zu einer Heterogenität der Patientenpopulation in Studien führen, was die Ergebnisse beeinträchtigt.[53,68] Eine angemessene Risikostratifizierung im klinischen Alltag hilft, Hochrisikopatient*innen zu identifizieren und zu behandeln.[69]

In diesem Kapitel liegt der Schwerpunkt auf der Risikostratifizierung bei Patient*innen mit Herzinsuffizienz und erhaltener Ejektionsfraktion (HFpEF). HFpEF stellt eine komplexe und heterogene Krankheitsentität dar, deren Pathophysiologie und klinisches Management sich von der Herzinsuffizienz mit reduzierter (HFrEF) und mittlerer Ejektionsfraktion (HFmrEF) unterscheidet. Angesichts der zunehmenden Prävalenz von HFpEF in der alternden Bevölkerung und der begrenzten therapeutischen Optionen ist eine präzise Risikostratifizierung für diese Patientengruppe von großer Bedeutung. Die folgenden Unterkapitel befassen sich mit den Methoden zur Risikostratifizierung bei HFpEF und diskutieren die Rolle der personalisierten Medizin in diesem Bereich.

3.5.1. Risikostratifizierung bei Herzinsuffizienz

Eine Risikostratifizierung bei HFpEF, d. h. eine Korrelation mit einer höheren Ereignisrate bezüglich HI-bedinger Hospitalisierung und Mortalität, ist möglich mit folgenden bekannten Risikoindikatoren:

a. Klinische Faktoren und Biomarker:
   Alter, Geschlecht, Komorbiditäten, Nierenfunktion und Biomarker wie natriuretische Peptide (BNP, NT-proBNP) oder der laborchemische Hinweis auf eine myokardiale Schädigung (Troponin-Erhöhung) sind wichtige Faktoren zur Risikostratifizierung.[70]
b. Bildgebende Verfahren:
   Echokardiographie ist das Hauptverfahren zur Beurteilung von HFpEF, während Kardio-MRT zusätzliche Informationen zur myokardialen Struktur und Funktion liefern

kann.[71-73]

c. Funktionsuntersuchungen:

   Belastungstests (z. B. Spiroergometrie) und invasives hämodynamisches Monitoring (z. B. Rechtsherzkatheter) können zur Beurteilung der funktionellen Kapazität und der hämodynamischen Veränderungen bei Belastung herangezogen werden.[16]

d. Scoring-Systeme und Risikomodelle:

   Der HFA-PEFF-Score ist ein Beispiel für ein Risikomodell, das verschiedene Parameter zur Risikostratifizierung von HFpEF-Patient*innen verwendet.[53]

Die Risikostratifizierung bei HFpEF ist ausschlaggebend für die individuelle Versorgung von Erkrankten und die Gestaltung klinischer Studien. Die genauere Charakterisierung der heterogenen Patientenpopulation mit HFpEF ist Voraussetzung für die Entwicklung neuer Therapieansätze. Die Integration von klinischen Faktoren, Biomarkern, bildgebenden Verfahren und funktionellen Tests in Risikomodelle könnte dazu beitragen, die Prognose und das Management von HFpEF-Patient*innen weiter zu verbessern.[53]

3.5.2. Personalisierte Medizin bei HFpEF

Personalisierte Medizin, auch *precision medicine* genannt, bezieht sich auf die Anpassung von medizinischen Behandlungen an die individuellen Charakteristika eines Erkrankten.[74] Sie hat das Potenzial, durch eine bessere Identifikation der Population, die von der Intervention profitieren wird, die Effektivität der Therapie zu erhöhen und unerwünschte Nebenwirkungen zu reduzieren.

HFpEF ist ein heterogenes Spektrum der Erkrankung, das von verschiedenen zugrunde liegenden pathophysiologischen Mechanismen und Komorbiditäten beeinflusst wird. Daher ist die personalisierte Medizin bei HFpEF besonders relevant. Eine genauere Herausbildung von Patientenclustern ermöglicht personalisierte Therapieansätze in homogeneren Studienpopulationen.[75] Beispielsweise wurde eine neuartige Klassifikation von HFpEF-Patient*innen basierend auf der *Phenomapping*-Methode etabliert und diskutiert.[75] Diese Methode nutzt maschinelles Lernen, um Patient*innen anhand ihrer klinischen, laborchemischen und echokardiographischen Merkmale zu klassifizieren. Die Studie identifizierte drei führende HFpEF-Phänotypen mit unterschiedlichen klinischen Merkmalen und prognostischen Implikationen, mittels ihrer Kerncharakteristika wurden sie wie folgt

beschrieben: (1) junge Patient*innen mit niedrigen Blutdruckwerten, (2) adipöse, Patient*innen mit obstruktivem Schlafapnoe-Syndrom, Diabetes mellitus und den höchsten Nüchternglukosewerten sowie (3) ältere Patient*innen mit chronischer Niereninsuffizienz, den höchsten Kreatininwerten und den höchsten natriuretischen Serumspiegeln.[75]

Die Integration von Risikostratifizierungsmethoden in die klinische Praxis kann dazu beitragen, personalisierte Therapieansätze bei HFpEF zu implementieren. Eine der Herausforderungen besteht darin, die Methoden zur Risikostratifizierung und Phänotypisierung in den klinischen Alltag zu integrieren.

Bei steigender Bedeutung der HFpEF wird der Bedarf einer adäquaten Therapiestrategie höher. Zukünftige Studiendesigns werden daher voraussichtlich den Weg der personalisierten Medizin einschlagen. Welche Parameter Teil der relevanten Differenzierungsstrategien sind, ist aktuell offen und unterliegt einer fortdauernden Pflicht zur Aktualisierung bei neuen wissenschaftlichen Erkenntnissen.

3.6. Ziele der Arbeit

In Anbetracht der Komplexität der Herzinsuffizienz, insbesondere der HFpEF, und ihrer weitreichenden Auswirkungen auf Patient*innen und das Gesundheitssystem, verfolgt diese Arbeit mehrere zentrale Ziele, um verschiedene Aspekte der Erkrankung zu beleuchten und potenzielle Verbesserungen in Diagnose und Versorgung aufzuzeigen.

I. Phänotypisierung:

   Das erste Ziel dieser Arbeit besteht darin, die Bedeutung einer ausführlichen klinischen Phänotypisierung und genauen Diagnosestellung der HFpEF für die Prognose der Patient*innen zu verdeutlichen. Dieser Aspekt ist relevant, um die bestmögliche Versorgung und Behandlung für betroffene Personen zu gewährleisten.

II. Kostenanalyse:

   Das zweite Ziel ist es, die gesundheitsökonomischen Kosten aufzuzeigen, die mit der HFpEF verbunden sind. Dies wird dazu beitragen, ein besseres Verständnis für die finanziellen Auswirkungen der Erkrankung zu gewinnen und möglicherweise Ansätze für Kosteneinsparungen und effizientere Behandlungsstrategien zu identifizieren.

III. Erweiterte Charakterisierung mittels Kardio-MRT:

   Im dritten Schritt wird die Anwendung der Kardio-MRT zur treffenderen

Charakterisierung von Patient*innen mit HI hinsichtlich ihrer myokardialen Funktion untersucht. Dieser innovative Ansatz könnte dazu beitragen, die Diagnose und das Management von HI-Betroffenen zu verbessern.

IV. Früherkennung in Risikokollektiv:

Als viertes Ziel wird die Arbeit Methoden der MRT-basierten Charakterisierung hinsichtlich einer Früherkennung einer Risikopopulation untersuchen. Dies könnte dazu beitragen, präventive Maßnahmen zu ergreifen und die Krankheitsprogression bei gefährdeten Personen zu verlangsamen.

V. Analyse von patientenorientierten Endpunkten:

Schließlich wird diese Arbeit untersuchen, ob und inwieweit die Befunde des Kardio-MRT bei HI-Patient*innen mit dem subjektiven Beschwerdeempfinden zusammenhängen. Diese Untersuchung soll daran mitwirken, das Verständnis für die individuellen Erfahrungen von Patient*innen mit HI zu erweitern und möglicherweise Ansätze zur Verbesserung der Lebensqualität zu identifizieren.

Zusammenfassend sollen die in dieser Arbeit vorgestellten Ziele dazu beitragen, ein tieferes Verständnis der HFpEF zu gewinnen, innovative diagnostische Ansätze zu erkunden und die Versorgung von Erkrankten mit HI zu optimieren.

4. Eigene Arbeiten

4.1. Evaluation der Diagnosestellung mittels HFA-PEFF-Algorithmus

Als numerische Erkrankung ist die korrekte Diagnose einer HFpEF essenziell mit einer Risikostratifizierung verbunden. *Korrekt* ist eine Diagnose in diesem Konzept zu verstehen, wenn sie mit einem schlechteren Outcome verbunden ist.

Der HFA-PEFF-Algorithmus dient der Diagnosestellung einer HFpEF.[53] Er wurde als Expertenkonsensus verfasst, sodass es einer Untersuchung hinsichtlich der prognostischen Aussagekraft bedurfte.

Diese Arbeit untersucht die prognostische Aussagekraft des HFA-PEFF-Algorithmus.

Der nachfolgende Text entspricht dem Abstrakt dieser Arbeit[76]:

Hashemi D, Mende M, Trippel TD, Petutschnigg J, Hasenfuss G, Nolte K, Herrmann-Lingen C, Feuerstein A, Langhammer R, Tschöpe C, Pieske B, Wachter R, Edelmann F. Evaluation of the HFA-PEFF Score: results from the prospective DIAST-CHF cohort. ESC Heart Fail. 2022 Dec;9(6):4120-4128. doi: 10.1002/ehf2.14131. Epub 2022 Sep 7. PMID: 36070881.

*"**Aims:** Although the number of patients suffering from heart failure with preserved ejection fraction (HFpEF) increases, the routine diagnosis remains a challenge. In the absence of a pathognomonic sign for HFpEF or specific treatment strategies, a prognosis-based characterization of suspected patients remains promising for both the risk stratification of the patients and a disease definition. The Heart Failure Association (HFA) of the European Society of Cardiology has introduced an algorithm with different levels of likelihood regarding the diagnosis of HFpEF, the HFA-PEFF score. We aimed to evaluate the predictive value of this algorithm in a large cohort regarding mortality, symptom burden, and the functional status.*

***Methods and results:** DIAST-CHF is a multicentre, population-based, prospective, observational study in subjects with at least one risk factor for HFpEF between the age of 50*

and 85. We calculated the HFA-PEFF score (n = 1668) and analysed the risk groups for overall mortality, cardiovascular hospitalization, and submaximal functional capacity (6-min walk distance) at baseline and after a follow-up period of 10 years. Patients with high HFA-PEFF score values 5&6 showed a higher mortality than those with an intermediate score (score values 2-4) and low score values (high 21.3% vs. intermediate 10.1% vs. low 4.3%, P < 0.001). Also, the burden of MACE (death, cardiovascular hospitalization, new myocardial infarction, first diagnosis of HF) was increased in the high score values group (high 40.7% vs. intermediate 25.9% vs. low 13.9%, P < 0.001). Similarly, patients with higher scores had higher cumulative incidences of cardiovascular hospitalizations (P = 0.011). Subjects with higher scores also had lower 6-min walk distance both at baseline and during follow-up.

Conclusions: *The HFA-PEFF score provides a reliable instrument to stratify suspected HFpEF patients by their risk for mortality, symptom burden, and functional status in cohort at risk with a follow-up period of 10 years. As high HFA-PEFF scores are associated with worse outcome, the HFA-PEFF algorithm describes a defining approach towards HFpEF."*[76]

ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 4120–4128
Published online 7 September 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14131

ORIGINAL ARTICLE

Evaluation of the HFA-PEFF Score: results from the prospective DIAST-CHF cohort

Djawid Hashemi[1,2,3], Meinhard Mende[4], Tobias D. Trippel[1,3], Johannes Petutschnigg[1,3], Gerd Hasenfuss[5,6], Kathleen Nolte[5,6], Christoph Herrmann-Lingen[5,7], Anna Feuerstein[1,3], Romy Langhammer[8], Carsten Tschöpe[1,3,9], Burkert Pieske[1,2,3], Rolf Wachter[5,8] and Frank Edelmann[1,3]*

[1]*Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany;* [2]*Department of Internal Medicine and Cardiology, German Heart Institute Berlin (DHZB), Berlin, Germany;* [3]*DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany;* [4]*Clinical Trial Centre and Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Leipzig, Germany;* [5]*DZHK (German Centre for Cardiovascular Research), partner site Göttingen, Berlin, Germany;* [6]*Department of Cardiology and Pneumology, Georg-August University, Göttingen, Germany;* [7]*Department of Psychosomatic Medicine and Psychotherapy, University of Göttingen Medical Centre, Göttingen, Germany;* [8]*Clinic and Policlinic for Cardiology, University Hospital Leipzig, Leipzig, Germany; and* [9]*Berlin Institute of Health (BIH) & Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany*

Abstract

Aims Although the number of patients suffering from heart failure with preserved ejection fraction (HFpEF) increases, the routine diagnosis remains a challenge. In the absence of a pathognomonic sign for HFpEF or specific treatment strategies, a prognosis-based characterization of suspected patients remains promising for both the risk stratification of the patients and a disease definition. The Heart Failure Association (HFA) of the European Society of Cardiology has introduced an algorithm with different levels of likelihood regarding the diagnosis of HFpEF, the HFA-PEFF score. We aimed to evaluate the predictive value of this algorithm in a large cohort regarding mortality, symptom burden, and the functional status.

Methods and results DIAST-CHF is a multicentre, population-based, prospective, observational study in subjects with at least one risk factor for HFpEF between the age of 50 and 85. We calculated the HFA-PEFF score (n = 1668) and analysed the risk groups for overall mortality, cardiovascular hospitalization, and submaximal functional capacity (6-min walk distance) at baseline and after a follow-up period of 10 years. Patients with high HFA-PEFF score values 5&6 showed a higher mortality than those with an intermediate score (score values 2–4) and low score values (high 21.3% vs. intermediate 10.1% vs. low 4.3%, $P < 0.001$). Also, the burden of MACE (death, cardiovascular hospitalization, new myocardial infarction, first diagnosis of HF) was increased in the high score values group (high 40.7% vs. intermediate 25.9% vs. low 13.9%, $P < 0.001$). Similarly, patients with higher scores had higher cumulative incidences of cardiovascular hospitalizations (P = 0.011). Subjects with higher scores also had lower 6-min walk distance both at baseline and during follow-up.

Conclusions The HFA-PEFF score provides a reliable instrument to stratify suspected HFpEF patients by their risk for mortality, symptom burden, and functional status in cohort at risk with a follow-up period of 10 years. As high HFA-PEFF scores are associated with worse outcome, the HFA-PEFF algorithm describes a defining approach towards HFpEF.

Keywords Heart failure; Heart failure with preserved ejection fraction; HFpEF; Prognosis; HFA-PEFF score

Received: 18 February 2022; Revised: 19 July 2022; Accepted: 18 August 2022
**Correspondence to: Frank Edelmann, Department of Internal Medicine and Cardiology, Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Email: frank.edelmann@charite.de*

Introduction

Patients suffering from heart failure (HF) account for nearly 1–2% of the adult population in developed countries, rising up to ≥10% among people above 70 years of age with increasing prevalence due to demographic changes.[1–4] Patients suffering from HF with preserved ejection fraction (EF, HFpEF) account for nearly half of the HF population.[5] Despite remarkable progress in HF research, it remained controversial which criteria suffice to diagnose HFpEF additional to a preserved (>50%) left ventricular ejection fraction (LVEF). HF, like most degenerative diseases, is a 'numerical disease', defined by a change in relative function.[5] Whereas 'categorical diseases' are defined as the presence or absence of a pathogenic condition, for

example, cancer or infections, *numerical diseases* are not defined by their presence but by the prognostic implications of an altered function.[5] The prognostic implication is either descriptive, a threshold of alteration associated with a worse prognosis, or therapeutic, when an intervention in prespecified setting is associated with an improved prognosis. HFpEF is a numerical disease as it results by the alteration of different characteristics, for example, diastolic function, left atrial (LA) dilatation, or LV hypertrophy. Because interventional strategies in major clinical trials have missed their hard clinical primary endpoint, the definition of HFpEF needs to be described by a multifactorial clinical approach to assess the prognosis.[6]

Current guidelines updated the diagnosis of HFpEF formerly based on the assessment of echocardiographic surrogates for elevated intra-cardiac filling pressures, serum biomarkers, and HF symptoms to the diagnostic approach of the HFA-PEFF algorithm.[6]

This new diagnostic algorithm, the HFA-PEFF score, was proposed by the Heart Failure Association (HFA) of the European Society of Cardiology.[6,7] The HFA-PEFF score is a multimodal approach based on a pre-test assessment and a second step including the assessment by echocardiography and natriuretic peptides, functional testing, and aetiology diagnostics to estimate the likelihood (low, intermediate, or high) of suffering from HFpEF. A high likelihood score is considered diagnostic for HFpEF and a low-likelihood score rules out HFpEF. The intermediate-likelihood group requires exercise testing for further evaluation. The HFA-PEFF score has been developed based on previous findings and expert opinion but was not based on calculations and prospectively performed cohorts to prove its clinical value and validity. So far, the HFA-PEFF score has only been either retrospectively tested on small cohorts or with only a short follow-up period.[8–15]

An analysis with a sufficient follow-up period to assess the prognostic value has been missing. Therefore, the aim of this study is to evaluate the diagnostic value of the HFA-PEFF algorithm by assessing the predictive value of the score in a large well-defined cohort with a long follow-up period considering overall mortality symptom burden as well as functional status.

Methods

Study design and subject population

The observational Diagnostic Study on Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart Failure (DIAST-CHF) is a multicentre population-based prospective study within the framework of the German Competence Network for HF (CNHF) and the German Centre for Cardiovascular Research (DZHK). It is a unique database with detailed clinical and echocardiographic data to describe characteristics with a focus on HFpEF. The CNHF constitutes one of Europe's largest HF research programmes funded by the German Federal Ministry of Education and Research. Its rationale and design have been previously described.[16,17] The design of the CNHF and the many analyses of DIAST-CHF have been previously published.[18–23] Briefly, the DIAST-CHF investigated outpatients aged 50–85 years who were recruited between 2004 and 2006 with a history of overt HF or at least one risk factor. These risk factors included a history of HF, coronary disease, diabetes mellitus, sleep apnoea syndrome, or arterial hypertension. Candidates were referred by primary care physicians. The only exclusion criterion was unwillingness to participate, insufficient understanding of the German language, or unavailability for logistic reasons.

The study protocol was reviewed and approved by the institutional review board of each participating centre, and all patients provided written informed consent prior to enrolment. DIAST-CHF was conducted in accordance with national laws, guidelines for good clinical practice, and the Declaration of Helsinki.

After study enrolment, all patients received a routine physical examination and a detailed cardiology assessment including extensive blood analyses and a transthoracic echocardiography. The follow-up in-person visits were planned after 12, 24, and 60 months as well as after 10 years. A telephone visit was performed after 9 years.

The HFA-PEFF diagnostic algorithm

The HFA-PEFF diagnostic algorithm is a clinical score including eight parameters in three categories (functional, morphological, and biomarker changes). These parameters include imaging signs for diastolic dysfunction, LV hypertrophy, left atrial dilatation, or increased natriuretic peptide levels. Each item is assigned to a category and is evaluated. Small changes will score 1 point, and larger changes 2 points. The possible range of the total score reaches from 0 to 6 points. Cumulative 5 or 6 points are considered diagnosed HFpEF. 0 or 1 point would rule out the presence of HFpEF. If the subject scored 2–4 points, stress testing is required to evaluate the presence of HFpEF.

Endpoint

The main aim of this analysis was to evaluate the prognostic value of the HFA-PEFF algorithm in subjects with diagnosed HF or at least one risk factor for HFpEF with regard to assess the symptom burden, the functional status, and clinical outcome parameters.

For this purpose, we assessed (i) overall mortality; (ii) major adverse cardiac events (MACE) including death, cardiovascular hospitalization, new myocardial infarction, and first diagnosis of HF; and (iii) CV hospitalization.

Symptom burden and functional status were assessed by quality of life measures [measured by the 36-Item Short Form Health Survey (SF-36) questionnaire] and functional capacity measured by 6-min walk test (6MWT).

We compared subjects with low vs. intermediate vs. high scores according to the proposed algorithm.

Statistical methods

Data preparation and descriptive statistics was performed by IBM SPSS, Version 28. We applied R, Version 4.1, inclusive the packages *ggplot2*, *survival*, and *Hmisc* to build multiple models and to generate graphs.

The study cohort was characterized by standard statistics: mean and standard deviation (SD) for continuous, count, and % for categorical characteristics. For three-group comparisons of endpoints, we applied ANOVA with Dunnett's test as post hoc analysis. P-values were adjusted for multiple testing by the method of Bonferroni and Holm.[24]

The 95% confidence intervals (CI) were calculated and displayed by longitudinal error bar plots. We calculated cumulative incidences of overall mortality by the Kaplan–Meier method, depicted it and tested it by log-rank test. The association of common risk factors different between HFA-PEFF groups in *Table 1* was analysed by a multiple model. We started with the full linear regression model and simplified it by stepwise exclusion of variables using the Akaike Information Criterion (AIC). The effect estimates were determined with 95% CI. We calculated the concordance (c-) statistics to assess the predictive power of our model.

Cardiovascular hospitalization and death are competing risks. Thus, they were compared between the subgroups by means of cumulative incidences following Gray and Pepe.

Results

Subject population

A total of 1937 participants were included in DIAST-CHF. For the present analysis, we excluded 269 subjects (n = 8 due to incomplete baseline characteristics and n = 174 due to missing or reduced LVEF values, n = 15 for valvular or congenital heart disease as well as n = 72 for missing natriuretic peptide levels), resulting in 1668 subjects for the complete analysis. Their baseline characteristics are presented in *Table 1*.

In line with the proposed algorithm, we separated those with a low score (0–1 points) from those with an intermediate (2–4 points) or a high score (5–6 points). This resulted in 115 subjects in the low, 980 subjects in the intermediate, and 573 in the high score group. Subsequently, we compared all three groups.

Clinical outcomes and assessment of symptom burden and functional status

Overall mortality

The overall mortality at 10-year follow-up increases monotonically with the HFA-PEFF score: low 5 (4.3%), intermediate 99 (10.1%), and high score 122 (21.3%), $P < 0.001$. Comparing the risk groups pairwise reconfirms this result: low vs. intermediate: $P = 0.046$; low vs. high: $P < 0.001$; intermediate vs. high: $P < 0.001$.

MACE

In line with the overall mortality, incidence of MACE grows monotonically across the groups: low 16 (13.9%), intermediate 254 (25.9%), and high score 233 (40.7%), $P < 0.001$. This effect is also shown in direct comparisons between the groups: low vs. intermediate score: $P = 0.005$; low vs. high score: $P < 0.001$; intermediate vs. high score: $P < 0.001$ (*Figure 1*).

Cardiovascular hospitalization

A higher score was also associated with a higher number of cardiovascular hospitalizations per patient: low 0.10 [0.04, 0.17], intermediate 0.19 [0.15, 0.23], and high score 0.32 [0.26, 0.39], $P < 0.001$ in the global test. Whereas the difference in hospitalization rate between the low and the intermediate group was not significant (low vs. intermediate score: $P = 0.25$), the differences between the low-risk and the high-risk group as well as the intermediate-risk and the high-risk group were significant (low vs. high score: $P = 0.003$; intermediate vs. high score: 0.003).

The cumulative incidences of both MACE and cardiovascular hospitalization are shown in *Figure S1*.

Functional capacity

Figure 2 shows the walking distance measured by the 6MWT both at baseline and at the 10-year follow-up (high vs. intermediate vs. low score at baseline: 588 ± 83 m vs. 558 ± 108 m vs. 537 ± 93 m, $P < 0.001$; low vs. intermediate score: $P < 0.001$; low vs. high score: $P < 0.001$; intermediate vs. high: $P < 0.001$). During 10-year follow-up, the differences between the groups grew: low 555 ± 76 m, intermediate 506 ± 116 m, and high score 473 ± 126 m (low vs. intermediate score: $P = 0.006$; low vs. high score: $P < 0.001$; intermediate vs. high score: $P = 0.051$).

Self-rated physical function

Assessing physical limitations, we compared the physical functioning (PF) scale on the SF-36 between the groups.

Table 1 Study population baseline characteristics

	HFA-PEFF score values 0–1		HFA-PEFF score values 2–4		HFA-PEFF score values 5 and 6		
	No HFpEF n = 115		Intermediate risk for HFpEF n = 980		HFpEF n = 573		P value
	Mean/ Number	SD/ %	Mean/ Number	SD/ %	Mean/ Number	SD/ %	Comparison across groups
Age [years]	57	7	65	8	70	8	<0.001
Female sex	49	42.6%	509	51.9%	314	54.8%	0.55
BMI [kg/m^2]	27.2	4.8	28.7	4.8	29.1	4.8	0.002
Waist–hip ratio	0.93	0.09	0.94	0.21	0.94	0.13	1.0
BP systolic [mmHg]	135	18	145	20	151	23	<0.001
BP diastolic [mmHg]	82	10	83	12	83	12	1.0
HR [bpm]	72	10	72	12	68	12	0.010
Diabetes mellitus	17	14.8%	220	22.4%	155	27.1%	0.11
Hypertension	56	48.7%	746	76.1%	515	89.9%	<0.001
Hyperlipidaemia	19	16.5%	384	39.2%	258	45.0%	0.000
Hyperuricaemia	9	7.8%	112	11.4%	97	16.9%	0.027
Non-smoker[a]	49	42.6%	504	51.5%	302	52.7%	0.019
Ex-smoker	40	34.8%	356	36.4%	220	38.4%	
Smoker	26	22.6%	118	12.1%	51	8.9%	
Sleep apnoea	4	3.5%	55	5.6%	35	6.1%	1.0
COPD	8	7.0%	74	7.6%	39	6.8%	1.0
History of resuscitation	0	0.0%	20	2.0%	9	1.6%	1.0
CAD	10	8.7%	127	13.0%	145	25.3%	<0.001
History of AMI	5	4.3%	64	6.5%	59	10.3%	0.12
History of PCI	6	5.2%	73	7.5%	79	13.9%	0.001
History of CABG	0	0.0%	26	2.7%	41	7.2%	<0.001
Atrial fibrillation	4	3.5%	57	5.8%	44	7.7%	1.0
Diagnosis of heart failure	4	3.5%	87	8.9%	83	14.5%	0.002
NYHA class[a]							1.0
I	0	0.0%	22	25.3%	20	23.8%	
II	4	100.0%	47	54.0%	44	52.4%	
III	0	0.0%	18	20.7%	20	23.8%	
LV-EF (%)	63	6.0	61	6.4	61	6.5	0.036
RV pacemaker	0	0.0%	9	0.9%	13	2.3%	0.39
BV pacemaker	0	0.0%	1	0.1%	0	0.0%	1.0
ICD	0	0.00%	1	0.10%	1	0.17%	0.86
Years since diagnosis of HF Median [quartiles]	0	[0, 7.5]	4	[2, 10]	3	[0, 9]	

AMI, acute myocardial infarction; BMI, body mass index; BP, blood pressure; BV, biventricular; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; LV, left ventricular; NYHA class: New York Heart Association functional class; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RV, right ventricular.
P-values provided for not randomized groups; level of significance was set at 5%.
[a]Delaney's and Vargha's A measurement of the effect size.

Patients with high score values have lower PF values at baseline (low vs. intermediate vs. high score: 85.1 ± 18.9 vs. 76.5 ± 23.1 vs. 68.3 ± 25.8, overall comparison $P < 0.001$; low vs. intermediate score: $P = 0.001$; low vs. high score: $P < 0.001$; intermediate vs. high score: $P < 0.001$).

Self-rated mental health

Comparing the mental health state by the mental health sub-scale of the SF-36 between the three groups showed a significant difference overall across the groups (low vs. intermediate vs. high score: 65.3 ± 18.1 vs. 62.3 ± 18.2 vs. 59.4 ± 18.0, overall comparison $P = 0.004$; low vs. intermediate score: $P = 0.39$; low vs. high score: $P = 0.020$; intermediate vs. high score: $P = 0.018$).

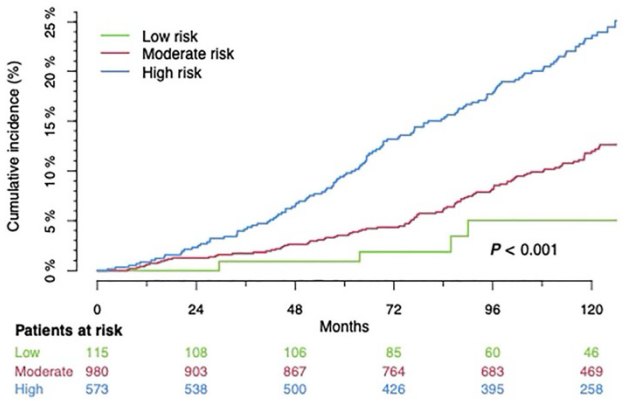
Analysis of the potential impact of single score items on prognosis in survival

As shown in *Table 2*, the items included in the HFA-PEFF score were analysed regarding their associations with mortality. Consistency of the score is confirmed, as major criteria are associated stronger than minor criteria with a higher risk for mortality. In our cohort, biomarkers and functional parameters showed stronger prognostic effects on the survival than morphological changes [HR 2.77 (1.99 3.85) for the major criterion of the biomarkers and HR 2.80 (1.55 5.07) for the major criterion of the functional parameters vs. HR 1.15 (0.66 2.01) for the major criterion of the morphological changes].

Multiple association of the risk factors with the HFA-PEFF score

Figure 3 represents relevant clinical risk factors and their effect estimates on HFA-PEFF score values. The illustrated parameters were the resulting relevant parameters after the reduction of baseline characteristics to a sparse model. The factors listed in *Figure 3* including their effect estimates (and 95% CI) might provide an insight to the causes leading to the parameters assessed by the HFA-PEFF score *Table 3*.

Figure 1 Cumulative overall mortality. Low score: score values 0 and 1; intermediate score: score values 2–4; high score: score values 5 and 6 in the HFA-PEFF algorithm.



Discussion

In a large prospective cohort of subjects with cardiovascular risk factors, we assessed the prognostic value of the HFA-PEFF diagnostic algorithm regarding mortality and morbidity as well as relevant clinical measures. Higher scores were associated with a higher overall mortality, incidence of MACE, a higher symptom burden, and a lower the functional status. Considering the definition of *numerical diseases*, the HFA-PEFF score identifies patients who have syndrome characterized by different altered parameters associated with a worse outcome. Therefore, the HFA-PEFF score provides a reliable definition of HFpEF. The higher risk reflected by a higher score value may be explained by contributing known risk factors (*Figure 3*). Hence, the diagnostic HFA-PEFF algorithm reflects high-risk clinical compositions of altered parameters associated with a worse outcome.

This analysis gained power and robustness through a large number of subjects, prospectively investigated with an elaborated protocol to follow them up over 10 years.

Previous analyses of smaller cohorts assessed the HFA-PEFF score with regard to hospitalization without mortality data as the primary endpoint over a follow-up period of 5 years.[25,26] Selvaraj *et al*. as well as Aizpurua *et al*. confirmed that the high score groups assessed by the HFA-PEFF algorithm suffered from a shorter hospitalization-free survival. Our analysis confirmed higher hospitalization rates in subjects with high scores. They showed even a lower overall survival during a 10-year follow-up period.

Figure 2 Six-minute walking distance in all three groups at baseline and at 10-year follow-up. Low score: score values 0 and 1; intermediate score: score values 2–4; high score: score values 5 and 6 in the HFA-PEFF algorithm. (A) Walk distance at baseline. (B) Walk distance at 10-year follow-up for the three groups. Results (average ± standard deviation): at baseline: low score 588 ± 83; median score 558 ± 108; high score 537 ± 93. At 10-year follow-up: low score 555 ± 76; median score 50 6 ± 116; high score 473 ± 126. Overall *P* value for changes over time: $P < 0.001$. Overall *P* value for differences between the groups at 10-year follow-up: $P = 0.001$. Low risk vs. median risk at 10-year follow-up: $P = 0.006$. Low risk vs. high risk: $P = < 0.001$. Median risk vs. high risk: $P = 0.051$.

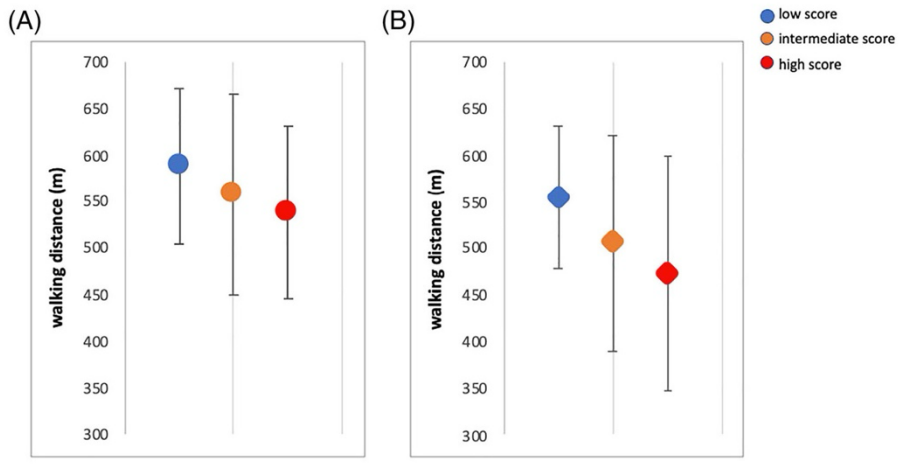
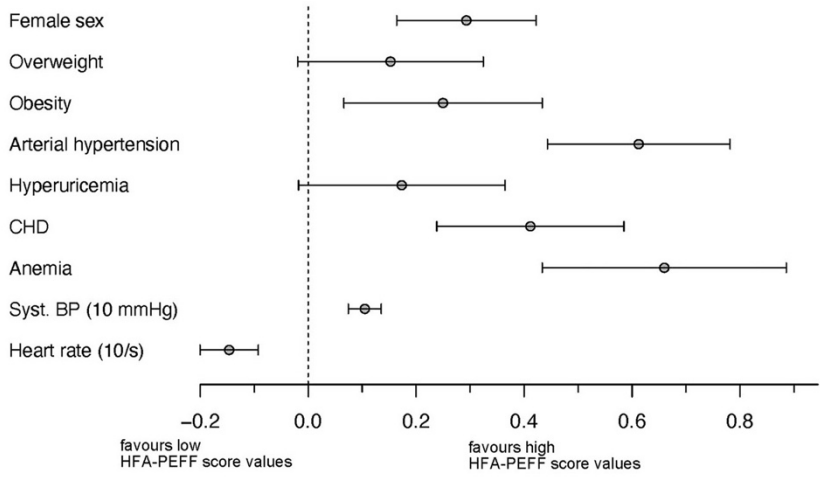


Table 2 Association of single items of the HFA-PEFF score on mortality

Characteristic	Threshold	OR	95% CI	
E/e' 1 pt.	E/e'_mean 9–14.99	1.65	0.98	2.76
E/e' 2 pts.	E/e'_mean ≥ 15	2.03	1.01	4.09
e' 2 pts.	Age <75 y: e'_sep < 7 cm/s, e'_lat < 10 cm/s; Age ≥75: e'_sep < 5 cm/s, e'_lat < 7 cm/s	1.61	0.82	3.17
PASP > 35	PASP > 35 mmHg	2.17	1.03	4.56
LAVi enlarged 1 pt.	LAVI > 29 mL/m^2	1.50	0.85	2.62
LAVi enlarged 2 pts.	LAVI > 34 mL/m^2	3.20	1.85	5.54
LVMi enlarged 1 pt.	Women: ≥95 g/m^2 or RWT > 0.42 Men: ≥115 g/m^2 or RWT > 0.42	0.95	0.48	1.86
LVMi enlarged 2 pts.	Women: ≥122 g/m^2 and RWT > 0.42 Men: ≥149 g/m^2 and RWT > 0.42	1.03	0.53	1.98
Biomarkers 1 pt.	Sinus rhythm: 125–220 pg/mL Atrial fibrillation 375–660 pg/mL	0.78	0.45	1.37
Biomarkers 2 pts.	Sinus rhythm: NT-proBNP > 220 pg/mL Atrial fibrillation: NT-proBNP > 660 pg/mL	1.44	0.88	2.36
RWT > 0.42	RWT > 0.42	1.06	0.66	1.70

LAVI, left atrial volume index; PASP, pulmonary artery systolic pressure; RWT, relative wall thickness, calculated as twice the LV posterior wall thickness divided by the LV internal diameter at end-diastole.
All items refer to the HFA-PEFF score.[8]

Figure 3 Risk factors associated with high score values. BP, blood pressure. Contribution of specific risk factors to the HFA-PEFF score value if present. Female sex [0.29, 95% CI (0.16, 0.42)], that is, the presence of female sex is associated with a 0.29 points contribution to the HFA-PEFF score value. Obesity [0.25 (0.07, 0.43)], arterial hypertension [0.61 (0.44, 0.78)], coronary heart disease [0.41 (0.24, 0.58)], anaemia [0.66 (0.43, 0.89)], systolic blood pressure [0.10 (0.07, 0.14) per 10 mmHg], and heart rate [per 10/min, −0.15 (−0.20, −0.09)].



Not only was the prognosis of patients with higher scores worse regarding mortality, MACE, and cardiovascular hospitalizations, but also the symptom burden and the functional status in these subjects were increased. Because functional capacity, for example, measured by the 6MWT, and worse prognosis are associated with higher score values, assessing the functional capacity is thought to be a parameter to identify high-risk subjects within the HFpEF population.[27] The 6MWT is evaluated during the first step of the HFA-PEFF algorithm, the pre-test probability assessment, which triggers the next step, the assessment by the HFA-PEFF score. The smaller decline in walking distance in the high score group is explained by the lower baseline values of this group. The two other groups were on a higher level at the beginning, implicating a higher chance of deterioration over time. Factors contributing to the restricted functional capacity include chronotropic incompetence, increased LV filling pressure, reduced cardiac output, and changes in the metabolism of peripheral muscular system. These reasons cannot be assessed in our population post hoc.

Table 3 Mortality, MACE, and CV hospitalization categorized by HFA-PEFF score values during the 10-year follow-up

	HFA-PEFF score value							Total
	0	1	2	3	4	5	6	
Dead	0	5	8	40	51	70	52	226
	0.0%	5.2%	7.4%	9.5%	11.4%	19.4%	24.5%	13.5%
MACE	1	15	20	98	136	145	88	503
	5.6%	15.5%	18.5%	23.2%	30.3%	40.2%	41.5%	30.2%
CV hospitalization	1	10	8	51	67	71	37	245
	5.6%	10.3%	7.4%	12.1%	14.9%	19.7%	17.5%	14.7%
Total	18	97	108	423	449	361	212	1668
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

CV hospitalization, cardiovascular hospitalization; MACE, major adverse cardiac events including death, cardiovascular hospitalization, new myocardial infarction, and first diagnosis of HF.

The DIAST-CHF cohort is close to a real-world scenario because its inclusion criteria are very broad and there are no cardiovascular exclusion criteria.

58.8% of the subjects from the DIAST-CHF study qualified for the intermediate score group. Therefore, most subjects of our analysed cohort would require a diastolic stress testing strategy with regard to the HFA-PEFF algorithm. This requirement of further testing challenges the current common practice as well as current care provider frameworks. Most probably, our cohort overestimates the number of subjects with intermediate scores because the study design augmented an at-risk population without signs or symptoms of HF. Future cohorts need to reassess this distribution by including parameters from the HFA-PEFF score at baseline.

Clinical implications

All studies evaluating the proposed diagnostic algorithm are challenged by the fact that there is no gold standard but expert opinion in diagnosing HFpEF. The HFA-PEFF algorithm provides an HFpEF definition characterized by its prognostic value. The disease definition allows further investigation of the HFpEF population with multiple advantages: high event rates for interventional trials as well as higher comparability of trial and study data by better characterization.

However, complex algorithms like the HFA-PEFF algorithm have a high threshold to be implemented in clinical or trial routine.

Limitations

The DIAST-CHF study was designed before the introduction of the HFA-PEFF score. Thus, not all components of the score were fully documented.

Within the intermediate score group, the HFA-PEFF algorithm suspected subjects both suffering and not suffering from HFpEF, distinguished by a diastolic stress examination. These stress examinations were not performed within DIAST-CHF. Therefore, we could not further analyse the differences within the intermediate score group.

SF-36 values were captured only in a relatively small number of patients. Moreover, the study population is at risk to develop HF, whereas the algorithm is primarily designed to assess the presence of HFpEF. Because the work-up for the intermediate HFA-PEFF group is not established routinely yet, invasive testing is often required but not routinely implemented.

Funding

This work was supported by the German Competence Network for Heart Failure, funded by the German Federal Ministry of Education and Research, the Charité – Universitätsmedizin Berlin, Germany, and the German Centre for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislaufforschung e.V., DZHK - funding number: 81X3100214).

Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

No conflict of interest was declared regarding the presented analysis. BP, FE and CT are authors of the HFA-PEFF consensus recommendation statement by the HFA/ESC. Honoraria and consultancy fees for pharmaceutical companies did not interfere with this analysis for any author.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cumulative incidences for death and cardiovascular hospitalization. Low score: score values 0 and 1; intermediate score: score values 2–4; high score: score values 5 and 6 in the HFA-PEFF algorithm. Times were truncated at 126 months.

References

1. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004; **351**: 2049–2057.
2. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, Witteman JCM, Stricker BHC. Quantifying the heart failure epidemic: Prevalence, incidence rate, lifetime risk and prognosis of heart failure - The Rotterdam study. *Eur Heart J*. 2004; **25**: 1614–1619.
3. Redfield MM, Jacobsen SJ, Burnett JJC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community. *JAMA*. 2003; **289**: 194–202, 202.
4. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; **93**: 1137–1146.
5. Stewart Coats AJ. Validating the HFA-PEFF score - or how to define a disease? *Eur J Heart Fail*. 2020; **22**: 428–431.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JG. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726.
7. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSPP, Lancellotti P. How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm: A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019; **40**: 3297–3317.
8. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca H-P, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VPM. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020; **22**: 413–421.
9. Parcha V, Malla G, Kalra R, Patel N, Sanders-van Wijk S, Pandey A, Shah SJ, Arora G, Arora P. Diagnostic and prognostic implications of heart failure with preserved ejection fraction scoring systems. *ESC Heart Fail*. 2021; **8**: 2089–2102.
10. Sotomi Y, Iwakura K, Hikoso S, Inoue K, Onishi T, Okada M, Fujii K, Okamura A, Tamaki S, Yano M, Hayashi T, Nakagawa A, Nakagawa Y, Nakatani D, Yasumura Y, Yamada T, Sakata Y, the OCVC-Heart Failure Investigators. Prognostic significance of the HFA-PEFF score in patients with heart failure with preserved ejection fraction. *ESC Heart Fail*. 2021; **8**: 2154–2164.
11. Tada A, Nagai T, Omote K, Iwano H, Tsujinaga S, Kamiya K, Konishi T, Sato T, Komoriyama H, Kobayashi Y, Takenaka S, Mizuguchi Y, Sato T, Yamamoto K, Yoshikawa T, Saito Y, Anzai T. Performance of the H(2)FPEF and the HFA-PEFF scores for the diagnosis of heart failure with preserved ejection fraction in Japanese patients: A report from the Japanese multicenter registry. *Int J Cardiol*. 2021; **342**: 43–48.
12. Nikorowitsch J, Bei der Kellen R, Kirchhof P, Magnussen C, Jagodzinski A, Schnabel RB, Blankenberg S, Wenzel J-P. Applying the ESC 2016, H(2) FPEF, and HFA-PEFF diagnostic algorithms for heart failure with preserved ejection fraction to the general population. *ESC Heart Fail*. 2021; **8**: 3603–3612.
13. Sun Y, Si J, Li J, Dai M, King E, Zhang X, Zhang Y, Xia Y, Tse G, Liu Y. Predictive value of HFA-PEFF score in patients with heart failure with preserved ejection fraction. *Front Cardiovasc Med*. 2021; **8**: 656536.
14. Egashira K, Sueta D, Komorita T, Yamamoto E, Usuku H, Tokitsu T, Fujisue K, Nishihara T, Oike F, Takae M, Hanatani S, Takashio S, Ito M, Yamanaga K, Araki S, Soejima H, Kaikita K, Matsushita K, Tsujita K. HFA-PEFF scores: Prognostic value in heart failure with preserved left ventricular ejection fraction. *Korean J Intern Med*. 2022; **37**: 96–108.
15. Amanai S, Harada T, Kagami K, Yoshida K, Kato T, Wada N, Obokata M. The H-(2)FPEF and HFA-PEFF algorithms for predicting exercise intolerance and abnormal hemodynamics in heart failure with preserved ejection fraction. *Sci Rep*. 2022; **12**: 13.
16. Mehrhof F, Löffler M, Gelbrich G, Özcelik C, Posch M, Hense HW, Keil U, Scheffold T, Schunkert H, Angermann C, Ertl G. A network against failing hearts-Introducing the German "Competence Network Heart Failure". *Int J Cardiol*. 2010; **145**: 135–138.
17. Hashemi D, Blum M, Mende M, Störk S, Angermann CE, Pankuweit S, Tahirovic E, Wachter R, Pieske B, Edelmann F, Düngen HD, the German Competence Network for Heart Failure. Syncopes and clinical outcome in heart failure: Results from prospective clinical study data in Germany. *ESC Heart Fail*. 2020; **7**: 942–952.
18. Meyer T, Chavanon M-L, Herrrmann-Lingen C, Roggenthien M, Nolte K, Pieske B, Wachter R, Edelmann F. Elevated plasma C-terminal endothelin-1 precursor fragment concentrations are associated with less anxiety in patients with cardiovascular risk factors. Results from the observational DIAST-CHF study. *PLoS ONE*. 2015; **10**: e0136739.
19. Edelmann F, Stahrenberg R, Polzin F, Kockskämper A, Düngen H-D, Duvinage A, Binder L, Kunde J, Scherer M, Gelbrich G, Hasenfuß G, Pieske B, Wachter R, Herrmann-Lingen C. Impaired physical quality of life in patients with diastolic dysfunction associates more strongly with neurohumoral activation than with echocardiographic parameters: Quality of life in diastolic dysfunction. *Am Heart J*. 2011; **161**: 797–804.
20. Bobenko A, Duvinage A, Mende M, Holzendorf V, Nolte K, Herrmann-Lingen C, Binder L, Düngen H-D, Hasenfuss G, Pieske B, Wachter R, Edelmann F. Outcome assessment using estimation of left ventricular filling pressure in asymptomatic patients at risk for heart failure with preserved ejection fraction. *IJC Heart Vasc*. 2020; **28**: 100525.
21. Haarmann H, Koch J, Bonsch N, Mende M, Werhahn SM, Lüers C, Stahrenberg R, Edelmann F, Holzendorf V, von Haehling S, Pieske B, Andreas S, Lüthje L, Wachter R. Morbidity and mortality in patients with cardiovascular risk factors and obstructive sleep apnoea: Results from the DIAST-CHF cohort. *Respir Med*. 2019; **154**: 127–132.
22. Stahrenberg R, Duvinage A, Mende M, Gelbrich G, Auf der Heide W, Düngen H-D, Binder L, Nolte K, Herrmann-Lingen C, Hasenfuß G, Pieske B. Determinants of submaximal exercise capacity in patients at risk for heart failure with preserved ejection fraction-results from the DIAST-CHF study. *ESC Heart Fail*. 2015; **2**: 76–84.
23. Lüers C, Trippel TD, Seeländer S, Wachter R, Hasenfuss G, Lindhorst R, Bobenko A, Nolte K, Pieske B, Edelmann F. Arterial stiffness and elevated left ventricular filling pressure in patients at risk for the development or a previous diagnosis of HF-A subgroup analysis from the DIAST-CHF study. *J Am Soc Hypertens*. 2017; **11**: 303–313.

24. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979; **6**: 65–70.
25. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca H-P, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VPM. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019: 1–9.
26. Selvaraj S, Myhre PL, Vaduganathan M, Claggett BL, Matsushita K, Kitzman DW, Borlaug BA, Shah AM, Solomon SD. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. *JACC Heart Fail*. 2020; **8**: 640–653.
27. Nayor M, Houstis NE, Namasivayam M, Rouvina J, Hardin C, Shah RV, Ho JE, Malhotra R, Lewis GD. Impaired exercise tolerance in heart failure with preserved ejection fraction: Quantification of multiorgan system reserve capacity. *JACC Heart Fail*. 2020; **8**: 605–617.

4.2. Gesundheitsökonomische Bedeutung der HFpEF-Behandlung

Die vorherige Arbeit hat die eingeschränkte Prognose bei der Diagnosestellung einer HFpEF mittels des HFA-PEFF-Scores aufgezeigt.[76] Ebenso wurde deutlich, dass auch Patient*innen, die bereits auffällige Untersuchungsbefunde zeigen, allerdings die HFpEF-Grenzwerte des Algorithmus nicht erreichen, bereits eine schlechtere Prognose haben als diejenigen, die nicht bzw. kaum auffällige Befunde vorweisen.[76]

Mit steigender Prävalenz der HFpEF bei einer Zunahme von Patient*innen mit kardiovaskulären Risikofaktoren nimmt die gesundheitsökonomische Belastung ebenso zu. Diese zu erfassen, bildet ein Kernstück in der Steuerung der Mittel zur Früherkennung, Diagnostik und Therapie von HFpEF auf Ebene der öffentlichen Gesundheitsfürsorge (Public Health).

Dieses Projekt analysiert die Gesundheitskosten einer Studienpopulation mit HFpEF.

Der nachfolgende Text entspricht dem Abstrakt dieser Arbeit[77]:

Hashemi D, Dettmann L, Trippel TD, Holzendorf V, Petutschnigg J, Wachter R, Hasenfuß G, Pieske B, Zapf A, Edelmann F. Economic impact of heart failure with preserved ejection fraction: insights from the ALDO-DHF trial. ESC Heart Fail. 2020 Jun;7(3):786-793. doi: 10.1002/ehf2.12606. Epub 2020 Jan 27. PMID: 31984661.

*"**Aims:** Although heart failure (HF) with preserved ejection fraction (HFpEF) is a leading cause for hospitalization, its overall costs remain unclear. Therefore, we assessed the health care-related costs of ambulatory HFpEF patients and the effect of spironolactone.*

***Methods and results:** The aldosterone receptor blockade in diastolic HF trial is a multicentre, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2011 at 10 sites in Germany and Austria that included 422 ambulatory patients [mean age: 67 years (standard deviation: 8); 52% women]. All subjects suffered from chronic New York Heart Association (NYHA) class II or III HF and preserved left ventricular ejection*

fraction of 50% or greater. They also showed evidence of diastolic dysfunction. Patients were randomly assigned to receive 25 mg of spironolactone once daily (n = 213) or matching placebo (n = 209) with 12 months of follow-up. We used a single-patient approach to explore the resulting general cost structure and included medication, number of general practitioner and cardiologist visits, and hospitalization in both acute and rehabilitative care facilities. The average annual costs per patient in this cohort came up to €1,118 (±2,475), and the median costs were €332. We confirmed that the main cost factor was hospitalization and spironolactone did not affect the overall costs. We identified higher HF functional class (NYHA), male patients with low haemoglobin level, with high oxygen uptake (VO2 max) and coronary artery disease, hyperlipidaemia, and atrial fibrillation as independent predictors for higher costs.

Conclusions: *In this relatively young, oligosymptomatic, and with regard to the protocol without major comorbidities patient cohort, the overall costs are lower than expected compared with the HFrEF population. Further investigation is needed to investigate the impact of, for example, comorbidities and their effect over a longer period of time. Simultaneously, this analysis suggests that prevention of comorbidities are necessary to reduce costs in the health care system."*[77]

ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 786–793
Published online 27 January 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12606

ORIGINAL RESEARCH ARTICLE

Economic impact of heart failure with preserved ejection fraction: insights from the ALDO-DHF trial

Djawid Hashemi[1,2], Ludwig Dettmann[3], Tobias D. Trippel[1,2], Volker Holzendorf[5], Johannes Petutschnigg[1,2], Rolf Wachter[6,7], Gerd Hasenfuß[3,6], Burkert Pieske[1,2,8], Antonia Zapf[4†] and Frank Edelmann[1,2*†]

[1]*Department of Internal Medicine and Cardiology, Charité—Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany;* [2]*DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany;* [3]*Department of Cardiology and Pneumology, University of Göttingen, Göttingen, Germany;* [4]*Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany;* [5]*Clinical Trial Centre, University of Leipzig, Leipzig, Germany;* [6]*DZHK (German Centre for Cardiovascular Research), partner site Göttingen, Göttingen, Germany;* [7]*Clinic and Policlinic for Cardiology, University Hospital Leipzig, Leipzig, Germany;* [8]*Department of Internal Medicine and Cardiology, German Heart Institute Berlin (DHZB), Berlin, Germany*

Abstract

Aims Although heart failure (HF) with preserved ejection fraction (HFpEF) is a leading cause for hospitalization, its overall costs remain unclear.
Therefore, we assessed the health care-related costs of ambulatory HFpEF patients and the effect of spironolactone.
Methods and results The aldosterone receptor blockade in diastolic HF trial is a multicentre, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2011 at 10 sites in Germany and Austria that included 422 ambulatory patients [mean age: 67 years (standard deviation: 8); 52% women]. All subjects suffered from chronic New York Heart Association (NYHA) class II or III HF and preserved left ventricular ejection fraction of 50% or greater. They also showed evidence of diastolic dysfunction.
Patients were randomly assigned to receive 25 mg of spironolactone once daily (n = 213) or matching placebo (n = 209) with 12 months of follow-up. We used a single-patient approach to explore the resulting general cost structure and included medication, number of general practitioner and cardiologist visits, and hospitalization in both acute and rehabilitative care facilities. The average annual costs per patient in this cohort came up to €1, 118 (±2,475), and the median costs were €332. We confirmed that the main cost factor was hospitalization and spironolactone did not affect the overall costs. We identified higher HF functional class (NYHA), male patients with low haemoglobin level, with high oxygen uptake (VO_2max) and coronary artery disease, hyperlipidaemia, and atrial fibrillation as independent predictors for higher costs.
Conclusions In this relatively young, oligosymptomatic, and with regard to the protocol without major comorbidities patient cohort, the overall costs are lower than expected compared with the HFrEF population. Further investigation is needed to investigate the impact of, for example, comorbidities and their effect over a longer period of time. Simultaneously, this analysis suggests that prevention of comorbidities are necessary to reduce costs in the health care system.

Keywords Heart failure; Heart failure with preserved ejection fraction; Economic costs; Economics

Received: 15 August 2019; Revised: 2 December 2019; Accepted: 9 December 2019
**Correspondence to: Frank Edelmann, Charité - Universitätsmedizin Berlin, Medizinische Klinik m. S. Kardiologie, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 (30) 450 653 731; Fax: +49 (30) 450 7 553 731 Email: frank.edelmann@charite.de*
†These authors share senior authorship.

Introduction

Patients suffering from heart failure (HF) account for nearly 1–2% of the adult population in developed countries, rising up to ≥10% among people above 70 years of age with increasing prevalence due to demographic changes.[1–4] HF patients are mainly categorized into HF with reduced (HFrEF) and preserved ejection fraction (HFpEF) due to different underlying aetiologies, demographics, comorbidities, and response to therapies.[5,6] The prevalence of both entities and their prognoses is comparable.[7] Despite remarkable progress in HF research, we still miss a specific treatment for HFpEF, at the moment the guidelines focus on optimizing the comorbidities.

However, the economic burden of HF treatment increases with its prevalence. Cardiovascular diseases are estimated to cost about $130 billion in Europe annually with HF as a major matter of expense.[8] HF cost estimates in the USA amount to $39.2 billion in direct costs,[9] which do not include the impact on the economic reduction in work force nor the informal care these patients receive. A key portion of HF direct costs is caused by hospitalization, while ~5% of all hospital admissions in Western countries are due to HF.[10–12] Projected total medical costs in 2030 will rise up $53.1 billion, and nearly 80% of these projected expenses are attributed to increased hospitalizations.[13–15] All these details are mainly based on databases from national registries and insurance companies.[16] These databases underestimate the costs of HF patients systematically because of differently attributed diagnoses for hospitalization due to common comorbidities of HF patients. In particular, HFpEF patients are inadequately represented because of various comorbidities and a systematic neglect due to the absence of direct treatment options.[17] Based on the recommended guideline treatment for HFrEF patients, monitoring HFrEF costs is easier on a non-individual-based approach in registries.

The aldosterone receptor blockade in diastolic HF (aldo-DHF) study was a randomized, controlled trial investigating the effects of chronic aldosterone receptor blockade in 422 outpatient stable HFpEF patients during a 12-month follow-up period.[18] Its co-primary endpoints were E/e' and peakVO_2.

Thus, in this analysis, we aim to (i) analyse the structure of the costs and to (ii) assess the direct health costs for this stable outpatient HFpEF population. Ultimately, we aim to (iii) evaluate the effect of spironolactone on the overall direct costs and the cost distribution and to (iv) identify predictors for higher costs in subjects based on these findings.

Methods

Study design and setting

The aldo-DHF trial was a multicentre, randomized, placebo-controlled, double-blind study within the framework of the German Competence Network Heart Failure (KNHI) between 2007 and 2012.[19] The study design and the primary results of the aldo-DHF trial have been previously published.[18,20] Briefly, eligible patients were enrolled and randomized to spironolactone 25 mg once daily or matching placebo. The diagnosis of HFpEF was based mainly on the Paulus criteria [symptomatic HF, left ventricular ejection fraction (LVEF) $\geq$ 50% at rest and echocardiographic signs of diastolic dysfunction (tissue doppler-derived E/e' $>$ 15 or E/e' $>$ 8 in combination with the presence of either elevated N terminal pro brain natriuretic peptide or brain natriuretic peptide or atrial fibrillation)][21] Ultimately, symptomatic patients with New York Heart Association class II or III, LVEF $\geq$ 50% at rest, echocardiographic evidence of grade $\geq$ I diastolic dysfunction or present atrial fibrillation, and peak $VO_2 \leq$ 25 mL/kg/min were eligible for participation.[20] Major exclusion criteria included prior documented LVEF $\leq$ 40%, significant coronary artery disease, myocardial infarction or coronary artery bypass graft surgery within 3 months, definite or probable pulmonary disease [vital capacity $<$ 80% or forced expiratory volume in 1 s $<$ 80% of reference values on spirometry], body mass index $\geq$ 36 kg/m, or serum creatinine $>$ 1.8 mg/dL. After the baseline examination and the randomization, patients were seen at visits after 1 week and 3, 6, 9, and 12 months. Examination results, questionnaires, and changes of medication were recorded at each visit. The study protocol was reviewed and approved by the institutional review board of each participating centre, and all patients provided written informed consent prior to enrolment. Aldo-DHF was conducted in accordance with national laws, guidelines for good clinical practice, and the Declaration of Helsinki.

Subject population

We analysed the data of 422 patients. The data collection also consisted of details regarding physician visits, rehabilitation, and hospital admissions as well as the concomitant medication at the screening, the baseline, and the follow-up visits every 3 months for a year.

Endpoint

The main endpoint in focus was defined as the overall direct costs. These direct costs were based on (i) structural costs assessed by the number of general practitioner (GP) and cardiologist visits, number of HF hospitalizations, duration of cardiac rehabilitation, and duration of required nursing care as well as (ii) medication costs assessed by the number of days the medication was taken and the individual composition of medication per day.

Cost parameter assessment

We analysed the cost of illness with a bottom-up-approach[22,23] based on the details of every single patient. We considered cardiovascular medication as relevant for our analysis and therefore as distinguishable from other medication. These considered medication included beta-blocker, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, cardiac glycosides, statines, other lipid-lowering agents, antiarrhythmic agents, calcium channel

blocker, anticoagulants, nitrates, oral antidiabetic medication, and insulin and pulmonary medication. For the calculations of the costs due to the concomitant medication, we used the price for the cheapest generic in the largest available package size on the German market in the year 2011 for our calculations.

Regarding outpatient physician visits, we considered visits to GPs, specialists in internal medicine, and cardiologists as relevant for our analysis. Reliable data for costs per physician visit were only available from the year 1999.[24] Therefore, we adjusted these for inflation and set the year 2011 as the reference point of time.

The direct costs of hospitalization were assessed when the hospitalization reported at the baseline visit for the previous 12 months or any other follow-up visit was due to HF. The direct economic costs of a hospitalization emerge from both the treatment costs and the infrastructural costs of the health care provider. We used an established approach to assess these costs by including the average HF costs based on diagnosis-related group statistics from the Federal Statistical Office of Germany and added the infrastructural state funding per day multiplied by the duration of the hospital stay to assess the hospitalization costs.[24]

Statistical methods

Study cohort and subgroups are described by absolute and relative frequencies for categorical data, by mean and standard deviation (SD) for symmetric continuous variables and in addition, median and quartiles/interquartile range for skewed continuous variables.

We compared frequencies by χ^2 test and Fisher's exact test. Continuous variables were compared by *t*-tests for independent samples with Satterthwaite approximation or by Mann–Whitney *U* tests.

For the analysis of both the physician visits and the hospitalizations, we summed up the details at each visit per patient. Medication costs were calculated as a product of daily dosage, price per dosage, and number of days taken.

In searching baseline variables associated with the total direct costs, we built various regression models. After simple linear regression models with variables from *Table 1*, we built a multiple regression model and excluded irrelevant variables by backward selection with probabilities for inclusion: p_in = 0.2 and exclusion p_out = 0.05. Final models were built with the variables selected that way to get correct estimates for incidence rate ratios, which were calculated including two-sided 95% confidence intervals.

Table 1 patient characteristics I

Variable	Spironolactone *n* (%)	Placebo *n* (%)	*P value*
Female	111 (52)	110 (53)	0.9150
CAD	92 (43)	78 (37)	0.2188
Arterial hypertension	197 (92)	190 (91)	0.5565
CVD	23 (11)	22 (11)	0.9279
PAD	7 (3)	10 (5)	0.4338
Atrial fibrillation	30 (14)	36 (17)	0.3746
Chronotropic incompetence	9 (4)	16 (8)	0.1356
NYHA III	33 (15)	26 (12)	0.3659
Hyperlipidemia	130 (61)	143 (68)	0.1123
Diabetes mellitus	36 (17)	34 (16)	0.8611
sleep apnoea	29 (14)	21 (10)	0.2569
COPD	11 (5)	3 (1)	0.0535
Depression	22 (10)	25 (12)	0.5939
Paulus criteria positive	111 (52)	109 (52)	0.9934

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; Paulus criteria, HFpEF criteria mentioned above.[21]

Results

Subject population

A total of 422 patients were randomly assigned to receive spironolactone (*n* = 213) or matching placebo (*n* = 209) with 12 months of follow-up. Patients who dropped out were analysed until their dropout. There was no relevant difference in the number of dropouts (9 vs. 13, *P* = 0.22) nor in the baseline characteristics (*Tables 1 and 2*) between both groups.

Costs per item: physician visits and hospitalizations

Because most data were collected in 2011, that year was also set as the reference point of time for all calculations.

The latest costs per outpatient physician visit given by the German physician's association were from 1999. We adjusted those values for inflation in 2011 and calculated 19.95 € per visit to the general practitioner and 71.16€ per visit to the cardiologist.

The average diagnosis-related group-based cost was 3168.03 € per hospitalization. We calculated additional 64.43 € per day in hospital for infrastructural costs. For rehabilitation, we calculated additional 121.12 € per day.

Overall direct cost

As shown in *Figure1*, the overall direct costs are the sum of the costs for outpatient physician visits, hospitalization, rehabilitation, and medication. The mean overall cost per patient was 1188€. The median cost was in contrast 332€ as a result

Table 2 Patient characteristics II

Variable	Spironolactone					Placebo					
	N	Mean	SD	Median	IQR	N	Mean	SD	Median	IQR	*P value*
Age [years]	213	66.9	7.7	67.0	12.0	209	66.7	7.5	68.0	11.0	0.8038
BMI [kg/m^2]	213	28.9	3.6	29.0	5.0	209	28.9	3.6	28.8	5.1	0.9644
MAP [mmHg]	213	97.6	11.4	96.3	16.0	209	98.2	12.2	98.0	14.7	0.5435
Pulse pressure [mmHg]	213	55.8	14.8	54.0	19.0	209	55.8	15.8	55.0	20.0	0.9667
HR in ECG [min^{-1}]	213	66.5	13.8	65.0	15.0	208	64.3	11.8	63.0	11.5	*0.0815*
eGFR [ml/min/1.73 m^2]	211	79.3	19.2	77.7	25.6	208	78.1	18.3	77.9	24.9	0.5095
VO_2max [ml/min/kg]	213	16.4	3.6	16.1	4.4	209	16.4	3.5	16.3	4.6	0.8731
E/e' (medial)	213	12.7	3.6	11.9	4.3	209	12.8	4.4	11.9	3.6	0.6252
log10NTproBNP	204	2.2	0.5	2.3	0.6	195	2.2	0.4	2.2	0.5	0.5052
LAVI [ml/m^2]	212	28.2	9.1	26.4	10.4	208	27.8	7.7	26.7	9.7	0.9586
LVMI [ml/m^2]	212	107.9	29.2	106.8	29.8	209	109.3	26.8	107.4	35.8	0.5347
Hb [g/dl]	213	13.8	1.2	13.8	1.5	209	13.8	1.3	13.8	1.8	0.8135
VACI	206	0.5	0.7	0.5	0.3	202	0.5	0.3	0.5	0.2	*0.0849*

Values in italic are smaller than 0.2, selection criterion before multiple regression model
BMI: body mass index; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HR: heart rate; IQR: interquartile range; LAVI: left atrial volume indexed to body surface area; LVMI left ventricular mass indexed to body surface area; MAP :mean arterial pressure; SD: standard deviation; VACI: Ventricular-atrial Coupling Index; VO_2max: maximal oxygen uptake

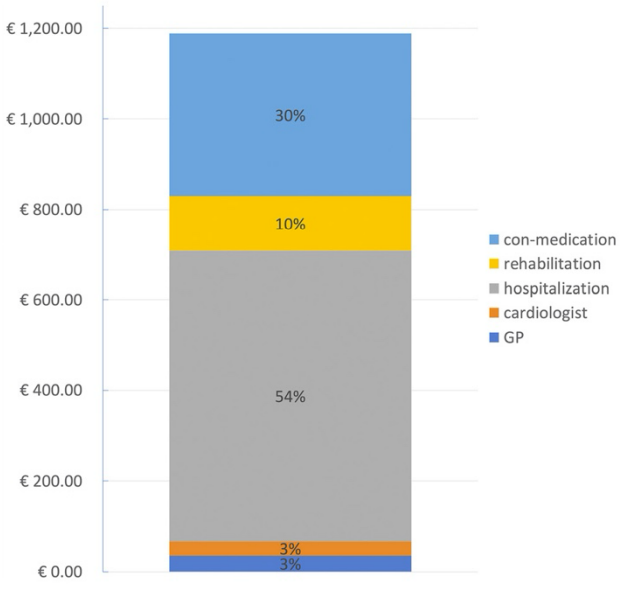
of most patients contributing to less than 1000€ per patient per year. The main component was hospitalization due to HF.

Hospitalization and rehabilitation

Because only 14.7% (62/422) of all subjects were hospitalized during the follow-up period, its contribution to the overall costs of the investigated HFpEF cohort was very limited. However, for patients who were hospitalized, hospitalization was the most expensive item. This resulted in 640.7€ [SD: ±1995.7€, median 0€ (Q_1: 0€; Q_3: 0€)] average costs for hospitalization per study subject during the 12 months of follow-up.

The same applies to patients who were admitted to rehabilitation and their costs. 5.5% (23/422) of subjects had at least one admission for rehabilitation care that generated an average cost of 122.3€ [SD: ±693.3€, median 0€ (Q_1: 0€; Q_3: 0€)] per rehabilitation treatment per patient annually.

Figure 1 Distribution of mean overall direct costs of the complete study population. Con-medication: medication taken besides study drug (spironolactone/placebo); cardiologist: outpatient visits to cardiologist; GP: outpatient visits to general practitioner; hospitalization: hospitalization due to heart failure (HF); rehabilitation: rehabilitation due to HF.



Outpatient visits

Among patients who were not hospitalized, outpatient visits, either to the cardiologist or the GP, were the most relevant cost item besides the prescribed medication.

One-third of the study population had no visit to the GP during the follow-up period. Seventy-five percent of patients had up to two visits, and one patient was outlying with 48 GP visits during the follow-up period. Thus, on average, 35.3€ [SD: ±67.9, median 20€ (Q_1: 0€; Q_3: 40€)] was spent for GP visits per patient during the follow-up period.

Visits to the cardiologist were noticeably fewer but with a similar pattern. Seventy-five percent of the study population had up to one visit to the cardiologist. The subject with the most visits to the cardiologist during the follow-up had 10 visits. In total, visits to the cardiologist added up to an average cost of 31.2€ [SD: ±68.5€, median 0€ (Q_1: 0€; Q_3: 71€)] per patient during the follow-up period.

Medication

Considering the follow-up visits at 3, 6, 9, and 12 months, about 29% of subjects on average reported altered

medication and 66.1% (279/422) reported none or one change in medication during the complete follow-up period. The con-medication taken from all participants is shown in *Table 3*.

Some of the frequently taken drugs created low median costs, like beta-blockers (17€) and statins (23€). Some of the less frequently taken drug groups generated higher median costs, like antiarrhythmic agents (1313.6 €) and antidepressants (1894.9€). Anticoagulation, which included antiplatelet therapy in our analysis, was frequently taken and contributed notably to the costs with a relatively high median cost (1109.5€). These findings resulted in median con-medication costs of 223€ per subject per year. The large distribution lead to nearly 100 subjects (one quartile) with costs less than 100 € and a quartile with costs more than 487€ per patient per year. These results are accompanied by mean costs of 358.7€ (SD: ±396.5) per patient per year.

Effect of spironolactone

The costs for outpatient visits to both the GP and the cardiologist, the hospitalizations, and rehabilitation care were not different in the two study arms. *Table 4* shows the distribution in the total patient cohort.

The medication costs between both treatment arms are not relevantly different ($P = 0.84$). Certain medication groups were different between these study arms but had no impact on the overall costs [calcium channel blockers were taken more often in the placebo group ($P = 0.01$) and loop diuretics more in the spironolactone group ($P = 0.02$)].

Table 3 Absolute and relative frequency of medication groups in both treatment arms

	Spironolactone (n = 213)		Placebo (n = 209)	
Medication group	No. (n)	Rel. (%)	No. (n)	Rel. (%)
Antiarrhythmic agents	12	6	21	10
Beta blockers	150	70	160	77
CCB	47	22	74	35
ACE inhibitors	103	48	92	44
ARBs	85	40	80	38
Loop diuretics	46	22	27	13
Other diuretics	97	46	99	47
Nitrates	23	11	18	9
Cardiac glycosides	4	2	4	2
Statins	117	55	119	57
Other cholesterol-lowering medication	19	9	15	7
Anticoagulants	132	62	119	57
Oral antidiabetic medication	30	14	20	10
Pulmonary medication	13	6	9	4
Insulins	4	2	11	5
Antidepressants	21	10	16	8

Mediation group was considered positive, when at least one drug from a medication group was reported to be part of the taken by patient at one of the study visits.
ACE: angiotensin-converting-enzyme inhibitor; anticoagulants: including antiplatelet therapy; ARBs: Angiotensin II receptor blockers; CCB: calcium channel blockers; Rel.: relative frequency.

Table 4 Comparison of the descriptive cost items without medication costs

	Total patient cohort (n = 422)				
Cost item	Min	Max	Med	Q_1	Q_3
GP	0	958	20	0	40
Cardiologist	0	712	0	0	71
Hospitalization	0	18,288	0	0	0
Rehabilitation	0	8,478	0	0	0

Costs in € (Euro).GP, costs of outpatient visits to the general practitioner; cardiologist, costs of outpatient visits to the cardiologist; hospitalization, costs of hospitalizations due to heart failure; rehabilitation, costs of rehabilitation care due to heart failure.

Predictors

Factors associated with impact on the costs are shown in *Table 5*. Factors like atrial fibrillation, coronary artery disease, and higher HF functional class were associated with higher costs, while higher haemoglobin levels in women predicted lower costs. Other factors, for example, age, arterial hypertension, and chronic obstructive pulmonary disease, as well as the level of diastolic dysfunction (E/e'), showed no impact on higher costs.

Discussion

In this analysis, we measure for the first time the costs of an ambulatory HFpEF cohort, which account for a median amount of 332 € per patient per year (1118€ on average). The analysis of the structure revealed hospitalization as the driving cost factor followed by medication, rehabilitation, and outpatient visits. Spironolactone did not change the overall costs or the distribution over the different items; however, it showed associations with certain compositions of the con-medication. Independent predictors for higher costs included men with lower haemoglobin values, better VO_2max, as well as the presence of coronary artery disease, hyperlipidaemia, and atrial fibrillation.

Table 5 Incidence rate ratio of relevant predictive factors for overall costs

Predictive factor	IRR	95% CI	P
Haemoglobin	0.791	0.706–0.887	<0.001
VO_2max	1.049	1.009–1.090	0.015
Female vs. male	0.619	0.464–0.824	0.001
CAD, yes vs. no	1.399	1.026–1.910	0.034
Hyperlipidaemia, yes vs. no	1.608	1.189–2.175	0.002
Atrial fibrillation, yes vs. no	2.164	1.516–3.093	<0.001
NYHA III vs. II	1.640	1.120–2.406	0.011

CAD: coronary artery disease; CI: confidence interval; IRR: incidence rate ratio; NYHA: New York Heart Association.

This analysis gained power through the bottom-up-approach, which focused on the use of resources on every level of each subject instead of referring to aggregated cohort data.

Analyses by other authors investigating HF populations and providing their use of medical resources focused mainly on a different selection of patients, for example, Biermann *et al.* investigated a pooled HF cohort with LVEF < 50%.[25] In that analysis, HFrEF and HF with mid-range ejection fraction patients showed higher need for medical resources indicating higher costs. There were more often outpatient visits to both GPs as well as cardiologists than in our cohort [6.1 (±9) and 1.7 (±2.5) vs. 1.8 (±3.4) and 0.4 (±1.0) per year]. Hospital admissions due to HF were more frequent in those patients [0.8 (±1.2) vs. 0.2 (±0.6) per year]. However, even the basic characteristics differed: the cohort was younger and there were more male subjects [25.2% female subjects and mean age 62.9 (± 13.6) years vs. 52% female subjects and mean age 67 (± 8) years]. Both analyses, theirs and ours, could show that higher HF functional classes were associated with higher costs.

Focusing on HFpEF populations only, similar effects could be shown, for example, by Redfield *et al.* In the RELAX trial, they investigated the effect of phosphodiesterase-5 inhibition with administration of sildenafil for 24 weeks, compared with placebo in an HFpEF cohort.[26] It did not result in significant improvement in exercise capacity or clinical status, but the data could be analysed in the same bottom-up-approach like ours and showed also a significant higher need for medical resources in both medication and hospitalization terms. Although the RELAX cohort was similar to the ALDO cohort regarding the basic baseline characteristics (mean age 69 years, 49% women), they differed in others, such as the comorbidities. In summary, comorbidities were more present in the RELAX than in the ALDO group, for example, arterial hypertension 85% vs. 92%, diabetes mellitus 43% vs. 17%, chronic obstructive pulmonary disease 19% vs. 3%, and atrial fibrillation 51% vs. 15%. Consequently, the number of con-medication was higher than in the ALDO cohort, for example, loop diuretics 77% vs. 17% or ACEi 70% vs. 46%. Even in laboratory and clinical testing, the RELAX group appeared to be sicker with median N-terminal pro brain natriuretic peptide values around 700 pg/mL vs. 158 pg/mL in the ALDO cohort. VO_2max was at 11.7 mL/min/kg vs. >16 mL/min/kg in the aldo-DHF data. Diastolic parameters like E/e' (16 vs. 11.8) and left atrial volume indexed to body surface area (44 mL/m^2 vs. 26 mL/m^2) were also different. This constellation indicates that patients with a higher disease burden have higher costs, represented by the fact that HF hospitalization was an inclusion criterion in RELAX but not in aldo-DHF. In contrast, only 37% of aldo-DHF patients had a hospitalization before baseline. Korves *et al.*[27] could show that hospitalization and especially the 6 months after HF hospitalization are the most costly periods of the patient journey.

Conclusively, we show that early stage HFpEF patients have lower costs and because managing the comorbidities is the main treatment approach at the moment, an early diagnosis and prevention as well as treatment of comorbidities reduces the economic costs even of an oligosymptomatic, relatively young HFpEF cohort.

In analysing the predictive factors for higher costs, the only item that we can change and improve besides optimal therapy of comorbidities is VO_2max. This underlines the idea that physical exercises could improve HFpEF population outcomes and lower the costs of their care.

Limitations to this analysis include focusing on direct costs. Indirect costs, for example, disability to work, early retirement, and commute to diagnosis or treatment, were not included. Incidental costs in an elderly population with HFpEF are negligible due to their higher age (67 ± 8 years) and the presumed retirement. Intangible costs were not observed in the study protocol.

Compared with many other studies focusing on HFpEF, our study population is relatively young. Being young and only oligosymptomatic with a relatively low rate of HF hospitalization created lower costs.

But even the number of outpatient visits was much lower than expected, especially regarding visits to the cardiologist. Regular study visits may have influenced the number of other outpatient visits to the GP or cardiologist although subjects were instructed to keep regular appointments, including those required for prescriptions for the con-medication.

Regarding the con-medication, we most likely underestimate the real costs because we always calculated for the cheapest generic per largest pack size drug of an agent. At the same time, we only calculated single medication therapies and did not include polypills, which are usually cheaper than the combination of two drugs.

We could calculate the costs of a stable, oligosymptomatic patient with HFpEF per year. Because the hospitalizations and the following patient monitoring create the highest costs, we need to find methods to reduce HF hospitalizations and processes to decrease their impact on the overall costs in future steps.

Conflict of interest

None declared.

Funding

This work was supported by the German Competence Network for Heart Failure, funded by the German Federal Ministry of Education and Research, and the Charité—Universitätsmedizin Berlin, Germany.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 2016; **18**: 891–975.
2. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, Witteman JCM, Stricker BHC. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure—The Rotterdam Study. *Eur Heart J* 2004; **25**: 1614–1619.
3. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community. *JAMA* 2003; **289**: 194–202.
4. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; **93**: 1137–1146.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail* 2016; **18**: 891–975.
6. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M, Butler J. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol Elsevier* 2017; **69**: 556–569.
7. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251–259.
8. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**: e146–e603.
9. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010; **121**: 948–954.
10. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? *Europace* 2011; **13**: 13–17.
11. Meerding WJ, Bonneux L, Polder JJ, Koopmanschap MA, van der Maas PJ. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. *BMJ* 1998; **317**: 111–115.
12. Rodríguez-Artalejo F, Guallar-Castillón P, Banegas Banegas JR, del Rey Calero J. Trends in hospitalization and mortality for heart failure in Spain, 1980–1993. *Eur Heart J* 1997; **18**: 1771–1779.
13. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016; **13**: 368–378.
14. Shafie AA, Tan YP, Ng CH. Systematic review of economic burden of heart failure. *Heart Fail Rev* 2018; **23**: 131–145.
15. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. *BMC Cardiovasc Disord* 2018; **18**: 74.
16. Hollingworth W, Biswas M, Maishman RL, Dayer MJ, McDonagh T, Purdy S, Reeves BC, Rogers CA, Williams R, Pufulete M. The healthcare costs of heart failure during the last five years of life: a retrospective cohort study. *Int J Cardiol* Elsevier Ireland Ltd 2016; **224**: 132–138.
17. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JGF. Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol* Elsevier Masson SAS 2002; **39**: 138–141.
18. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen H-D, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013; **309**: 781–791.
19. Mehrhof F, Löffler M, Gelbrich G, Özcelik C, Posch M, Hense HW, Keil U, Scheffold T, Schunkert H, Angermann C, Ertl G, Jahns R, Pieske B, Wachter R, Edelmann F, Wollert KC, Maisch B, Pankuweit S, Erbel R, Neumann T, Herzog W, Katus H, Müller-Tasch T, Zugck C, Düngen HD, Regitz-Zagrosek V, Lehmkuhl E, Störk S, Siebert U, Wasem J, Neumann A, Göhler A, Anker SD, Köhler F, Möckel M, Osterziel K-J, Dietz R, Rauchhaus M. A network against failing hearts—introducing the German 'competence Network Heart Failure'. *Int J Cardiol* 2010; **145**: 135–138.
20. Edelmann F, Schmidt AG, Gelbrich G, Binder L, Herrmann-Lingen C, Halle M, Hasenfuss G, Wachter R, Pieske B. Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in pa. *Eur J Heart Fail* 2010; **12**: 874–882.
21. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Édes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**: 2539–2550.
22. Schöffski O, Glaser P, Schulenburg J-M G v.d, eds. *Gesundheitsökonomische Evaluationen*. Berlin, Heidelberg: Springer Berlin Heidelberg; 1998.
23. Icks A, Chernyak N, Bestehorn K, Brüggenjürgen B, Bruns J, Damm O, Dintsios C-M, Dreinhöfer K, Gandjour A, Gerber A, Greiner W, Hermanek P, Hessel F, Heymann R, Huppertz E, Jacke C, Kächele H, Kilian R, Klingenberger D, Kolominsky-Rabas P, Krämer H, Krauth C, Lüngen M, Neumann T, Porzsolt F, Prenzler A, Pueschner F, Riedel R, Rüther A, Salize HJ, Scharnetzky E, Schwerd W, Selbmann HK, Siebert H, Stengel D, Stock S, Völler H, Wasem J, Schrappe M. Methoden der gesundheitsökonomischen Evaluation in der Versorgungsforschung TT - Methods of Health Economic Evaluation for Health Services Research. *Gesundheitswesen* 2010; **72**: 917–933.
24. Krauth C, Hessel F, Hansmeier T, Wasem J, Seitz R, Schweikert B. Empirical standard costs for health economic evaluation in Germany—a proposal by the working group methods in health

economic evaluation. *Gesundheitswesen Germany* 2005; **67**: 736–746.
25. Biermann J, Neumann T, Angermann CE, Erbel R, Maisch B, Pittrow D, Regitz-Zagrosek V, Scheffold T, Wachter R, Gelbrich G, Wasem J, Neumann A. Economic burden of patients with various etiologies of chronic systolic heart failure analyzed by resource use and costs. *Int J Cardiol Elsevier Ireland Ltd* 2012; **156**: 323–325.
26. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E, for the RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction. *JAMA* 2013; **309**: 1268–1277.
27. Korves C, Eldar-Lissai A, McHale J, Lafeuille M-H, Hwa Ong S, Sheng Duh M. Resource utilization and costs following hospitalization of patients with chronic heart failure in the US. *J Med Econ* 2012; **15**: 925–937.

4.3. Charakterisierung von HI mittels Kardio-MRT

Wie bereits gezeigt wurde, sind präventive Maßnahmen in Ermangelung direkt therapeutischer Ansätze nicht nur das Kernstück der Krankheitsvorbeugung bei HFpEF, sondern auch ein zentrales Instrument zur Reduktion der Krankheitskosten.[77]

Die bisherige Klassifikation der Herzinsuffizienz erfolgt unter therapeutischen Gesichtspunkten entlang der Gruppierung der LVEF.[1] Neben der LVEF, die als Indikator der globalen systolischen LV-Funktion dient, haben sich auch Strain-Messungen als Maßzahlen für die globale myokardiale Deformation etabliert. Diese korrelieren eng mit der LVEF, was darauf hindeutet, dass regionale Einschränkungen bei der Darstellung der globalen Funktion nicht ausreichend abgebildet sind. Zudem wird die Herzinsuffizienz im Kontext als Spektrum über die LVEF betrachtet.

In dieser Arbeit wird ein neuer Parameter zur Abbildung der myokardialen Deformation bei Herzinsuffizienz mit höherer Granularität untersucht.

Der nachfolgende Text entspricht dem Abstrakt dieser Arbeit[78]:

Hashemi D, Motzkus L, Blum M, Kraft R, Tanacli R, Tahirovic E, Doeblin P, Zieschang V, Zamani SM, Kelm M, Kuehne T, Pieske B, Alogna A, Edelmann F, Duengen HD, Kelle S. Myocardial deformation assessed among heart failure entities by cardiovascular magnetic resonance imaging. ESC Heart Fail. 2021 Apr;8(2):890-897. doi: 10.1002/ehf2.13193. Epub 2021 Feb 4. PMID: 33539681.

*"**Aims:** Although heart failure (HF) is a leading cause for hospitalization and mortality, normalized and comparable non-invasive assessment of haemodynamics and myocardial action remains limited. Moreover, myocardial deformation has not been compared between the guideline-defined HF entities. The distribution of affected and impaired segments within the contracting left ventricular (LV) myocardium have also not been compared. Therefore, we assessed myocardial function impairment by strain in patients with HF and control subjects by magnetic resonance imaging after clinically phenotyping these patients.*

Methods and results: *This prospective study conducted at two centres in Germany between 2017 and 2018 enrolled stable outpatient subjects with HF [n = 56, including HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF)] and a control cohort (n = 12). Parameters assessed included measures for external myocardial function, for example, cardiac index and myocardial deformation measurements by cardiovascular magnetic resonance imaging, left ventricular global longitudinal strain (GLS), the global circumferential strain (GCS) and the regional distribution of segment deformation within the LV myocardium, as well as basic phenotypical characteristics. Comparison of the cardiac indices at rest showed no differences neither between the HF groups nor between the control group and HF patients (one-way ANOVA P = 0.70). The analysis of the strain data revealed differences between all groups in both LV GLS (One-way ANOVA: P < 0.01. Controls vs. HFpEF: -20.48 ± 1.62 vs. -19.27 ± 1.25. HFpEF vs. HFmrEF: -19.27 ± 1.25 vs. -15.72 ± 2.76. HFmrEF vs. HFrEF: -15.72 ± 2.76 vs. -11.51 ± 3.97.) and LV GCS (One-way ANOVA: P < 0.01. Controls vs. HFpEF: -19.74 ± 2.18 vs. -17.47 ± 2.10. HFpEF vs. HFmrEF: -17.47 ± 2.10 vs. -12.78 ± 3.47. HFrEF: -11.41 ± 3.27). Comparing the segment deformation distribution patterns highlighted the discriminating effect between the groups was much more prominent between the groups (one-way ANOVA P < 0.01) when compared by a score combining regional effects and a global view on the LV. Further analyses of the patterns among the segments affected showed that while the LVEF is preserved in HFpEF, the segments impaired in their contractility are located in the ventricular septum. The worse the LVEF is, the more segments are affected, but the septum remains an outstanding location with the most severe contractility impairment throughout the HF entities.*

Conclusions: *While cardiac index at rest did not differ significantly between controls and stable HF patients suffering from HFrEF, HFmrEF, or HFpEF, the groups did differ significantly in LV GLS and LV GCS values. Regional strain analysis revealed that the LV septum is the location affected most, with reduced values already visible in HFpEF and further reductions in HFmrEF and HFrEF."*[78]

ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 890–897
Published online 4 February 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13193

ORIGINAL RESEARCH ARTICLE

Myocardial deformation assessed among heart failure entities by cardiovascular magnetic resonance imaging

Djawid Hashemi[1,2], Laura Motzkus[1], Moritz Blum[1], Robin Kraft[1], Radu Tanacli[3], Elvis Tahirovic[1,2], Patrick Doeblin[2,3], Victoria Zieschang[3], S. Mahsa Zamani[3], Marcus Kelm[4], Titus Kuehne[2,4], Burkert Pieske[1,2,3], Alessio Alogna[1,2], Frank Edelmann[1,2], Hans-Dirk Duengen[1,2†] and Sebastian Kelle[1,2,3*†]

[1]*Department of Internal Medicine and Cardiology, Charité—Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany;* [2]*DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany;* [3]*Department of Internal Medicine and Cardiology, German Heart Institute Berlin (DHZB), Augustenburger Platz 1, Berlin, 13353, Germany;* [4]*Charité—Universitätsmedizin Berlin, Institute for Computational and Imaging Science in Cardiovascular Medicine, Berlin, Germany*

Abstract

Aims Although heart failure (HF) is a leading cause for hospitalization and mortality, normalized and comparable non-invasive assessment of haemodynamics and myocardial action remains limited. Moreover, myocardial deformation has not been compared between the guideline-defined HF entities. The distribution of affected and impaired segments within the contracting left ventricular (LV) myocardium have also not been compared. Therefore, we assessed myocardial function impairment by strain in patients with HF and control subjects by magnetic resonance imaging after clinically phenotyping these patients.

Methods and results This prospective study conducted at two centres in Germany between 2017 and 2018 enrolled stable outpatient subjects with HF [n = 56, including HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF)] and a control cohort (n = 12). Parameters assessed included measures for external myocardial function, for example, cardiac index and myocardial deformation measurements by cardiovascular magnetic resonance imaging, left ventricular global longitudinal strain (GLS), the global circumferential strain (GCS) and the regional distribution of segment deformation within the LV myocardium, as well as basic phenotypical characteristics. Comparison of the cardiac indices at rest showed no differences neither between the HF groups nor between the control group and HF patients (one-way ANOVA P = 0.70). The analysis of the strain data revealed differences between all groups in both LV GLS (One-way ANOVA: $P < 0.01$. Controls vs. HFpEF: −20.48 ± 1.62 vs. −19.27 ± 1.25. HFpEF vs. HFmrEF: −19.27 ± 1.25 vs. −15.72 ± 2.76. HFmrEF vs. HFrEF: −15.72 ± 2.76 vs. −11.51 ± 3.97.) and LV GCS (One-way ANOVA: $P < 0.01$. Controls vs. HFpEF: −19.74 ± 2.18 vs. −17.47 ± 2.10. HFpEF vs. HFmrEF: −17.47 ± 2.10 vs. −12.78 ± 3.47. HFrEF: −11.41 ± 3.27). Comparing the segment deformation distribution patterns highlighted the discriminating effect between the groups was much more prominent between the groups (one-way ANOVA $P < 0.01$) when compared by a score combining regional effects and a global view on the LV. Further analyses of the patterns among the segments affected showed that while the LVEF is preserved in HFpEF, the segments impaired in their contractility are located in the ventricular septum. The worse the LVEF is, the more segments are affected, but the septum remains an outstanding location with the most severe contractility impairment throughout the HF entities.

Conclusions While cardiac index at rest did not differ significantly between controls and stable HF patients suffering from HFrEF, HFmrEF, or HFpEF, the groups did differ significantly in LV GLS and LV GCS values. Regional strain analysis revealed that the LV septum is the location affected most, with reduced values already visible in HFpEF and further reductions in HFmrEF and HFrEF.

Keywords Heart failure; Myocardial deformation; CMR; Strain; Cardiac MRI

Received: 11 May 2020; Revised: 30 September 2020; Accepted: 21 December 2020
**Correspondence to: Sebastian Kelle, Department of Internal Medicine and Cardiology, German Heart Institute Berlin (DHZB), Augustenburger Platz 1, 13353 Berlin, Germany. Tel.: +49 30 4593 1182; Fax: +49 30 4593 2500. Email: kelle@dhzb.de*
†Hans-Dirk Duengen and Sebastian Kelle contributed equally to this paper

Introduction

While the causes for heart failure (HF) have been broadly explored and HF is becoming increasingly important due to demographic changes in the western world, mechanisms and haemodynamic have remained insufficiently understood.[1,2] Patients with HF include those with reduced left ventricular (LV) ejection fraction (LVEF, HFrEF), mid-range LVEF (HFmrEF) and preserved LVEF (HFpEF)—all with different degrees of systolic and diastolic alterations.[3] Phenotypically, patients with HFrEF, HFmrEF, and HFpEF suffer from a systemic disease with different comorbidities with great overlaps.[4,5] Classic approaches to categorize these phenotypes include functional classes of symptoms on exertion, for example, by the New York Heart Association (NYHA) classification, global cardiac function assessed by global systolic or diastolic parameters, for example, LVEF or E/e. While the discriminatory effect of LVEF among HF patients has been broadly criticized for decades, especially in distinguishing healthy hearts from HFpEF patients, increasing evidence challenged its meaning because it covers poorly actual cardiac action.[6–9] While echocardiographic parameters are extensively used in HF guidelines, they have significant detractions, especially in an era when HFpEF is becoming the dominant presentation.[10]

Measurements of cardiac contractility and the assessment of myocardial deformation by strain analyses are an emerging and promising tool to better characterize patients.[10]

Strain imaging provides the opportunity to render the spatial contractility parameters (longitudinal, circumferential, and radial strain) measurable at each voxel level over the cardiac cycle, as the LVEF is limited in discriminating HF patients and both global longitudinal and circumferential strain provide the chance to assess these subjects more accurately—especially by cardiovascular magnetic resonance imaging (CMR).[11] Since HFmrEF was just introduced in 2016 by the European Society of Cardiology (ESC) guidelines, assessment of strain imaging in HFmrEF patients has been very limited.

However, usually myocardial deformation is reported as a global value either for the longitudinal axis or the circumferential axis. Recent studies showed the relevance of both myocardial deformation per se and the distribution of its impairment—a comparison between the HF entities regarding their regional differences within the LV myocardium has not been performed. Combining the regional differences and a global view on the affected LV resulted in a summarizing score based on 37 segments of the LV, which has already been introduced.[12] The ratio of segments with preserved strain values to all 37 LV segments represents a number reflecting the share of the myocardium that provides a normal strain value of the LV with a global view—allowing for comparisons of how many segments are affected between the HF entities.

While HF entities per se have been characterized regarding strain values, there has not been a comparison of cardiac contractility with regard to the cardiac work or cardiac index.

The aim of this study is to assess the longitudinal and circumferential strain as well as the distribution of the myocardial deformation in an HF population including HFrEF, HFmrEF, and HFpEF patients as well as subjects without HF.

Methods

This study was a prospective study conducted at two centres in Berlin, Germany, the Charité—University Medicine Berlin and the German Heart Centre Berlin, between 2017 and 2018.

Briefly, subjects were screened for diagnosed HF NYHA functional Classes II and III and an age of at least 45 years. The initial diagnosis of HF should have been older than 30 days; the patients were required to be in a stable state with no changes in their HF medication and no HF hospitalization within the previous 7 days. HFrEF was defined as diagnosis of HF, increased N terminal pro brain natriuretic peptide (NT-proBNP) (>220 pg/mL) and LVEF <40%, HFmrEF as the diagnosis of HF, increased NT-proBNP (>220 pg/mL) and 40% ≥ LVEF < 50% as well as HFpEF as diagnosis of HF, increased NT-proBNP (>220 pg/mL) and LVEF ≥50% at the time of study inclusion. We did not distinguish between the causes for HF for recruiting patients.

Additionally, we recruited subjects without HF or major cardiovascular diseases as controls—for this analysis, we excluded those with cardiovascular risk factors, for example, coronary artery disease or diabetes.

All studies included complied with the Declaration of Helsinki, the protocols were approved by the responsible ethics committees, and all patients gave written informed consent. It was registered at the German Clinical Trials Register (DRKS, registration number: DRKS00015615). The detailed inclusion and exclusion criteria are listed on the webpage of the DRKS. Further analyses of this study have already been published.[13–16]

Cardiac magnetic resonance

All CMR images were acquired using 1.5 T (Achieva, Philips Healthcare, Best, The Netherlands) magnetic resonance imaging (MRI) scanners with a five-channel cardiac surface coil in a supine position. All study participants were scanned using identical comprehensive imaging protocol. The study protocol included initial scouts to determine cardiac imaging planes. Cine images were acquired using a retrospectively gated cine-CMR in cardiac short-axis, vertical long-axis, and horizontal long-axis orientations using a steady-state free precession sequence for volumetry as

previously described.[13] The calculation of the cardiac indices (CIs) is based on the volumetry of the ventricles. Fast strain-encoded (fast-SENC) MRI was used for strain evaluation, as it has been shown to enable quantification of longitudinal and circumferential strain in free breathing and with high reproducibility.[17] Images were blinded to strain analysis, cine, and volumetric measurements, respectively. We waived interobserver analyses based on an analysis that highlighted the robustness of fast-SENC analyses regarding intraoberserver and interobserver variabilities.[18]

Image analysis

All images were analysed offline using commercially available software (Medis Suite, version 3.1, Leiden, The Netherlands) in accordance to recent consensus document for quantification of LV function using CMR.[19] In the analysis were included 2Ch, 3Ch, and 4Ch cine images, and respectively, three preselected mid-ventricle slices from the LV short-axis stack. Image analysis was performed using the software Medis® Suite MR (Medis medical imaging systems, Leiden, The Netherlands, version 3.1) for volume measurements and the software MyoStrain (Myocardial Solutions, Inc., Morrisville, North Carolina, USA, version 5.0) for fast-SENC strain measurements.

Statistical analysis

Statistical analysis was carried out with GraphPad Prism software version 8.4.2 and R version 3.5.1 (2018-07-02) (R Foundation for Statistical Computing, Vienna, Austria).

Normality of variables was assessed by visual assessment of normality curves and the Shapiro–Wilk test. Comparison between groups for continuous variables was performed with a one-way ANOVA for normally distributed data. When a significant P value was obtained using one-way ANOVA, the group means were examined by the Holm–Bonferroni method. Values of $P < 0.05$ were considered statistically significant.

Results

Study population

There were 68 subjects analysed, including 56 HF patients (HFrEF: $n = 19$; HFmrEF: $n = 19$; HFpEF: $n = 18$) and 12 without HF. We considered the subjects without HF and cardiovascular risk factors as controls in our study. The baseline characteristics are shown in *Table 1*.

Haemodynamic differences

Figure 1C illustrates the cardiac indices of all four analysed groups, which illustrates that there is no difference in cardiac indices neither between controls and HF groups nor between the HF groups (one-way ANOVA: $P = 0.64$). In the same manner, the stroke volume indexed to the body surface area was not relevantly different between the groups—while the LVEF and the LV end-diastolic volume index were different among the groups, which underlines der reliability of our data (*Table 1*).

Strain analyses

While the majority of segments are impaired regarding the contractility measured in strain values in HFrEF patients, the majority is preserved in HFpEF patients (*Figure 2A,B*). Nonetheless, we see a significant difference in the global, averaged strain value between controls and HFpEF while most segments are intact (*Figure 2C*). Obviously, there are a restricted number of segments in HFpEF patients that are mostly affected to make the global value different. Further analyses showed that these segments are mainly located in the LV septum. The lower the LVEF is, the more segments are affected—this correlates with higher LV septum impairment.

Discussion

In this analysis, we compared for the first time the cardiac indices as well as myocardial deformation pattern changes measured by MRI at rest in a stable but symptomatic outpatient cohort suffering from HFrEF, HFmrEF, and HFpEF as well as a controls cohort without HF. While CI was not different among these groups at rest, strain values showed differences. This finding stayed in contrast to the clinically common perception that a lower LVEF is indicative of a lower cardiac output but was in line with the haemodynamic key rule that in HF, CI is impaired or only maintained at the expense of increased filling pressures.

We explain our findings by the fact that the HF patients investigated in our study were stable and showed symptoms only at exertion, reflected by the NYHA functional Classes II and III—therefore, showing no impairment of CI at rest.

Analysing strain values, we saw differences between the groups in both LV GLS and LV GCS. This finding is also in alignment with previous studies, which showed that both GLS and GCS are robust to LV volume changes, especially more robust compared with LVEF.[11,18,20] Latest works support the idea that myocardial shortening is a superior parameter for myocardial contraction and function.[21] Similar to our analysis, other studies have also shown that septal contraction is

Table 1 Baseline characteristics of the population analysed

		Controls *N* = 12 *n* (%) *mean ± SD*	HFpEF *N* = 19 *n* (%) *mean ± SD*	HFmrEF *N* = 19 *n* (%) *mean ± SD*	HFrEF *N* = 18 *n* (%) *mean ± SD*	*P* value
Female sex (%)		5 (41.7)	9 (47.4)	6 (31.6)	3 (16.7)	0.24
Age (years)		58.92 (6.84)	77.58 ± 8.11	67.00 ± 9.64	64.22 ± 10.09	<0.01
BMI (kg/m^2)		24.84 ± 3.48	27.32 ± 3.78	26.56 ± 4.16	28.83 ± 4.10	0.06
Blood pressure, systolic (mmHg)		130.5 ± 12.0	141.7 ± 17.4	131.1 ± 12.5	133.7 ± 17.41	0.14
Blood pressure, diastolic (mmHg)		75.00 ± 7.1	76.00 ± 14.62	77.16 ± 8.8	79.71 ± 13.7	0.72
Heart rate (bpm)		58.91 ± 7.3	64.94 ± 9.5	67.26 ± 7.3	67.24 ± 12.4	0.10
Presence of CAD (%)		0 (0.0)	12 (66.7)	15 (79.0)	13 (76.5)	<0.01 for HF only: *P* = 0.68
Hypertension (%)		4 (33.3)	14 (88.9)	15 (79.0)	16 (82.4)	<0.01 for HF only: *P* = 0.73
Diabetes mellitus (%)		0 (0)	5 (27.8)	3 (15.8)	5 (29.4)	0.1867 for HF only: *P* = 0.59
LVEF (%)		62.00 ± 5.34	61.42 ± 5.88	44.84 ± 2.93	32.89 ± 4.71	<0.01 for HF only: <0.01
LVEDVi (mL/m^2)		80.75 ± 12.00	69.50 ± 15.02	93.63 ± 15.29	130.70 ± 24.74	<0.01 for HF only: <0.01
SVi (mL/m^2)		49.75 ± 5.79	43.79 ± 9.81	41.74 ± 5.75	42.56 ± 7.28	0.03 for HF only: *P* = 0.72
Cardiac output (L/min)		5.73 ± 0.66	5.14 ± 1.40	5.37 ± 1.01	5.70 ± 1.26	0.42
Cardiac index (L/min/m^2)		2.96 ± 0.39	2.71 ± 0.58	2.79 ± 0.42	2.83 ± 0.56	0.64
Septal wall thickness		8.7 ± 1.2	11.0 ± 2.2	11.8 ± 2.0	11.8 ± 2.7	<0.01 for HF only: *P* = 0.51
NYHA class	II	—	9 (50)	16 (84.2)	12 (70.6)	0.08
	III	—	8 (44.4)	3 (15.8)	5 (29.4)	0.17
MLHFQ		5.3 ± 6.2	31.0 ± 23.1	27.4 ± 22.5	28.5 ± 24.9	<0.01 for HF only: *P* = 0.90
6MWT (m)		547.8 ± 130.0	344.4 ± 118.3	415.5 ± 85.2	413.5 ± 125.4	<0.01 for HF only: *P* = 0.12
Concomitant medication						
Beta-blocker (%)		4 (33.3)	11 (57.9)	14 (73.7)	17 (94.4)	<0.01
ACEi (%)		1 (8.3)	4 (21.1)	7 (36.8)	9 (52.9)	0.0481
MRA (%)		0 (0.0)	3 (15.8)	4 (21.1)	11 (64.7)	<0.01
ARNI (%)		0 (0.0)	0 (0)	0 (0)	5 (27.8)	<0.01
Loop diuretic (%)		0 (0.0)	4 (21.1)	7 (36.8)	6 (35.3)	<0.01 for HF only: *P* = 0.53
Thiazide diuretic (%)		1 (8.3)	4 (21.1)	2 (10.5)	1 (0.1)	0.51
Blood testing						
Haemoglobin (g/dL)		14.22 ± 0.94	13.0 ± 1.3	13.7 ± 1.1	15.0 ± 1.1	<0.01
Haematocrit		0.41 ± 0.03	0.38 ± 0.03	0.40 ± 0.03	0.44 ± 0.04	<0.01
eGFR (mL/min/1.73 m^2)		81.08 ± 10.43	69.89 ± 15.13	71.21 ± 17.92	71.76 ± 20.58	0.31
NT-proBNP (ng/L)		68.92 ± 28.14	554.2 ± 609.3	790.2 ± 1,138	2,247 ± 3,447	0.01 for HF only: *P* = 0.04
Troponin T hs (ng/L)		6.83 ± 3.66	19.56 ± 17.72	19.22 ± 19.52	18.38 ± 11.98	0.11

ACEi, ACE/angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BSA, body surface area using the Mosteller method; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate using the CKD-EPI formula; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end diastolic volume indexed to BSA; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptors antagonist; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA class, New York Heart Association Functional Classification; SVi, LV stroke volume indexed to BSA; 6MWT, 6 min walk test.
Absolute (relative) numbers.

Figure 1 Synopsis of LVEF, SVi, and cardiac index in all four groups. (A) LVEF in all subject groups. All marked differences are statistically significant in percentage (mean ± SD): *controls vs. HFmrEF: 62.00 ± 5.34 vs. 44.84 ± 2.93, $P < 0.01$; ***HFpEF vs. HFmrEF 61.42 ± 5.88 vs. 44.84 ± 2.93, $P < 0.01$; ****HFpEF vs. HFrEF: 61.42 ± 5.88 vs. 32.89 ± 4.71, $P < 0.01$. (B) Stroke volume indexed to body surface area in all subject groups. Marked difference is significant in B in millilitre per square meter (mL/m^2): *controls vs. HFmrEF: 49.75 ± 5.79 vs. 41.74 ± 5.75, $P = 0.031$. Other descriptive values in millilitre per square meter (mL/m^2) (mean ± SD): HFpEF: 43.79 ± 9.81; HFrEF: 42.56 ± 7.28. (C) Cardiac index in all subject groups. Other descriptive values in L/min/m^2 (mean ± SD): controls: 2.96 ± 0.39; HFpEF: 2.71 ± 0.58; HFmrEF: 2.79 ± 0.42; HFrEF: 2.83 ± 0.56. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; SVi, left ventricular stroke volume indexed to body surface area.

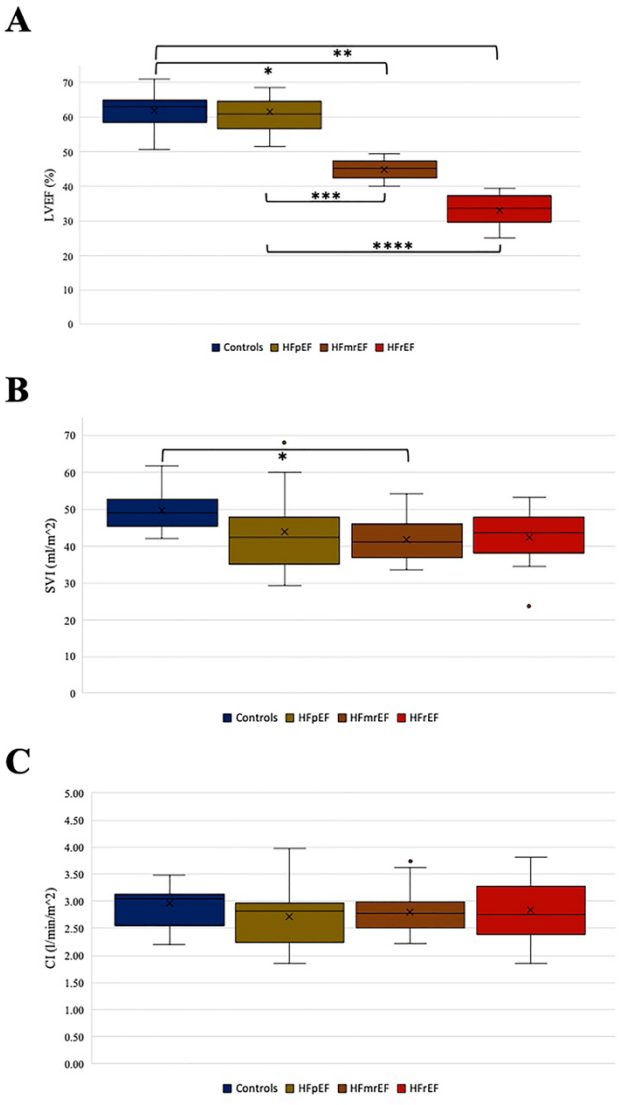
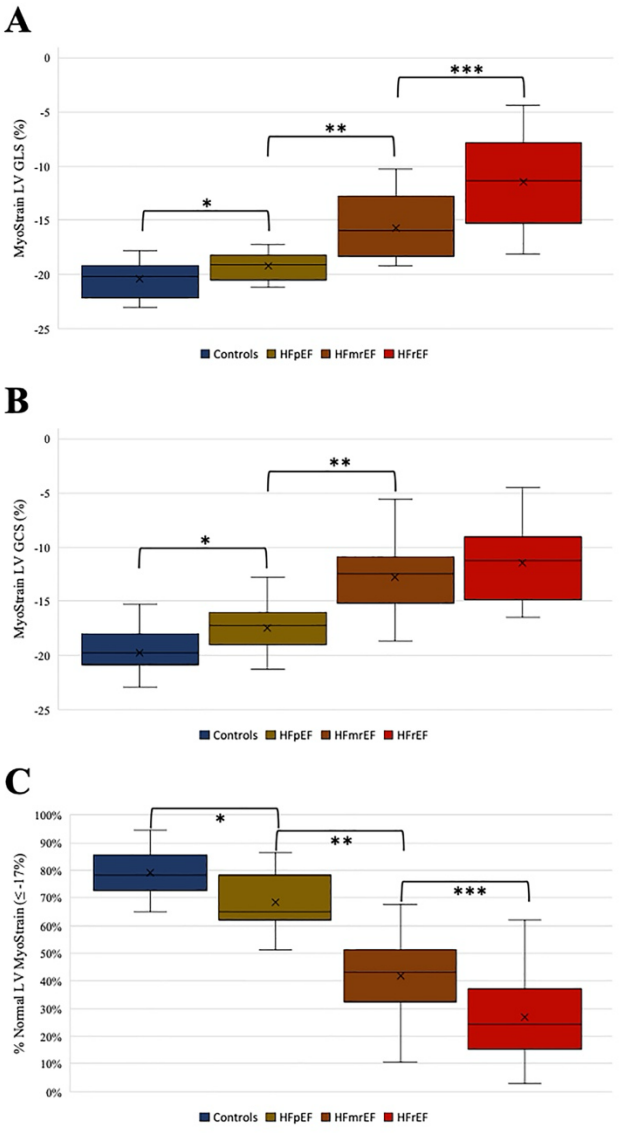


Figure 2 Synopsis of LV GLS, LV GCS and fraction of preserved strain in all subject groups. (A) LV GLS in all subject groups. All marked differences are statistically significant: *controls vs. HFpEF: −20.48 ± 1.62 vs. −19.27 ± 1.25, $P = 0.041$. **HFpEF vs. HFmrEF: −19.27 ± 1.25 vs. −15.72 ± 2.76, $P < 0.01$. ***HFmrEF vs. HFrEF: −15.72 ± 2.76 vs. −11.51 ± 3.97, $P < 0.01$. (B) LV GCS in all subject groups. All marked differences are statistically significant in B: *controls vs. HFpEF: −19.74 ± 2.18 vs. −17.47 ± 2.10, $P = 0.017$. **: HFpEF vs. HFmrEF: −17.47 ± 2.10 vs. −12.78 ± 3.47, $P < 0.01$. Other descriptive values (mean ± SD): HFrEF: −11.41 ± 3.27. (C) Fraction of preserved strain in all subject groups. All marked differences are statistically significant in C in percentage: *controls vs. HFpEF: 79.00 ± 8.50 vs. 68.11 ± 9.54, $P < 0.01$. **HFpEF vs. HFmrEF: 68.11 ± 9.54 vs. 42.16 ± 14.89, $P < 0.01$. ***HFmrEF vs. HFrEF: 42.16 ± 14.89 vs. 26.72 ± 15.72, $P < 0.01$. GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricular; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.



primarily impaired—even though in different cardiac diseases leading to HF. Changes of myocardial contraction in HF of different origins require further investigation (*Figures 3* and *4*).[22]

The relationship between LV GCS and LV GLS regarding additional value needs to be further evaluated, especially because there are myocardial compensation mechanisms reported, which showed increase of the one when the other is impaired—which are in contrast to our results, possibly due to different techniques, fast-SENC on the one hand, and tissue tracking on the other.[11]

The prognostic value of GLS was initially limited, but recent studies showed a significant added value in prognosis with improved techniques, mainly in HFrEF patients—the prognostic aspect of the GCS value has not been conclusively evaluated.[23]

Our calculations are limited by the moderate number of LVEF values at the extremes and the stable outpatient state of the HF patients (NYHA Classes II and III). An analysis including patients with NYHA Class IV might provide a more elaborate approach to these questions, but it is more challenging to perform a diagnostic CMR in those patients due to their supine position at the time of the exam. Alternatively, a physical stress method at which the patients report symptoms could be added to the protocol to assess the point of time of discomfort—this is not yet an established part of routine MRI diagnostic protocols. Additionally, the optimal stressor is not yet defined. The results of our study are in line and supportive with the recent ESC Heart Failure Association (HFA) position statement for shifting paradigms in the assessment of cardiac function.[24] In particular, going away from ejection fraction to myocardial strain evaluation and also from rest to stress assessment of LV function is accompanied by the latest expert panel statement of the HFA regarding HF classification.[7] Correspondingly, the newest ESC HFA diagnostic work-up recommendation for HFpEF highlights the relevance of stress imaging to unmask impaired cardiac function in HF.[25] We consider our results as a key component in changing the understanding of HF dynamics challenging the current HF classification. In summary, we have to state that the current HF classification of HF patients into LVEF-based entities is only of relevance in HFrEF patients from a treatment point of view. HFrEF is the only entity with an evidence-based treatment while chronic HFmrEF and HFpEF still lack tailored therapy.[3] Better characterization of the myocardial action impairment provides both a better pathomechanistic understanding of the underlying disease and better parameters for patient phenotyping as well as trial endpoints.

Figure 3 Regional disparity of myocardial contraction preserved in all four groups. Ratio of segments with both LV GLS and LV GCS in the reference range, that is, ≤ − 17% divided by the amount of LV segments in every patient (n = 37). (A) Septal segments strain in all subject groups. All marked differences are statistically significant: *controls vs. HFpEF: −19.63 ± 1.95 vs. −16.61 ± 2.57, $P < 0.01$. **HFpEF vs. HFmrEF: −16.61 ± 2.57 vs. 13.69 ± 4.91, $P = 0.013$. ***HFmrEF vs. HFrEF: 13.69 ± 4.91 vs. −9.04 ± 5.27, $P < 0.01$. (B) Anterior segments strain in all subject groups. All marked differences are statistically significant: *controls vs. HFpEF: −19.73 ± 1.77 vs. −18.25 ± 1.83, $P = 0.017$. **HFpEF vs. HFmrEF: −18.25 ± 1.83 vs. −13.54 ± 4.20, $P < 0.01$. ***HFmrEF vs. HFrEF: −13.54 ± 4.20 vs. −9.22 ± 4.41, $P < 0.01$. (C) Inferior segments strain in all subject groups. All marked differences are statistically significant: **HFpEF vs. HFmrEF: −20.64 ± 2.87 vs. −15.29 ± 3.19, $P < 0.01$. Other descriptive values: controls: −21.81 ± 2.06. HFrEF: −12.97 ± 4.22. (D) Lateral segments strain in all subject groups. All marked differences are statistically significant: **HFpEF vs. HFmrEF: −20.69 ± 2.49 vs. −14.47 ± 3.38, $P < 0.01$. Other descriptive values: controls: −20.82 ± 1.84. HFrEF: −13.81 ± 3.18. GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricular; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

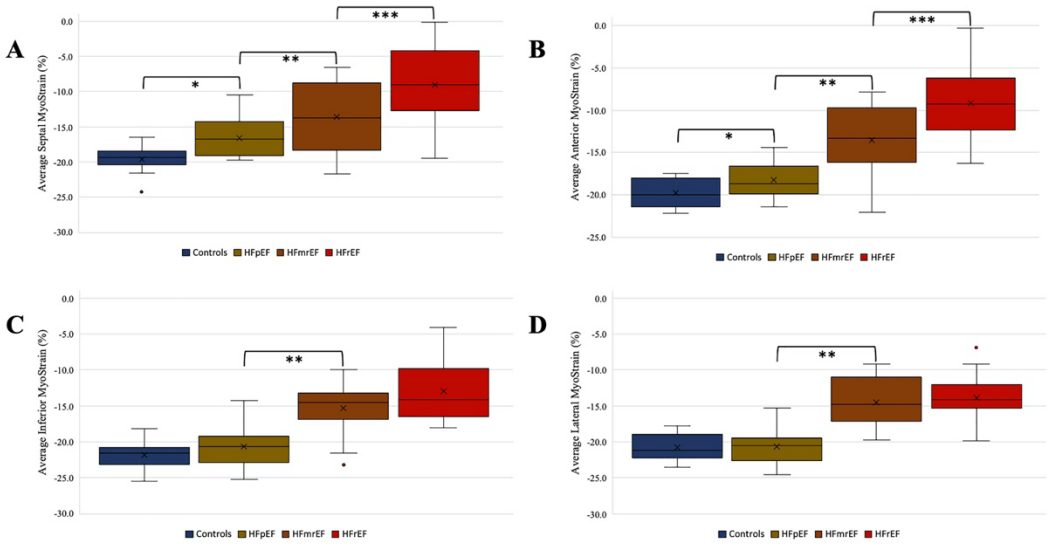
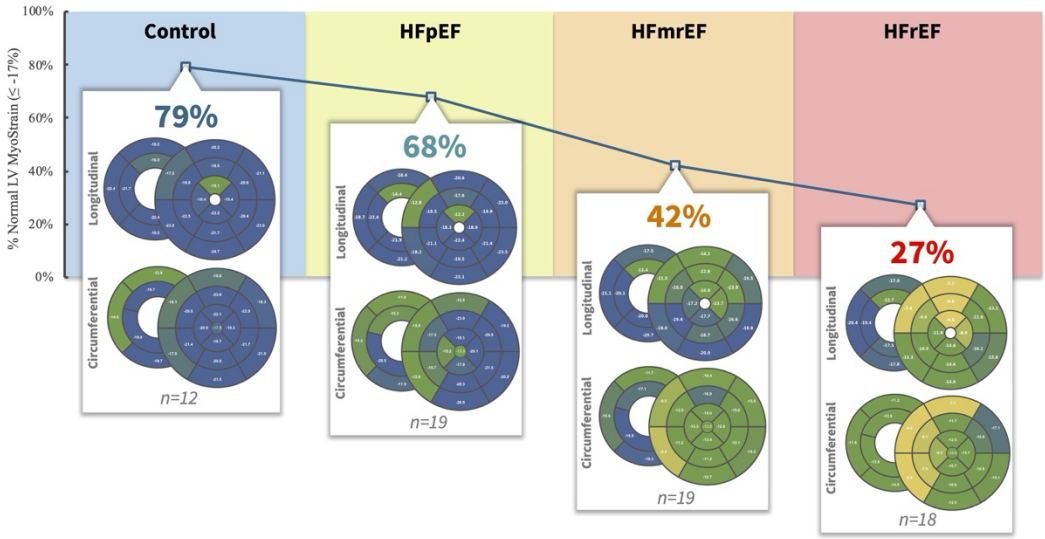


Figure 4 Distribution of regional strain impairment in all four groups. LV, left ventricular; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



Limitations

This study was performed at two centres cooperating, one focusing on MRI acquisition and analysis and the other with the remainder of the comprehensive study. The MRI centre used the same scanner for all subjects providing a high level of comparability.

Examinations in an magnetic resonance scanner may cause psychological stress due to the confined space and examination in a hospital setting. We cannot rule out that in some patients, this might have resulted in potentially slightly higher CI values compared with the CI at complete rest at home.

While including more patients than previous studies evaluating the discriminatory effect of strain values across HF groups and a control cohort, our sample size was still small.

We had to exclude patients with implanted ICDs and pacemakers due to MRI contraindications. This limits the generalizability of our study to the general HF population, especially in patients with HFrEF. However, our findings should primarily be considered hypothesis generating.

Conclusions

While cardiac index at rest did not differ significantly between controls and stable HF patients suffering from HFrEF, HFmrEF, or HFpEF, the groups did differ significantly in LV GLS and LV GCS values. Regional strain analysis revealed that the LV septum is the location affected most, with reduced values already visible in HFpEF and further reductions in HFmrEF and HFrEF.

Acknowledgements

We like to express our sincere thanks to all the patients and volunteers who agreed to participate in our study. Likewise, we appreciate the support by the team maintaining the study, especially the image acquisition.

Conflict of interest

S. K. reports grants and other support by the DZHK (German Center for Cardiovascular Research), Partner Site Berlin, Philips Healthcare, BioVentrix, Berlin-Chemie, Merck/Bayer, Novartis, Astra Zeneca, Siemens, and Myocardial Solutions outside of the submitted work. S. K. is also on the advisory board for Merck/Bayer, BioVentrix, and Myocardial Solutions. B. P. has provided steering committee and advisory board services for Bayer Healthcare and MSD and has received steering committee and advisory board/speaker honoraria from Novartis. P. D. is a shareholder of Siemens and Bayer. All other authors declare that they have no relationships relevant to the contents of this paper to disclose.

Funding

This work was supported by the German Centre for Cardiovascular Research (DZHK), funded by the German Federal Ministry of Education and Research, and the Charité—Universitätsmedizin Berlin, Germany, as well as the German Heart Institute Berlin, Germany, Myocardial Solutions, and Novartis.

References

1. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN, African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351**: 2049–2057.
2. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, Witteman JCM, Stricker BHC. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure—the Rotterdam Study. *Eur Heart J* 2004; **25**: 1614–1619.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail* 2016; **18**: 891–975.
4. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1624–1634.
5. Rastogi A, Novak E, Platts AE, Mann DL. Epidemiology, pathophysiology and clinical outcomes for heart failure patients with a mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1597–1605.
6. Katsi V, Georgiopoulos G, Laina A, Koutli E, Parissis J, Tsioufis C, Nihoyannopoulos P, Tousoulis D. Left ventricular ejection fraction as therapeutic target: is it the ideal marker? *Heart Fail Rev* 2017; **22**: 641–655.
7. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, Backs J, Bauersachs J, Burkhoff D, Bonow RO, Chopra VK, de Boer RA, de Windt L, Hamdani N, Hasenfuss G, Heymans S, Hulot J-S, Konstam M, Lee RT, Linke WA, Lunde IG, Lyon AR, Maack C, Mann DL, Mebazaa A, Mentz RJ, Nihoyannopoulos P, Papp Z, Parissis J, Pedrazzini T, Rosano G, Rouleau J, Seferovic PM, Shah AM, Starling RC, Tocchetti CG, Trochu JN, Thum T, Zannad F, Brutsaert DL, Segers VF, de Keulenaer GW. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J* 2019; **40**: 2155–2163.
8. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J* 2016; **37**: 1642–1650.
9. Roul G, Moulichon ME, Bareiss P, Gries P, Koegler A, Sacrez J, Germain P, Mossard JM, Sacrez A. Prognostic factors of chronic heart failure in NYHA class II or III: value of invasive exercise haemodynamic data. *Eur Heart J* 1995; **16**: 1387–1398.
10. Marwick TH, Shah SJ, Thomas JD. Myocardial strain in the assessment of patients with heart failure: a review. *JAMA Cardiol* 2019; **4**: 287–294.
11. Pedrizzetti G, Lapinskas T, Tonti G, Stoiber L, Zaliunas R, Gebker R, Pieske B, Kelle S. The relationship between ef and strain permits a more accurate assessment of LV systolic function. *JACC Cardiovasc Imag* American College of Cardiology Foundation 2019; **12**: 1893–1895.
12. Steen H, Montenbruck M, Gerzak B, Schwarz AK, Kelle S, Giusca S, Korosoglou G, Dent S, Lenihan D. Cardiotoxicity during cancer treatment causes more regional than global dysfunction: the Prefect Study. *J Am Coll Cardiol* 2020; **75**: 1824.
13. Doeblin P, Hashemi D, Tanacli R, Lapinskas T, Gebker R, Stehning C, Motzkus LA, Blum M, Tahirovic E, Dordevic A, Kraft R, Zamani SM, Pieske B, Edelmann F, Düngen H-D, Kelle S. CMR tissue characterization in patients with HFmrEF. *J Clin Med MDPI AG* 2019; **8**.
14. Tanacli R, Hashemi D, Lapinskas T, Edelmann F, Gebker R, Pedrizzetti G, Schuster A, Nagel E, Pieske B, Düngen HD, Kelle S. Range variability in CMR feature tracking multilayer strain across different stages of heart failure. *Sci Rep Nature Publishing Group* 2019; **9**.
15. Tanacli R, Hashemi D, Neye M, Motzkus LA, Blum M, Tahirovic E, Dordevic A, Kraft R, Zamani SM, Pieske B, Düngen H-D, Kelle S. Multilayer myocardial strain improves the diagnosis of heart failure with preserved ejection fraction. *ESC Hear Fail* 2020.
16. Blum M, Hashemi D, Motzkus LA, Neye M, Dordevic A, Zieschang V, Zamani SM, Lapinskas T, Runte K, Kelm M, Kühne T, Tahirovic E, Edelmann F, Pieske B, Düngen H-D, Kelle S. Variability of myocardial strain during isometric exercise in subjects with and without heart failure. *Front Cardiovasc Med* 2020; **7**: 111.
17. Lapinskas T, Zieschang V, Erley J, Stoiber L, Schnackenburg B, Stehning C, Gebker R, Patel AR, Kawaji K, Steen H, Zaliunas R, Backhaus SJ, Schuster A, Makowski M, Giusca S, Korosoglou G, Pieske B, Kelle S. Strain-encoded cardiac magnetic resonance imaging: a new approach for fast estimation of left ventricular function. *BMC Cardiovasc Disord* 2019; **19**: 52.
18. Bucius P, Erley J, Tanacli R, Zieschang V, Giusca S, Korosoglou G, Steen H, Stehning C, Pieske B, Pieske-Kraigher E, Schuster A, Lapinskas T, Kelle S. Comparison of feature tracking, fast-SENC, and myocardial tagging for global and segmental left ventricular strain. *ESC Hear Fail* 2020; **7**: 523–532.
19. Suinesiaputra A, Bluemke DA, Cowan BR, Friedrich MG, Kramer CM, Kwong R, Plein S, Schulz-Menger J, Westenberg JJM, Young AA, Nagel E. Quantification of LV function and mass by cardiovascular magnetic resonance: multi-center variability and consensus contours. *J Cardiovasc Magn Reson* 2015; **17**: 63.
20. Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, Edvardsen T, Remme EW. Geometry as a confounder when assessing ventricular systolic function: comparison between ejection fraction and strain. *J Am Coll Cardiol* 2017; **70**: 942–954.
21. Maurer MS, Packer M. How should physicians assess myocardial contraction?: redefining heart failure with a preserved ejection fraction. *JACC Cardiovasc Imaging* Elsevier 2020; **13**: 873–878.
22. Tops LF, Delgado V, Marsan NA, Bax JJ. Myocardial strain to detect subtle left ventricular systolic dysfunction. *Eur J Heart Fail* m 2017; **19**: 307–313.
23. Chimura M, Onishi T, Tsukishiro Y, Sawada T, Kiuchi K, Shimane A, Okajima K, Yamada S, Taniguchi Y, Yasaka Y, Kawai H. Longitudinal strain combined with delayed-enhancement magnetic resonance improves risk stratification in patients with dilated cardiomyopathy. *Heart* 2017; **103**: 679–686.
24. Čelutkienė J, Plymen CM, Flachskampf FA, de Boer RA, Grapsa J, Manka R, Anderson L, Garbi M, Barberis V, Filardi PP, Gargiulo P, Zamorano JL, Lainscak M, Seferovic P, Ruschitzka F, Rosano GMC, Nihoyannopoulos P. Innovative imaging methods in heart failure: a shifting paradigm in cardiac assessment. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018; **20**: 1615–1633.
25. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSPP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* Oxford University Press 2019; i: 1–21.

4.4. Risikostratifizierung zur Früherkennung von HFpEF

In der vorangegangenen Arbeit wurde gezeigt, dass eine kleinere LVEF (linksventrikuläre Ejektionsfraktion) mit einer geringeren Anzahl von Segmenten mit erhaltener myokardialer Deformation einhergeht. Zudem treten Veränderungen bei reduzierter LVEF häufiger als Segmente mit reduziertem regionalem Strain im septalen Bereich auf.[78]

Es ist jedoch zu beachten, dass Risikofaktoren, die mit HFpEF (Herzinsuffizienz mit erhaltener Ejektionsfraktion) assoziiert sind, hauptsächlich auf weit verbreitete Erkrankungen wie arterielle Hypertonie und Diabetes mellitus zurückzuführen sind.[1] Daher liegt der Fokus auf der Identifikation von Personen, die diese Risikofaktoren aufweisen und bereits kardiale Veränderungen zeigen, ohne an einer Herzinsuffizienz zu leiden.

Die asymptomatische Kontrollgruppe ohne Herzinsuffizienz weist normale systolische LV-Funktionswerte auf. In der folgenden Studie wird die zuvor beschriebene Methode der regionalen Verteilung der myokardialen Deformation untersucht, um festzustellen, ob sie als Instrument zur Identifizierung von Patient*innen mit myokardialen Veränderungen in der Gruppe der Gesunden geeignet ist.

Der nachfolgende Text entspricht dem Abstrakt dieser Arbeit[79]:

Hashemi D, Doeblin P, Blum M, Weiss KJ, Schneider M, Korosoglou G, Beyer RE, Pieske B, Edelmann F, Kelle S. CMR detects decreased myocardial deformation in asymptomatic patients at risk for heart failure. Front Cardiovasc Med. 2023 Jan 5;9:1091768. doi: 10.3389/fcvm.2022.1091768. PMID: 36684590.

*"**Aims:** The main management strategy of heart failure with preserved ejection fraction (HFpEF) is prevention since HFpEF is associated with many cardiovascular (CV) risk factors, especially since HFpEF is linked to a high risk for both mortality and recurrent heart failure (HF) hospitalizations. Therefore, there is a need for new tools to identify patients with a high risk profile early. Regional strain assessment by CMR seems to be superior in describing*

deformation impairment in HF. The MyoHealth score is a promising tool to identify cardiac changes early.

Methods and results: *Heart failure patients irrespective of LVEF and asymptomatic controls were recruited, and CMR based measures were obtained. For this analysis the asymptomatic control group (n = 19) was divided into asymptomatic subjects without CV co-morbidities or evidence of cardiac abnormalities and (n = 12) and asymptomatic subjects with CV co-morbidities or evidence of cardiac abnormalities (n = 7) as well as patients with HFpEF (n = 19). We performed CMR scans at rest and during a stress test using isometric handgrip exercise (HG). Assessing the MyoHealth score at rest revealed preserved regional strain in 85 ± 9% of LV segments in controls, 73 ± 11% in at Risk subjects and 73 ± 8% in HFpEF patients. During stress the MyoHealth score was 84 ± 7% in controls, 83 ± 7 in at risk subjects and 74 ± 11 in HFpEF patients.*

Conclusion: *In summary, we show for the first time that asymptomatic subjects with increased CV risk present with HFpEF like impaired myocardial deformation at rest, while they show results like controls under HG stress. The potential of preventive treatment in this group of patients merits further investigation in future."*[79]

frontiers | Frontiers in Cardiovascular Medicine

TYPE Brief Research Report
PUBLISHED 05 January 2023
DOI 10.3389/fcvm.2022.1091768

OPEN ACCESS

EDITED BY
Mark J. Schuuring,
University Medical Center Utrecht,
Netherlands

REVIEWED BY
Moritz Hundertmark,
University of Oxford, United Kingdom
Farbod Sedaghat,
University Hospital Heidelberg,
Germany

*CORRESPONDENCE
Djawid Hashemi
djawid.hashemi@charite.de

SPECIALTY SECTION
This article was submitted to
Cardiovascular Imaging,
a section of the journal
Frontiers in Cardiovascular Medicine

RECEIVED 07 November 2022
ACCEPTED 09 December 2022
PUBLISHED 05 January 2023

CITATION
Hashemi D, Doeblin P, Blum M, Weiss KJ, Schneider M, Korosoglou G, Beyer RE, Pieske B, Edelmann F and Kelle S (2023) CMR detects decreased myocardial deformation in asymptomatic patients at risk for heart failure.
Front. Cardiovasc. Med. 9:1091768.
doi: 10.3389/fcvm.2022.1091768

CMR detects decreased myocardial deformation in asymptomatic patients at risk for heart failure

Djawid Hashemi[1,2,3,4]*, Patrick Doeblin[2,3], Moritz Blum[5], Karl Jakob Weiss[2,3], Matthias Schneider[1,2], Grigorios Korosoglou[6,7], Rebecca Elisabeth Beyer[1,2,3], Burkert Pieske[1,2,3], Frank Edelmann[1,3] and Sebastian Kelle[1,2,3]

[1]Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Charité Campus Virchow Clinic, Berlin, Germany, [2]Department of Internal Medicine and Cardiology, German Heart Institute Berlin (DHZB), Berlin, Germany, [3]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany, [4]BIH Charité Digital Clinician Scientist Program, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, Berlin, Germany, [5]Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [6]Department of Cardiology, Vascular Medicine and Pneumology, Gesundheitszentrum Rhein-Neckar Hospital Weinheim, Weinheim, Germany, [7]Cardiac Imaging Center Weinheim, Hector Foundation, Weinheim, Germany

Aims: The main management strategy of heart failure with preserved ejection fraction (HFpEF) is prevention since HFpEF is associated with many cardiovascular (CV) risk factors, especially since HFpEF is linked to a high risk for both mortality and recurrent heart failure (HF) hospitalizations. Therefore, there is a need for new tools to identify patients with a high risk profile early. Regional strain assessment by CMR seems to be superior in describing deformation impairment in HF. The MyoHealth score is a promising tool to identify cardiac changes early.

Methods and results: Heart failure patients irrespective of LVEF and asymptomatic controls were recruited, and CMR based measures were obtained. For this analysis the asymptomatic control group (n = 19) was divided into asymptomatic subjects without CV co-morbidities or evidence of cardiac abnormalities and (n = 12) and asymptomatic subjects with CV co-morbidities or evidence of cardiac abnormalities (n = 7) as well as patients with HFpEF (n = 19). We performed CMR scans at rest and during a stress test using isometric handgrip exercise (HG). Assessing the MyoHealth score at rest revealed preserved regional strain in 85 ± 9% of LV segments in controls, 73 ± 11% in at Risk subjects and 73 ± 8% in HFpEF patients. During stress the MyoHealth score was 84 ± 7% in controls, 83 ± 7 in at risk subjects and 74 ± 11 in HFpEF patients.

Conclusion: In summary, we show for the first time that asymptomatic subjects with increased CV risk present with HFpEF like impaired myocardial deformation at rest, while they show results like controls under HG stress. The potential of preventive treatment in this group of patients merits further investigation in future.

Clinical trial registration: [https://drks.de/search/de/trial/DRKS00015615], identifier [DRKS00015615].

KEYWORDS

heart failure, cardiovascular magnetic resonance imaging, myocardial deformation, strain, handgrip exercise, risk, asymptomatic

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is defined as symptomatic heart failure (HF), a left ventricular ejection fraction (LVEF) $\geq$ 50% and evidence of diastolic dysfunction and/or raised LV filling pressures (1). HFpEF is associated with a variety of cardiovascular (CV) risk factors and a high risk for both mortality and recurrent HF hospitalization (2, 3).

With very limited and only recently introduced treatment options, prevention including the early identification of vulnerable patients with CV risk factors, remains the focus of HFpEF management (4, 5). This challenge is intensified by the increasing prevalence of HFpEF, triggered by the lower mortality of cardiovascular risk factors, e.g., diabetes or arterial hypertension (6, 7). Hence, the Universal Definition and Classification of HF considers myocardial changes in still asymptomatic patients already as Stage A and B of HF and encourages earlier action to prevent a transition in clinical apparent HF (8).

Once, HFpEF is suspected, the introduced algorithm to diagnose HFpEF is a comprehensive approach requiring multiple steps (2). The more pronounced the characteristic details of HFpEF are, the worse is the patients' prognosis (3). It has been shown that patients at risk for HFpEF have already an increased mortality and risk for HF hospitalization (3). The scarcity of resources forces health care providers to identify patients at risk to optimize their therapy continuously.

Hence, there is an urgent need to screen for patients at risk in clinical routine to prevent HFpEF.

Cardiovascular magnetic resonance imaging (CMR) provides anatomical and functional cardiac parameters. Myocardial strain analysis may detect impaired myocardial contractility in patients despite a preserved LVEF (9). Regional strain assessment seems to be superior to global strain analysis in describing deformation impairment in HF (10). The MyoHealth score reflects the share of LV segments with preserved strain values ($\leq -17\%$) in a 37 segment model (10).

We hypothesize that asymptomatic healthy subjects with CV co-morbidities may demonstrate detectable impairments in regional strain compatible with pre-clinical HFpEF.

2. Method

This study was a prospective study conducted in Berlin, Germany, approved by the local Ethics Committee (registration: EA4/112/16; German Clinical Trials Registry, DRKS, DRKS00015615). Its rationale and design have been described previously (10–13).

Briefly, HF patients irrespective of LVEF and controls without HF were recruited, and CMR based measures of cardiac structure and function, including assessment of cardiac contractility were obtained. For this analysis, we included the control subjects and the HFpEF patients.

We divided the control group into (a) subjects without HF and no CV co-morbidities or evidence of cardiac dysfunction and (b) those without HF but CV co-morbidities or evidence of cardiac dysfunction. CV co-morbidities or evidence of cardiac dysfunction were defined as the presence of diabetes, suboptimal managed arterial hypertension (hypertensive values at rest despite medication), increased NT-proBNP levels (>120 pg/dL), or LV hypertrophy (LV wall thickness > 11 mm) on CMR (minimum 1 criterion). They were compared to (c) patients with HFpEF (10). We performed CMR scans at rest and during a non-invasive, medication-free stress test. For stress testing we used isometric handgrip exercise (HG), which was effective and changed both blood pressure and heart rate significantly (11). All patients were in sinus rhythm, *nota bene* patients with atrial fibrillation were excluded to maintain better CMR image quality.

All CMR images were acquired using 1.5 T, fast strain-encoded MRI was used for strain evaluation. Volume measurements were performed with Medis® Suite MR (Medis medical imaging systems, Leiden, The Netherlands, version

TABLE 1 Baseline characteristics.

Parameters	Controls (n = 12)	At risk (n = 7)	HFpEF (n = 19)	P-value
Age – median [IQR], years	59.00 [54.75–65.00]	67.00 [62.00–72.00]	78.00 [75.00–82.00]	<0.01*
Female sex – no. (%)	6 (50.00)	4 (57.14)	9 (47.37)	0.914
LVEF – median [IQR], %	63.00 [59.22–64.70]	61.52 [57.88–64.58]	61.12 [58.17–64.17]	0.888
LA area – median [IQR], cm^2	20.00 [16.50–22.75]	21.00 [19.00–21.00]	22.50 [16.75–25.00]	0.73
NT-proBNP – median [IQR]), pg/dL	66.00 [50.50–88.00]	114.00 [58.50–175.50]	314.00 [266.00–617.00]	<0.01*
hs-TroponinT – median [IQR], (ng/l)	6.00 [4.00–7.50]	8.00 [5.5–10.00]	13.50 [9.00–20.00]	0.02*
eGFR – median [IQR]), mL/min/1.73 m^2	86.00 [71.50–90.00]	82.00 [72.50–85.50]	74.00 [60.25–82.75]	0.06
Coronary artery disease – no. (%)	0 (0)	0 (0)	12 (66.67)	<0.01*
Arterial hypertension [n (%)]	4 (33.33)	3 (42.86)	17 (89.47)	<0.01*
Diabetes – no. (%)	0 (0)	3.00 (42.86)	7.00 (36.84)	0.04*
Dyslipidemia – no. (%)	2.00 (16.67)	2.00 (28.57)	12 (66.67)	0.02*

eGFR, estimated glomerular filtration rate; IQR, interquartile range (first quartile – third quartile); LV, left ventricular; LVEF, left ventricular ejection fraction; N, number. *Statistically significant. Further details on the baseline characteristics described by Blum et al. (11).

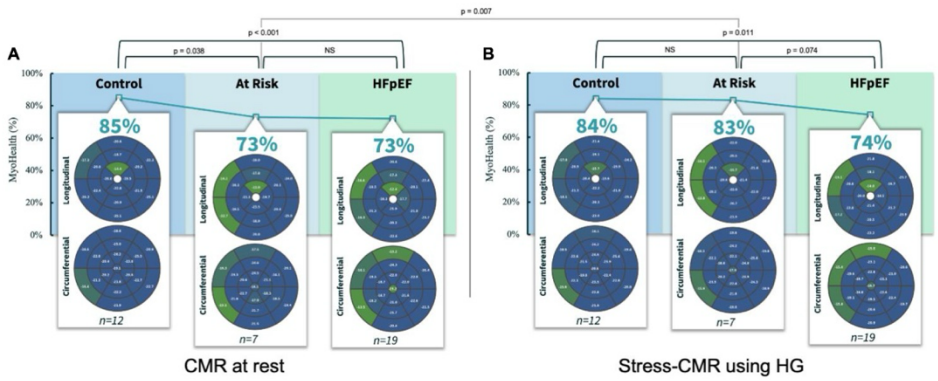


FIGURE 1
MyoHealth score at rest **(A)** and under stress **(B)** in healthy controls, controls with CV risk factors and HFpEF patients. CMR, cardiovascular magnetic resonance imaging; HG, handgrip exercise; NS, statistically not significant. Preserved regional strain values are blue, altered regional strain values are green. Color code reflects that early affected regions are primarily septal segments. In the at risk group the altered septal segments improve during HG stress, reflected by a color change from green to blue.

TABLE 2 Comparison of the MyoHealth results.

	MyoHealth values at rest	MyoHealth values during HG stress	P-value, student's t-test
Controls –%, median [IQR]	86.49 [82.77–89.19]	86.49 [78.14–87.51]	0.71
At risk –%, median [IQR]	73.33 [69.82–78.38]	83.33 [79.50–87.08]	0.01
HFpEF –%, median [IQR]	72.97 [68.92–78.38]	72.97 [70.27–78.38]	1.00
P-value, one-way ANOVA	<0.01	<0.01	

ANOVA, analysis of variance; HG, handgrip exercise; IQR, interquartile range.

3.1), strain analysis by MyoStrain (Myocardial Solutions, Inc., Morrisville, North Carolina, USA, version 5.2) (10, 11).

Pairwise comparisons were conducted using a student's t-test, comparisons across three groups were conducted using one-way analysis of variance (one-way ANOVA). A P-value < 0.05 was considered statistically significant.

The endpoint was the MyoHealth score at rest and under HG.

3. Results

The baseline characteristics of the three groups (controls without CV risk factors: n = 12; controls with CV risk factors: n = 7 and HFpEF: n = 19) are shown in Table 1. The LVEF was similar in all three cohorts: LVEF median [IQR; Q_1–Q_3]: control: 63.00 [59.22–64.70]%; at risk: 61.52 [57.88–64.58]%; HFpEF: 61.12 [58.17–64.17]%.

Assessing the MyoHealth score at rest revealed preserved regional strain in 85 ± 9% of LV segments in controls, 73 ± 11% in at risk subjects and 73 ± 8% in HFpEF patients (comparisons in Figure 1A and Table 2). During stress the MyoHealth score was 84 ± 7% in controls, 83 ± 7 in at Risk subjects and 74 ± 11 in HFpEF patients (comparisons in Figure 1B and Table 2).

At rest, the MyoHealth score in at the risk cohort was reduced compared to the healthy controls (p = 0.04), at the same level as the HFpEF cohort (p = 0.45). This is in line with our recent finding that demonstrated the potential diagnostic window across different heart-failure stages using CMR-strain-analysis (14). However, during stress, at the risk cohort showed a higher MyoHealth score and was similar to the healthy controls (p = 0.32) and higher than the HFpEF values (p = 0.07). The "at risk" group improved significantly between rest and stress (p = 0.01, Figures 1A, B), while there were no relevant changes in healthy controls (p = 0.36) or HFpEF (p = 0.35). Like the HFpEF pattern, the impaired segments were mainly septal. During stress the impaired septal segments improved primarily in terms of circumferential strain (Figure 1B). It has been shown that septal impairment precedes global systolic dysfunction, highlighting the relevance of septal assessments in the future (10).

4. Discussion

In summary, we show for the first time that asymptomatic subjects with evidence of CV risk present with HFpEF like impaired myocardial deformation at rest. The absence of HF symptoms in these subjects is well explained by the compensation capacities during stress when their deformation capacities are similar to healthy subjects.

Performing a quick medication-free CMR-stress-test as HG in asymptomatic patients provides the chance to assess cardiac manifestations of their individual risk-profile. In patients with pathological changes, a stricter management of co-morbidities and shorter follow-up intervals may be adequate to prevent the transition to HFpEF. The potential of preventive treatment in this group of patients merits further investigation in future studies. The feasibility of its use in clinical practice is underlined by the quick acquisition of the exam as it added only up to 10 min. to the regular scan protocol during our study. This time included the more extensive informed consent process regarding the HG application and the additional image acquisition during the HG test.

Table 1 shows an age difference between the three groups, the difference between the youngest, the control subjects, and the HFpEF group was 19 years. This finding might suggest that the results reflect changes in elderly constitutions also supported by higher NT-proBNP values in the older group (15). However, we believe that our findings reflect different disease stages which are also influenced by age, but the main age-depended factor influencing both serum biomarkers and cardiac constitutions is atrial fibrillation which was excluded while recruiting the subjects. Therefore, we see the data has representative for theoretical patient trajectory from healthy to suffering from HF (16).

However, the limited number of subjects included in this study restrains the generalizability of the results. Nonetheless, the reasoning that changes in cardiac function do not develop at a certain tipping point but are present to some degree even at a preclinical state is both shown and intuitive – we propose an emerging tool promising to detect changes early.

Therefore, CMR scans including HG are a promising tool in future preventive cardiology trials for better risk stratification and phenotyping.

Data availability statement

The datasets presented in this article are not readily available because data safety regulations of the informed consent process limit open access. Requests to access the datasets should be directed to DH, djawid.hashemi@charite.de.

Ethics statement

The studies involving human participants were reviewed and approved by the Charité – Universitätsmedizin Berlin Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DH, FE, and SK: conception and design of the study and literature review. DH, MB, and SK: analysis and interpretation of the data. DH: drafting of the manuscript. DH, PD, and MB: data collection. All authors contributed to revising and editing the manuscript.

Funding

This work was supported by the German Centre for Cardiovascular Research (DZHK), funded by the German Federal Ministry of Education and Research, the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – CRC-1470 – B06 and the Charité – Universitätsmedizin Berlin, Germany, as well as the German Heart Institute Berlin, Germany, and Myocardial Solutions. Our research was also supported by an unrestricted research grant from Philips Healthcare. DH received a CMR specific research grant from the DZHK (Grant number: 81X3100214). DH was participant in the BIH Charité Digital Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health at Charité (BIH).

Acknowledgments

We express our gratitude toward all participating patients and subjects. We acknowledge the contribution of James G. Whayne and Hayden Whayne who supported this analysis.

Conflict of interest

SK reports grants and other support by the DZHK (German Center for Cardiovascular Research), Partner Site Berlin, Philips Healthcare, BioVentrix, Berlin Chemie, Merck/Bayer, Novartis, AstraZeneca, Siemens, and Myocardial Solutions outside of the submitted work. SK was also on the advisory board for Merck/Bayer, BioVentrix, and Myocardial Solutions.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* (2021) 42:3599–726.

2. Pieske B, Tschope C, de Boer R, Fraser A, Anker S, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J.* (2019) 40:3297–317. doi: 10.1093/eurheartj/ehz641

3. Hashemi D, Mende M, Trippel T, Petutschnigg J, Hasenfuss G, Nolte K, et al. Evaluation of the HFA-PEFF Score: results from the prospective DIAST-CHF cohort. *ESC Heart Fail.* (2022) doi: 10.1002/ehf2.14131 [Epub ahead of print].

4. Solomon S, McMurray J, Claggett B, de Boer R, DeMets D, Hernandez A, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med.* (2022) 387:1089–98.

5. Anker S, Butler J, Filippatos G, Ferreira J, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* (2021) 385:1451–61.

6. Steinberg B, Zhao X, Heidenreich P, Peterson E, Bhatt D, Cannon C, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation.* (2012) 126:65–75. doi: 10.1161/CIRCULATIONAHA.111.080770

7. Oktay A, Rich J, Shah S. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep.* (2013) 10:401–10. doi: 10.1007/s11897-013-0155-7

8. Bozkurt B, Coats A, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure. *J Cardiac Fail.* (2021) 27:387–413. doi: 10.1016/j.cardfail.2021.01.022

9. Kraigher-Krainer E, Shah A, Gupta D, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol.* (2014) 63:447–56. doi: 10.1016/j.jacc.2013.09.052

10. Hashemi D, Motzkus L, Blum M, Kraft R, Tanacli R, Tahirovic E, et al. Myocardial deformation assessed among heart failure entities by cardiovascular magnetic resonance imaging. *ESC Heart Fail.* (2021) 8:890–7. doi: 10.1002/ehf2.13193

11. Blum M, Hashemi D, Motzkus L, Neye M, Dordevic A, Zieschang V, et al. Variability of myocardial strain during isometric exercise in subjects with and without heart failure. *Front Cardiovasc Med.* (2020) 7:111. doi: 10.3389/fcvm.2020.00111

12. Tanacli R, Hashemi D, Neye M, Motzkus L, Blum M, Tahirovic E, et al. Multilayer myocardial strain improves the diagnosis of heart failure with preserved ejection fraction. *ESC Heart Fail.* (2020) 7:3240–5. doi: 10.1002/ehf2.12826

13. Doeblin P, Hashemi D, Tanacli R, Lapinskas T, Gebker R, Stehning C, et al. CMR tissue characterization in patients with HFmrEF. *J Clin Med.* (2019) 8:1877. doi: 10.3390/jcm8111877

14. Korosoglou G, Giusca S, Montenbruck M, Patel A, Lapinskas T, Gotze C, et al. Fast strain-encoded cardiac magnetic resonance for diagnostic classification and risk stratification of heart failure patients. *JACC Cardiovasc Imaging.* (2021) 14:1177–88. doi: 10.1016/j.jcmg.2020.10.024

15. Welsh P, Campbell R, Mooney L, Kimenai D, Hayward C, Campbell A, et al. Reference ranges for NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) and risk factors for higher NT-proBNP concentrations in a large general population cohort. *Circ Heart Fail.* (2022) 15:e009427. doi: 10.1161/CIRCHEARTFAILURE.121.009427

16. Stewart Coats A. Validating the HFA-PEFF score – or how to define a disease? *Eur J Heart Fail.* (2020) 22:428–31. doi: 10.1002/ejhf.1770

4.5. Assoziation von myokardialer Deformation und Beschwerdeempfinden

Die beiden vorangegangenen Studien haben die Möglichkeit zur Analyse der regionalen Verteilung der myokardialen Deformation bei Herzinsuffizienz (HI) und bei Personen mit erhöhtem HI-Risiko aufgezeigt.[78,79]

Wie die universelle HI-Definition verdeutlicht, besteht das zentrale Unterscheidungsmerkmal zwischen Betroffenen mit erhöhtem HI-Risiko (Stufen A und B der universellen HI-Definition) und HI-Patient*innen (Stufen C und D) in der Präsenz von HI-Symptomen oder auffälligen Untersuchungsbefunden.[3]

In dieser Studie wurde untersucht, ob die beschriebenen regionalen Unterscheidungsmuster der Segmente mit eingeschränkter myokardialer Deformation in Zusammenhang mit dem Beschwerdebild und der Symptomatik der Patient*innen stehen.

Der nachfolgende Text entspricht dem Abstrakt dieser Arbeit[80]:

Hashemi D, Doeblin P, Blum M, Weiss KJ, Schneider M, Beyer R, Pieske B, Duengen HD, Edelmann F, Kelle S. Reduced functional capacity is associated with the proportion of impaired myocardial deformation assessed in heart failure patients by CMR. Front Cardiovasc Med. 2023 Feb 9;10:1038337. doi: 10.3389/fcvm.2023.1038337. PMID: 36844739; PMCID: PMC9947709.

*"**Aims:** Heart failure (HF) does not only reduce the life expectancy in patients, but their life is also often limited by HF symptoms leading to a reduced quality of life (QoL) and a diminished exercise capacity. Novel parameters in cardiac imaging, including both global and regional myocardial strain imaging, promise to contribute to better patient characterization and ultimately to better patient management. However, many of these methods are not part of clinical routine yet, their associations with clinical parameters have been poorly studied. An imaging parameters that also indicate the clinical symptom burden of HF patients would make cardiac imaging more robust toward incomplete clinical information and support the clinical decision process.*

Methods and results: *This prospective study conducted at two centers in Germany between 2017 and 2018 enrolled stable outpatient subjects with HF [n = 56, including HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF)] and a control cohort (n = 19). Parameters assessed included measures for external myocardial function, for example, cardiac index and myocardial deformation measurements by cardiovascular magnetic resonance imaging, left ventricular global longitudinal strain (GLS), the global circumferential strain (GCS), and the regional distribution of segment deformation within the LV myocardium, as well as basic phenotypical characteristics including the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the 6-minute walk test (6MWT). If less than 80% of the LV segments are preserved in their deformation capacity the functional capacity by 6MWT (6 minutes walking distance: MyoHealth ≥ 80%: 579.8 ± 177.6 m; MyoHealth 60-<80%: 401.3 ± 121.7 m; MyoHealth 40-<60%: 456.4 ± 68.9 m; MyoHealth < 40%: 397.6 ± 125.9 m, overall p-value: 0.03) as well as the symptom burden are significantly impaired (NYHA class: MyoHealth ≥ 80%: 0.6 ± 1.1 m; MyoHealth 60-<80%: 1.7 ± 1.2 m; MyoHealth 40-<60%: 1.8 ± 0.7 m; MyoHealth < 40%: 2.4 ± 0.5 m; overall p-value < 0.01). Differences were also observed in the perceived exertion assessed by on the Borg scale (MyoHealth ≥ 80%: 8.2 ± 2.3 m; MyoHealth 60-<80%: 10.4 ± 3.2 m; MyoHealth 40-<60%: 9.8 ± 2.1 m; MyoHealth < 40%: 11.0 ± 2.9 m; overall p-value: 0.20) as well as quality of life measures (MLHFQ; MyoHealth ≥ 80%: 7.5 ± 12.4 m; MyoHealth 60-<80%: 23.4 ± 23.4 m; MyoHealth 40-<60%: 20.5 ± 21.2 m; MyoHealth < 40%: 27.4 ± 24.4 m; overall p-value: 0.15)-while these differences were not significant.*

Conclusion: *The share of LV segments with preserved myocardial contraction promises to discriminate between symptomatic and asymptomatic subjects based on the imaging findings, even when the LV ejection fraction is preserved. This finding is promising to make imaging studies more robust toward incomplete clinical information."*[80]

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 09 February 2023
DOI 10.3389/fcvm.2023.1038337

OPEN ACCESS

EDITED BY
Frédéric Schnell,
Centre Hospitalier Universitaire (CHU) de Rennes, France

REVIEWED BY
Oliver Bruder,
Elisabeth-Krankenhaus Essen, Germany
Roman Johannes Gertz,
University Hospital of Cologne, Germany

*CORRESPONDENCE
Djawid Hashemi
djawid.hashemi@charite.de

SPECIALTY SECTION
This article was submitted to Cardiovascular Imaging, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 06 September 2022
ACCEPTED 23 January 2023
PUBLISHED 09 February 2023

CITATION
Hashemi D, Doeblin P, Blum M, Weiss KJ, Schneider M, Beyer R, Pieske B, Duengen H-D, Edelmann F and Kelle S (2023) Reduced functional capacity is associated with the proportion of impaired myocardial deformation assessed in heart failure patients by CMR.
Front. Cardiovasc. Med. 10:1038337.
doi: 10.3389/fcvm.2023.1038337

Reduced functional capacity is associated with the proportion of impaired myocardial deformation assessed in heart failure patients by CMR

Djawid Hashemi[1,2,3]*, Patrick Doeblin[2,3], Moritz Blum[4], Karl Jakob Weiss[2,3], Matthias Schneider[1,2], Rebecca Beyer[2,3], Burkert Pieske[1,2,3], Hans-Dirk Duengen[1,2], Frank Edelmann[1,2] and Sebastian Kelle[1,2,3]

[1]Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Berlin, Germany, [2]Department of Internal Medicine and Cardiology, German Heart Institute Berlin, Berlin, Germany, [3]German Centre for Cardiovascular Research, Partner Site Berlin, Berlin, Germany, [4]Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Aims: Heart failure (HF) does not only reduce the life expectancy in patients, but their life is also often limited by HF symptoms leading to a reduced quality of life (QoL) and a diminished exercise capacity. Novel parameters in cardiac imaging, including both global and regional myocardial strain imaging, promise to contribute to better patient characterization and ultimately to better patient management. However, many of these methods are not part of clinical routine yet, their associations with clinical parameters have been poorly studied. An imaging parameters that also indicate the clinical symptom burden of HF patients would make cardiac imaging more robust toward incomplete clinical information and support the clinical decision process.

Methods and results: This prospective study conducted at two centers in Germany between 2017 and 2018 enrolled stable outpatient subjects with HF [n = 56, including HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF)] and a control cohort (n = 19). Parameters assessed included measures for external myocardial function, for example, cardiac index and myocardial deformation measurements by cardiovascular magnetic resonance imaging, left ventricular global longitudinal strain (GLS), the global circumferential strain (GCS), and the regional distribution of segment deformation within the LV myocardium, as well as basic phenotypical characteristics including the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the 6-minute walk test (6MWT). If less than 80% of the LV segments are preserved in their deformation capacity the functional capacity by 6MWT (6 minutes walking distance: MyoHealth $\geq$ 80%: 579.8 $\pm$ 177.6 m; MyoHealth 60–<80%: 401.3 $\pm$ 121.7 m; MyoHealth 40–<60%: 456.4 $\pm$ 68.9 m; MyoHealth < 40%: 397.6 $\pm$ 125.9 m, overall p-value: 0.03) as well as the symptom burden are significantly impaired (NYHA class: MyoHealth $\geq$ 80%: 0.6 $\pm$ 1.1 m; MyoHealth 60–<80%: 1.7 $\pm$ 1.2 m; MyoHealth 40–<60%: 1.8 $\pm$ 0.7 m; MyoHealth < 40%: 2.4 $\pm$ 0.5 m; overall p-value < 0.01). Differences were also observed in the perceived exertion assessed by on the Borg scale (MyoHealth $\geq$ 80%: 8.2 $\pm$ 2.3 m;

MyoHealth 60–<80%: 10.4 ± 3.2 m; MyoHealth 40–<60%: 9.8 ± 2.1 m; MyoHealth < 40%: 11.0 ± 2.9 m; overall *p*-value: 0.20) as well as quality of life measures (MLHFQ; MyoHealth ≥ 80%: 7.5 ± 12.4 m; MyoHealth 60–<80%: 23.4 ± 23.4 m; MyoHealth 40–<60%: 20.5 ± 21.2 m; MyoHealth < 40%: 27.4 ± 24.4 m; overall *p*-value: 0.15)–while these differences were not significant.

Conclusion: The share of LV segments with preserved myocardial contraction promises to discriminate between symptomatic and asymptomatic subjects based on the imaging findings, even when the LV ejection fraction is preserved. This finding is promising to make imaging studies more robust toward incomplete clinical information.

KEYWORDS

heart failure, cardiovascular magnetic resonance imaging, myocardial deformation, quality of life, CMR, score, strain, quantitative

1. Introduction

Patients with heart failure (HF) are at high risk for mortality and hospitalization and have a high burden of symptoms that alter their function and health-related quality of life (QoL) (1–5). QoL and functional capacities contributing to QoL are major goals in monitoring and treating patients with HF. Although patients with HF and a low QoL may have a higher potential for improvement, they may also be in a stage of the disease that is too advanced to improve (6). Therefore it is important to measure other contributing parameters associated with QoL, disease state and prognosis to better assess the patients (7). QoL measures are often evaluated in clinical trials as patient reported outcome measures become increasingly important, but they are rarely implement in clinical routine. Hence, identifying routine measures reflecting insights into QoL as well as functional capacities will contribute to an improved assessment of HF patients.

Various dimensions including physical capacity influence QoL. Routine measures to assess physical capacities include the semi-objective 6-minute walk tests and the subjective New York Heart Association (NYHA) functional class, often used in clinical trials but rarely in daily routine (8).

Cardiovascular magnetic resonance imaging (CMR) is a comprehensive technique, increasingly accessible and providing not only a high resolution of information on functional cardiac parameters but also information of tissue characteristics. Measurements of cardiac contractility and the assessment of myocardial deformation by strain analyses are an emerging and promising tool to better characterize patients compared to traditional parameters, e.g., left ventricular ejection fraction (LVEF) (9). While LVEF as well as routine strain measurements provide a global impression of cardiac contractility, recent studies showed the relevance of both myocardial deformation *per se* and the distribution of its impairment assessed by strain measurements characterizes HF patients in more detail (10). The added value of strain compared to LVEF in HF has been highlighted in HFpEF where LVEF is preserved. The MyoHealth score has been introduced as a parameter highlighting the heterogeneity of regions with altered myocardial deformation compared to preserved regional myocardial strain values (10–12). The score is calculated by the ratio of LV segments with preserved myocardial deformation to the total number of LV segments in a 37 segment LV model (10). It has been shown that cardiac remodeling does not present itself simultaneously across all LV segments in HF (10). Various reasons lead to the regional differences of both systolic and diastolic changes including shearing stress induced diffuse fibrosis, altered local gene expression patterns or global metabolic changes of cardiomyocytes (13–16).

We hypothesize that the better characterization of cardiac deformation in HF patients provides information on QoL and functional capacity. Therefore, we aim to evaluate the association of cardiac deformation assessed by the MyoHealth score and parameters for QoL and functional capacity in this analysis.

2. Materials and methods

This study was a prospective study conducted at two centers in Berlin, Germany, the Charité—University Medicine Berlin and the German Heart Centre Berlin, between 2017 and 2018. Its rationale and design have been previously described (10, 17–20).

Briefly, subjects were screened for diagnosed HF and an age of at least 45 years. The initial diagnosis of HF should have been older than 30 days; the patients were required to be in a stable state with no changes in their HF medication and no HF hospitalization within the previous 7 days. HFrEF was defined as diagnosis of HF, increased N terminal pro brain natriuretic peptide (NT-proBNP) (>220 pg/mL) and LVEF < 40%, HFmrEF as the diagnosis of HF, increased NT-proBNP (>220 pg/mL) and 40% ≥ LVEF < 50% as well as HFpEF as diagnosis of HF, increased NT-proBNP (>220 pg/mL) and LVEF ≥ 50% at the time of study inclusion. We did not distinguish between the causes for HF for recruiting patients (10).

Additionally, we recruited subjects without HF or advanced cardiovascular (CV) diseases as controls.

All studies included complied with the Declaration of Helsinki, the protocols were approved by the responsible ethics committees, and all patients gave written informed consent. It was registered at the German Clinical Trials Register (DRKS, registration number: DRKS00015615). The detailed inclusion and exclusion criteria are listed on the webpage of the DRKS.

TABLE 1 Baseline characteristics by study subgroup.

	Control (*n* = 19) Mean ± SD [median]	HFpEF (*n* = 19) Mean ± SD [median]	HFmrEF (*n* = 19) Mean ± SD [median]	HFrEF (*n* = 18) Mean ± SD [median]	*P*-value
Age–years	59.0 ± 6.84	77.6 ± 8.1	67.0 ± 9.6	64.2 ± 10.1	<0.01
Female sex–no. (%)	9 (47.4)	9 (47.4)	6 (31.6)	3 (16.7)	0.16
LVEF, mean–%	61.6 ± 5.37	61.5 ± 5.87	44.8 ± 2.90	32.9 ± 4.71	<0.01
NT-proBNP–ng/l	88.7 ± 61.1 [79]	586.4 ± 612.1 [314]	790.2 ± 1,138.1 [379]	2,247.5 ± 3,447.3 [886]	<0.01
Presence of CAD–no. (%)	0 (0)	12 (66.7)	15 (78.9)	13 (76.5)	<0.01

CAD, coronary artery disease; HFmrEF, heart failure mid-range preserved ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; n, number; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

TABLE 2 Baseline characteristics by the ratio of non-altered LV segments (MyoHealth).

	MyoHealth ≥ 80% (*n* = 7) Mean ± SD [median]	MyoHealth 60–<80% (*n* = 30) Mean ± SD [median]	MyoHealth 40–<60% (*n* = 17) Mean ± SD [median]	MyoHealth < 40% (*n* = 21) Mean ± SD [median]
Age–years	62.9 ± 15.2	71.5 ± 9.1	65.6 ± 11.1	65.6 ± 9.9
Female sex–no. (%)	3 (42.9)	18 (60)	3 (17.6)	3 (14.3)
LVEF, mean–%	62.1 ± 4.1	60.0 ± 8.5	47.1 ± 7.3	36.0 ± 7.3
NT-proBNP–ng/l	387.9 ± 791.3 [63]	341.7 ± 415.6 [254]	498.4 ± 389.9 [366]	2,189.1 ± 3,306.4 [653]
Presence of CAD–no. (%)	1 (14.3)	13 (43.3)	12 (70.6)	14 (66.7)
Cardiac index–l/min/m^2	2.5 ± 0.3	2.7 ± 1.1	2.7 ± 0.7	2.7 ± 0.5
GCS–%	−19.7 ± 2.3	−17.4 ± 1.6	−14.4 ± 2.6	−10.3 ± 2.1
GLS–%	−20.6 ± 1.6	−19.2 ± 1.1	−16.0 ± 2.2	−11.0 ± 3.4
Controls–no. (%)	5 (71.4)	12 (40.0)	2 (11.8)	0 (0)
HFpEF–no. (%)	2 (28.6)	14 (46.7)	3 (17.6)	0 (0)
HFmrEF–no. (%)	0 (0)	3 (10)	9 (52.9)	7 (33.3)
HFrEF–no. (%)	0 (0)	1 (3.3)	3 (17.6)	14 (66.7)

CAD, coronary artery disease; GCS, LV global circumferential strain; GLS, LV global longitudinal strain; HFmrEF, heart failure mid-range preserved ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; n, number; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

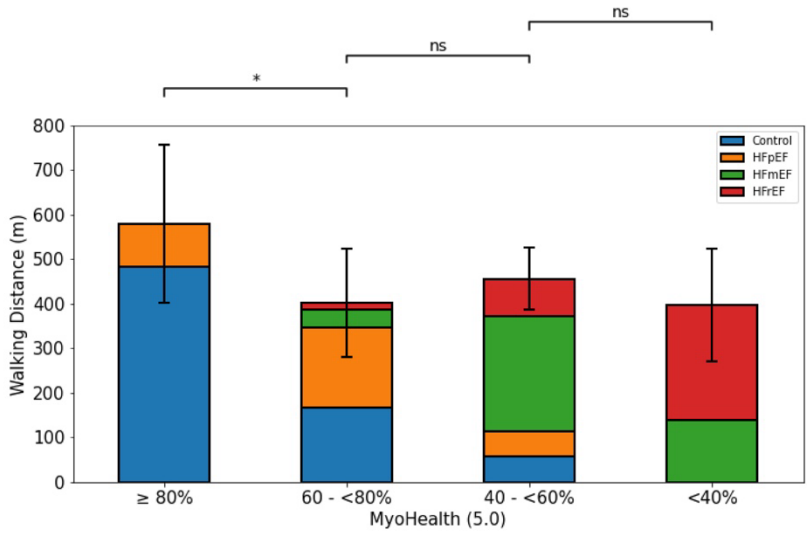


FIGURE 1
6-minute walk distance across MyoHealth groups. MyoHealth: ratio of myocardial segments with preserved deformation to the total number of myocardial segments. MyoHealth ≥ 80% vs. MyoHealth 60–<80%: $p = 0.03$; MyoHealth 60–<80% vs. MyoHealth 40–<60%: $p = 0.31$; MyoHealth 40–<60% vs. MyoHealth < 40%: $p = 0.59$. *Significant; ns, not significant.

2.1. Cardiac magnetic resonance

As previously described, all CMR images were acquired using a 1.5 T (Achieva, Philips Healthcare, Best, The Netherlands) magnetic resonance imaging (MRI) scanner with a five-channel cardiac surface coil in a supine position. All study participants were scanned using the identical comprehensive imaging protocol. The study protocol included initial scouts to determine cardiac imaging planes. Cine images were acquired using a retrospectively gated cine-CMR in cardiac short-axis, vertical long-axis, and horizontal long-axis orientations using a steady-state free precession sequence for volumetry (10, 20). The calculation of the cardiac indices (CIs) is based on the volumetry of the ventricles. Fast strain-encoded (fast-SENC) MRI was used for strain evaluation, as it has been shown to enable quantification of longitudinal and circumferential strain in free breathing and with high reproducibility (21). Images were blinded to strain analysis, cine, and volumetric measurements, respectively. We waived reproducibility analyses based on an analysis that highlighted the robustness of fast-SENC analyses regarding intraobserver and reproducibility variabilities (22).

2.2. Image analysis

All images were analyzed offline using commercially available software in accordance with the recent consensus document for quantification of LV function using CMR (23). In the analysis, we included 2 chamber, 3chamber, and 4chamber cine images, and respectively, three preselected mid-ventricle slices from the LV short-axis stack. Image analysis was performed using the software Medis® Suite MR (Medis medical imaging systems, Leiden, The Netherlands, version 3.1) for voluinterme measurements and the software MyoStrain (Myocardial Solutions, Inc., Morrisville, NC, USA, version 5.0) for fast-SENC strain measurements.

2.3. Endpoints

The study population was not only categorized by traditional HF entities, but also by the ratio of myocardial segments with preserved deformation to the total number of myocardial segments (n = 37), described as MyoHealth score (illustrated in S1 of **Supplementary material**; 10–12). Briefly, the MyoHealth score assess the 37 segments of the LV separately, whether the myocardial deformation is altered, i.e., whether the strain value of that segment is $> -17\%$. The MyoHealth score is the proportion of LV segments with preserved and not altered myocardial deformation from the total 37 segments. The MyoHealth entities introduced include 4 groups: MyoHealth > 80%, MyoHealth 60–<80%, MyoHealth 40–<60%, and MyoHealth < 40%.

Based on the MyoHealth score distribution following parameters were assessed: QoL, 6-minute walk test (6MWT) key parameters as well as the New York Heart Association (NYHA) functional classification.

Patients were instructed to cover the maximum distance in 6 min (6-minute walk distance, 6MWD) at a self-graded walking speed, pausing to rest when needed. The test was supervised by the same study staff to minimize the variability. The 6MWD as well as the level of perceived exertion indicated as specific level on the Borg score were recorded. The functional capacities indicated by the New York Heart Association (NYHA) functional classification were also part of the baseline information collected.

In accordance with the study protocol, study participants completed a QoL questionnaire, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (24).

2.4. Statistical analysis

Statistical analysis was carried out with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Normality of variables was assessed by visual assessment of normality curves and the Shapiro–Wilk test. Comparison between groups for continuous variables was performed with a one-way ANOVA for normally distributed data. When a significant P-value was obtained using one-way ANOVA, the group means were examined by the Holm–Bonferroni method. Values of $P < 0.05$ were considered statistically significant. For the comparison of categorical variables between the groups were used the χ^2 test.

3. Results

3.1. Baseline characteristics

The ratio of non-altered myocardial deformation was assessed in 71 patients. The baseline characteristics of these patients have been previously reported, in brief the details are presented in **Tables 1**, **2** (10, 17–20). The difference in the sex distribution between the groups is not significant (χ^2 = 5.21, p = 0.157, n = 71) in **Table 1**. Due to the non-major numbers in each group, we refrain from further testing. **Table 2** shows the increasing global strain values, including both global circumferential (GCS) and longitudinal strain (GLS), with smaller MyoHealth values. Simultaneously, the cardiac index remains on the same level across all groups.

3.2. Functional capacity—6MWD

The 6MWD was significantly different across groups separated by the MyoHealth score (overall p-value: 0.03). **Figure 1** shows the longest 6MWD in the group with the preserved MyoHealth score (MyoHealth ≥ 80%: 579.8 ± 177.6 m) and shorter distances in the other groups (MyoHealth 60–<80%: 401.3 ± 121.7 m; MyoHealth 40–<60%: 456.4 ± 68.9 m; MyoHealth < 40%: 397.6 ± 125.9 m). S2 of **Supplementary material** highlights the major role of the MyoHealth score in the prediction of the 6MWD when compared to LVEF and the LV global longitudinal strain.

3.3. Perceived exertion—Borg scale

Figure 2 illustrates the level of perceived exertion at the end of the 6MWT. The overall comparison revealed no difference between the groups (MyoHealth ≥ 80%: 8.2 ± 2.3 m; MyoHealth 60–<80%: 10.4 ± 3.2; MyoHealth 40–<60%: 9.8 ± 2.1; MyoHealth < 40%: 11.0 ± 2.9; overall p-value: 0.20).

3.4. Quality of life–MLHFQ

Figure 3 demonstrates the QoL measure assessed by the MLHFQ with lower numbers indicating a higher QoL. It shows the lowest MLHFQ score values in the group with preserved myocardial deformation. However, the comparison did not reveal a reliable difference across the study population (MyoHealth ≥ 80%: 7.5 ± 12.4; MyoHealth 60–<80%: 23.4 ± 23.4; MyoHealth 40–<60%: 20.5 ± 21.2; MyoHealth < 40%: 27.4 ± 24.4; overall *p*-value: 0.15).

3.5. Symptom burden—NYHA functional class

Figure 4 displays the significant association of the NYHA functional class and the proportion of preserved myocardial segments. While the NYHA class was lowest in the group with a preserved MyoHealth score, it was similarly higher in the groups with decreased score values (MyoHealth ≥ 80%: 0.6 ± 1.1; MyoHealth 60–<80%: 1.7 ± 1.2; MyoHealth 40–<60%: 1.8 ± 0.7; MyoHealth < 40%: 2.4 ± 0.5; overall *p*-value < 0.01).

4. Discussion

In this study, aiming to better characterize HF patients and imaging parameters indicating their symptom burden, we found that the proportion of myocardial segments with preserved myocardial deformation indicates better functional capacity. Furthermore, this exploratory analysis suggests an association of the MyoHealth score with quality of life surrogate parameters in larger study population.

Table 2 shows the consistency of our data. The cardiac index remains on a similar level across all groups who were either healthy subjects or HF patients in a stable outpatient condition. The global strain values (GCS and GLS) were increasing with smaller MyoHealth score values, as the MyoHealth score *per se* represents the proportion of segments with preserved strain values.

Our observational study of consecutive patients with HF as well as control subjects was carefully designed to better characterize myocardial contraction. After focusing on the contraction pattern and describing the onset of changes in HF in interventricular septal segments, we sought to highlight that CMR scans in HF are not only relevant to characterize HF but to better phenotype patients with regards to parameters limiting their lives on a daily basis (10).

Given the high prevalence of HF and a nearly half of these patients showing nearly normal values with regards to traditional HF parameters, e.g., LVEF, there is an unmet need for innovative tools to diagnose patients and identify those at risk (8). In this analysis we sought to identify a parameter that reflects both an insight to the cardiac contraction with its regional differences and key parameters limiting patients' everyday experience, functional capacity, and quality of life (8, 25).

The MyoHealth score allows for the estimation of the clinical condition when functional capacity data is not available. If the signal with regards to the QoL assessed by the MLHFQ prove feasible and the differences are significantly different in a larger study population, this might lead to fewer resources than assessing the symptom burden systematically aside from the image acquisition, e.g., by conducting a 6MWT or questionnaires for QoL.

Impaired functional capacity, often assessed by 6MWT, is the main symptom in patients with HF, regardless of LVEF (26–28). With the 6MWD being relevantly reduced in both patients and subjects with a reduced ratio of segments with preserved myocardial deformation, as seen in **Figure 1**, we could show the association of an innovative parameter reflecting the myocardial contraction with its regional disparities. The validity of this finding is shown in **Figure 2**, as patients in all groups reached a comparable level of exhaustion indicated by values on the Borg scale. The comparable values on the Borg scale indicate that patients were tested with the same rigor to maintain a comparable, adjusted intensity to test their capacities.

While there is some evidence indicating a worse prognosis based on CMR characteristics in HFpEF, the association with the symptom burden remains to be further explored (29–31).

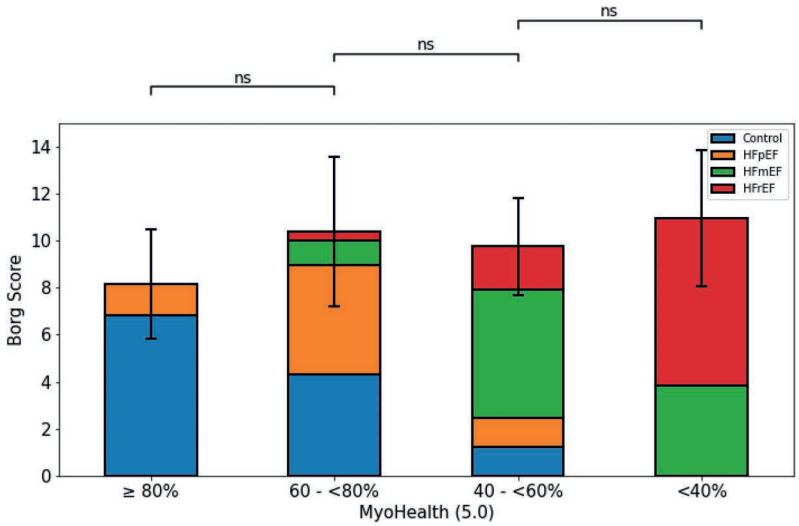


FIGURE 2
Perceived exertion at the end of the 6-minute walk test across MyoHealth groups. MyoHealth ≥ 80% vs. MyoHealth 60–<80%: $p = 0.45$; MyoHealth 60–<80% vs. MyoHealth 40–<60%: $p = 1$; MyoHealth 40–<60% vs. MyoHealth < 40%: $p = 0.43$. ns, not significant.

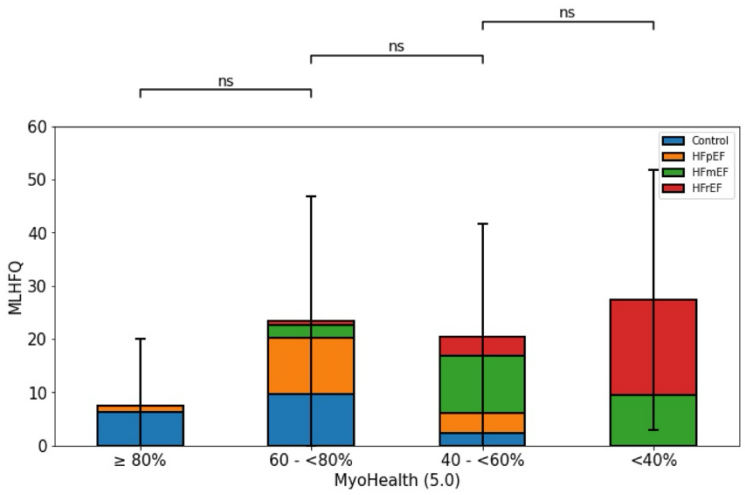


FIGURE 3
Quality of life by MLHFQ across MyoHealth groups. MyoHealth ≥ 80% vs. MyoHealth 60–<80%: $p = 0.15$; MyoHealth 60–<80% vs. MyoHealth 40–<60%: $p = 1$; MyoHealth 40–<60% vs. MyoHealth < 40%: $p = 1$. ns, not significant.

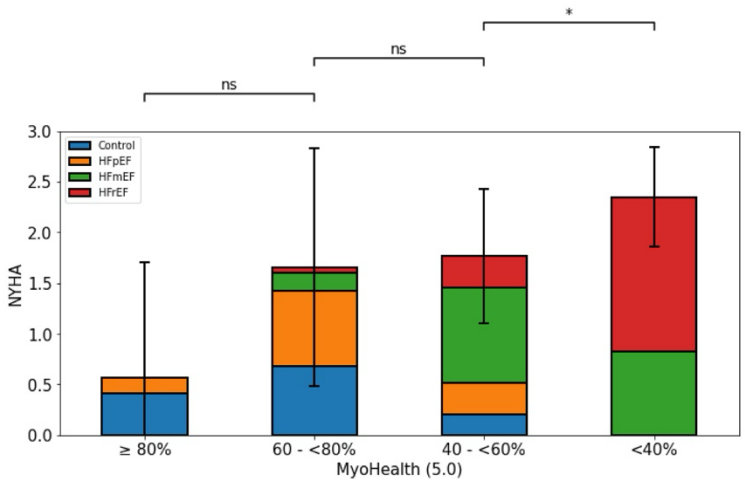


FIGURE 4
Limitations and symptom burden by NYHA functional class across MyoHealth groups. MyoHealth ≥ 80% vs. MyoHealth 60–<80%: $p = 0.15$; MyoHealth 60–<80% vs. MyoHealth 40–<60%: $p = 1$; MyoHealth 40–<60% vs. MyoHealth < 40%: $p < 0.01$. *Significant; ns, not significant.

The HFA-PEFF algorithm introduced imaging parameters to diagnose HFpEF, e.g., E/e', tricuspid regurgitation velocity, left atrial volume index, and LV wall thickness (32). In brief, the HFA-PEFF algorithm leads to a score value for an individual patient based on functional, morphological and biomarker parameters, that may diagnose HFpEF, exclude HFpEF or indicate further investigation for a diagnosis by stress testing. Many of the highlighted functional and morphological parameters are derived from echocardiography and cannot be acquired reliably by routine CMR techniques. Nonetheless, it has been shown that the application of a CMR stress testing technique is a feasible strategy for further investigations in suspected HFpEF patients (33). All these efforts aim to better understand patients with a symptom burden leading to a suspected diagnosis of HF and a preserved traditional parameter, LVEF. Identifying those with altered cardiac function, like our analysis of regional differences of myocardial deformation, is at the core of recent findings, which aspire to lead to an earlier diagnosis as well as a better differentiation of the broad spectrum of patients diagnosed with HFpEF.

HFA-PEFF parameters as well as other HFpEF criteria have been often analyzed for a prognostic value regarding survival, but only recently a few studies focused on functional capacity (26, 34, 35). These analyses focused on clinical features and their impact on the 6MWT (26). Clinical information is often neither at the disposal of the physician reporting on cardiac imaging nor of the team managing the patient, which stresses the relevance of this analysis highlighting a method to increase the robustness of images to interpret.

With regards to the QoL the greatest difference could be observed between the group with preserved MyoHealth score and the impaired

groups, as illustrated in S1, indicating that this parameter indicates QoL. While many patients with HF suffer from depression, QoL was only recently used as a clinical trial outcome parameter in HF—very rarely in cardiac imaging and CMR studies (36–40).

Figure 4 reflects the harmony of the presented data, as the subjects with a preserved ratio of altered myocardial deformation are those with the lowest symptom burden with regards to the subjective NYHA classification.

4.1. Limitations

The main limitation of our study is that we cannot provide prognostic information of the subjects and patients examined. Nonetheless, the main objective of this analysis was to evaluate the predictive value of regional myocardial deformation on functional capacity as well as the quality of life in HF patients, especially HFpEF.

However, our explorative analyses to better understand the differences between the study subgroups are limited due to the smaller subgroup sizes the more fragmented they become. Comparing HF entities from different subgroups against each other within our analyses (Figures 1–4) will include subgroups with very few subjects, which restricts massively the claim of transferability. Further analyses of our exploratory indications require replication in larger cohorts. Due to this restriction, we also did not perform a *post hoc* subject sex or age matched analysis, as it would lead to even smaller numbers of subgroup subjects.

The small numbers also limit some of our analyses where we see quantitative difference, which do not reach the level of statistical significance, e.g., the assessment of QoL by the MLHFQ. Revisiting this analysis in a larger study population would lead to results that are more reliable. However, we believe that these not significant results are a signal to further analyses.

5. Conclusion

The results of this study promise an association between regional LV strain impairment and the symptom burden of HF patients with regards to functional capacity and quality of life, especially relevant in patients with a preserved LVEF that requires future prospective validation.

Data availability statement

The original contributions presented in this study are included in this article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Charité – Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DH, HDD, FE, and SK: conception and design of the study and literature review. DH, MB, and SK: analysis and interpretation of the data. DH: drafting of the manuscript. DH, PD, and MB: data collection. All authors revising and editing the manuscript and approved the submitted version.

Funding

This work was supported by the German Centre for Cardiovascular Research (DZHK), funded by the German Federal Ministry of Education and Research, the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—CRC-1470—B06, and the Charité – Universitätsmedizin Berlin, Germany, as well as the German Heart Institute Berlin, Germany, and Myocardial Solutions. This research was also supported by an unrestricted research grant from Philips Healthcare. DH received a CMR specific research grant from the DZHK (grant number: 81X3100214).

Acknowledgments

We wish to express our gratitude toward all participating patients and subjects. We would especially like to acknowledge the contribution of James G. Whayne and Hayden Whayne, who supported this analysis.

Conflict of interest

SK reported grants and other support by the Philips Healthcare, BioVentrix, Berlin-Chemie, Merck/Bayer, Novartis, Astra Zeneca, Siemens, and Myocardial Solutions outside of the submitted work. SK was also on the advisory board for Merck/Bayer, BioVentrix, and Myocardial Solutions.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1038337/full#supplementary-material

References

1. Lewis E. Assessing the impact of heart failure therapeutics on quality of life and functional capacity. *Curr Treat Options Cardiovasc Med.* (2013) 15:425–36. doi: 10.1007/s11936-013-0249-2

2. Butler J, Stebbins A, Melenovsky V, Sweitzer N, Cowie M, Stehlik J, et al. Vericiguat and health-related quality of life in patients with heart failure with reduced ejection fraction: insights from the VICTORIA trial. *Circ Heart Fail.* (2022) 15:e009337. doi: 10.1161/CIRCHEARTFAILURE.121.009337

3. Vaishnava P, Lewis E. Assessment of quality of life in severe heart failure. *Curr Heart Fail Rep.* (2007) 4:170–7. doi: 10.1007/s11897-007-0037-y

4. Bui A, Horwich T, Fonarow G. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol.* (2011) 8:30–41. doi: 10.1038/nrcardio.2010.165

5. Johansson I, Joseph P, Balasubramanian K, McMurray J, Lund L, Ezekowitz J, et al. Health-related quality of life and mortality in heart failure: the global congestive heart failure study of 23 000 patients from 40 countries. *Circulation.* (2021) 143:2129–42. doi: 10.1161/CIRCULATIONAHA.120.050850

6. Butler J, Khan M, Mori C, Filippatos G, Ponikowski P, Comin-Colet J, et al. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. *Eur J Heart Fail.* (2020) 22:999–1005. doi: 10.1002/ejhf.1810

7. Fitz J, Edelmann F, Hasenfuss G, Sandek A, Nolte K, Hashemi D, et al. Influence of baseline parameters on one-year physical, mental, and health-related quality of life in patients with heart failure and preserved ejection fraction. *ESC Heart Fail.* (2021) 8:4635–43. doi: 10.1002/ehf2.13593

8. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eu Heart J.* (2021) 42:3599–726. doi: 10.1093/eurheartj/ehab368

9. Marwick T, Shah S, Thomas J. Myocardial strain in the assessment of patients with heart failure: a review. *JAMA Cardiol.* (2019) 4:287–94. doi: 10.1001/jamacardio.2019.0052

10. Hashemi D, Motzkus L, Blum M, Kraft R, Tanacli R, Tahirovic E, et al. Myocardial deformation assessed among heart failure entities by cardiovascular magnetic resonance imaging. *ESC Heart Fail.* (2021) 8:890–7. doi: 10.1002/ehf2.13193

11. Gersak B, Kukec A, Steen H, Montenbruck M, Sostaric M, Schwarz A, et al. Relationship between quality of life indicators and cardiac status indicators in chemotherapy patients. *Zdr Varst.* (2021) 60:199–209. doi: 10.2478/sjph-2021-0028

12. Steen H, Montenbruck M, Gerzak B, Schwarz A, Kelle S, Giusca S, et al. Cardiotoxicity during cancer treatment causes more regional than global dysfunction: the prefect study. *J Am Coll Cardiol.* (2020) 75:1824. doi: 10.1016/s0735-1097(20)32451-7

13. Parikh V, Caleshu C, Reuter C, Lazzeroni L, Ingles J, Garcia J, et al. Regional variation in RBM20 causes a highly penetrant arrhythmogenic cardiomyopathy. *Circ Heart Fail.* (2019) 12:e005371. doi: 10.1161/CIRCHEARTFAILURE.118.005371

14. Achenbach S, Fuchs F, Goncalves A, Kaiser-Albers C, Ali Z, Bengel F, et al. Non-invasive imaging as the cornerstone of cardiovascular precision medicine. *Eur Heart J Cardiovasc Imaging.* (2022) 23:465–75. doi: 10.1093/ehjci/jeab287

15. Bertero E, Sequeira V, Maack C. Hungry hearts. *Circ Heart Fail.* (2018) 11:e005642. doi: 10.1161/CIRCHEARTFAILURE.118.005642

16. Voros G, Ector J, Garweg C, Droogne W, Van Cleemput J, Peersman N, et al. Increased cardiac uptake of ketone bodies and free fatty acids in human heart failure and hypertrophic left ventricular remodeling. *Circ Heart Fail.* (2018) 11:e004953. doi: 10.1161/CIRCHEARTFAILURE.118.004953

17. Tanacli R, Hashemi D, Neye M, Motzkus L, Blum M, Tahirovic E, et al. Multilayer myocardial strain improves the diagnosis of heart failure with preserved ejection fraction. *ESC Heart Fail.* (2020) 7:3240–5. doi: 10.1002/ehf2.12826

18. Blum M, Hashemi D, Motzkus L, Neye M, Dordevic A, Zieschang V, et al. Variability of myocardial strain during isometric exercise in subjects with and without heart failure. *Front Cardiovasc Med.* (2020) 7:111. doi: 10.3389/fcvm.2020.00111

19. Tanacli R, Hashemi D, Lapinskas T, Edelmann F, Gebker R, Pedrizzetti G, et al. Range variability in CMR feature tracking multilayer strain across different stages of heart failure. *Sci Rep.* (2019) 9:16478. doi: 10.1038/s41598-019-52683-8

20. Doeblin P, Hashemi D, Tanacli R, Lapinskas T, Gebker R, Stehning C, et al. CMR tissue characterization in patients with HFmrEF. *J Clin Med.* (2019) 8:1877. doi: 10.3390/jcm8111877

21. Lapinskas T, Zieschang V, Erley J, Stoiber L, Schnackenburg B, Stehning C, et al. Strain-encoded cardiac magnetic resonance imaging: a new approach for fast estimation of left ventricular function. *BMC Cardiovasc Disord.* (2019) 19:52. doi: 10.1186/s12872-019-1031-5

22. Bucius P, Erley J, Tanacli R, Zieschang V, Giusca S, Korosoglou G, et al. Comparison of feature tracking, fast-SENC, and myocardial tagging for global and segmental left ventricular strain. *ESC Heart Fail.* (2020) 7:523–32. doi: 10.1002/ehf2.12576

23. Suinesiaputra A, Bluemke D, Cowan B, Friedrich M, Kramer C, Kwong R, et al. Quantification of LV function and mass by cardiovascular magnetic resonance: multi-center variability and consensus contours. *J Cardiovasc Magn Reson.* (2015) 17:63. doi: 10.1186/s12968-015-0170-9

24. Garin O, Herdman M, Vilagut G, Ferrer M, Ribera A, Rajmil L, et al. Assessing health-related quality of life in patients with heart failure: a systematic, standardized comparison of available measures. *Heart Fail Rev.* (2014) 19:359–67. doi: 10.1007/s10741-013-9394-7

25. Mant J, Doust J, Roalfe A, Barton P, Cowie M, Glasziou P, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. *Health Technol Assess.* (2009) 13:1–207. doi: 10.3310/hta13320

26. Berisha-Muharremi V, Henein M, Dini F, Haliti E, Bytyci I, Ibrahimi P, et al. Diabetes is the strongest predictor of limited exercise capacity in chronic heart failure and preserved ejection fraction (HFpEF). *Front Cardiovasc Med.* (2022) 9:883615. doi: 10.3389/fcvm.2022.883615

27. Nadruz W Jr., West E, Sengelov M, Santos M, Groarke J, Forman D, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. *J Am Heart Assoc.* (2017) 6:e006000. doi: 10.1161/JAHA.117.006000

28. Batalli A, Ibrahimi P, Bytyci I, Ahmeti A, Haliti E, Elezi S, et al. Different determinants of exercise capacity in HFpEF compared to HFrEF. *Cardiovasc Ultrasound.* (2017) 15:12. doi: 10.1186/s12947-017-0103-x

29. Golukhova E, Bulaeva N, Alexandrova S, Gromova O, Berdibekov B. Prognostic value of characterizing myocardial tissue by cardiac MRI with T1 mapping in HFpEF patients: a systematic review and meta-analysis. *J Clin Med.* (2022) 11:2531. doi: 10.3390/jcm11092531

30. Schonbauer R, Kammerlander A, Duca F, Aschauer S, Koschutnik M, Dona C, et al. Prognostic impact of left atrial function in heart failure with preserved ejection fraction in sinus rhythm vs. persistent atrial fibrillation. *ESC Heart Fail.* (2022) 9:465–75. doi: 10.1002/ehf2.13723

31. Pezel T, Hovasse T, Sanguineti F, Kinnel M, Garot P, Champagne S, et al. Long-term prognostic value of stress CMR in patients with heart failure and preserved ejection fraction. *JACC Cardiovasc Imaging.* (2021) 14:2319–33. doi: 10.1016/j.jcmg.2021.03.010

32. Pieske B, Tschope C, de Boer R, Fraser A, Anker S, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the heart failure association (HFA) of the European society of cardiology (ESC). *Eur Heart J.* (2019) 40:3297–317. doi: 10.1093/eurheartj/ehz641

33. Backhaus S, Lange T, George E, Hellenkamp K, Gertz R, Billing M, et al. Exercise stress real-time cardiac magnetic resonance imaging for noninvasive characterization of heart failure with preserved ejection fraction: the HFpEF-stress trial. *Circulation.* (2021) 143:1484–98. doi: 10.1161/CIRCULATIONAHA.120.051542

34. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca H, Henkens M, Heymans S, Beussink-Nelson L, et al. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail.* (2020) 22:413–21. doi: 10.1002/ejhf.1614

35. Sotomi Y, Iwakura K, Hikoso S, Inoue K, Onishi T, Okada M, et al. Prognostic significance of the HFA-PEFF score in patients with heart failure with preserved ejection fraction. *ESC Heart Fail.* (2021) 8:2154–64. doi: 10.1002/ehf2.13302

36. Angermann C, Ertl G. Depression, anxiety, and cognitive impairment: comorbid mental health disorders in heart failure. *Curr Heart Fail Rep.* (2018) 15:398–410. doi: 10.1007/s11897-018-0414-8

37. Angermann C, Gelbrich G, Stork S, Gunold H, Edelmann F, Wachter R, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA.* (2016) 315:2683–93. doi: 10.1001/jama.2016.7635

38. Piepoli M, Hussain R, Comin-Colet J, Dosantos R, Ferber P, Jaarsma T, et al. OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. *Eur J Heart Fail.* (2021) 23:127–35. doi: 10.1002/ejhf.2076

39. Armstrong P, Lam C, Anstrom K, Ezekowitz J, Hernandez A, O'Connor C, et al. Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. *JAMA.* (2020) 324:1512–21. doi: 10.1001/jama.2020.15922

40. Khandwalla R, Birkeland K, Heywood J, Steinhubl S, McCague K, Fombu E, et al. Activity sensors to evaluate the effect of sacubitril/valsartan on quality-of-life in heart failure: rational and design of the AWAKE-HF study. *ESC Heart Fail.* (2019) 6:1313–21. doi: 10.1002/ehf2.12514

5. Diskussion

Herzinsuffizienz, insbesondere HFpEF, ist eine komplexe Erkrankung, die die Lebensqualität und -erwartung von Patient*innen beeinträchtigt und das Gesundheitssystem erheblich belastet. Diese Arbeit verfolgte mehrere Ziele, um verschiedene Aspekte der Erkrankung zu beleuchten und potenzielle Verbesserungen in Diagnose und Versorgung aufzuzeigen.
Die vorgestellten Studien untersuchten die Bedeutung einer ausführlichen klinischen Phänotypisierung und die gesundheitsökonomischen Kosten der HFpEF. Die Anwendung der Kardio-MRT zur besseren Charakterisierung von Patient*innen mit Herzinsuffizienz und die MRT-basierte Charakterisierung zur Früherkennung von Risikopopulationen wurden ebenfalls thematisiert. Letztlich wurde der Zusammenhang zwischen neuartigen Kardio-MRT-Charakteristika und dem subjektiven Beschwerdeempfinden von Patient*innen untersucht.[76-80]

Um die Versorgung von Patientinnen mit Herzinsuffizienz zu optimieren, ist es erforderlich, ein tieferes Verständnis der HFpEF zu gewinnen und innovative diagnostische Ansätze zu erkunden. Die in dieser Arbeit vorgestellten Studien haben die Bedeutung einer ausführlichen klinischen Phänotypisierung und genauen Diagnosestellung der HFpEF sowohl aus individueller Sicht der Erkrankten als auch unter gesundheitsökonomischen Aspekten hervorgehoben.

<u>Prognostische Bedeutung der Diagnosestellung</u>

Eine präzise Diagnose und eine Phänotypisierung der HFpEF sind entscheidend, da sie sowohl das Verständnis der Krankheitsmechanismen verbessern als auch eine gezielte, individualisierte Therapie ermöglichen können. Die Analyse des HFA-PEFF-Algorithmus zeigt auf, dass es keine dichotome Aufteilung (HFpEF nach HFA-PEFF-Algorithmus vs. Nicht-HFpEF nach HFA-PEFF-Algorithmus) hinsichtlich einer Pathologie bzw. einem negativen Ergebnis im Verlauf gibt. Studienteilnehmer*innen, die bereits Auffälligkeiten in den genannten Parametern des Algorithmus zeigen, aber den HFpEF-Grenzwert nicht erreichen, weisen auch eine schlechtere Prognose auf als der Teil der Studienpopulation, der keine Auffälligkeiten aufzeigt. Der HFA-PEFF-Algorithmus sieht zwar bei den Patient*innen dieser Gruppe *in der Grauzone* vor, dass eine erweiterte Diagnostik mittels Belastungsuntersuchung zur

erweiterten Risikostratifizierung erfolgen soll, um eine maskierte HFpEF-Diagnose aufzuzeigen. In Anbetracht der fehlenden Konsequenz im klinischen Alltag wurde in der Analyse von einer weiteren Diagnostik bei der DIAST-CHF-Studienpopulation abgesehen. Die Populationen der einzigen beiden Studien, die zu einem positiven Ergebnis im Rahmen einer Phase-III-Zulassungsstudie eines Medikaments gekommen sind, DELIVER und EMPEROR-preserved, haben nicht den HFA-PEFF-Algorithmus oder den H2FPEF als bestimmendes Instrument zum Studieneinschluss genutzt.[60,61]

Mittlerweile konnten auch andere Analysen den prädiktiven Wert des HFA-PEFF-Algorithmus bestätigen, sodass das Ergebnis der vorliegenden Studie bestätigt wurde und die Aussagekraft des Algorithmus als gesichert gilt.[81-85] Zeitgleich muss festgestellt werden, dass mit den Analysen auch eine Kritik hinsichtlich der klinischen Anwendbarkeit einherging und bisher keine klinische Studie bekannt ist, die prospektiv den Algorithmus hinsichtlich eines Einschlusskriteriums nutzt. Anzuführen ist hier beispielhaft die größte aktuell rekrutierende, nach der Vorstellung des HFA-PEFF-Scores begonnene Interventionsstudie bei HFpEF, FINEARTS-HF genannt, die die Wirkung des nicht-steroidalen Aldosteron-Antagonisten Finerenone bei HFpEF untersucht (ClinicalTrials.gov identifier: NCT04435626). FINEARTS-HF nutzt zwar Bestandteile des HFA-PEFF-Algorithmus, jedoch nicht den Score selbst. Die größte Limitation in der Anwendung des vollständigen Algorithmus ist die abverlangte invasive hämodynamische Evaluation bei nicht eindeutiger Punktzahl im ersten Schritt der Beurteilung, um eine HFpEF zu bestätigen bzw. auszuschließen. Dies wurde aufgezeigt und diskutiert in der prospektiven Beobachtungsstudie PROMIS-HF.[86] Somit bleibt im klinischen Alltag bei HI und erhaltener LVEF der Nachweis einer diastolischen Dysfunktion mit weniger positiven Parametern, als der HFA-PEFF-Score vorgibt. Da die prädiktive Aussagekraft des Algorithmus allerdings bestätigt ist, kann der HFA-PEFF-Algorithmus im Rahmen der ohnehin erhobenen Parameter als Instrument der präspezifizierten Analysen von Interventionsstudien angewandt werden, um der Herausforderung der heterogenen HFpEF-Kohorten mittels einer besseren Charakterisierung zu begegnen.

Gesundheitsökonomische Herausforderung durch HFpEF

Anreiz für eine treffendere Charakterisierung und konsekutiv geeignetere Versorgung ist nicht nur die aufgezeigte prognostische Bedeutung für Patient*innen, sondern auch die

gesundheitsökonomische Belastung der HFpEF, deren Prävalenz steigt. Die ökonomische Belastung von HFpEF ist von volkswirtschaftlicher Relevanz, da etwa 2 % der gesamten Gesundheitsausgaben in industrialisierten Ländern auf die Versorgung von Patient*innen mit HI entfallen, wovon etwa die Hälfte für nicht-fatale HI-Hospitalisationen aufgewendet wird.[87-89] In der vorliegenden Analyse wurden die direkten Gesundheitskosten in der ALDO-DHF-Kohorte verglichen. Spironolacton hat ökonomisch keine signifikante Besserung zur Behandlung bei HFpEF gezeigt und wies im Durchschnitt 1118 € an Gesundheitsausgaben auf.[77] Die meisten Patient*innen verursachten mit medianen Ausgaben von 332 € geringere Kosten, während diese bei einem kleineren, älteren Teil der Studienteilnehmenden deutlich höher waren.[77]

Herz-Kreislauf-Erkrankungen sind bereits jetzt die führende Todesursache in Deutschland, HI die häufigste Ursache für stationäre Aufnahme und HFpEF nimmt in ihrer Prävalenz zu – zeitgleich erschöpft sich die Kernaufgabe der Therapie der HFpEF darin, Komorbiditäten zu optimieren.[1,90] Im Rahmen des demographischen Wandels wird der *healthy volunteer effect* der ALDO-DHF-Studie überwunden, sodass vorrangig das kostenintensivere Kollektiv der HFpEF zum Tragen kommen wird.[91] Diese Breite der Kostenstruktur spiegelt die Heterogenität der Patientenpopulation wider, in Ermangelung hinreichender Therapieoptionen bleibt zur Vermeidung der Krankheitskosten die Prävention von HFpEF entscheidend. Insgesamt zeigen die Ergebnisse die dringende Notwendigkeit, die Versorgung und Charakterisierung von Patient*innen mit HFpEF zu optimieren. Die prädiktive Aussagekraft des HFA-PEFF-Algorithmus kann dazu beitragen, der Herausforderung der heterogenen HFpEF-Kohorten durch eine umfassendere Charakterisierung zu begegnen. Durch diese und durch die konsekutive Verbesserung der Versorgung können nicht nur prognostische Vorteile für die Patient*innen erreicht werden, sondern es kann auch die ökonomische Belastung der HFpEF reduziert werden.

Die prognostische und gesundheitsökonomische Herausforderung verlangt ein zielgerichteteres, individualisiertes Management, um die Effektgröße der Maßnahmen zu erhöhen.

Bedeutung der Kardio-MRT

Bildgebende Verfahren spielen eine entscheidende Rolle bei der Diagnose der HFpEF. Die

Echokardiographie ist nach wie vor die primäre Modalität zur Evaluation der diastolischen Dysfunktion und damit zur HFpEF-Diagnostik.[53,92] Kernelement der Bildgebung ist ein Kompositum aus Parametern, um den erhöhten linksventrikulären enddiastolischen Druck (LVEDP) indirekt abzuschätzen, beispielsweise durch das aus der Gewebedopplerechokardiografie abgeleitete E/e'-Verhältnis.[92]

Eine weitere Methode, den myokardialen Kontraktionsablauf zu evaluieren, ist die Strainbildgebung, die ihre prognostische Bedeutung bereits gezeigt hat. Denn sie weist die systolische Dysfunktion, die bei erhaltener LVEF maskiert ist, auf.[55,93] Die Strainbildgebung, die zunächst in der Echokardiographie etabliert war, wurde auch vom Kardio-MRT als leistungsfähige Modalität für hochauflösende Bildgebung zur detaillierten Gewebecharakterisierung adaptiert.[93,94] Die etablierten Parameter der Strainbildgebung sind die der globalen longitudinalen (GLS, *global longitudinal strain*) und zirkumferentiellen Deformation (GCS, *global circumferential strain*).[93] Die Analyse der segmentbasierten Strainevalution hat aufgezeigt, dass die myokardiale Deformation im Rahmen des Kontraktionsablaufes regionale Heterogenitäten aufweist und bei besserer LVEF mit einer eher septal-betonten Strainreduktion einhergeht.[78] Die Korrelation des Strainwertes mit der LVEF legt nahe, dass bei hochgradig eingeschränkter LVEF eine größere Anzahl an Segmenten mehr Einschränkungen der myokardialen Deformation aufzeigt. Dennoch ist über die Entitäten der HI hinweg eine septale Betonung zu sehen, die als mögliche Primärmanifestation einer Dysfunktion gewertet werden kann und sich auch in anderen Populationen bereits als solche herausstellt.[95] Obgleich die vorliegende Analyse keine prognostische Bedeutung evaluiert hat, ist diese Methode eine Fortführung der Granularität der Erfassung systolischer Funktionseinschränkungen bei erhaltener LVEF. Die globalen Strainwerte zeigten bereits einen Mehrwert bezüglich der Patientencharakterisierung. Eine Aufschlüsselung der Patient*innen hinsichtlich der regionalen Verteilung der Straineinschränkungen ist eine Fortsetzung dieses Ansatzes. Ein Unterschied zwischen HFpEF-Patient*innen mit und ohne regionale Straineinschränkungen auch im Therapieansprechen und in der Prognose kann angenommen werden kann, jedoch steht eine prognostische Evaluation noch aus.

Die Identifikation von Personen, die einem höheren Risiko für HFpEF ausgesetzt sind, ist ein zentraler Aspekt bei der Prävention dieser Erkrankung. Aktuell basiert die Identifikation von gefährdeten Patient*innen hauptsächlich auf der Anamnese von Vorerkrankungen oder

kardiovaskulären Risikofaktoren, die zu der Auswahl einer optimierten Therapie führen sollen. Da jedoch die Hauptkomorbiditäten, die mit HFpEF in Verbindung stehen, weit verbreitete Krankheiten sind, bleibt die Eingrenzung der gefährdeten Personen unvollständig.

Die Untersuchung des heterogenen Verteilungsmusters der kardialen Deformation bietet eine Möglichkeit zur Identifikation von Patient*innen, die bereits myokardiale Veränderungen bei erhaltener LVEF aufweisen, jedoch asymptomatisch sind. Dies wurde durch den Vergleich von gesunden Personen, Studienteilnehmenden mit Risikofaktoren und HFpEF-Patient*innen verdeutlicht.[79] Bei dieser Auswertung wurden nicht nur Parameter der Ruhebildgebung, sondern auch der Stress-Bildgebung mittels *handgrip test*, einer Messung der submaximalen willkürlichen Handkraft mittels eines Dynamometers, evaluiert. Die Patient*innen mit Risikofaktoren zeigten in Ruhe ein den HFpEF-Patient*innen ähnliches Verteilungsmuster der Segmente mit eingeschränkter Deformation auf. Dagegen verbesserte sich ihre globale Pumpfunktion unter Belastung und das Verteilungsmuster der myokardialen Segmente entsprach dem der Probanden ohne kardiovaskuläres Risikoprofil. Die HFpEF-Patient*innen hingegen wiesen ihre Einschränkungen auch unter Belastung auf.

Asymptomatische Patient*innen mit Risikofaktoren zählen nach der universellen Definition der Herzinsuffizienz bereits zum Stadium A der Erkrankung, beim Vorliegen kardialer Veränderungen sogar zum Stadium B.[3] Dieses ist durch etablierte LV-Parameter wie LV-Hypertrophie oder LVEF-Einschränkung gekennzeichnet. Ob das Heterogenitätsmuster der regionalen Verteilung von Strainwerten hier hinzugefügt werden kann oder einen Mehrwert gegenüber anderen Parametern bietet, muss noch untersucht werden. In dieser Patientengruppe wurden jedoch zunächst die Machbarkeit und die Rationale des Parameters bestätigt.

Die Verfügbarkeit eines Dynamometers ist ebenso nicht universell gewährleistet, zumal es nicht zur Standardausstattung der Kardio-MRT gezählt wird. Obgleich sich der *handgrip test* als machbar und zielführend dargestellt hat, wird diskutiert, ob die Analyse der willkürlichen Handkraft repräsentativ für eine physiologische Belastung aus dem Alltag der Patient*innen gewertet werden darf.[96,97] Inhaltlich wirkt das gezeichnete Bild kohärent: Patient*innen, die Belastungsbeschwerden zeigen, weisen auch bei Belastung einen Befund auf, der sich von Gesunden unterscheidet. Asymptomatische Proband*innen mit Risikofaktoren, bei denen eine frühe kardiale Veränderung vermutet wird, weisen hingegen zwar in Ruhe veränderte

Messwerte, unter Belastung allerdings unauffällige Werte auf.

Im Kardio-MRT sind diastolische Parameter noch nicht etabliert. Die Integration neuer Parameter in die klinische Praxis gestaltet sich schwierig, weil prospektive klinische Studien zur Evaluation dieser Parameter häufig fehlen – ein Problem, das viele diagnostische Instrumente teilen. Bei modernen Modalitäten ist diese Schwierigkeit besonders ausgeprägt, da die limitierte Verfügbarkeit der Methode an akademischen Zentren eine zusätzliche Hürde darstellt. Beispielsweise hat der HFpEF-Stress-Trial die LVEDP abschätzende Belastungsuntersuchung, die im HFA-PEFF-Algorithmus in Bezug auf die Echokardiographie Erwähnung findet, im Kardio-MRT generiert.[98] Die Untersuchung hinsichtlich der prognostischen Aussagekraft oder eines diagnostischen Mehrwertes steht noch aus, auch wenn die Ergebnisse vielversprechend sind.

In dieser Studie zeigte sich eine signifikante Verschlechterung der funktionellen Kapazität und der Symptombelastung in Abhängigkeit vom Anteil der erhaltenen LV-Segmente.[80] Die Untersuchung, inwiefern der Anteil von erhaltenen LV-Segmenten hinsichtlich des myokardialen Strains mit der funktionalen Kapazität verbunden ist, bildet einen patientenorientierten Endpunkt ab. Die Ergebnisse legen nahe, dass der Anteil an LV-Segmenten mit erhaltener myokardialer Kontraktion dazu beitragen kann, zwischen symptomatischen und asymptomatischen Patient*innen zu unterscheiden, selbst wenn die LVEF erhalten ist. Dieser Befund ist vielversprechend für die Verbesserung der Patientencharakterisierung und des Patientenmanagements und könnte dazu beitragen, die kardiale Bildgebung robuster gegenüber unvollständigen klinischen Informationen zu gestalten.

<u>Limitationen</u>

Die Granularität der Informationen aus dieser Betrachtung ist begrenzt, da bei kleineren Subgruppen die Übertragbarkeit auf andere Patient*innen deutlich behindert wird – zumal die Ausgangspopulation bereits Limitationen hinsichtlich ihrer Größe aufweist. Vor diesem Hintergrund ist diese Analyse als primär explorativ zu werten.

Prospektive diagnostische Studien sind in diesem Umfang zur Etablierung selten, ihre Kraft setzen Methoden häufig durch, wenn eine ergebnisabhängige klinische Konsequenz abgeleitet werden kann und der neue Parameter entscheidungsrelevant wird. Bei der noch

eingeschränkten generellen Verfügbarkeit von Kardio-MRT (v. a. in klinischen Studienzentren) ist dieser Aspekt ein Nachteil, der sich erst im zeitlichen Verlauf mit einer höheren Verfügbarkeit und geringeren infrastrukturellen Kosten wird ändern können.

Eine maßgebliche Limitation dieser Kardio-MRT-Analysen und auch der methodologischen Arbeiten im Kardio-MRT stellt regelhaft die geringe Stichprobengröße und das Fehlen von Verlaufsdaten dar. Um diese Aspekte zu überwinden, sind prospektive Studien zur Evaluierung der prognostischen Aussagekraft und des diagnostischen Mehrwerts von regionaler und globaler myokardialer Deformation notwendig. Die Ergebnisse solcher Studien könnten dazu beitragen, den Stellenwert der myokardialen Deformation bei der Identifikation von Patient*innen mit HFpEF weiter zu klären und möglicherweise neue Ansätze für das Patientenmanagement zu entwickeln.

Aktuell basiert der Standard, Kardio-MRT-Parameter bei HFpEF zu evaluieren, auf zwei Hauptsäulen: (a) Machbarkeitsstudien (*feasibility studies*), wie die vorgestellten Kardio-MRT-Studien oder der HFpEF-Stress-Trial, sowie (b) retrospektive Registerstudien.[78-80,98]

Während Registerstudien häufig den Vorteil einer höheren Fallzahl aufweisen und damit den vermeintlichen Charakter der explorativen Analyse reduzieren, unterstehen sie anderen Verzerrungsfaktoren wie spezifischen Indikationen, die zur Untersuchung führten. Auch andere Faktoren, die retrospektiv nicht zu identifizieren sind, können die Ergebnisse von Registerstudien beeinflussen. Illustrierend kann eine viel diskutierte HFpEF-Registerauswertung dienen, die bei 1203 HFpEF-Patient*innen, die ein Stress-MRT erhalten haben, durchgeführt wurde.[99] Ziel war es die prognostischen Bedeutung eines Nachweises einer myokardialen Ischämie bei HFpEF zu analysieren. Die These bestätigte sich: HFpEF Patient*innen mit induzierbarer Ischämie haben mehr kardiovaskuläre Ereignisse im Langzeitverlauf erlebt als diejenigen ohne Ischämie. Dadurch, dass die ausgewertete Stress-MRT-Bildgebung des Herzens allerdings aus klinischer Indikation heraus durchgeführt wurde, ist ein Selektionsprozess der Analyse vorgeschaltet, der eine Übertragbarkeit auf HFpEF-Patient*innen nicht vorbehaltlos zulässt. Darüber hinaus könnte es ein HFpEF-unabhängiger Effekt sein, dass Patient*innen mit Nachweis einer myokardialen Ischämie häufiger ischämische Ereignisse wie Herzinfarkte und Schlaganfälle erleiden werden.

Den Kritikpunkten der retrospektiven Verzerrung bei Registerstudien und der geringen Fallzahl bei prospektiven Auswertungen begegnend, haben sich auch systemische Reviews

und Meta-Analysen hervorgetan. Eine Meta-Analyse, die die prognostische Bedeutung von Gewebecharakterisierung bei HFpEF ausgewertet hat, identifizierte zwar 1930 Patient*innen aus sieben Studien, deren Daten in ihre Auswertung geflossen sind.[73] Bemerkenswert ist aber bei der Zusammenschau der Studien, dass 1174 der 1930 Patient*innen auf eine Studie fallen und sich die übrigen auf die anderen sechs Studien verteilen; in der weiteren Spezifikation der Studie zeigt sich, dass 801 Patient*innen der 1930 zwar eine HI haben, aber die Entität unbekannt ist. Diese wurden für die Auswertung dennoch berücksichtigt. Die methodologische Kritik der Auswertung außer Acht lassend zeigt sich allerdings auch bei dieser Meta-Analyse, dass die einzelnen Studien auch den Charakter einer *feasibility study* verfolgt haben und ihre Limitationen hinsichtlich der Fallzahl hier keine Möglichkeit zur statistischen Aufwertung hinsichtlich der Studienpower aufweisen.

Um die notwendige statistische Power zu generieren, könnten perspektivisch die Hypothesen der erfolgreichen *feasiblity studies* demonstriert werden. Das Kardio-MRT könnte stärker in Interventionsstudien, als Einschlusskriterium oder Biomarker einer Substudie eingebunden werden. Interventionsstudien kalkulieren ihre Studienpopulation basierend auf moderaten Effektgrößen, sodass bei HI große Fallzahlen zustande kommen und in der Regel auch eine Auswertung der Bedeutung des Kardio-MRT, unabhängig korrigiert für die Intervention, analysiert werden kann. Zeitgleich wird dem Parameter des Kardio-MRT damit nicht nur eine deskriptive Bedeutung beigemessen, da die klinische Implikation bei Nachweis der klinischen Interventionsstudie direkt abgeleitet werden kann.

Conclusio

Diese Arbeit illustriert, dass die Anwendung von Kardio-MRT zur Analyse der myokardialen Deformation mittels segmentaler Strainevaluation bei Patient*innen mit HFpEF vielversprechend ist und möglicherweise zur verbesserten Identifizierung von Patient*innen sowie zur Entwicklung neuer Ansätze für das Patientenmanagement beitragen kann. Die erweiterte Charakterisierung der Patient*innen (beispielsweise durch Einbindung des HFA-PEFF-Scores) kann die diagnostische Präzision noch erhöhen, da mit ihr eine adäquate Risikostratifikation möglich ist. Zukünftige Studien sind prädisponiert dazu, das Kardio-MRT im klinischen Kontext weiter zu untersuchen, insbesondere in Bezug auf gesundheitsökonomische Aspekte wie Verfügbarkeit, Kosten und Nutzen der Technologie.

Eine stärkere Integration von Kardio-MRT in Interventionsstudien sowie die Generierung von größeren Stichprobengrößen und längeren Verlaufsstudien werden entscheidend sein, um die prognostische Aussagekraft und den diagnostischen Mehrwert von Kardio-MRT bei der Behandlung von Patient*innen mit HFpEF zu etablieren und damit die Grundlage für eine verbesserte Patientenversorgung zu schaffen.

6. Zusammenfassung

Diese Arbeit untersucht Herzinsuffizienz, insbesondere HFpEF, und zeigt innovative Kardio-MRT-Methoden für Diagnostik und Präventions- sowie Behandlungsstrategien auf.

HFpEF ist eine Erkrankung mit limitierten Behandlungsmöglichkeiten und komplexer Diagnostik und Risikostratifizierung. Der HFA-PEFF-Algorithmus verspricht eine adäquate Diagnosestellung der HFpEF. Dass dieser Algorithmus zuverlässige Prognosen für Morbidität und Mortalität bei HFpEF-Patient*innen bietet, wurde untersucht und bestätigt. Aufgrund der limitierten therapeutischen Maßnahmen steht hier vor allem die Prävention im Vordergrund der Behandlungsstrategie.

Die Notwendigkeit eines besseren Managements von HFpEF ergibt sich auch aus den gesundheitsbezogenen Kosten der ambulanten HFpEF-Patient*innen der ALDO-DHF-Studie, bei denen Krankenhausaufenthalte die Hauptkostenfaktoren sind.

Um eine Risikostratifizierung für HFpEF zu etablieren, wurde die Myokarddeformation im Kontraktionsablauf mittels Kardio-MRT in höherer Granularität untersucht, wobei einzelne myokardiale Segmente und das resultierende Verteilungsmuster der Deformationsveränderung ausgewertet wurden. Mit dieser Methode können Proband*innen mit kardiovaskulären Risikofaktoren von denen ohne Risikofaktoren unterschieden werden, da sie in Ruhe ein Verteilungsmuster wie HFpEF-Patient*innen und unter Belastung ein Muster wie Gesunde zeigen. Zudem konnte der Trend identifiziert werden, dass dieser Verteilungsparameter auch die funktionale Kapazität von HI-Patientinnen abbildet, selbst wenn die LVEF erhalten ist.

Die gewonnenen Erkenntnisse könnten dazu beitragen, die Versorgung von Patient*innen mit HI zu verbessern, indem sie neue Wege zur Identifizierung von Risikopatient*innen und verbesserte Diagnosemethoden aufzeigen, die zu präventiven Behandlungsstrategien führen können. Die Validierung der prognostischen Bedeutung von HI-Parametern des Kardio-MRT in Interventionsstudien bildet den nächsten Schritt, da neben Validierung auch eine klinische Konsequenz prospektiv mit den Methoden verbunden und untersucht wird. Diese Kombination verspricht, die Behandlung von HFpEF-Patient*innen zu optimieren und dem Kardio-MRT einen angemessenen Stellenwert im Management-Prozess der Erkrankten und der von HI Bedrohten zu verleihen.

7. Literaturangaben

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European heart journal*. 2021;42:3599-3726. doi: 10.1093/eurheartj/ehab368
2. Stewart Coats AJ. Validating the HFA-PEFF score - or how to define a disease? *European journal of heart failure*. 2020;22:428-431. doi: 10.1002/ejhf.1770
3. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, et al. Universal Definition and Classification of Heart Failure. *Journal of Cardiac Failure*. 2021;27:387-413. doi: 10.1016/j.cardfail.2021.01.022
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *European journal of heart failure*. 2016;18:891-975. doi: 10.1002/ejhf.592
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147-239. doi: 10.1016/j.jacc.2013.05.019
6. Alba AC, Rao V, Ivanov J, Ross HJ, Delgado DH. Usefulness of the INTERMACS scale to predict outcomes after mechanical assist device implantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2009;28:827-833. doi: 10.1016/j.healun.2009.04.033
7. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263-e421. doi: 10.1016/j.jacc.2021.12.012
8. Frantz S, Anker SD, Bauersachs J, Boer J, Böhm M, Busch S, Frey N, Perings CA, Rudolph TK, Schulze PC, et al. *Pocket-Leitlinie: Akute und chronische Herzinsuffizienz (Version 2021) || 2021 ESC Pocket Guidelines for the diagnosis and treatment of acute and chronic heart failure - German version.* Grünwald: Bruckmeier Verlag GmbH; 2022.
9. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2006;8:417-426. doi: 10.1080/10976640600572889
10. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3:7-11. doi: 10.15420/cfr.2016:25:2
11. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25:1614-1619. doi: 10.1016/j.ehj.2004.06.038
12. Stork S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S. Epidemiology of heart failure in Germany: a retrospective database study. *Clin Res Cardiol*. 2017;106:913-922. doi: 10.1007/s00392-017-1137-7
13. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J*. 1999;20:447-455.

14. Tisdale RL, Fan J, Calma J, Cyr K, Podchiyska T, Stafford RS, Maron DJ, Hernandez-Boussard T, Ambrosy A, Heidenreich PA, et al. Predictors of Incident Heart Failure Diagnosis Setting: Insights From the Veterans Affairs Healthcare System. *JACC Heart Fail*. 2022. doi: 10.1016/j.jchf.2022.11.013
15. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2011;13:18-28. doi: 10.1093/eurjhf/hfq121
16. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nature reviews Cardiology*. 2014;11:507-515. doi: 10.1038/nrcardio.2014.83
17. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*. 2013;62:263-271. doi: 10.1016/j.jacc.2013.02.092
18. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC, Get With the Guidelines Scientific Advisory C, Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation*. 2012;126:65-75. doi: 10.1161/CIRCULATIONAHA.111.080770
19. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. *Nat Rev Cardiol*. 2022;19:100-116. doi: 10.1038/s41569-021-00605-5
20. McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. *Heart*. 2000;83:596-602. doi: 10.1136/heart.83.5.596
21. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1574-1585. doi: 10.1002/ejhf.813
22. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. *Circ Res*. 2019;124:1598-1617. doi: 10.1161/CIRCRESAHA.119.313572
23. Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA*. 2009;302:394-400. doi: 10.1001/jama.2009.1062
24. Piano MR, Phillips SA. Alcoholic cardiomyopathy: pathophysiologic insights. *Cardiovasc Toxicol*. 2014;14:291-308. doi: 10.1007/s12012-014-9252-4
25. Ronco C, Bellasi A, Di Lullo L. Cardiorenal Syndrome: An Overview. *Adv Chronic Kidney Dis*. 2018;25:382-390. doi: 10.1053/j.ackd.2018.08.004
26. Meder B, Ruhle F, Weis T, Homuth G, Keller A, Franke J, Peil B, Lorenzo Bermejo J, Frese K, Huge A, et al. A genome-wide association study identifies 6p21 as novel risk locus for dilated cardiomyopathy. *Eur Heart J*. 2014;35:1069-1077. doi: 10.1093/eurheartj/eht251
27. Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circ Res*. 2017;121:749-770. doi: 10.1161/CIRCRESAHA.117.311059
28. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10:531-547. doi: 10.1038/nrcardio.2013.105
29. Munzel T, Sorensen M, Schmidt F, Schmidt E, Steven S, Kroller-Schon S, Daiber A. The Adverse Effects of Environmental Noise Exposure on Oxidative Stress and Cardiovascular Risk. *Antioxid Redox Signal*. 2018;28:873-908. doi: 10.1089/ars.2017.7118
30. Munzel T, Gori T, Babisch W, Basner M. Cardiovascular effects of environmental noise exposure. *Eur Heart J*. 2014;35:829-836. doi: 10.1093/eurheartj/ehu030
31. Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, et al. Particulate matter air pollution and cardiovascular disease:

An update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331-2378. doi: 10.1161/CIR.0b013e3181dbece1
32. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14:591-602. doi: 10.1038/nrcardio.2017.65
33. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, Harjola VP, Drexler H, Dickstein K, Tavazzi L, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J*. 2009;30:478-486. doi: 10.1093/eurheartj/ehn539
34. Komajda M, Hanon O, Hochadel M, Follath F, Swedberg K, Gitt A, Cleland JG. Management of octogenarians hospitalized for heart failure in Euro Heart Failure Survey I. *Eur Heart J*. 2007;28:1310-1318. doi: 10.1093/eurheartj/ehl443
35. Feltner C, Jones CD, Cene CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJ, Arvanitis M, Lohr KN, Middleton JC, Jonas DE. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med*. 2014;160:774-784. doi: 10.7326/M14-0083
36. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail*. 2014;1:4-25. doi: 10.1002/ehf2.12005
37. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021;143:e254-e743. doi: 10.1161/CIR.0000000000000950
38. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204-1222. doi: 10.1016/S0140-6736(20)30925-9
39. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, et al. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health*. 2017;5:e665-e672. doi: 10.1016/S2214-109X(17)30196-1
40. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004-2016. *BMC Cardiovasc Disord*. 2018;18:74. doi: 10.1186/s12872-018-0815-3
41. Schwinger RHG. Pathophysiology of heart failure. *Cardiovasc Diagn Ther*. 2021;11:263-276. doi: 10.21037/cdt-20-302
42. Braunwald E. Heart failure. *JACC Heart Fail*. 2013;1:1-20. doi: 10.1016/j.jchf.2012.10.002
43. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. 2000;35:569-582. doi: 10.1016/s0735-1097(99)00630-0
44. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac Fibrosis: The Fibroblast Awakens. *Circ Res*. 2016;118:1021-1040. doi: 10.1161/CIRCRESAHA.115.306565
45. Marks AR. Calcium cycling proteins and heart failure: mechanisms and therapeutics. *J Clin Invest*. 2013;123:46-52. doi: 10.1172/JCI62834
46. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009;54:1747-1762. doi: 10.1016/j.jacc.2009.05.015
47. Eisner DA, Caldwell JL, Kistamas K, Trafford AW. Calcium and Excitation-Contraction Coupling in the Heart. *Circ Res*. 2017;121:181-195. doi: 10.1161/CIRCRESAHA.117.310230
48. Rosca MG, Hoppel CL. Mitochondrial dysfunction in heart failure. *Heart Fail Rev*. 2013;18:607-622. doi: 10.1007/s10741-012-9340-0

49. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953-1959. doi: 10.1056/NEJMoa032566
50. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32:670-679. doi: 10.1093/eurheartj/ehq426
51. Zile MR, Baicu CF. Biomarkers of diastolic dysfunction and myocardial fibrosis: application to heart failure with a preserved ejection fraction. *J Cardiovasc Transl Res*. 2013;6:501-515. doi: 10.1007/s12265-013-9472-1
52. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, Francis GS, Lenihan D, Lewis EF, McNamara DM, et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e579-e646. doi: 10.1161/CIR.0000000000000455
53. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297-3317. doi: 10.1093/eurheartj/ehz641
54. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation*. 2018;138:861-870. doi: 10.1161/CIRCULATIONAHA.118.034646
55. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63:447-456. doi: 10.1016/j.jacc.2013.09.052
56. Huntjens PR, Zhang KW, Soyama Y, Karmpalioti M, Lenihan DJ, Gorcsan J, 3rd. Prognostic Utility of Echocardiographic Atrial and Ventricular Strain Imaging in Patients With Cardiac Amyloidosis. *JACC Cardiovasc Imaging*. 2021;14:1508-1519. doi: 10.1016/j.jcmg.2021.01.016
57. Guder G, Ertl G, Angermann CE. [Diagnostics and treatment of chronic heart failure : Update 2020]. *Herz*. 2020. doi: 10.1007/s00059-019-04877-z
58. Mullens W, Martens P, Testani JM, Tang WHW, Skouri H, Verbrugge FH, Fudim M, Iacoviello M, Franke J, Flammer AJ, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*. 2022;24:603-619. doi: https://dx.doi.org/10.1002/ejhf.2471
59. Bauersachs J. Heart failure drug treatment: the fantastic four. *Eur Heart J*. 2021;42:681-683. doi: 10.1093/eurheartj/ehaa1012
60. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387:1089-1098. doi: 10.1056/NEJMoa2206286
61. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385:1451-1461. doi: 10.1056/NEJMoa2107038
62. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med*. 2018;379:2307-2318. doi: 10.1056/NEJMoa1806640
63. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-847. doi: 10.1161/CIRCULATIONAHA.113.005119

64. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, Winkler S, Vettorazzi E, Bruch L, Oeff M, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet*. 2018;392:1047-1057. doi: 10.1016/S0140-6736(18)31880-4
65. Guder G, Stork S, Gelbrich G, Brenner S, Deubner N, Morbach C, Wallenborn J, Berliner D, Ertl G, Angermann CE. Nurse-coordinated collaborative disease management improves the quality of guideline-recommended heart failure therapy, patient-reported outcomes, and left ventricular remodelling. *Eur J Heart Fail*. 2015;17:442-452. doi: 10.1002/ejhf.252
66. Riley JP, Masters J. Practical multidisciplinary approaches to heart failure management for improved patient outcome. *Eur heart j suppl*. 2016;18:G43-G52. doi: 10.1093/eurheartj/suw046
67. Luedike P, Papathanasiou M, Schmack B, Kamler M, Perings C, Ruhparwar A, Rassaf T. Structural components for the development of a heart failure network. *ESC Heart Fail*. 2022. doi: 10.1002/ehf2.14266
68. Reddy YN, Borlaug BA. Heart Failure With Preserved Ejection Fraction. *Curr Probl Cardiol*. 2016;41:145-188. doi: 10.1016/j.cpcardiol.2015.12.002
69. Shah SJ, Katz DH, Deo RC. Phenotypic spectrum of heart failure with preserved ejection fraction. *Heart Fail Clin*. 2014;10:407-418. doi: 10.1016/j.hfc.2014.04.008
70. McGranaghan P, Dungen HD, Saxena A, Rubens M, Salami J, Radenkovic J, Bach D, Apostolovic S, Loncar G, Zdravkovic M, et al. Incremental prognostic value of a novel metabolite-based biomarker score in congestive heart failure patients. *ESC Heart Fail*. 2020;7:3029-3039. doi: 10.1002/ehf2.12928
71. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321-1360. doi: 10.1093/ehjci/jew082
72. Opitz CF, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, Scelsi L, D'Alto M, Olsson KM, Ulrich S, et al. Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. *J Am Coll Cardiol*. 2016;68:368-378. doi: 10.1016/j.jacc.2016.05.047
73. Golukhova E, Bulaeva N, Alexandrova S, Gromova O, Berdibekov B. Prognostic Value of Characterizing Myocardial Tissue by Cardiac MRI with T1 Mapping in HFpEF Patients: A Systematic Review and Meta-Analysis. *J Clin Med*. 2022;11. doi: 10.3390/jcm11092531
74. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010;363:301-304. doi: 10.1056/NEJMp1006304
75. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269-279. doi: 10.1161/CIRCULATIONAHA.114.010637
76. Hashemi D, Mende M, Trippel TD, Petutschnigg J, Hasenfuss G, Nolte K, Herrmann-Lingen C, Feuerstein A, Langhammer R, Tschope C, et al. Evaluation of the HFA-PEFF Score: results from the prospective DIAST-CHF cohort. *ESC Heart Fail*. 2022. doi: 10.1002/ehf2.14131
77. Hashemi D, Dettmann L, Trippel TD, Holzendorf V, Petutschnigg J, Wachter R, Hasenfuß G, Pieske B, Zapf A, Edelmann F. Economic impact of heart failure with preserved ejection fraction: insights from the ALDO-DHF trial. *ESC Heart Failure*. 2020;7. doi: 10.1002/ehf2.12606
78. Hashemi D, Motzkus L, Blum M, Kraft R, Tanacli R, Tahirovic E, Doeblin P, Zieschang V, Zamani SM, Kelm M, et al. Myocardial deformation assessed among heart failure entities by cardiovascular magnetic resonance imaging. *ESC Heart Failure*. 2021. doi: 10.1002/ehf2.13193
79. Hashemi D, Doeblin P, Blum M, Weiss KJ, Schneider M, Korosoglou G, Beyer RE, Pieske B, Edelmann F, Kelle S. CMR detects decreased myocardial deformation in asymptomatic patients

at risk for heart failure. *Front Cardiovasc Med*. 2022;9:1091768. doi: 10.3389/fcvm.2022.1091768
80. Hashemi D, Doeblin P, Blum M, Weiss KJ, Schneider M, Beyer R, Pieske B, Duengen HD, Edelmann F, Kelle S. Reduced functional capacity is associated with the proportion of impaired myocardial deformation assessed in heart failure patients by CMR. *Front Cardiovasc Med*. 2023;10:1038337. doi: 10.3389/fcvm.2023.1038337
81. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca H-P, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VPM. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *European journal of heart failure*. 2019:1-9. doi: 10.1002/ejhf.1614
82. Tada A, Nagai T, Omote K, Iwano H, Tsujinaga S, Kamiya K, Konishi T, Sato T, Komoriyama H, Kobayashi Y, et al. Performance of the H(2)FPEF and the HFA-PEFF scores for the diagnosis of heart failure with preserved ejection fraction in Japanese patients: A report from the Japanese multicenter registry. *International journal of cardiology*. 2021;342:43-48. doi: 10.1016/j.ijcard.2021.08.001
83. Sun Y, Si J, Li J, Dai M, King E, Zhang X, Zhang Y, Xia Y, Tse G, Liu Y. Predictive Value of HFA-PEFF Score in Patients With Heart Failure With Preserved Ejection Fraction. *Frontiers in cardiovascular medicine*. 2021;8:656536-656536. doi: 10.3389/fcvm.2021.656536
84. Egashira K, Sueta D, Komorita T, Yamamoto E, Usuku H, Tokitsu T, Fujisue K, Nishihara T, Oike F, Takae M, et al. HFA-PEFF scores: prognostic value in heart failure with preserved left ventricular ejection fraction. *The Korean journal of internal medicine*. 2022;37:96-108. doi: 10.3904/kjim.2021.272
85. Amanai S, Harada T, Kagami K, Yoshida K, Kato T, Wada N, Obokata M. The H(2)FPEF and HFA-PEFF algorithms for predicting exercise intolerance and abnormal hemodynamics in heart failure with preserved ejection fraction. *Scientific reports*. 2022;12:13-13. doi: 10.1038/s41598-021-03974-6
86. Faxen UL, Venkateshvaran A, Shah SJ, Lam CSP, Svedlund S, Saraste A, Beussink-Nelson L, Lagerstrom Fermer M, Gan L-M, Hage C, et al. Generalizability of HFA-PEFF and H2FPEF Diagnostic Algorithms and Associations With Heart Failure Indices and Proteomic Biomarkers: Insights From PROMIS-HFpEF. *Journal of Cardiac Failure*. 2021;00. doi: 10.1016/j.cardfail.2021.02.005
87. Hollenberg SM, Warner Stevenson L, Ahmad T, Amin VJ, Bozkurt B, Butler J, Davis LL, Drazner MH, Kirkpatrick JN, Peterson PN, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2019;74:1966-2011. doi: 10.1016/j.jacc.2019.08.001
88. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482-1487. doi: 10.1161/CIRCULATIONAHA.107.696906
89. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004-2016. *BMC cardiovascular disorders*. 2018;18:74-74. doi: 10.1186/s12872-018-0815-3
90. Robert-Koch-Institut. Gesundheit in Deutschland. www.gbe-bund.de. 2015.
91. Li CY, Sung FC. A review of the healthy worker effect in occupational epidemiology. *Occup Med (Lond)*. 1999;49:225-229. doi: 10.1093/occmed/49.4.225
92. Smiseth OA, Morris DA, Cardim N, Cikes M, Delgado V, Donal E, Flachskampf FA, Galderisi M, Gerber BL, Gimelli A, et al. Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of

Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2022;23:e34-e61. doi: 10.1093/ehjci/jeab154
93. Pedrizzetti G, Lapinskas T, Tonti G, Stoiber L, Zaliunas R, Gebker R, Pieske B, Kelle S. The Relationship Between EF and Strain Permits a More Accurate Assessment of LV Systolic Function. *JACC Cardiovasc Imaging*. 2019;12:1893-1895. doi: 10.1016/j.jcmg.2019.03.019
94. Telles F, Marwick TH. Imaging and Management of Heart Failure and Preserved Ejection Fraction. *Curr Treat Options Cardiovasc Med*. 2018;20:90. doi: 10.1007/s11936-018-0689-9
95. Becker MAJ, van der Lingen ACJ, Wubben M, van de Ven PM, van Rossum AC, Cornel JH, Allaart CP, Germans T. Characteristics and prognostic value of right ventricular (dys)function in patients with non-ischaemic dilated cardiomyopathy assessed with cardiac magnetic resonance imaging. *ESC Heart Fail*. 2021;8:1055-1063. doi: 10.1002/ehf2.13072
96. von Knobelsdorff-Brenkenhoff F, Dieringer MA, Fuchs K, Hezel F, Niendorf T, Schulz-Menger J. Isometric handgrip exercise during cardiovascular magnetic resonance imaging: set-up and cardiovascular effects. *J Magn Reson Imaging*. 2013;37:1342-1350. doi: 10.1002/jmri.23924
97. Rommel KP, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, Besler C, Sandri M, Lucke C, Gutberlet M, et al. Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol*. 2016;67:1815-1825. doi: 10.1016/j.jacc.2016.02.018
98. Backhaus SJ, Lange T, George EF, Hellenkamp K, Gertz RJ, Billing M, Wachter R, Steinmetz M, Kutty S, Raaz U, et al. Exercise Stress Real-Time Cardiac Magnetic Resonance Imaging for Noninvasive Characterization of Heart Failure With Preserved Ejection Fraction: The HFpEF-Stress Trial. *Circulation*. 2021;143:1484-1498. doi: 10.1161/CIRCULATIONAHA.120.051542
99. Pezel T, Hovasse T, Sanguineti F, Kinnel M, Garot P, Champagne S, Toupin S, Unterseeh T, Garot J. Long-Term Prognostic Value of Stress CMR in Patients With Heart Failure and Preserved Ejection Fraction. *JACC Cardiovasc Imaging*. 2021;14:2319-2333. doi: 10.1016/j.jcmg.2021.03.010

8. Danksagung

Es ist mir eine aufrührende Ehre, die Gelegenheit zu haben, eine Handvoll Menschen zu würdigen, die meine akademische Reise maßgeblich geprägt und bereichert haben. Meine Habilitation ist das Resultat eines Kollektivs von Unterstützung, Anregung und Ausdauer, sowohl auf privater als auch auf professioneller Ebene.

Zuallererst möchte ich meine tiefe Dankbarkeit gegenüber meiner wunderbaren Frau, Friederike Hashemi, ausdrücken. Sie verkörpert eine stärkende Kraft, eine unbeirrbare Willensstärke, die mir immer wieder Mut gemacht hat. Sie hat persönliche Ambitionen zurückgestellt, damit ich meinem akademischen Wunsch nachgehen konnte, und dies bei den besonderen Herausforderungen unseres Familienlebens. Rieke, Deine Liebe und Deine Unterstützung haben diese Arbeit erst möglich gemacht.

An meine Tochter Neda, deren Neugier so lebendig ist, dass sie förmlich aus ihren Augen strahlt. Dein ständiger Wissensdurst ist eine Inspiration für mich und erinnert mich stets an die Wichtigkeit des ständigen Lernens.

Mein Sohn Navid, dem stärksten und wärmsten Menschen, den ich kenne, war mir eine Inspiration bei allen Herausforderungen mit positiver Kraft immer weiterzumachen. Deine Energie und Lebensfreude haben mir stets Kraft gegeben.

Meiner Schwester Farieba bin ich dankbar, dass sie in den schwierigsten Zeiten immer da war, um den Moment zu halten, damit ich kurz Luft holen konnte, um weiterzumachen.

Im professionellen Kontext gibt es viele, denen ich zu danken habe.

Professor Sebastian Kelle, der mich früh in meine Karriere einband und als Mentor meine Entwicklung zu einem unabhängigen Wissenschaftler gefördert hat. Professor Frank Edelmann, der mich in konkreten Projekten und in der Entwicklung wissenschaftlicher Netzwerke unterstützte. PD Dr. Tobias Daniel Trippel, der seit meinem praktischen Jahr an mich geglaubt und mich durch private und berufliche Herausforderungen geleitet hat.

Mein Dank gilt ebenfalls Professor Burkert Pieske, der meine Eigenart und Stärke erkannte und mich in seiner Klinik früh förderte. Herrn Professor Dr. Hans-Dirk Düngen und Herrn Dr. Elvis Tahirovic danke ich für die Wegbereitung in die klinische Forschung.

Ich danke dem Deutschen Zentrum für Herz-Kreislauf-Forschung (DZHK), das mich stets finanziell und ideell unterstützt hat. Ein besonderer Dank gilt hier Professor Holger Gerhardt, der eine tiefgreifende Verpflichtung zur Förderung des wissenschaftlichen Nachwuchses zeigt und mich mit hilfreichen Ratschlägen und seiner schützenden Hand unterstützt hat.

An meine Kursdirektoren, Professor Jane Armitage und Louise Bowman, und meine Kommilitonen im Masterstudium in Oxford, danke ich für die strukturierte Lehre des akademischen Denkens in klinischen Studien. Und schließlich danke ich den Kolleginnen und Kollegen der Charité, mit denen ich mich entwickelt habe, für ihre Geduld und die zahlreichen anregenden Diskussionen.

Ich bin mir bewusst, dass es noch viele weitere Menschen gibt, die zu meiner wissenschaftlichen Entwicklung beigetragen haben und denen ich hiermit meine Anerkennung und meinen Dank ausspreche. Sie alle haben einen unschätzbaren Einfluss auf meine Arbeit und auf mein Leben gehabt.

Schließlich möchte ich meine Dankbarkeit gegenüber meinen Freunden und meiner erweiterten Familie ausdrücken, die mich immer mit ihren Gedanken, Gebeten und besten Wünschen unterstützt haben. Eure unerschütterliche Unterstützung und eure ermutigenden Worte in Zeiten des Zweifels und der Erschöpfung haben mir geholfen, diesen Weg zu beschreiten.

Ich bin tief dankbar für diese Gemeinschaft von Menschen, die mich auf meiner Reise begleitet haben, und ich freue mich darauf, die Früchte dieser Arbeit mit euch allen zu teilen. Eure Rolle in diesem wichtigen Kapitel meines Lebens wird immer in Ehren gehalten werden.

Danke.

9. Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, den 16.05.2023

……

Dr. med. Djawid Hashemi, MSc