Herzinsuffizienz mit erhaltener Pumpfunktion

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Entwicklung therapeutischer Konzepte durch pathomechanistische Charakterisierung und klinische Phänotypisierung

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Herzinsuffizienz mit erhaltener Pumpfunktion – Entwicklung therapeutischer Konzepte durch pathomechanistische Charakterisierung und klinische Phänotypisierung

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Die wissenschaftlichen Arbeiten in dieser Habilitationsschrift belegen die phänotypische Heterogenität der Herzinsuffizienz mit erhaltener Pumpfunktion (HFpEF) und zeigen, dass eine erweiterte pathomechanistische und klinische Phänotypisierung geeignet ist um homogenere Subgruppen und Therapieziele zu identifizieren.

Eine erweiterte pathomechanistische Charakterisierung mittels kardialer Magnetresonanztomographie und invasiver Druck-Volumenanalyse ermöglichte dabei die Identifikation zweier hämodynamischer Phänotypen, die sich anhand des Ausmaßes der interstitiellen linksventrikulären (LV) Fibrosierung unterscheiden. Eine so durchgeführte Stratifizierung ermöglicht die Individualisierung potentieller Therapien anhand des Vorliegens einer LV Fibrose, wobei aktuelle Studien die Reduktion der myozytären Steifigkeit und Fibroseentwicklung in der einen und eine spezifische Fibrosereduktion in der anderen Gruppe untersuchen. Mittels pathomechanistischer Charakterisierung konnten außerdem potentiell neue Therapieziele identifiziert werden. So konnte gezeigt werden, dass eine Störung der phasischen linksatrialen (LA) Funktion unabhängig von LV Funktionsstörungen mit einer eingeschränkten Belastbarkeit in HFpEF assoziiert ist. Gemeinsam mit Untersuchungen anderer Gruppen wurde so das Konzept der LA Myopathie als maßgeblicher pathophysiologischer Faktor der HFpEF etabliert, auf deren Grundlage aktuell spezifische Therapien zur Modulation der LA Drücke in HFpEF untersucht werden. Außerdem wurde dargelegt, dass eine diastolische rechtsventrikuläre und rechtsatriale Dysfunktion bereits früh im Verlauf einer HFpEF auftreten und maßgeblich zur Unfähigkeit der Steigerung des Herzzeitvolumens unter Belastung beitragen. Dies legt zum einen nahe, dass zukünftig potentielle Therapien auch insbesondere hinsichtlich ihrer Effekte auf diese Funktionsstörungen beurteilt werden sollten und bildet zum anderen den Ausgangspunkt für weitere mechanistische Studien zur Entwicklung spezifischer Therapien.

Eine klinische Phänotypisierung anhand der Stratifizierung von HFpEF Patienten nach dem Vorliegen einer hochgradigen Trikuspidalklappeninsuffizienz (TI) identifizierte ein HFpEF Kollektiv mit hoher Symptomlast und eingeschränkter Prognose. Für eine interventionelle Reduktion der TI konnte gezeigt werden, dass diese die biventrikuläre Hämodynamik und das klinische Outcome verbessert und sie damit eine attraktive Therapieoption in dieser Gruppe darstellt. In dieser Habilitationsschrift konnte weiterhin demonstriert werden, dass HFpEF Patienten mit resistenter arterieller Hypertonien einen Phänotyp in einem frühen Erkrankungsstadium darstellen, der durch einen erhöhten Sympathikotonus, eine arterielle und ventrikuläre Steifigkeit sowie eine relative LV Hyperkontraktilität als potentielle Therapieziele charakterisiert ist. Die interventionelle renale Denervation stellt ein vielversprechendes Therapiekonzept für diesen Phänotyp dar.

Die dargestellten Arbeiten und Ergebnisse zur Phänotypisierung von HFpEF Patienten bieten neue Einblicke und eröffnen neue Wege für zukünftige Studien auf diesem Gebiet. Offene Fragen verbleiben hinsichtlich der therapeutischen Relevanz pathomechanistisch identifizierter Phänotypen und deren Rolle in der Modulierung des natürlichen Verlaufs der HFpEF. Therapiestudien unter Beachtung der aktuellen Ergebnisse und longitudinale Studien zur Identifizierung von Faktoren, die mit der Entwicklung einer HFpEF beziehungsweise deren Progression einhergehen, werden zur Klärung dieser Zusammenhänge notwendig sein.

INHALTSVERZEICHNIS

1 EINFÜHRUNG IN DIE THEMATIK

1.1 EINLEITUNG

Die chronische Herzinsuffizienz stellt eine der häufigsten internistischen Erkrankungen dar. Ihre Prävalenz steigt mit zunehmendem Alter und ist einer der wichtigsten Mortalitäts- und Morbiditätsfaktoren in der westlichen Gesellschaft (1). Neben der Sterblichkeit führen insbesondere die Belastungsintoleranz, chronische Luftnot und wiederholte Krankenhausaufnahmen (27.382 Fälle pro Jahr allein in Sachsen, deutschlandweit etwa 500 Fälle pro 100.000 Einwohner jährlich) zu einer erheblichen Einschränkung der Lebensqualität und Kosten für das Gesundheitssystem (2,3).

Bis vor kurzem stand vor allem eine Einschränkung der linksventrikulären Pumpfunktion (systolische Dysfunktion) im Fokus der Diagnose und Behandlung der Herzinsuffizienz (HFrEF). In den letzten drei Jahrzenten etablierte sich zunehmend das Konzept einer Füllungsstörung des linken Ventrikels (diastolische Dysfunktion) als bedeutender Faktor für die Ausprägung einer Herzinsuffizienz. Verbesserungen der invasiven, serologischen und echokardiographischen Diagnostik in den 1990er und 2000er Jahren führten zu einer zunehmenden Detektion von Patienten mit Herzinsuffizienz und normaler linksventrikulärer Pumpfunktion (HFpEF) (4).

Aktuell ist die HFpEF die dominierende Herzinsuffizienzform weltweit, insbesondere ab einem Alter von 65 Jahren, mit steigender Inzidenz und Prävalenz und deutlich erhöhter Morbidität und Mortalität (5). Während in den letzten Jahren multiple effektive Therapien für die Behandlung von HFrEF Patienten etabliert wurden, konnte in den meisten klinischen Studien zur Behandlung der HFpEF bis dato keine Therapieerfolg gezeigt werden (6,7).

Insgesamt ergibt sich aus dem Zusammentreffen eines häufigen Krankheitsbildes mit ungünstiger Prognose und fehlenden Therapieoptionen die dringende Notwendigkeit der Entwicklung neuer therapeutischer und präventiver Konzepte.

Als Hauptargument der bisherigen therapeutischen Misserfolge wird die pathophysiologische Heterogenität der Gesamtheit der HFpEF Patienten ins Feld geführt. Unterschiede in den vorliegenden klinischen Komorbiditäten aber auch hämodynamischen oder molekularen Merkmalen könnten Gründe für ein nicht einheitliches Therapieansprechen sein (7). Die Mechanismen der Krankheitsentstehung sind bis dato auch vor dem Hintergrund der pathophysiologischen Heterogenität unzureichend verstanden, wodurch eine Prädiktion und damit Prävention gehindert wird.

In dieser Habilitationsschrift werden Arbeiten dargestellt und diskutiert, deren Ziel es war mittels detaillierter Patientencharakterisierung individuelle Pathologien zu identifizieren um die Heterogenität des Gesamtkollektivs zu verringern, neue pathophysiologische Zusammenhänge aufzudecken und interventionelle Therapien für spezifische klinische Subgruppen zu entwickeln.

1.2 ZIELSETZUNGEN UND AUFBAU DER ARBEIT

In den folgenden einführenden Kapiteln wird zunächst die klinische Problematik der der HFpEF diskutiert (Kapitel 1.3). Zum einen ergibt sich daraus die dringliche Notwendigkeit der ausführlichen pathomechanistischen Charakterisierung von HFpEF Patienten mit Identifikation von Subgruppen homogenerer Pathophysiologie. Zum anderen soll verdeutlicht werden wie die Identifikation von Subgruppen mit dominierender Pathophysiologie der Zuführung individualisierter Therapien dienlich sein kann. Kapitel 1.4 gibt einen Überblick über potentielle Möglichkeiten der pathomechanistischen Phänotypisierung und interventionellen Therapie klinischer HFpEF Subgruppen am Beispiel der interventionellen Trikuspidalklappenrekonstruktion (TTVR) und der renalen Sympathikusmodulation (RDN).

Im ersten Kapitel der Originalarbeiten (2.1) werden Ergebnisse zur pathomechanistischen Phänotypisierung von HFpEF Patienten mittels kardialer Magnetresonanztomographie (MRT) und weiterführender hämodynamischer Charakterisierung durch Aufzeichnung invasiver Druck-Volumenbeziehungen dargestellt. Dabei wird in Kapitel 2.1.1 dargelegt wie mittels neuartiger nicht-invasiver Gewebecharakterisierung zur Quantifizierung der myokardialen Fibrosierung in der kardialen MRT hämodynamische Phänotypen identifiziert werden können. In den Kapitel 2.1.2 bis 2.1.4 werden Funktionsstörungen des rechten Ventrikels, sowie des linken und rechten Vorhofs als neue und eigenständige pathomechanistische Faktoren für Patienten mit HFpEF analysiert.

Im Kapitel 2.2 wird die klinische Etablierung und der potentielle Nutzen einer interventionellen Therapie der Trikuspidalklappeninsuffizienz (TI) in HFpEF dargestellt. Kapitel 2.2.1 beschreibt die biventrikulären hämodynamischen Effekte dieses neuartigen Therapiekonzeptes. In Kapitel 2.2.2 wird der klinische Nutzen für Patienten mit Herzinsuffizienz im Sinne einer Reduktion der Hospitalisierungsrate beschrieben. Da das Auftreten einer relevanten TI bei HFpEF Patienten in erster Linie durch die Entwicklung

einer pulmonalen Hypertonie (PHT) erklärt wird, werden klinische Effekte der TTVR vor dem Hintergrund des Vorliegens einer PHT in Kapitel 2.2.3 analysiert. In Kapitel 2.2.4 wird der klinische Nutzen der Therapie für Patienten mit HFpEF im Vergleich zu Patienten mit HFrEF und einer medikamentös behandelten Kontrollgruppe dargelegt.

Die Arbeiten in Kapitel 2.3 widmen sich der Etablierung der interventionellen Sympathikusmodulation mittels renaler Denervation (RDN) als potentielles Therapiekonzept für HFpEF Patienten. Kapitel 2.3.1 gibt einen Überblick über mögliche physiologische Effekte der RDN, während in Kapitel 2.3.2 die hämodynamischen Ursachen einer Blutdrucksenkung nach RDN genauer untersucht werden. Hierbei zeigt sich, dass eine Blutdruckreduktion maßgeblich über eine linksventrikuläre Schlagvolumenreduktion vermittelt wird. Im Kapitel 2.3.3 wird dargestellt, dass HFpEF Patienten mit resistenter Hypertonie phänotypisch durch ein erhöhtes linksventrikuläres Schlagvolumen sowie erhöhte vaskuläre und ventrikuläre Steifigkeit charakterisiert sind und dass diese Veränderungen durch eine RDN teilweise normalisiert werden können.

Die Ergebnisse dieser Arbeiten führten zur Formulierung und Untersuchung folgender Hypothesen:

1. HFpEF ist charakterisiert durch eine pathomechanistische und klinische Heterogenität die der Entwicklung einheitlicher therapeutischer Konzepte entgegensteht.
2. Eine pathomechanistische Phänotypisierung ermöglicht die Identifikation neuer Therapieziele und homogener Subgruppen für die Untersuchung spezifischer und individualisierter Therapien.
3. Eine klinische Phänotypisierung ermöglicht die direkte Adressierung homogener Pathophysiologien als erfolgversprechende therapeutische Interventionsziele.

In Kapitel 3 werden die Resultate dieser Habilitationsschrift zusammengefasst und diskutiert, mit einem abschließenden Ausblick auf bestehende Limitationen und Bereiche möglicher zukünftiger Forschung auf diesem Gebiet.

1.3 DIE KLINISCHE PROBLEMATIK DER HERZINSUFFIZIENZ MIT ERHALTENER PUMPFUNKTION

1.3.1 Definition

Eine Herzinsuffizienz ist ein klinisches Syndrom, das charakterisiert ist durch Dyspnoe, Belastungsintoleranz und Kongestion infolge kardialer Veränderungen. Hämodynamisch beruht die Definition auf der Unfähigkeit des Herzens eine adäquate Blutperfusion zur Abdeckung des metabolischen Bedarfs des Körpers bei normalen Füllungsdrücken in Ruhe oder unter Belastung zu gewährleisten (7).

Im Wesentlichen werden zwei Mechanismen der linksventrikulären Funktion (LV) für diesen Zustand verantwortlich gemacht: eine Einschränkung der systolischen Funktion, die eine eingeschränkte kontraktile Funktion des Ventrikels beschreibt und eine Einschränkung der diastolischen Funktion, wobei eine abnorme ventrikuläre Relaxation, Steifigkeit und Füllung vorliegt. Anhand dieser Mechanismen werden Patienten mit Herzinsuffizienz in zwei grundsätzliche Gruppen klassifiziert.

HFpEF Patienten weisen eine normale LV Ejektionsfraktion (LVEF), als Maß der systolische Funktion, normale LV Dimensionen und eine gestörte diastolische Funktion, häufig mit konzentrischem LV Remodeling auf (7). In aktuellen Leitlinien wird HFpEF mit einer LVEF ≥50 Prozent definiert (1,8).

HFrEF ist hauptsächlich charakterisiert durch Einschränkungen der LVEF, häufig mit Dilatation des Ventrikels und exzentrischem Remodeling. Zumeist gilt für diese Herzinsuffizienzgruppe ein Grenzwert der LVEF von ≤40 Prozent (1,8).

Verschiedene Studien konnten eine dritte Patientengruppe herausarbeiten, die durch eine LVEF zwischen 40 und 49 Prozent charakterisiert ist (HFmrEF) und verschiedene Merkmale sowohl mit HFpEF als auch HFrEF Patienten teilt. Trotz weniger prospektiver Studien zu diesem Kollektiv legen einige Daten nahe, dass diese Patienten im therapeutischen Ansprechen und klinischen Verlauf eher der Gruppe der HFrEF Pateinten zugeordnet werden können (9,10).

HFrEF und HFpEF sind unterschiedliche Syndrome und nicht Teils eines kontinuierlichen Krankheitsspektrums (11). Unterschiede zwischen HFpEF und HFrEF bestehen auf epidemiologischer, LV morphologischer bis hin zur kardiomyozytären Ebene (11). Der Übergang von einer HFpEF in eine HFrEF ist selten und in der Regel mit einem kardiovaskulären Ereignis, wie etwa einem Myokardinfarkt, assoziiert (12-14).

1.3.2 Epidemiologie und Prognose

Die Gesamtprävalenz der Herzinsuffizienz liegt bei etwa zwei bis vier Prozent der deutschen Bevölkerung und ist mit der Situation in anderen europäischen Ländern und den Vereinigten Staaten von Amerika vergleichbar (15,16). Für letztere wird geschätzt, dass zwischen 2013 und 2016 über sechs Millionen Menschen eine Herzinsuffizienz hatten, wobei weltweit von über 64 Millionen Betroffenen ausgegangen wird (17).

Die HFpEF Prävalenz steigt altersabhängig und lag Krankenkassendaten zufolge in Deutschland zwischen 2009 und 2013 bei vier Prozent in der Gruppe der 60 bis 69 Jährigen, bei elf Prozent bei den 70 bis 79 Jährigen, 26 Prozent bei den 80 bis 89 Jährigen und 46 Prozent bei den über 90 Jährigen (16). Inzidenzdaten legen über 600 neue Fälle pro 100 000 Einwohner und über 500 000 Fälle jährlich in Deutschland nahe (15). Etwa 455 000 Patienten wurden im Jahr 2018 in Deutschland aufgrund einer Herzinsuffizienz stationär behandelt, womit die Herzinsuffizienz eine der häufigsten Gründe für Hospitalisierungen in Deutschland ist (2).

Aktuell stellt die Gruppe der HFpEF Patienten mit über 70 Prozent den Großteil der Patienten mit Herzinsuffizienz im Alter über 65 Jahren dar (5,18). Sowohl die Prävalenz als auch die Inzidenz der HFpEF steigt im Vergleich zur HFrEF um etwa zehn Prozent pro Dekade. Es wird erwartet, dass sich dieser Trend weiter fortsetzt vor dem Hintergrund der steigenden Lebenserwartung und der steigenden Prävalenz der mit HFpEF assoziierten Komorbiditäten wie Adipositas, arterieller Hypertension und Diabetes mellitus (18-20).

Populationsbezogene Studien zeigen, dass mehr Frauen als Männer von HFpEF betroffen sind. Zum einen kann dies mit der höheren HFpEF Inzidenz in den höchsten Lebensdekaden und der höheren Lebenserwartung von Frauen und dem damit verbundenen höheren geschlechtsspezifischen Lebenszeitrisiko begründet werden. Zum anderen ist das weibliche Geschlecht mit einem niedrigeren Mortalitätsrisiko nach einer HFpEF Diagnose assoziiert (21). Dahingegen wird für HFrEF eine starke männliche Dominanz beobachtet, entsprechend der höheren Prävalenz einer koronaren Herzkrankheit als wichtigstem ätiologischem Faktor bei Männern. In einem amerikanischen Bericht von über 100 000 Hospitalisierungen aufgrund einer akut dekompensierten Herzinsuffizienz waren HFpEF Patienten durchschnittlich älter, häufiger weiblich, häufiger hypertensiv und hatten weniger häufig vorausgegangene Myokardinfarkte, eine geringere Krankenhaussterblichkeit, aber ähnliche Aufenthaltszeiten im Krankenhaus und auf der Intensivstation (22).

Die Anzahl der nicht kardialen Komorbiditäten, wie etwa eine arterielle Hypertonie, ein Diabetes mellitus, eine Adipositas oder eine obstruktive Lungenerkrankungen, ist

durchschnittlich höher bei HFpEF als bei HFrEF Patienten. Ihr Vorliegen erlaubt aber im Einzelnen keine zuverlässige Diskrimination zwischen den beiden Entitäten und individuell tragen die Komorbiditäten in beiden Gruppen in ähnlichem Maße zur ungünstigen Prognose bei (23).

Unabhängig von der LV Funktion ist die Herzinsuffizienz mit einer deutlich erhöhten Mortalität und Morbidität assoziiert. Dies gilt insbesondere auch für die HFpEF im Vergleich zu Personen ohne Herzinsuffizienz (5). Die Prognose der Gesamtheit der HFpEF Patienten scheint etwas besser zu sei als die von HFrEF Patienten (jährliche Mortalität zwischen acht und neun Prozent versus 19 Prozent), obwohl einige Autoren ähnliche Mortalitätsraten für HFpEF und HFrEF, insbesondere nach vorausgegangener Hospitalisierung, berichten (24-28).

Vor dem Hintergrund der Entwicklung effektiver Therapiekonzepte für HFrEF Patienten und dem Fehlen effektiver Therapien für das HFpEF Kollektiv legen populationsbezogene Daten eine Verbesserung der Prognose für HFrEF Patienten, nicht aber für HFpEF Patienten nahe (27). Hospitalisierungsraten, Hospitalisierungsdauer und Einschränkungen der Lebensqualität ähneln sich für Patienten mit HFpEF und HFrEF (29,30). Neben der Bedeutung der Hospitalisierungen für die Gesundheitsökonomie, sind diese auch mit einer deutlich erhöhten Mortalität verbunden (31). Die differierenden Mortalitätszahlen in verschiedenen HFpEF Kohorten spiegeln am ehesten auch Unterschiede im Einschluss von Patienten verschiedener Erkrankungsstadien wieder. In der Tat zeigen HFpEF Patienten mit den größten Veränderungen der kardialen Funktion, Natriumretention, Überwässerung und erhöhten natriuretischen Peptiden ein höheres Risiko für Mortalität oder Herzinsuffizienzhospitalisierung verglichen mit Patienten welche eine normale Hämodynamik in Ruhe aber eine pathologische Belastungsreaktion aufweisen (32). Dennoch muss auch in diesen letztgenannten Patienten eine HFpEF diagnostiziert werden. Trotz normaler Ruhehämodynamik entwickeln diese Patienten eine myokardiale Schädigung und Einschränkung der myokardialen Funktion unter körperlicher Belastung, die in einer PHT und Lungenstauung sowie einer eingeschränkten Atemmechanik und Dyspnoe münden (33-36). Über die Zeit führen diese Veränderungen zu einer reduzierten körperlichen Fitness, einem erhöhten Risiko für Hospitalisierungen und sind verbunden mit einer erhöhten Mortalität (32,37-39).

Letzteres gilt auch für Patienten mit Erfüllung der strukturellen HFpEF Kriterien, die keine Symptome aufweisen und daher als sich in einem sehr frühen Stadium befindliche Gruppe betrachtet werden kann (40-43).

1.3.3 Pathophysiologie

Aus klinischer Sicht bilden HFpEF Patienten in der Regel eine Belastungsintoleranz und Dyspnoe aus. Mit fortschreitendem Krankheitsstadium tritt diese Symptomatik bei zunehmend geringeren Belastungsstufen auf und das Risiko einer pulmonalen und peripheren Stauung mit konsekutiver Herzinsuffizienzhospitalisierung steigt.

Verursacht werden die Zeichen und Symptome der HFpEF durch Veränderungen der Hämodynamik, die, wie im Folgenden beschrieben, mit morphologischen und funktionellen kardialen Veränderungen assoziiert sind.

Neuere Daten legen nahe, dass zusätzlich zu kardialen Veränderungen auch Veränderungen der Peripherie zum HFpEF Syndrom beitragen. Hier seien unter anderem Veränderung der systemischen Gefäße, des Endothels, der Skelettmuskulatur und des sympathischen Nervensystems genannt (5).

Das verbindende Element aller pathophysiologischen Konzepte ist die reduzierte Belastungsreserve im Sinne der Unfähigkeit zur adäquaten Steigerung des Herzzeitvolumens unter Belastung. Trotz der Möglichkeit einer erhaltenen Ruhehämodynamik ist die Anpassungsfähigkeit an körperliche Belastung der kardialen, vaskulären und peripheren Funktionen eingeschränkt (34).

1.3.3.1 Morphologische linksventrikuläre Veränderungen

Sowohl für die HFrEF als auch für die HFpEF gilt, wie in Kapitel 1.3.1 dargelegt, der Zusammenhang zwischen strukturellen und funktionellen kardialen Störungen und einer kompromittierten Hämodynamik. Die kardialen strukturellen Veränderungen unterscheiden sich jedoch zwischen den verschiedenen Herzinsuffizienztypen.

Bei ähnlich erhöhten LV Füllungsdrücken haben HFpEF Patienten ein erhaltenes LV enddiastolisches Volumen und weisen häufiger eine LV Hypertrophie mit konzentrischem Remodeling entsprechend einer höheren Wandstärke im Verhältnis zum Ventrikelvolumen bei gleichsam auftretender linksatrialer (LA) Dilatation auf (44-46).

Als pathognomonische Veränderungen von HFpEF Patienten gelten steife, hypertrophierte Herzwände mit erhöhter myokardialer Fibrose und relativ kleiner Ventrikelgröße (47,48). Klinisch auffällig ist jedoch, dass die Gesamtheit der HFpEF Patienten von einem heterogenen Bild eines kardialen Remodelings betroffen ist (49). Epidemiologische Daten belegen eine normale LV Größe mit variabler Hypertrophie. Während 40 bis 60 Prozent der Patienten eine signifikante LV Hypertrophie aufweisen, wird ein konzentrisches Remodeling nur in etwa der Hälfte der Patienten beobachtet, während etwa

jeder achte Patient eine exzentrische Hypertrophie und beinahe ein Drittel der Patienten eine normale LV Geometrie aufweist (45,50). Im klinischen Verlauf ist der Nachweis einer LV Hypertrophie mit einer schlechten Prognose verbunden, inklusive eines erhöhten Mortalitäts- und Herzinsuffizienzhospitalisierungsrisikos (51,52).

Die Veränderungen der kardialen Morphologie und Geometrie gehen im Allgemeinen mit Veränderungen auf der zellulären Ebene des Myokards einher. Es konnte gezeigt werden, dass Kardiomyozyten von HFpEF Patienten in der Breite, nicht aber in der Länge hypertrophiert sind, was einer vergrößerten Wandstärke bei geringem ventrikulärem Volumen entspricht. Zudem weisen die Kardiomyozyten eine erhöhte intrazelluläre Steifigkeit auf. Als nicht myozytäre Ursache einer erhöhten myokardialen Steifigkeit wird eine vergrößerte extrazelluläre Fibrosierung des LV Myokards von HFpEF Patienten beschrieben (53,54). Obwohl HFpEF Patienten in der Regel mehr interstitielle myokardiale Fibrose aufweisen als gesunde Kontrollen sind die Unterschiede im Einzelnen gering und viele Patienten zeigen keine relevant erhöhte myokardiale Fibrosierung (55).

1.3.3.2 Diastolische linksventrikuläre Dysfunktion

Auf funktioneller Ebene ist die prominenteste kardiale Störung bei HFpEF Patienten die der diastolischen Funktion (5). In taxonomischer Abgrenzung zur HFrEF, die auch als „systolische Herzinsuffizienz“ bezeichnet wird, war für HFpEF initial der Begriff der „diastolischen Herzinsuffizienz“ geläufig. Diese vereinfachte Darstellung negiert allerdings die komplexe und heterogene Pathophysiologie und sollte daher verlassen werden (56).

Nach hämodynamischer Definition treten bei HFpEF Patienten erhöhte LV Füllungsdrücke auf, die mit dem Ausmaß der Herzinsuffizienzsymptomatik korrelieren (34-37). Diese erhöhte LV Füllungsdrücke entstehen vornehmlich durch das Auftreten einer diastolischen Dysfunktion (57). Die kardiale Funktion hängt stark von den physiologischen Vorgängen während der Diastole ab, die über eine adäquate LV Füllung einen suffizienten Auswurf ermöglichen. Der LV enddiastolische Druck (LVEDP) wird durch das Blutvolumen im Ventrikel, die Steifigkeit und Dehnbarkeit des Ventrikels und externe Drücke auf den LV etwa durch das Perikard oder die rechtsseitigen Herzkammern bestimmt. In der Diastole bilden der LV, das linke Atrium (LA) und die Pulmonalvenen eine verbundene Einheit, die mit dem pulmonalen Kapillarbett in Verbindung steht. Jede Druckerhöhung im LV und LA wird so passiv auf die Lungengefäße weitergeleitet (57).

Die ventrikuläre Diastole beginnt mit einem dynamischen, energieabhängigen Prozess, der Relaxation des kontrahierten Myokards. Die isovolumetrische Relaxation beschreibt die

Phase zwischen Aortenklappenschluss und Mitralklappenöffnung, mit Abfall des LV Drucks ohne LV Volumenänderung. Während der physiologischen isovolumetrischen Relaxation beobachtet man einen schnellen LV Druckabfall, der mit den LV Deformationsänderungen „untwisting“ und „recoiling“ einhergeht. Dies ermöglicht die LV Füllung durch einen „Saugeffekt“ mit Erhöhung des LA-LV Druckgradienten (58). In der Folgephase, der Diastase, erfolgt eine Volumenzunahme des LV unter verschiedenen Druckverhältnissen zumeist bis zur zeitlichen Mitte der Diastole. In der letzten Phase der Diastole erfolgt die atriale Füllung des LV mit Kontraktion des LA und LV Volumenzunahme um etwa 20 Prozent. Das LV Myokard ist dabei vollständig relaxiert, der LV maximal dehnbar, sodass im Gesunden ein nur geringer zusätzlicher LV Druckanstieg beobachtet werden kann (59).

Unter physiologischer Belastung muss das Herzzeitvolumen um ein Vielfaches gesteigert werden um eine adäquate Abdeckung des erhöhten peripheren Sauerstoffbedarfs zu ermöglichen. Zu dieser Steigerung tragen eine Reihe von Mechanismen bei, darunter die Erhöhung der Herzfrequenz, eine Reduktion des peripheren Widerstands, eine geringe Erhöhung des LV Schlagvolumens und der LV Kontraktilität. Der erhöhte Auswurf bedingt eine Steigerung der LV Füllung, deren Mechanismen mit denen des erhöhten Auswurfs zum Teil interferieren. Hier sei die Herzfrequenzerhöhung als Beispiel angeführt, die das Herzzeitvolumen global steigert aber die Zeit für die Füllung, die Diastolendauer, verkürzt. Kompensatorisch muss die diastolische Füllungsgeschwindigkeit gesteigert werden, um den erhöhten LV Auswurf zu ermöglichen (60). Eine vermehrte LV Füllung bedingt eine Erhöhung des diastolischen Flusses über der Mitralklappe, mit der Notwendigkeit eines ausgeprägten LA-LV Druckgradienten. Unter physiologischen Bedingungen kann die LV Füllungsgeschwindigkeit deutlich gesteigert werden mit einem schnellen Druckabfall in der frühen Diastole durch einen verstärkten „Saugeffekt“ und Erhöhung des LA-LV Gradienten ohne Erhöhung der LA Drücke. Einige Mechanismen die zu einem erhöhten LV Auswurf und einer verbesserten LV Füllung führen sind kombinierte Effekte der systolischen und diastolischen Funktion. Eine gesteigerte Kontraktilität führt über eine Verstärkung der frühdiastolischen „Recoil“ Kräfte und Erhöhung der LV Füllungsgeschwindigkeit zu einer verbesserten Füllung unter Erhaltung moderater LA- und LV Füllungsdrücke (57).

Eine Störung dieser diastolischen Mechanismen ist typisch für HFpEF Patienten und führt zu einer Erhöhung der LV enddiastolischen Drücke, einer Erhöhung der LA Drücke und resultierend auch zu einer Druckerhöhung im pulmonalvenösen und -kapillären System (58). Im Vergleich zu gesunden Kontrollen zeigen Patienten mit HFpEF eine nach oben und links verschobene LV enddiastolische Druck-Volumenbeziehung als Ausdruck einer erhöhten

ventrikulären Steifigkeit (61). Unter körperlicher Belastung nimmt das LV enddiastolische Druck-Volumenverhältnis akut und quantitativ deutlich stärker zu verglichen mit Patienten ohne Herzinsuffizienz (62). Patienten mit HFpEF weisen eine verlängerte LV Relaxation und eine eingeschränkte Anpassungsfähigkeit der LV Relaxation im Verhältnis zur Herzfrequenzzunahme unter Belastung auf (61,63). Insgesamt sind HFpEF Patienten damit durch eine erhöhte Sensibilität für Vorlaständerungen des LV und eine eingeschränkte diastolische Reserve gekennzeichnet (58).

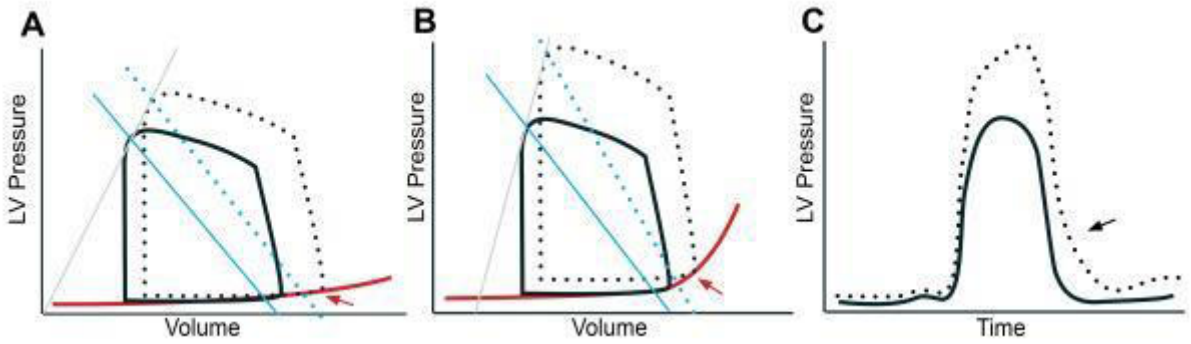

Abbildung 1 LV Druck-Volumen-Schleifen eines Patienten ohne Herzinsuffizienz (A) und mit HFpEF (B) in Ruhe (fette Linie) und unter Belastung (gestrichelte Linie), die eine erhöhte Steigung des enddiastolischen Druck-Volumenverhältnisses (rote Line), als Ausdruck der erhöhten ventrikulären Steifigkeit, zeigt. Die blauen Linien demonstrieren eine erhöhte arterielle Elastanz als Ausdruck einer erhöhten vaskulären Steifigkeit und LV Nachlast in HFpEF Patienten. Im Vergleich zu Patienten ohne Herzinsuffizienz (fette Linie in C) sind HFpEF Patienten (gestrichelte Linie in C) neben einer erhöhten LV Nachlast durch eine Verzögerung des LV Druckabfalls in der isovolumetrischen Relaxationsphase, als Ausdruck einer eingeschränkten aktiven Relaxation (schwarzer Pfeil), charakterisiert; modifiziert nach (64).

Als Goldstandard für den Nachweis dieser Veränderungen und einer detaillierten pathomechanistischen Charakterisierung der diastolischen Funktion gilt die invasive hämodynamische Untersuchung (Abbildung 1). Die zeitlich hochaufgelöste Druckmessung im linken Ventrikel ermöglicht die Charakterisierung der isovolumetrischen Relaxation unter anderem über die Bestimmung der Zeitkonstante der isovolumetrischen Relaxation „Tau“ (65). Eine simultane Messung von Druck und Volumen ermöglicht zusätzlich die individuelle Bestimmung ladungsunabhängiger Parameter, wie die der enddiastolischen Druck-Volumenbeziehung, als Maß der ventrikuläre Steifigkeit (66).

Sowohl in der klinischen Praxis als auch im Großteil klinischer und epidemiologischer Studien beruht die Untersuchung der diastolischen Funktion auf nicht-invasiven Methoden, vornehmlich der Echokardiographie. Verschiedene Parameter wurden etabliert um die oben genannten hämodynamischen Änderungen abzuleiten, wobei diese auch physiologisch altersabhängigen Änderungen unterliegen und als Surrogat nur hinweisend sein können für die tatsächlichen hämodynamischen Verhältnisse (67).

Epidemiologische Daten legen eine echokardiographisch nachweisbare diastolische Dysfunktion in etwa 80 Prozent der HFpEF Patienten nahe (26). Der Anteil von Patienten mit

echokardiographischem Nachweis einer diastolischen Dysfunktion in klinischen Studien ist variabler und tendenziell oft geringer. Beispielweise wies knapp die Hälfte der Patienten in der TOPCAT-Studie (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) eine echokardiographisch normale diastolische LV Funktion auf (51). Sowohl epidemiologische Daten als auch Daten klinischer Studien belegen eine direkte Korrelation der gestörten diastolischen Funktion mit einem ungünstigen klinischen Outcome, inklusive Mortalität und Herzinsuffizienzhospitalisierung (51,52).

1.3.3.3 Systolische linksventrikuläre Dysfunktion

Definitionsgemäß ist die LVEF, als klinisch etabliertester systolischer Funktionsparameter, normal oder erhalten bei HFpEF Patienten. Die LVEF ist allerdings ein unspezifischer Marker der globalen systolischen LV Funktion, da sie wesentlich durch LV Ladungsbedingungen und die LV Geometrie bestimmt wird und selbst im Falle des Vorliegens einer systolischen myokardialen Dysfunktion normal sein kann (68). Während die ventrikuläre endsystolische Elastanz (Ees; Steigung der grauen Linien in Abbildung 1) als invasiver Marker der ladungsunabhängigen Kontraktilität gerade in Anfangsstadien der HFpEF erhöht sein kann (69), weisen Studien mit komplexerer echokardiographischer Beurteilung der systolischen LV Funktion auf eine subtile Einschränkung der systolischen Ventrikelfunktion von HFpEF Patienten im Vergleich zu Patienten mit arterieller Hypertonie und gesunden Kontrollen hin. Die Einschränkungen beziehen sich dabei hauptsächlich auf die longitudinale LV Kontraktion und sind prädiktiv für das Auftreten eines schlechten klinischen Outcomes der HFpEF (70-72). Die relativ milden systolischen Funktionsstörungen in dieser Patientengruppe sind dabei bereits in Ruhe nachweisbar, werden allerdings unter körperliche Belastung aggraviert. Eine fehlende Augmentation der systolischen Funktion führt über die negative Beeinflussung der frühdiastolischen „recoil-“ und „Saugeffekte“ zu einer Verschlechterung der diastolischen Funktion wie oben beschrieben (35). In Kombination mit Faktoren, die eine erhöhte ladungsunabhängige enddiastolische LV Steifigkeit bedingen, führt dies zu einer unzureichenden Steigerung des Herzzeitvolumens und Endorganperfusion unter Belastung (34,35,73).

1.3.3.4 Linksatriale Veränderungen

Im Verlauf der Entwicklung intermittierender oder chronisch erhöhter LV Füllungsdrücke mit konsekutiver LA Druckerhöhung kommt es zu einem LA Remodeling mit LA Dilatation. Diese in der pathophysiologischen Überlegung als HFpEF typisch zu wertende morphologische Änderung hat daher Eingang in diagnostische Algorithmen zur HFpEF Diagnose gefunden, wie in Kapitel 1.3.4 weiter ausgeführt (1,74). Dies wird dadurch unterstützt, dass sowohl das Vorliegen einer LA Dilatation als auch deren Zunahme prognostisch ungünstige Faktoren der HFpEF sind (51,75,76). Eine LA Funktionsstörung wird häufig mit dem Auftreten von Vorhofflimmern assoziiert. Dies betrifft etwa ein Drittel der HFpEF Patienten zu einem Zeitpunkt über die Dauer der Erkrankung. Das Auftreten von Vorhofflimmern ist verbunden mit einem ausgeprägterem LA Remodeling, dem Nachweis einer PHT, ausgeprägterem rechtsventrikulärem (RV) Remodeling sowie einer eingeschränkten Belastbarkeit und Prognose (77,78).

1.3.3.5 Pulmonale Hypertonie und rechtsventrikuläre Dysfunktion

Bei etwa 70 bis 80 Prozent der HFpEF Patienten kann eine PHT in Ruhe oder unter Belastung nachgewiesen werden (79,80). Mit gesteigerten LA und pulmonalvenösen Drücken bedingt durch eine bestehende diastolische LV Dysfunktion steigen auch pulmonalarterielle (PA) Drücke durch passive hydrostatische Übertragung. Eine intermittierende, unproportionale LA Druckerhöhung unter Belastung führt zunächst zum oben beschriebenen LA Remodeling. Im weiteren Verlauf führen chronisch erhöhte LA und PA Drücke zu reaktiven Veränderungen der pulmonalen Zirkulation und Ausbildung eines erhöhten PA Widerstands, einer rechtsatrialen (RA) Dilatation, einer RV Dilatation und der Ausbildung einer Trikuspidalklappeninsuffizienz (TI)(81).

Das Auftreten einer PHT ist assoziiert mit einem ungünstigen klinischen Outcome der HFpEF, inklusive einer erhöhten Mortalität und Herzinsuffizienzhospitalisierungsrate (79,80). Entsprechend eines zu postulierenden fortgeschrittenen Stadiums im Falle einer PA Widerstandserhöhung zeigt diese Patientengruppe die ungünstigste Prognose (82). Die Reduktion von PA Drücken durch Diuretikatherapie (und der damit verbundenen Reduktion von LV und LA Drücken) reduziert die Hospitalisierungsrate in HFpEF (83,84). Ein klinischer Nutzen spezifischer pharmakologischer Therapien der PHT konnte bisher nicht demonstriert werden (85-87).

Hämodynamisch verursacht die Entwicklung einer fortgeschrittenen PHT eine Druckbelastung des RVs mit eingeschränkter RV Reserve durch einen reduzierten RV

Auswurf, eine RV Dilatation und erhöhten LV Füllungsdrücken trotz einer relativen LV Unterfüllung (88). Eine systolische RV Dysfunktion tritt bei etwa einem Drittel der HFpEF Patienten auf und wird in der Regel als Folge der Nachlaststeigerung durch Druckerhöhung im pulmonalen Kreislauf interpretiert (80,89,90). Die Ausbildung einer systolischen RV Dysfunktion ist verbunden mit einer niedrigeren LVEF, höheren PA Drücken sowie dem Vorliegens eines Vorhofflimmerns und ist ein starker Prädiktor für eine ungünstige Prognose unabhängig vom Ausmaß der PHT (80,91).

1.3.3.6 Arterielle Hypertonie und vaskuläre Veränderungen

Neben einer erhöhten LV Steifigkeit ist die HFpEF durch eine erhöhte Steifigkeit des arteriellen Gefäßsystems gekennzeichnet, häufig als Folge vorliegender Komorbiditäten wie eines Diabetes mellitus oder einer arteriellen Hypertonie (69,92). Die Änderung der vaskulären Eigenschaften führen zu einem Anstieg der pulsatilen Blutdruckkomponenten (systolischer Blutdruck, Pulsdruck, Druckwellenreflektion), die wesentliche Risikofaktoren für die Entwicklung einer Herzinsuffizienz im Allgemeinen und einer HFpEF im Besonderen sind (69,93-96). Während unter physiologischen Zuständen die Druckwellenreflektion in der Diastole eine Erhöhung diastolischer Organperfusionsdrücke bewirkt, ist eine erhöhte Steifigkeit der großen Arterien mit einer erhöhten und verfrühten Druckwellenreflexion und damit einhergehender Verstärkung der spätsystolischen Nachlast verbunden. Dies beeinflusst auch die frühe diastolische Funktion des LV, was durch die Demonstration eines Zusammenhangs zwischen diastolischen Funktionsstörungen und erhöhter arterieller Steifigkeit mit verstärkten arteriellen Wellenreflexionen in verschiedenen Populationen bestätigt wurde (97,98). Als Reaktion einer gesteigerten ventrikulären Nachlast im Zusammenhang mit erhöhter arterieller Steifigkeit wird eine gesteigerte LV Ees beobachtet (69). Vor allem in frühen Stadien dieser Veränderungen dient dies der Kompensation zur Erhaltung einer energetisch günstigen ventrikulo-arteriellen Kopplung (99). Eine erhöhte arterielle Steifigkeit über die Zeit geht allerdings mit einem erhöhten Risiko für die Ausbildung einer arteriellen Hypertonie einher, prädisponiert zu reduziertem koronaren Perfusionsdruck, konzentrischem LV Remodeling, myokardialer Fibrose und einer kontraktilen Dysfunktion (100). Entsprechend der bedeutenden Rolle der arteriellen Funktion in der zentralen Hämodynamik geht ein pathologisches vaskuläres Remodeling im Sinne einer erhöhten Steifigkeit mit einem erhöhten Risiko für kardiovaskuläre Ereignisse und insbesondere sowohl der Entwicklung einer Herzinsuffizienz als auch einer Herzinsuffizienzhospitalisierung einher (101). Hämodynamische Grundlage dafür ist eine

erhöhte Sensitivität für Nachlast- und Volumenänderungen bei HFpEF Patienten, die aus der gleichzeitigen Erhöhung der Elastanz des LV und der großen Arterien folgt (Abbildung 2). Kleine Volumenänderungen führen dabei zu unproportional erhöhten arteriellen Drücken und LV Füllungsdrücken unter Belastung, zu Belastungsintoleranz und prädisponieren zur Herzinsuffizienzdekompensation (92,102,103).

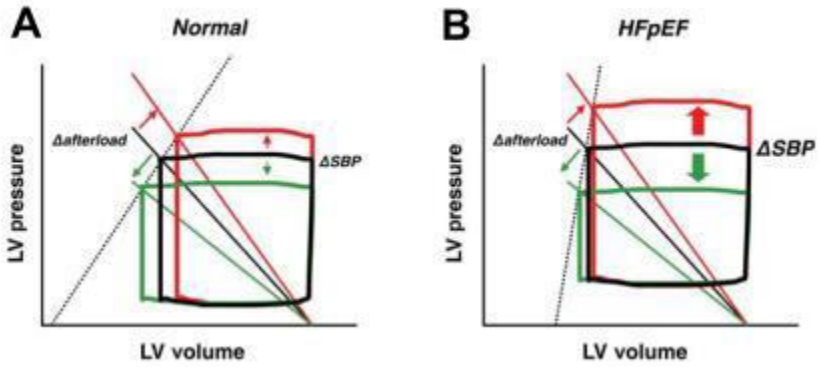

Abbildung 2 Im Vergleich zu Patienten ohne Herzinsuffizienz (A) weisen HFpEF Patienten (B) eine gesteigerte LV Elastanz (gestrichelte Linie) auf. Dies führt zu größeren Veränderungen des systemischen Blutdrucks (SBP) bei gleicher Änderung der LV Nachlast (afterload) in HFpEF Patienten; modifiziert nach (92).

Aggraviert wird diese Problematik durch eine gesteigerte systemische Sympathikusaktivität, die zunehmend als wichtiger pathomechanistischer Faktor bei Herzinsuffizienzpatienten beschrieben wird und mit einer eingeschränkten Prognose assoziiert ist (104-107). Eine gesteigerte Sympathikusaktivierung führt dabei zu einer erhöhten Blutdruckpulsatilität und somit zu einer weiteren Verschlechterung der oben beschriebenen ventrikulo-vaskulären Interaktion (108).

Eine vermehrte Steifigkeit der Gefäße wird ultrastrukturell durch Veränderungen der Gefäßwände in Abhängigkeit vom Vorliegen einer systemischen Inflammation und durch eine reduzierte Endothelfunktion mit reduzierter Stickstoffmonooxidverfügbarkeit vermittelt (34,109).

In ähnlicher Weise sind auch mikrovaskuläre Veränderungen zentraler Teil der Pathogenese von HFpEF, die bei etwa drei Viertel der Patienten vorliegen (110). Morphologisch wurde in einer autoptischen Studie eine reduzierte Dichte der myokardialen Mikrozirkulation beobachtet, deren Ausmaß mit dem Grad der interstitiellen myokardialen Fibrosierung korrelierte (55). Auch auf funktioneller Ebene kommt es zu Veränderungen im Sinne einer eingeschränkten Vasodilatation auf Ebene der Mikrozirkulation infolge einer reduzierten Stickstoffmonooxidverfügbarkeit (111). Patienten mit HFpEF entwickeln häufig serologische Marker einer latenten myokardialen Schädigung unter körperlicher Belastung, die auf eine myokardiale Ischämie hindeutet (33). Diese Ischämie kann durch ein Missverhältnis von Sauerstoffangebot und -bedarf im Kontext erhöhter LV Füllungsdrücke,

Koronarstenosen und vor allem durch eine eingeschränkte mikrovaskuläre Funktion bedingt sein (14,33,55,110). Der Nachweis einer funktionellen Einschränkung der myokardialen Mikrozirkulation ist dabei mit fortgeschritten Krankheitsstadien und einer erhöhten Rate an Herzinsuffizienzhospitalisierungen verbunden (110,112).

1.3.3.7 Periphere Veränderungen

Zusätzlich zu zentralen kardialen und vaskulären Veränderungen legen Beobachtungen nahe, dass auch periphere Veränderungen zum HFpEF Syndrom beitragen. Exemplarisch sei hier die Skelettmuskulatur genannt, die einen erhöhten Fettgehalt und eine reduzierte Muskelmasse sowie einen eingeschränkten Sauerstoffmetabolismus aufweist (113-115).

1.3.3.8 Zelluläre Mechanismen

Während in zahlreichen Studien verschiedene organspezifische Pathologien beschrieben wurden, bleiben die zugrunde liegenden zellulären Mechanismen weiterhin nicht vollständig verstanden. Epidemiologische Daten weisen ein höheres Alter, eine arterielle Hypertonie, Adipositas, Diabetes mellitus, Bewegungsmangel und eine myokardiale Ischämie als häufige Komorbiditäten und Risikofaktoren für die Entwicklung einer HFpEF aus (5).

Verantwortlich für das morphologische und funktionelle Remodeling ist nach gängigem pathophysiologischen Model von Paulus et al. die mit dem Vorliegen verschiedener Komorbiditäten assoziierte niedriggradige systemische Inflammation. Diese führt zu endothelialer mikrovaskulärer Aktivierung mit Überexpression von E-Selektin und interzellulärem Zelladhäsionsmolekül-1. Über diese Moleküle treten Monozyten ins myokardiale Interstitium aus, differenzieren zu Makrophagen und stimulieren über die Sekretion von Transforming-Growth-Factor-β Myofibroblasten zur Kollagenproduktion mit resultierender erhöhter interstitieller Fibrosierung, die zu einer Versteifung des Myokards führt (116). Daten aus einem HFpEF Tiermodell und Untersuchungen an myokardialen Biopsien von HFpEF Patienten legen nahe, das eine systemische Inflammation, charakterisiert durch das Zirkulieren von Tumornekrosefaktor-α, Interleukin-1ß und Interleukin-6, zu einer reduzierten endothelialen Stickstoffmonoxidproduktion (NO) führt. Dies reduziert die Aktivität der myokardialen cyclischem Guanosinmonophosphat (cGMP) und die Proteinkinase G (PKG) Aktivität, was eine Reduktion der Phosphorylierung des Strukturproteins Titins zur Folge hat (117,118). Die systemische Inflammation führt außerdem über die Produktion von reaktiven Sauerstoffspezies zur Entstehung von

Disulfidbindugen des Titins. Sowohl Hypophosphorylierung und die Entstehung dieser Verbindungen führen zu einer Versteifung der Titinmoleküle mit resultierender myozytärer Steifigkeit (119).

Kürzlich wurde von Schiattarella und Kollegen eine dritte Säule der systemischen Inflammationshypothese vorgeschlagen: eine Kompromittierung des evolutionär hoch konservierten zellulären Reparaturmechanismus, des „Unfolded Protein Response“. Die Autoren etablierten eine HFpEF Mausmodell durch eine Kombination von metabolischem und hämodynamischem Stress (hyperkalorische Diät und medikamentöse Induktion einer arteriellen Hypertonie) als sogenanntes „two-hit-model”. In diesem Modell beobachteten sie ein deutlich gesteigertes myokardiales NO Vorkommen durch eine inflammationsgetriggerte Induktion der induzierbaren NO Synthase. Der resultierende nitrosative Stress führte zur Herabregulierung und Veränderung von Proteinen die für den Ablauf des „Unfolded Protein Response“ verantwortlich sind. Diese gestörte zellulären Stressantwort führt zu einer myokardialen Ansammlung von destabilisierten Proteinen (120).

Die zentrale Bedeutung einer systemischen Inflammation wird gestützt durch die Beobachtung, dass eine Erhöhung von inflammatorischen Biomarkern prädiktiv für die Entwicklung einer HFpEF ist und dass diese stärker erhöht sind bei HFpEF im Vergleich zu HFrEF Patienten (121,122).

Andere zelluläre Mechanismen, die als pathophysiologische Faktoren in HFpEF vorgeschlagen wurden, sind unter anderem ein eingeschränkter myozytärer Calciumstoffwechsel, eine beschleunigte myozytäre Seneszenz, eine Lipotoxizität und gestörte Autophagievorgänge (123-127).

Natriuretische Peptide werden als physiologische Antwort auf eine erhöhte ventrikuläre Wandspannung von Kardiomyozyten sezerniert. Diese wirken protektiv auf eine Reihe kardiovaskulärer Funktionen, inklusive eines diuretischen und blutdrucksenkenden Effekts. Sie inhibieren die Renin-Angiotensin-Aldosteron Achse, die Endothelinsekretion und die systemische und renale Sympathikusaktivierung (128,129). Präklinische Daten legen außerdem einen protektiven Effekt von natriuretischen Peptiden auf die Entwicklung einer myokardialen Fibrose und auf den Phosphorylierungsstatus des Strukturproteins Titin nahe (130,131). Natriuretische Peptide sind erhöht in Herzinsuffizienzpatienten im Vergleich zu Patienten ohne Herzinsuffizienz und prognostisch relevant sowohl in HFpEF als auch in HFrEF Kollektiven. Das Ausmaß dieser Erhöhung ist jedoch bei HFrEF Patienten deutlich größer, wobei für HFpEF oft eine relative natriuretische Peptiddefizienz postuliert wird. Begründet wird dies mit der geringeren Wandspannung vor dem Hintergrund eines

konzentrischen Remodelings mit kleineren Ventrikelvolumina und größerer Wandstärke in HFpEF Patienten im Vergleich zu HFrEF Patienten. Zu weiteren Faktoren zählen eine verminderte Produktion und ein erhöhter Abbau natriuretischer Peptide im Kontext der in HFpEF hochprävalenten Adipositas, genetischen Polymorphismen und möglicherweise einer erhöhten Aktivität des Degradationsenzyms Neprilysin. Eine relativ verminderte natriuretische Peptidaktivität führt zu Natriumretention und Hypertension mit Aggravation der Klinik der HFpEF (132).

1.3.4 Diagnose der Herzinsuffizienz mit erhaltener Pumpfunktion

1.3.4.1 Klinische Diagnose

Patienten verschiedener Herzinsuffizienztypen präsentieren sich mit ähnlicher Symptomatik und ähnlichen Funktionseinschränkungen und die Diagnose beruht historisch gesehen maßgeblich auf dem Nachweis einer venösen Stauung in Ruhe (133,134). Diese Zeichen sind aber oft nicht nachweisbar in kompensierten und frühen Herzinsuffizienzstadien und in Patienten, die hämodynamische Pathologien nur unter Belastung entwickeln (135). Einige Symptome, wie Orthopnoe und paroxysmale nächtliche Dyspnoe, sind sehr spezifisch für eine Herzinsuffizienzdiagnose, aber selten und weisen daher eine geringe Sensitivität auf (136). Klinisches Leitsymptom ist eine Belastungsdyspnoe und Belastungsintoleranz. Diese Symptome sind häufig und daher sehr sensitiv aber weniger spezifisch für das Vorliegen einer Herzinsuffizienz. Während die Diagnose einer HFrEF in diesem klinischen Kontext in der Regel einfach mit dem Nachweis einer eingeschränkten LV Funktion gelingt, ist die Diagnosestellung einer HFpEF anspruchsvoller, da die LV Funktion sich, ähnlich wie bei Patienten mit nicht kardialer Dyspnoe, normal darstellt. Anamnestisch gehen das Vorliegen verschiedener Komorbiditäten und Risikofaktoren (Alter über 60 Jahre, Adipositas, Diabetes mellitus, Bewegungsmangel, arterielle Hypertonie, Vorhofflimmern und eine chronische Niereninsuffizienz) mit einer höheren Wahrscheinlichkeit für eine HFpEF Diagnose einher (137).

Letztlich beruht die Diagnose auf dem Nachweis der definierenden LV Füllungsdrücke beziehungsweise auf dem Nachweis einer strukturellen Herzerkrankung, die mit der zuvor beschriebenen Pathophysiologie vereinbar ist (1,137,138).

1.3.4.2 Echokardiographie

Der Echokardiographie kommt eine zentrale Rolle in der initialen Diagnostik zu. Neben der Bestimmung der LV Funktion zum Ausschluss einer HFrEF und Beurteilung des

morphologischen LV Remodelings können hiermit auch andere Pathologien ausgeschlossen werden die zum klinischen Bild einer Herzinsuffizienz führen, wie etwa valvuläre oder perikardiale Erkrankungen (7). Mittels Doppler- und Gewebedopplerverfahren kann das Vorliegen einer diastolischen Dysfunktion oder erhöhter LV Füllungsdrücke abgeschätzt werden. Die etabliertesten Parameter sind dabei das Verhältnis der Geschwindigkeit des frühdiastolischen LV Einstroms (E) zur frühdiastolischen basalen LV Gewebegeschwindigkeit (E/e‘), das mit akut erhöhten LV Füllungsdrücken korreliert. Eine Erhöhung der Geschwindigkeit des systolischen Rückflusses über der Trikuspidalklappe deutet auf einen erhöhten systolischen PA Druck infolge eines erhöhten LA Drucks hin (79,137). Andere Befunde, die mit einer erhöhten Wahrscheinlichkeit für eine HFpEF Diagnose einhergehen, sind Marker chronisch erhöhter LV Füllungsdrücke oder Ausdruck des Vorliegens einer subtilen systolischen LV Funktionsstörung (139). Hierzu gehören das Vorliegen einer LA Dilatation, RV Dilatation oder –Dysfunktion, ein reduzierte longitudinale LV Deformation und eine eingeschränkte frühdiastolische LV Gewebegeschwindigkeit (e′). Die meisten dieser Parameter weisen eine hohe Spezifität aber niedrige Sensitivität für eine invasiv bestätigte HFpEF Diagnose auf und sind daher hilfreich für den Einschluss, weniger aber für den Ausschluss der Diagnose (137,140).

1.3.4.3 Natriuretische Peptide

Serumkonzentrationen natriuretischer Peptide sind im gesamten Spektrum der Herzinsuffizienzpatienten erhöht. Sie können daher als diagnostische Marker eingesetzt werden und bieten prognostische Informationen (141,142). In Verbindung mit der einfachen Bestimmbarkeit hat sich eine NT-pro-BNP (N-terminal pro-B-type natriuretic peptide) Erhöhung in den letzten zehn Jahren daher als Einschlusskriterium für klinische HFpEF Studien und als HFpEF Diagnosekriterium in den Leitlinien etabliert (1,5,138).

Serumkonzentrationen natriuretischer Peptide müssen vor dem Hintergrund verschiedener Störfaktoren interpretiert werden, die ihre Sensitivität und Spezifität für eine HFpEF Diagnose einschränken. Dazu tragen die bereits beschriebene relative natriuretische Peptiddefizienz in HFpEF bei, als auch Effekte der Niereninsuffizienz und anderen differentialdiagnostischen Zuständen die eine Erhöhung natriuretischer Peptide bedingen (142). Kürzlich konnte gezeigt werden, dass 18 Prozent, 30 Prozent und 40 Prozent von Patienten mit invasiv diagnostizierter HFpEF Serumkonzentrationen des NT-proBNPs unterhalb der Grenzwerte von 125pg/ml, 225pg/ml und 300pg/ml aufweisen, die als Diagnosekriterien in der klinischen Praxis und klinischen Studien genutzt werden (140).

Während niedrige natriuretische Peptidkonzentration daher nicht zwangsläufig eine HFpEF ausschließen können, steigern erhöhte Konzentrationen die Wahrscheinlichkeit einer HFpEF Diagnose (137,138).

1.3.4.4 Nicht-invasive Diagnose

Basierend auf den genannten diagnostischen Erwägungen beruht die Diagnose einer HFpEF auf einem klinischen Herzinsuffizienzsyndrom, dem Nachweis einer erhaltenen LVEF und einer mit der HFpEF Pathophysiologie zu vereinbarenden strukturellen Herzerkrankung sowie einer möglichen Erhöhung natriuretischer Peptide (1,143).

Entsprechend der aktuellen Herzinsuffizienz Leitlinien der europäischen kardiologischen Gesellschaft ergibt sich eine HFpEF Diagnose beim Vorliegen herzinsuffizienztypischer Zeichen und Symptome, dem Nachweis einer LVEF ≥50 Prozent und einem Nachweis erhöhter natriuretischer Peptide sowie zusätzlich dem Nachweis des Vorliegens einer LV Hypertrophie oder einer LA Dilatation oder einer diastolischen LV Dysfunktion (1).

Differenziertere diagnostische Kriterien wurden kürzlich anhand evidenzbasierter Daten und eines Expertenkonsensus vorgeschlagen (137,138). In der ersten Studie wurden über 400 Patienten mit Luftnot mittels des diagnostischen Goldstandards, einer invasiven Belastungsuntersuchung, auf das Vorliegen einer HFpEF untersucht und klinische, laborchemische, elektrokardiographische und echokardiographische Prädiktoren einer HFpEF Diagnose bestimmt (137). Während die Erhöhung natriuretischer Peptide, das Vorliegen einer LA Dilatation oder einer LV Hypertrophie univariate Prädiktoren waren, flossen als unabhängige Prädiktoren in einen gewichteten Diagnosescore, den H²FPEF Score, das Vorliegen einer Adipositas (2 Punkte), das Vorliegen einer mit zwei Medikamentenklassen behandelten arteriellen Hypertonie (1 Punkt), einer Vorhofflimmeranamnese (3 Punkte), einer echokardiographisch abgeschätzten PHT (1 Punkt), echokardiographischer Hinweise auf erhöhte LA Drücke (E/e‘ über 9, 1 Punkt) und eines Alters über 60 Jahren (1 Punkt) ein. Die Wahrscheinlichkeit einer HFpEF Diagnose steigt linear pro Punkt des Scores, wobei diese bei einem Score von 6-9 als wahrscheinlich gilt, während sie mit einem Score von 0-1 nahezu ausgeschlossen werden kann. Die Anwendbarkeit und der prognostische Nutzen dieses Scores konnte in weiteren Patientenkollektiven validiert werden (144,145).

Ein ähnliches diagnostisches Modell wurde von der europäischen Gesellschaft für Kardiologie und der europäischen Gesellschaft für Herzinsuffizienz vorgeschlagen (138). Der Algorithmus umfasst eine klinische Vortest-Beurteilung, spezifische Diagnostik mittels

Echokardiographie, Bestimmung natriuretischer Peptide und eine weiterführende Diagnostik mit Belastungsuntersuchung in unklaren Fällen sowie eine ätiologische Abklärung zum differentialdiagnostischen Ausschluss anderer Kardiomyopathien. Der HFA-PEFF Score beurteilt Kriterien in den drei Domänen: Funktion, Morphologie und Biomarker, von denen jede maximal 2 Punkte bis zu einem Maximalscore von 6 Punkten beitragen kann (138). Bei einem Score von 5-6 kann eine HFpEF Diagnose gestellt, bei 0-1 ausgeschlossen werden und im Falle von 2-4 Punkten wird eine Belastungsuntersuchung gefordert. Der diagnostische Wert in Bezug auf den Ein- oder Ausschluss einer klinischen HFpEF Diagnose und der prognostische Wert des HFA-PEFF Scores konnte an zwei unabhängigen Kohorten nachgewiesen werden (146). Beide Scores besitzen eine ähnliche prognostische Wertigkeit, identifizieren aber nur geringfügig überlappende Hochrisikogruppen und weisen eine eingeschränkte diagnostische Übereinstimmung auf (147,148).

Die Heterogenität nicht-invasiver diagnostischer Kriterien in der klinischen Praxis und in klinischen Studien muss als Faktor eines uneinheitlichen Therapieansprechens in verschiedenen Studien diskutiert werden und ist ein starkes Argument für eine erweiterte Phänotypisierung der Patienten, die auf das Vorliegen einer HFpEF untersucht werden (149).

1.3.4.5 Invasive Diagnose

Beide Scores umfassen neben dem Ein- und Ausschluss einer HFpEF Diagnose die Identifikation einer großen Patientengruppe mit intermediärer Diagnosewahrscheinlichkeit, für deren Differenzierung weitere Diagnostik notwendig ist (137,138). Entsprechend der hämodynamischen Definition der Herzinsuffizienz gilt eine Erhöhung invasiv abgeschätzter LA oder LV Füllungsdrücke als diagnostische Referenz. Ein erheblicher Anteil von HFpEF Patienten entwickeln solche nur unter körperlicher Belastung, sodass eine invasive Belastungsuntersuchung für die endgültige Diagnosefindung vorgeschlagen wird (140).

In der klinischen Praxis kann dies durch einen Belastungstest während der Rechtsherzkatheteruntersuchung realisiert werden. Der Nachweis eines pulmonalkapillären Verschlussdrucks (PCWP) ≥15mmHg in Ruhe oder ≥25mmHg unter körperlicher Belastung ist dabei beweisend für eine HFpEF Diagnose. Außerdem können weitere hämodynamische Parameter, wie PA Drücke und die Herzzeitvolumenreserve abgeschätzt werden (7).

1.3.5 Therapeutische Konzepte

Im Gegensatz zur Etablierung multipler effektiver Therapien für Patienten mit HFrEF haben bis dato alle bisherigen großen klinischen Studien zur Effektivität pharmakologischer Therapien neutrale Ergebnisse erbracht (7).

Eine wichtige Säule der HFrEF Therapie ist die Blockade des Angiotensin konvertierenden Enzyms oder Angiotensin-II-Rezeptors, die in großen klinischen Studien sowohl einen Überlebensvorteil als auch einen positiven Effekt auf die Hospitalisierungsrate bewirken konnten (41,150). Für HFpEF Patienten konnte für diese Medikamentenklassen kein Mortalitätsunterschied und eine nur numerische, statistisch nicht signifikante, Reduktion von Hospitalisierungen demonstriert werden (151-153).

Auch Betablocker reduzieren die oben genannten „harten“ klinischen Endpunkte in HFrEF ohne klinischen Effekt in HFpEF (154-157).

Mineralokorticoidrezeptorantagonisten bieten gleichfalls einen klinischen Vorteil in HFrEF Patienten (158,159). Im HFpEF Kollektiv konnte in der ALDO-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) Studie zwar eine Verbesserung der diastolischen Funktion aber keine Änderung der körperlichen Belastbarkeit oder Lebensqualität im Zusammenhang mit einer Medikation mit Spironolacton beobachtet werden (160). Die TOPCAT-Studie untersuchte in der Folge den Effekt dieser Medikation auf die Hospitalisierung und Mortalität in über 3400 Patienten und konnte keinen statistisch signifikanten Therapievorteil nachweisen (161).

In ähnlicher Weise zeigte sich für die HFpEF Therapie mittels kombinierter Inhibition des Angiotensin-2-Rezeptors und des natriuretische Peptide spaltenden Enzyms Neprilysin eine numerische, aber nicht signifikante Reduktion der kardiovaskulären Mortalität und Hospitalisierungsrate (162). Für den gleichen therapeutischen Ansatz hatte sich eine signifikante Reduktion dieser Endpunkte um 20 Prozent in HFrEF Patienten ergeben (163).

Außerdem stehen für HFrEF weitere medikamentöse Optionen zur Verfügung. Eine Herzfrequenzsenkung mittels Ivabradin reduziert Mortalität und Hospitalisierungen in HFrEF, wohingegen für HFpEF keine klinischen Effekte, zum Teil sogar eine Reduktion der körperlichen Belastbarkeit beobachtet wurde (164,165). Kürzlich konnte für die Klasse der Gliflozine eine Mortalitäts- und Hospitalisierungsratenreduktion in HFrEF vor dem Hintergrund einer bereits optimierten medikamentösen Herzinsuffizienztherapie gezeigt werden. Outcomedaten für diese Substanzgruppe in HFpEF werden für dieses Jahr erwartet (166-168).

Auch für pharmakologische Therapien, die spezifisch die im Kapitel 1.3.3.8 beschriebenen zellulären Pathomechanismen adressieren, konnte bislang kein Nutzen belegt werden. Für die orale Kompensation der endothelialen NO Defizienz mittels Nitratsubstitution zeigte sich gar eine reduzierte körperliche Belastung unter Therapie ohne Effekt auf andere klinische Endpunkte (169). Auch eine Inhibierung der Phosphodiesterase 5 zur Verbesserung der intrazellulären PKG Aktivität konnte keinen klinischen Vorteil in Bezug auf Symptome und Belastbarkeit von HFpEF Patienten erbringen (85).

Wie für HFrEF Patienten stellen Diuretika eine effektive Therapie zur Symptomreduktion in HFpEF dar (1,170). Obwohl deren therapeutischer Effekt in HFpEF nicht direkt in klinischen Studien getestet wurde, gibt es indirekte Evidenz für deren Wirksamkeit in dieser Patientengruppe. In der randomisierten CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) Studie konnte gezeigt werden, das ein implantierbarer Monitor zur Erfassung der PA Drücke Herzinsuffizienzhospitalisierungen reduzieren kann. Eine kurzfristige Erhöhung der PA Drücke spiegelt in der Regel eine Erhöhung der LA und LV Füllungsdrücke und die Notwendigkeit von deren Reduktion wieder. Der klinische Vorteil in der Interventionsgruppe ging mit einer intensiveren Auftitrierung der diuretischen Therapie und niedrigeren PA Drücken über die Zeit sowohl in HFpEF als auch in HFrEF einher. Diese Ergebnisse legen einen klinischen Nutzen von Diuretika in HFpEF nahe und suggerieren, dass LA und LV Füllungsdrücke als Therapieziele geeignet sind um den klinischen Verlauf zu verbessern (83,84).

Im Vordergrund der HFpEF Therapie stehen folglich eine symptomorientierte antikongestive Therapie sowie die Behandlung der assoziierten Komorbiditäten (1,8). In Studien zur Blutdruckreduktion von Patienten mit arterieller Hypertonie konnte gezeigt werden, dass eine effektive Blutdrucktherapie ein Neuauftreten von HFpEF verhindert (171-173). Therapiestudien mit medikamentöser neurohumoraler Blutdrucktherapie bei Patienten mit bereits bestehender HFpEF zeigten dagegen neutrale Ergebnisse wie im vorhergehenden Abschnitt beschrieben, sodass diese Intervention aktuell als präventive Maßnahme gewertet werden muss. Für Lebensstilinterventionen, wie Ausdauertraining und Gewichts-normalisierung konnte eine Verbesserung der körperlichen Belastbarkeit und Lebensqualität demonstriert werden (174,175).

1.4 PHÄNOTYPISIERUNG ALS WEG ZUR ETABLIERUNG EFFEKTIVER THERAPIEN

Die Gründe für den bisher fehlenden Nachweis effektiver Therapiekonzepte für HFpEF Patienten können auf mehreren Ebenen diskutiert werden. Die Tatsache, dass ein Syndrom nicht wie sonst üblich über ein pathologisches Untersuchungsergebnis (etwa eine eingeschränkte LVEF bei HFrEF), sondern über die Norm (erhaltene LVEF bei HFpEF) definiert wird, impliziert dass das auf diese Weise betrachtete Kollektiv eine große Heterogenität aufweisen müsste, deren zugrunde liegende pathophysiologischen Faktoren nicht einer einheitlichen Therapie zugänglich sind. Auch die fehlende Spezifität und Heterogenität weiterer zur Diagnosestellung genutzter Kriterien in der klinischen Praxis und in klinischen Studien müssen als Faktoren eines uneinheitlichen Therapieansprechens in verschiedenen Studien ins Feld geführt werden (149).

Dies wird deutlich, wenn man die Evolution nicht-invasiver diagnostischer Kriterien in der klinischen Praxis und in klinischen Studien betrachtet. Frühe Outcome Studien nutzten als HFpEF Diagnosekriterium einen LVEF cut-off von 40 Prozent in Verbindung mit einer stattgehabten Herzinsuffizienzhospitalisierung (152). Diese Definition beruhte im Wesentlichen auf der pragmatischen Überlegung, dass für diese Patientengruppe keine evidenzbasierte Behandlung vorlag und weniger auf der Beobachtung pathomechanistischer Zusammenhänge (5). Auf der Suche nach diesen Zusammenhängen wurde in der Folge der Hauptfokus auf die diastolische Dysfunktion des LV gelegt, wobei im Verlauf klar wurde, dass auch andere Mechanismen, wie morphologische kardiale und vaskuläre Pathologien zentrale Bestandteile der HFpEF Pathophysiologie sind (47,51,57). Um diesen Aspekten Rechnung zu tragen hat sich die HFpEF Definition in den letzten zwei Jahrzenten weg von einer rein klinischen Herzinsuffizienzdiagnose vor dem Hintergrund einer erhaltenen LV Funktion, hin zu einer Definition unter Einbeziehung des Nachweises typischer Komorbiditäten, kardialer struktureller und funktioneller Veränderungen, einer Erhöhung der natriuretischen Peptide, dem Nachweis erhöhter LA und LV Füllungsdrücke und dem Ausschluss spezifischer alternativer Kardiomyopathien entwickelt, wie in Kapitel 1.3.4 ausgeführt. Dazu gehört auch die Fokussierung auf eine LVEF Bereich über 50 Prozent, da Patienten mit niedrigeren LVEF Werten ein homogeneres Therapieansprechen aufweisen (9,157,176).

Trotz der mit der Präzisierung der Definition einhergehenden Reduktion der Heterogenität des HFpEF Kollektivs, stellt sich die Frage, ob die multiplen in diesen Patienten zu beobachtende Pathologien auf einen gemeinsamen Mechanismus zurückzuführen

sind oder es sich um pathophysiologische Implikationen verschiedener Komorbiditäten handelt. Das Vorliegen eines HFpEF spezifischen Pathomechanismus wird gestützt durch die Tatsache, dass Patienten in klinischen Studien mit HFpEF ein deutlich schlechteres Outcome haben, als Patienten die in Studien zur Behandlung vergleichbarer Komorbiditäten aber ohne Diagnose einer Herzinsuffizienz eingeschlossen wurden (177).

Nach der Hypothese von Paulus und Tschöpe (116), wie in Kapital 1.3.3.8 ausgeführt, kann auf zellulärer Ebene ein verbindender Pathomechanismus identifiziert werden. Dieser beruht auf einer systemischen Inflammation mit resultierender Reduktion von NO Bioverfügbarkeit sowie cGMP und PKG Aktivität und führt letztlich zu einer erhöhten myozytären Steifigkeit, interstitiellen myokardialen Fibrosierung und vaskulärer Dysfunktion. Für therapeutische Interventionen, die auf eine spezifische Modulation dieses pathomechanistischen Wegs abzielten, konnte jedoch kein klinischer Vorteil gezeigt werden wie in Kapitel 1.3.5 dargestellt. Neben der Möglichkeit der Ungültigkeit dieses Modells könnte dies bedeuten, dass hier bisher nur ein Teilaspekt der zentralen Pathologie erfasst wurde (178). In der Tat konnte gezeigt werden, dass weitere molekulare Mechanismen an der kardialen Pathologie beteiligt und dass physiologische Veränderung bei HFpEF Patienten nicht ausschließlich kardial, sondern auch in anderen Organsystemen nachweisbar sind (120,179).

Unabhängig von der Frage, ob HFpEF durch einen zentralen Pathomechanismus oder durch eine zentrale Präsentation verschiedener Pathomechanismen charakterisiert ist, beinhaltet das Syndrom auch mit spezifischer klinischer Definition ein heterogenes phänotypisches Spektrum. Dies mag unter anderem mit der unterschiedlichen Interaktion vorrangiger Komorbiditäten und dem natürlichen individuellen Alterungsprozess aber auch mit unterschiedlichen Phasen des natürlichen Verlaufs der Erkrankung erklärbar sein. Ein Weg zur Entwicklung effektiver therapeutischer Konzepte ist daher eine Phänotypisierung mit Erarbeitung homogenerer Patientenkollektive zur Ermöglichung einer gerichteten Therapie. Ein wichtiger Aspekt ist, dass diese Phänotypisierung flexibel und klinisch praktikabel ist. Aus diesem Grund wurden in der Vergangenheit verschiedene Klassifizierungssysteme auf der Basis klinischer Informationen und Komorbiditäten vorgeschlagen (180). Die Phänotypisierung auf Grundlage mechanistischer Abnormitäten erlaubt eine gerichtete Intervention zur Therapie pathologischer biologischer Prozesse mit der Möglichkeit einer tatsächlich „individualisierten“ Therapie. Dieser Ansatz macht eine detaillierte Charakterisierung verschiedener zellulärer und gewebsspezifischer Prozesse notwendig, die mitunter dynamisch sind. Aus diesem Grund scheinen mechanistische Studien

besonderes geeignet um eine Verbindung zwischen klinischer Phänotypisierung und individueller Pathophysiologie herzustellen. Darüber hinaus bieten sie die Möglichkeit neue Pathomechanismen zu identifizieren, die in der Folge sowohl Grundlage für klinische, als auch pathomechanistische Charakterisierungen sein können.

1.4.1 Pathomechanistische Charakterisierung

1.4.1.1 Hämodynamische Charakterisierung mittels Konduktanzmessung

Wie in Kapitel 1.3.1 und 1.3.3 beschrieben kann für HFpEF Patienten die gemeinsame zentrale hämodynamische Beobachtung der erhöhten LV Füllungsdrücke in Ruhe oder unter Belastung definiert werden. Wie in Kapitel 1.3.3 ausgeführt kann dies jedoch auf verschiedene Aspekte morphologischer und funktioneller Störungen vor allem der diastolischen LV Funktion zurückzuführen sein. Als Goldstandard der hämodynamischen Funktionsbestimmung des LV gilt die invasive Aufzeichnung von Druck-Volumenbeziehungen (66). Durch die simultane Messung von Druck und Volumen über den Herzzyklus können ladungsunabhängige Funktionsparameter bestimmt und damit die systolische und diastolische myokardiale Funktionsstörung weiter charakterisiert werden. Dies gelingt durch den Einsatz spezieller Konduktanzkatheter, die neben einem Druckabnehmer aus einer unterschiedlichen Anzahl von Elektroden für die Erzeugung eines elektrischen Feldes bestehen. Die Messung von Potentialunterschieden zwischen den Elektroden ermöglicht die Änderung des intrakavitären Blutvolumens als Konduktanzunterschiede zu quantifizieren (Abbildung 3).

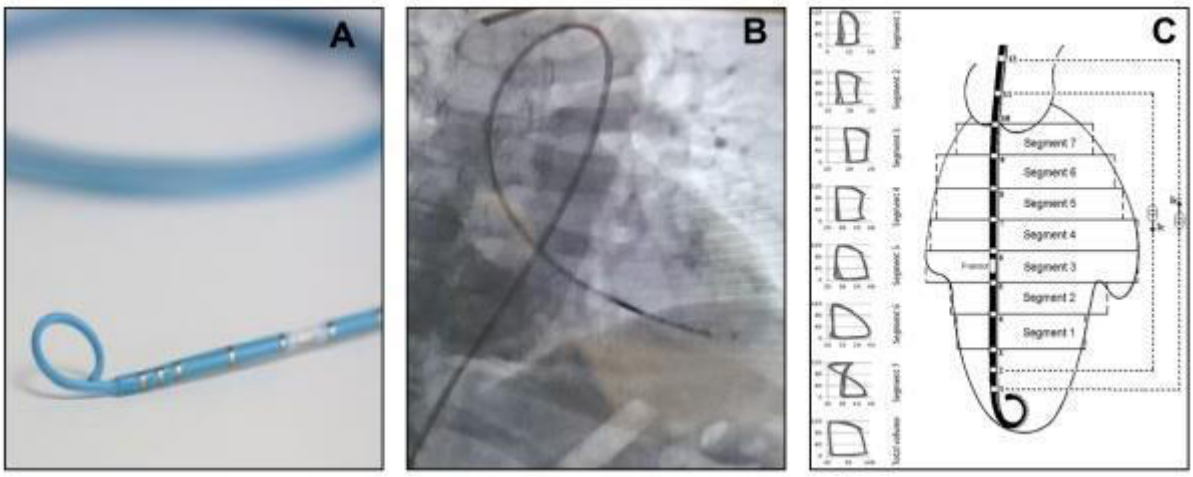

Abbildung 3 Pigtail Konduktanzkatheter (A) mit Drucksensor (weiß) zwischen der fünften und sechsten Elektrode (silber) und dessen fluoroskopisch korrekte Positionierung von transfemoral im LV Apex (B). Die Änderungen der Potentialunterschiede zwischen den Elektroden im elektrischen Feld zwischen distaler und proximaler Elektrode geben Auskunft über segmentale Volumenänderungen und werden in Verbindung mit dem simultan registrierten Druck zu gesamtventrikulären Druck-Volumen-Schleife summiert (C).

Durch Manöver der Vorlastreduktion, zum Beispiel durch Ballonokklusion der Vena cava inferior, beziehungsweise der Nachlaststeigerung, zum Beispiel durch isometrische Handgriffübungen, werden verschiedene Ladungsbedingungen simuliert und so ventrikuläre Funktionskonstanten bestimmt. Die enddiastolische-Druck-Volumenbeziehung (EDPVR), ventrikuläre Steifigkeitskonstante (Beta) und die Rate des Druckabfalls zum Zeitpunkt der isovolumetrischen Relaxation (Tau) sind gängige Maße zur Quantifizierung der diastolischen Funktion. Die endsystolische Elastizität (Ees), die endsystolische Druck-Volumenbeziehung (ESPVR) und die ventrikulo-arterielle Kopplung geben Auskunft über die ventrikuläre Kontraktilität und die ventrikuläre Interaktion mit der Nachlast (66). In ähnlicher Weise kann eine Beurteilung der RV Funktion vorgenommen werden (181).

Eine solche Untersuchung ist gut geeignet um HFpEF spezifische hämodynamische Pathologien und Phänotypen zu identifizieren, übersteigt aber im personellen, zeitlichen und finanziellen Aufwand die Möglichkeiten der klinischen Routinediagnostik. Eine Phänotypisierung sollte damit idealerweise darauf abzielen invasive Untersuchungsergebnisse mit nicht-invasive Messungen zu approximieren.

1.4.1.2 Kardiale Magnetresonanztomographie

Die kardiale Magnetresonanztomographie (MRT) ist ein Bildgebungsverfahren, das die intrinsischen magnetischen molekularen Eigenschaften nutzt um Bildkontraste und Gewebecharakteristika darzustellen. Damit können kardiale Morphologie, kardiale Funktion und Blutflüsse mit guter zeitlicher und exzellenter räumlicher Auflösung beurteilt werden. Die im Vergleich zur Echokardiographie bessere Reproduzierbarkeit ermöglicht die Detektion geringer Unterschiede bei kleineren Patientenzahlen in klinischen Studien. Die Methode ist unabhängig von akustischen Fenstern, und reduziert geometrische Annahmen, die oft eine Limitation in der Echokardiographie darstellen und einer detaillierten Struktur- und Funktionsbeurteilung insbesondere der rechtsseitigen Herzhöhlen entgegenstehen (182). In aktuellen Empfehlungen zur Diagnostik bei HFpEF Patienten ist eine kardiale MRT zentraler Teil des Ausschlusses differentialdiagnostisch zu erwägender Kardiomyopathien (74).

Die diastolische Funktion kann mittels Flussmessungen, Deformationsmessungen und Zeit-Volumen-Kurven ähnlich zur Echokardiographie bestimmt werden. Im Gegensatz zu anderen Bildgebungsverfahren bietet die kardiale MRT auch die Möglichkeit der myokardialen Gewebecharakterisierung. Die kardiale MRT kann dabei Informationen zum Vorhandensein von Ödemen, fokaler Fibrose und Fettinfiltrationen geben. Insbesondere neu entwickelte Bildgebungstechniken (T1-Mapping, Abbildung 4) erlauben die Quantifizierung

einer diffusen myokardialen Fibrosierung mit Ermittlung der extrazellulären Volumenfraktion, die histologisch mit dem Ausmaß einer interstitiellen Myokardfibrose korreliert (182).

Die Vielseitigkeit dieser Bildgebungsmodalität und die Möglichkeit der direkten Visualisierung der myokardialen Struktur machen die kardiale MRT zu einem geeigneten Instrument um eine Phänotypisierung von HFpEF Patienten vorzunehmen. Die Methode ist weitaus universeller einsetzbar als eine invasive hämodynamische Evaluation mittels Konduktanzmessung. Limitierende Faktoren sind die Notwendigkeit einer aktiven Mitarbeit und eine relativ lange Untersuchungsdauer. Außerdem bestehen spezifische Kontraindikationen wie ein hochgradig eingeschränkte Nierenfunktion oder das Vorhandensein von nicht MRT-kompatiblen Implantaten.

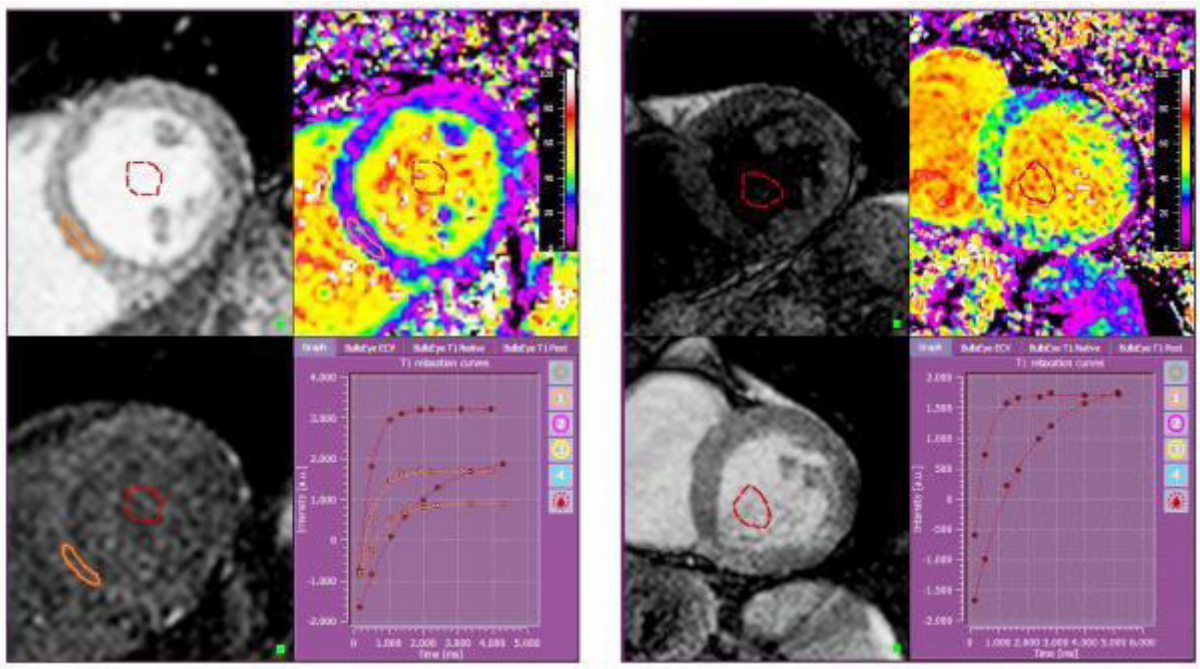

Abbildung 4 Quantifizierung der extrazellulären Volumenfraktion mittels T1-Mapping vor und nach Gadoliniumkontrastgabe in einem Patienten ohne Herzinsuffizienz und einer extrazellulären Volumenfraktion von 22 Prozent (links) und einem HFpEF Patienten mit einer extrazellulären Volumenfraktion von 36 Prozent (rechts); modifiziert nach (64).

1.4.2 Klinische Phänotypisierung

1.4.2.1 Herzinsuffizienz mit erhaltener Pumpfunktion und Trikuspidalklappeninsuffizienz

Fortgeschrittene Stadien der HFpEF sind mit dem Auftreten und dem Ausmaß einer funktionellen, das heißt nicht mit einer primären Pathologie der Klappen assoziierten, TI verbunden. Bis zu einem Fünftel der HFpEF Patienten weisen eine signifikante (moderate oder schwere) TI auf, wobei die höchsten Raten in Patienten mit der ausgeprägtesten RV Dilatation und RV Dysfunktion zu verzeichnen sind (90,183). Die allgemeine Prävalenz der Patienten mit signifikanter TI nimmt zu und diese Zunahme ist, wie die der generellen HFpEF

Prävalenz, mit höherem Alter und weiblichem Geschlecht assoziiert (184). Aus ätiologischer Sicht wird für das Auftreten einer TI im HFpEF Kollektiv eine Anulusdilatation als Folge der in Kapitel 1.3.3.5 beschriebenen Entwicklung einer PHT mit Dilatation von RV und RA postuliert (81,90).

Hämodynamisch führt das Vorhandensein einer hochgradigen TI zu einer Volumenbelastung des RV mit Kompression des LV (ventrikuläre Interdependenz) und konsekutiver Behinderung der LV Füllung mit weiterer Erhöhung der ohnehin schon erhöhten LV Füllungsdrücke. Eine Reduktion des effektiven RV Schlagvolumens infolge des erhöhten Pendelvolumens im RV trägt zudem zu einer chronischen Unterfüllung des LV bei (185). Eine signifikante TI ist mit höherer Symptomlast, verminderter Lebensqualität, höheren Hospitalisierungsraten und einer erhöhten Mortalität verbunden (186). Für HFpEF Patienten besteht eine klare Assoziation dieses Vitiums mit der Mortalität (187,188).

Nur ein geringer Anteil der Patienten mit signifikanter, funktioneller TI wird einer chirurgischen Therapie zugeführt. Dies liegt an der häufig späten Vorstellung der Patienten mit hohem perioperativen Risiko und einer deutlich erhöhten perioperativen Mortalität (186,189,190). Aus diesem Grund wurden kürzlich verschiedene interventionelle, katheterbasierte Verfahren vorgeschlagen um dieses klinische Problem zu adressieren (191). Neben hetero- oder orthotopen Klappenersatz- und direkten beziehungsweise indirekten Anuloplastieverfahren wird weltweit mehrheitlich das Prinzip der „edge-to-edge“ Rekonstruktion angewendet (192). Dabei werden jeweils zwei Segel mit dem Reparatursystem an ihren Segelspitzen gegriffen und mittels Clipimplantation angenähert (Abbildung 5).

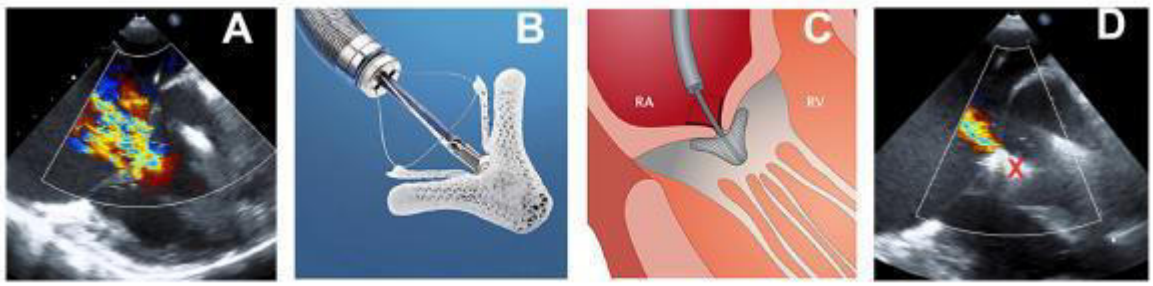

Abbildung 5 Transösophageale echokardiographische Darstellung einer hochgradigen TI (A) mit breiten Insuffizienzjet (Farbe). Verschiedene Systeme zur katheterinterventionellen „edge-to-edge“ Klappenrekonstruktion stehen zur Verfügung, in B ist das am häufigsten verwendete Device, der Mitraclip (Abott, USA), dargestellt. Über einen venösen femoralen Zugang wird das Koaptationsdevice in den RV geführt und im Rückzug die beabsichtigten Segel gegriffen (C). Nach Implantation und Ablösung des Device (rotes Kreuz) zeigt sich eine Reduktion des Koaptationsdefekts mit deutlich reduziertem Insuffizienzjet (D); modifiziert nach (193).

Dies verbessert die Koaptation der Segel und reduziert die Durchtrittsfläche des Insuffizienzjets sowie die Dimensionen des Anulus. Dieses Verfahren wurde initial für die Therapie der hochgradigen Mitralklappeninsuffizienz entwickelt und wird in dieser Indikation

heute weltweit angewandt (194). Aufgrund der langjährigen Erfahrung mit dieser Methode wurde das Prinzip auf die TI übertragen (195). Diese Technik stellt vor dem Hintergrund des durchschnittlich hohen Alters und der hohen Morbiditätslast von HFpEF Patienten mit relevanter TI einen interessanten Therapieansatz für diese Patientengruppe dar.

1.4.2.2 Herzinsuffizienz mit erhaltener Pumpfunktion und resistenter arterieller Hypertonie

Die arterielle Hypertonie gehört mit einer Prävalenz von etwa 90 Prozent zu den häufigsten Komorbiditäten der HFpEF und steht in engem Zusammenhang mit den in 1.3.3.6 beschriebenen vaskulären Veränderungen. Vor allem eine Sympathikusüberaktivität scheint ein gemeinsamer treibender Pathomechanismus zu sein (196). Eine sympathische Überaktivität ist für Patienten mit arterieller Hypertonie und HFpEF beschrieben, wobei eine gesteigerte renale Sympathikusaktivität gar von prognostischer Relevanz ist (196,197).

Eine Sympathikusüberaktivierung wird mit einem erhöhten Gefäßtonus im Splanchnikusgebiet in Verbindung gebracht. Dies führt zu einer Erhöhung des effektiv zirkulierenden Blutvolumens. Eine unproportionaler Erhöhung der LV Vorlast, vor allem unter Belastung, führt in Verbindung mit der in Kapitel 1.3.3.2 beschrieben Vorlastsensitivität bei bestehender diastolischer LV Dysfunktion zu einer starken Steigerung der LV Füllungsdrücke (198).

Unter den Patienten mit arterieller Hypertonie zeigen vor allem Patienten mit einer Therapieresistenz (unkontrollierter arterieller Hypertonus trotz drei oder mehr antihypertensiver Medikamente) eine gesteigerte Sympathikusaktivität und ein erhöhtes Risiko für kardiovaskuläre Mortalität und Morbidität (199,200). In der TOPCAT Studie konnte bei etwa 23 Prozent der Patienten eine resistente arterielle Hypertonie diagnostiziert werden. Interessanterweise wiesen diese Patienten eine erhöhte LVEF im Vergleich zu nicht resistenten Hypertonikern auf. Dies kann sowohl als kompensatorischer hyperkontraktiler Zustand im Zusammenhang mit einer erhöhten LV Nachlast als auch in Verbindung mit einer gesteigerten LV Vorlast infolge einer Sympathikusüberaktivierung interpretiert werden (201). Die Bedeutung dieser Befunde wird unterstützt durch den kürzlich postulierten U-förmigen Zusammenhang zwischen Mortalität und LVEF in einer bevölkerungsbezogenen Studie mit einer erhöhten Mortalität in Patienten mit einer LVEF > 65 Prozent (202).

Dementsprechend haben Therapiekonzepte, die auf die Behandlung der renalen und systemischen Sympathikusaktivität zielen das Potential den klinischen Verlauf und die Prognose von Patienten mit HFpEF zu verbessern (203). Die Modulation der renalen Sympathikusaktivität wurde bereits in den 50er Jahren als operatives Verfahren evaluiert

(204,205). Ende des ersten Jahrzehnts der 2000er Jahre konnten katheterbasierte Verfahren zur Modulation des renalen Sympathikotonus entwickelt und erstmals in klinischen Studien getestet werden (Abbildung 6). Dabei werden sympathische Nervenfasern mittels Radiofrequenz oder Ultraschallenergie von endovaskulär abladiert und damit der Sympathikotonus reduziert (206). Unsere und andere Gruppen konnten in den letzten Jahren unmissverständlich zeigen, dass diese Methode zu einer effektiven Blutdrucksenkung bei hypertensiven Patienten führt. (207-210). Die mannigfaltigen Effekte einer Reduktion des Sympathikotonus könnten darüber hinaus gerade für Patienten mit HFpEF und resistenter Hypertonie einen Therapieansatz bieten (206).

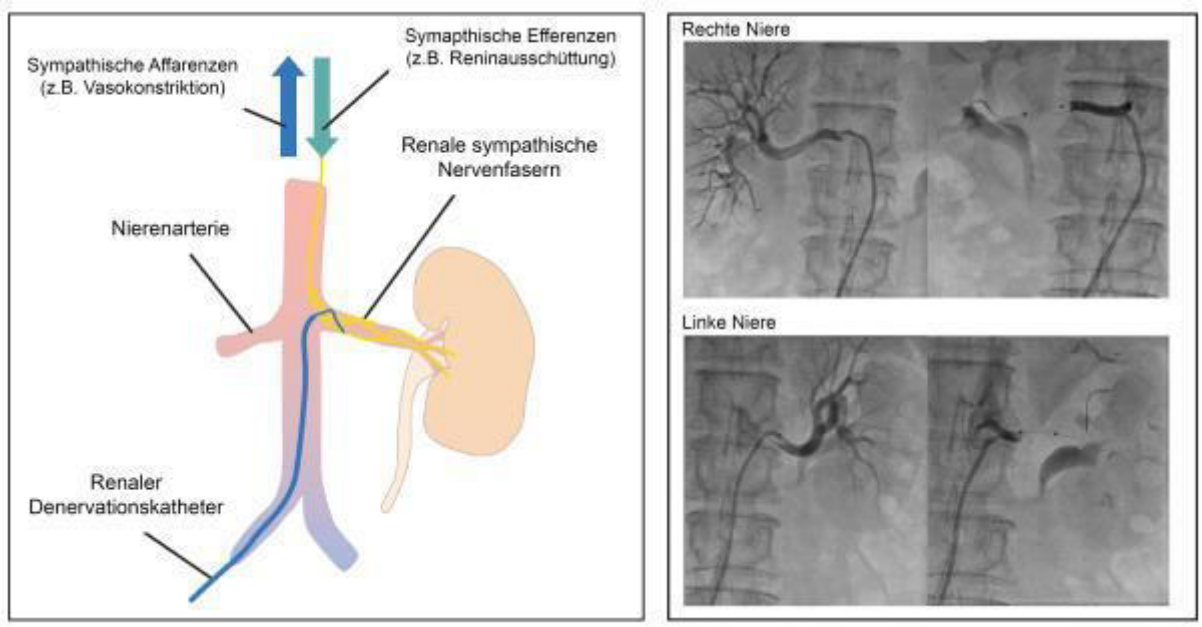

Abbildung 6 Schematische Darstellung des Prinzips der interventionellen renalen Denervation (links). Über einen femoralen arteriellen Zugang wird ein Denervationskatheter in die Nierenarterie vorgebracht und mittels Energieabgabe eine Reduktion der Signalübertragung der renalen sympathischen Nervenfasern entlang der Nierenarterie erreicht. Dadurch werden sympathische Efferenzen mit Effekten auf den renalen Sympathikotonus und Afferenzen mit Effekten auf den systemischen Sympathikotonus moduliert. Fluoroskopische Darstellung der Prozedur (rechts) mit selektivere Angiographie der Nierenarterien und anschließender Platzierung des Ablationskatheters. Es erfolgt eine mehrfache Energieabgabe an verschiedenen Positionen in den Nierenarterien.

2 PUBLIKATIONEN

2.1 PATHOMECHANISTISCHE PHÄNOTYPISIERUNG DER HERZINSUFFIZIENZ MIT ERHALTENER PUMPFUNKTION

2.1.1 Identifikation hämodynamischer Phänotypen mittels kardialer Magnetresonanztomographie

Zitierweise:

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Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Optimal patient characterization in heart failure with preserved ejection fraction (HFpEF) is essential to tailor successful treatment strategies. Cardiac magnetic resonance (CMR)–derived T_1 mapping can noninvasively quantify diffuse myocardial fibrosis as extracellular volume fraction (ECV).

OBJECTIVES This study aimed to elucidate the diagnostic performance of T_1 mapping in HFpEF by examining the relationship between ECV and invasively measured parameters of diastolic function. It also investigated the potential of ECV to differentiate among pathomechanisms in HFpEF.

METHODS We performed T_1 mapping in 24 patients with HFpEF and 12 patients without heart failure symptoms. Pressure-volume loops were obtained with a conductance catheter during basal conditions and handgrip exercise. Transient pre-load reduction was used to extrapolate the diastolic stiffness constant.

RESULTS Patients with HFpEF showed higher ECV ($p < 0.01$), elevated load-independent passive left ventricular (LV) stiffness constant (beta) ($p < 0.001$), and a longer time constant of active LV relaxation ($p = 0.02$). ECV correlated highly with beta ($r = 0.75$; $p < 0.001$). Within the HFpEF cohort, patients with ECV greater than the median showed a higher beta ($p = 0.05$), whereas ECV below the median identified patients with prolonged active LV relaxation ($p = 0.01$) and a marked hypertensive reaction to exercise due to pathologic arterial elastance ($p = 0.04$). On multiple linear regression analyses, ECV independently predicted intrinsic LV stiffness ($\beta = 0.75$; $p < 0.01$).

CONCLUSIONS Diffuse myocardial fibrosis, assessed by CMR-derived T_1 mapping, independently predicts invasively measured LV stiffness in HFpEF. Additionally, ECV helps to noninvasively distinguish the role of passive stiffness and hypertensive exercise response with impaired active relaxation. (Left Ventricular Stiffness vs. Fibrosis Quantification by T_1 Mapping in Heart Failure With Preserved Ejection Fraction [STIFFMAP]; NCT02459626) (J Am Coll Cardiol 2016;67:1815–25) © 2016 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) is an increasingly common condition accounting for almost one-half of heart failure (HF) cases, thus presenting a major challenge in modern cardiology (1). The prognosis of patients with HF symptoms and sustained systolic function is comparable to patients with reduced systolic function (2). Despite extensive research, all efforts to develop successful treatment strategies have led to unsatisfactory results (3–6). The lack of consistent therapeutic success might partly be explained by the heterogeneous cohort of patients investigated in previous studies, who exhibit exercise intolerance elicited by different pathophysiological mechanisms (7–11). Thus, there is a need to optimize patient characterization to enable scientists and clinicians to successfully tailor individual treatments.

Diastolic dysfunction can frequently be diagnosed in HFpEF patients and is associated with an impairment of active left ventricular (LV) relaxation and/or

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ABBREVIATIONS AND ACRONYMS

beta = left ventricular stiffness constant

Ea = arterial elastance

ECV = extracellular volume fraction

EDPVR = end-diastolic pressure volume relation

Ees = end-systolic elastance

ESPVR = end-systolic pressure-volume relations

PV = pressure volume

tau = time-constant of active left ventricular relaxation

LV compliance, which in turn results in a disproportional rise in LV filling pressures during exercise (7,12).

Diffuse myocardial fibrosis and an increase in extracellular matrix have been suggested as potential mechanisms for increased LV stiffness and diastolic dysfunction (13–15).

Cardiac magnetic resonance (CMR) imaging is a noninvasive tool that allows reliable characterization of myocardial tissue. With the recent advent of T_1 mapping techniques, it has become possible to quantify diffuse changes to the extracellular space. Post-contrast T_1 times and extracellular volume fraction (ECV) correlate with histological collagen volume fraction in vivo and in vitro (16,17). The diagnostic value of T_1 mapping techniques in patients with HFpEF needs to be further determined.

Invasive tracings of pressure-volume (PV) relations represent the gold standard for assessing left ventricular (LV) load-independent mechanical diastolic properties. Moreover, this technique provides the opportunity to instantly assess different aspects of diastolic function and the end-diastolic pressure-volume relation (EDPVR) under altering loading conditions (18,19).

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This study examined the relationship between ECV and invasively measured parameters of diastolic function, and also investigated the potential of ECV to differentiate between different pathomechanisms in HFpEF.

METHODS

This was a prospective study conducted at the Heart Center, Leipzig University, Germany. Patients with clinical and echocardiographic evidence for HFpEF were included, and patients without HF symptoms but indication for invasive coronary angiography served as control subjects. HFpEF patients were identified according to a consensus paper of the European Society of Cardiology (20), using specific inclusion criteria: left ventricular ejection fraction (LVEF) ≥50%; New York Heart Association functional class ≥II; and E/E′ (explanation in next section) 15 or E/E′ 8 to 15 combined with elevated B-type natriuretic peptide. Patients without HF symptoms served as control subjects; specific inclusion criteria were LVEF >50%, E/E′ <8, as well as normal values of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Exclusion criteria included any relevant coronary artery diseases (CADs), any contraindication to CMR imaging (e.g., pacemaker or cardioverter-defibrillator implants), an estimated glomerular filtration rate <30 ml/min/1.73 m^2, acute coronary syndrome, more than moderate valvular diseases, or persistent atrial fibrillation. NT-proBNP levels were analyzed centrally with a standard assay (Cobas, Elecsys NT-proBNP II, Roche, Basel, Switzerland). Assay-specific elevations >220 pg/ml were considered relevant.

To ensure comparable levels of intravascular volumes, CMR imaging and cardiac catheterization were preceded by an intravenous infusion of 500 ml saline solution. To reduce significant confounding, oral medication was withheld on the day of diagnostic workup.

The study was approved by the local ethics committee, and all patients gave written informed consent.

IMAGING AND TESTING PROTOCOLS. Echocardiographic studies were performed on a Vivid 9 system (General Electric Healthcare, Chalfont St. Giles, Great Britain). Mitral valve inflow pattern (E and A velocity), septal and lateral mitral valve annular velocities (E′), as well as the duration of the A wave and the duration of the pulmonary venous flow reversal (Ar), were recorded in an apical 4-chamber view. The ratios of E/A, E/E′ septal, E/E′ lateral, an averaged E/E′, and the difference of Ar-A duration were calculated as markers of diastolic function according to American Society of Echocardiography guidelines (21). Data were analyzed from stored images by an experienced operator (M.vR.) who was unaware of other test results. Measurements were made in 3 cardiac cycles; the average was used for statistical analysis.

Cardiopulmonary exercise testing was performed on a bicycle ergometer. Work rate was increased with a ramp protocol. Breath-by-breath respiratory gas exchange measurements were recorded throughout the test and averaged over a peak width of 20 s at the end of exercise to determine maximum values. Patients were encouraged to exercise until exhaustion.

CMR was performed immediately before invasive catheterization. All scans were performed on an Intera 1.5-T scanner (Koninklijke Philips N.V., Amsterdam, the Netherlands).

The CMR protocol consisted of cine-sequences, T_1-weighted spin-echo, and 2-dimensional inversion recovery gradient echo sequences for late enhancement assessment after gadobutrol administration.

T_1 mapping was performed with a modified Look-Locker inversion recovery sequence with a 3(3)5 scheme before and 15 min after contrast application (22). Mapping was performed over all available short-axis slices. ECV was calculated on the basis of the combination of pre- and post-contrast T_1

mapping data according to the approach proposed by Arheden et al. (23) using the formula: ECV = ($\Delta R1_{myocardium}/\Delta R1_{blood}$) • (1 − hematocrit), where R1 = $1/T_1$ time. A detailed description of the CMR protocol is provided in the Online Appendix.

According to the amount of ECV, we further assigned HFpEF patients to a group on the basis of an ECV greater or less than the median. Data were interpreted by 2 experienced readers who were unaware of the subjects' clinical information and the results of other diagnostic tests (C.L. and M.G.).

CARDIAC CATHETERIZATION PROTOCOL. Standard invasive coronary angiography was performed via right femoral artery access to exclude significant CAD; patients were excluded if they had an indication for the treatment of epicardial stenosis. A conductance catheter (CD Leycom, Hengelo, the Netherlands) was then introduced to record simultaneous LV pressure and volumes as previously described (12). For reduction of pre-load, transient occlusion of the inferior vena cava was achieved by inflation of an Amplatzer sizing balloon (St. Jude Medical, St. Paul, Minnesota). The end-systolic elastance (Ees) was determined as the linear slope through the end-systolic pressure-volume relations (ESPVR), and the load-independent LV stiffness constant (beta) was extrapolated from the EDPVR using the formula $EDP = C \bullet e^{beta \bullet EDV}$, where EDP is LV end-diastolic pressure, C is a fitting constant, and EDV is LV end-diastolic volume (24).

To increase afterload, patients were asked to perform handgrip exercise for 1 min, and PV data were acquired at baseline and throughout peak exercise.

The time constant of active relaxation, or tau, was calculated after the method of Mirsky (25), which evaluates the time needed for LV pressure to fall to one-half of its value from peak rate of LV pressure fall (dP/dt_{min}). Arterial elastance (Ea) was calculated as end-systolic pressure/stroke volume, whereas ventricular arterial coupling was assessed by the formula of end-systolic volume/stroke volume. An experienced operator without knowledge of other test results analyzed the conductance catheter data (K.-P.R.). Further details are provided in the Online Appendix.

STATISTICAL ANALYSIS. Normality of data was assessed using Shapiro-Wilk tests. Data for continuous variables are presented as mean ± SD, if normally distributed, or as median and interquartile range (IQR) if nonnormally distributed. Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using chi-square tests for categorical variables. Continuous variables were compared with unpaired Student *t* tests or the nonparametric Mann-Whitney *U* test where appropriate.

TABLE 1 Baseline Characteristics

	HFpEF (n = 24)	Control Subjects (n = 12)	p Value
Age, yrs	66.1 ± 8.2	56.6 ± 12.1	0.01
Female	21 (88)	2 (17)	<0.01
BMI, kg/m²	29.8 ± 4.3	26.7 ± 2.6	0.01
Abdominal girth, cm	99 ± 13	95 ± 11	0.40
Systolic BP, mm Hg	155 ± 13	149 ± 16	0.27
Diastolic BP, mm Hg	80 ± 9	79 ± 10	0.86
Hematocrit	40 (39-42)	44 (42-46)	0.01
Heart rate, beats/min	67 ± 9	74 ± 9	0.07
eGFR, ml/min•1.73 m²	74.4 ± 17.4	86.4 ± 14.2	0.05
Fasting glucose, mmol/l	5.8 ± 1.8	8.2 ± 6.3	0.20
hs-CRP, mg/l	3.0 (0.8-5.0)	1.6 (1.4-2.0)	0.40
NT-proBNP, ng/l	342 (222-614)	44 (22-68)	<0.01
NT-proBNP, elevation	17 (71)	0 (0)	<0.01
NYHA functional class			
I	0 (0)	12 (100)	<0.01
II	20 (83)	0 (0)	<0.01
III	4 (16)	0 (0)	0.28
Smoking	3 (14)	9 (83)	<0.01
Hypertension	23 (96)	7 (58)	0.01
Hypercholesterolemia	21 (88)	11 (92)	0.71
Diabetes mellitus	3 (13)	4 (33)	0.19
COPD	2 (8)	0 (0)	0.54
Paroxysmal AF	6 (25)	0 (0)	0.08
OSA	2 (8)	0 (0)	0.54
Beta-blockers	11 (46)	2 (17)	0.14
ACEI/ARB	17 (71)	4 (33)	0.07
Calcium antagonist	8 (33)	3 (25)	0.72
Statins	9 (38)	4 (33)	0.81
Diuretic agents	8 (33)	1 (8)	0.22

Values are mean ± SD, n (%), or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; hs-CRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OSA = obstructive sleep apnea.

Univariate and stepwise multivariate linear regression analyses were performed to identify predictors of beta. Correlations were analyzed with the Pearson method (r = Pearson product moment or standardized coefficient of univariate linear regression).

In a first step, comparisons were made between patients with HFpEF and control subjects. In a second step, HFpEF patients were classified and compared according to their extent of ECV (greater or less than the median). PV loops of 14 patients (providing a total of 28 measurements for each parameter) were assessed by a second observer (K.F.). Reproducibility of PV measurements was tested by the use of linear regression and Bland-Altman limits of agreement. The reproducibility coefficient was calculated as 1.96 × the SD of the differences, as proposed by Bland and Altman (26).

TABLE 2 CMR and TTE Results

	HFpEF (n = 24)	Control (n = 12)	p Value
LVEDV, ml	140 ± 38	139 ± 31	0.98
LVEDV index, ml/m²	71.6 ± 14.0	69.5 ± 13.7	0.68
LVESV, ml	56 ± 21	58 ± 21	0.66
LVESV index, ml/m²	28.4 ± 9.4	28.9 ± 9.6	0.88
LVEF, %	60.2 ± 7.2	58.5 ± 7.6	0.76
LV mass, g	185 (156-240)	170 (146-189)	0.13
LV mass index, g/m²	99 (85-128)	82 (72-100)	0.04
Myocardial T_1 pre-contrast, ms	1,074 (1,044-1,107)	1,061 (1,000-1,097)	0.21
Blood T_1 pre-contrast, ms	1,607 (1,576-1,652)	1,526 (1,477-1,599)	<0.01
Myocardial T_1 post-contrast, ms	453 (418-498)	488 (456-503)	0.08
Blood T_1 post-contrast, ms	344 (309-373)	356 (325-378)	0.30
Focal LGE present	4 (17)	0 (0)	0.12
Extracellular volume fraction, %	32.9 ± 3.2	28.9 ± 3.0	<0.01
LAESVi, ml/m²	39.9 ± 14.5	22.6 ± 6.3	<0.01
E velocity max, m/s	0.89 ± 0.2	0.66 ± 0.1	<0.01
A velocity max, m/s	0.80 ± 0.2	0.68 ± 0.2	0.12
E/A ratio	1.0 (0.8-1.6)	0.9 (0.8-1.3)	0.46
E' septal, m/s	0.06 ± 0.02	0.09 ± 0.02	<0.01
E' lateral, m/s	0.07 ± 0.02	0.12 ± 0.03	<0.01
E/E' septal ratio	16.4 ± 4.8	7.9 ± 1.1	<0.01
E/E' lateral ratio	13.4 ± 4.9	5.9 ± 1.2	<0.01
E/E' mean ratio	14.8 ± 4.1	6.9 ± 0.9	<0.01
E deceleration time, ms	200 ± 51	206 ± 40	0.76
Ar-A duration, ms	38 (26-42)	4 (0-23)	<0.01

Values are mean ± SD, median (interquartile range), or n (%).

Ar = pulmonary venous flow reversal; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HFpEF = heart failure with preserved ejection fraction; LAESVi = left atrial end-systolic volume index; LV = left ventricular; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; TTE = transthoracic echocardiography.

A 2-tailed p value <0.05 was considered statistically significant. SPSS version 20.0 (IBM, Armonk, New York) was used for statistical analyses.

RESULTS

During the study period, 45 patients were considered suitable after echocardiographic assessment. Of these, 2 patients were excluded due to incomplete CMR studies, another 5 excluded due to significant CAD, and 2 due to atrial fibrillation during catheterization. Therefore, 12 patients served as control subjects and 24 patients with HFpEF were included for final analyses.

HFpEF patients were older, were more frequently female, had a higher body mass index, were more likely to have hypertension, and had a numerically higher rate of paroxysmal atrial fibrillation (Table 1). An elevation of NT-proBNP was present in two-thirds of HFpEF patients, who all reported exertional dyspnea, predominantly New York Heart Association functional class II. Patients without HF symptoms presented with indication for coronary angiography due to chest pain and had a significant cardiovascular risk profile. A trend toward a more frequent use of antihypertensive and HF medications was noted in HFpEF patients.

TESTING AND IMAGING RESULTS. Patients with HFpEF had a significantly impaired exercise capacity in comparison with control subjects (97 W [IQR: 76 to 104 W] vs. 152 W [IQR: 114 to 193 W]; $p < 0.01$) and a reduced maximal oxygen uptake (16 ml/kg•min [IQR: 14 to 21 ml/kg•min] vs. 25 ml/kg•min [IQR: 21 to 38 ml/kg•min]; $p < 0.01$).

All patients in the final analysis had complete data for CMR and echocardiographic examinations; patients with HFpEF had bigger left atrial volumes, higher E/E' ratios, and longer Ar-A durations (Table 2).

Late gadolinium enhancement (LGE) was observed in 4 patients: 2 had inferolateral midwall LGE of unknown etiology, and 2 patients with marked hypertrophy showed focal LGE at the posterior right ventricle insertion. Areas of focal LGE were manually excluded from the analysis. T_1 maps were created from a median of 5 (IQR: 5 to 6) ventricular short-axis slices. The ECV was significantly higher in patients with HFpEF.

CORRELATION OF MEASURES OF DIASTOLIC FUNCTION. Markers of intrinsic systolic performance (contractility as defined by Ees) and arterial elastance (Ea) were comparable between groups. HFpEF patients had higher LV EDPs at baseline and during exercise as well as a more pronounced increase in EDPVR in response to physical exertion (ΔEDPVR) (Table 3). Patients in the HF group showed prolonged active relaxation during exercise as well as a significantly higher beta. Univariate linear regression demonstrated a significant correlation of the LV stiffness constant with pre-contrast T_1 time ($r = 0.48$; $ß_{nonstandardized} = 0.00007$; $p = 0.003$), post-contrast T_1 time ($r = -0.34$; $ß_{nonstandardized} = -0.00006$; $p = 0.04$), and ECV ($r = 0.75$; $ß_{nonstandardized} = 0.212$; $p < 0.01$) (Figure 1), as well as with E/E' ($r = 0.59$; $ß_{nonstandardized} = 0.001$; $p = 0.04$) and left atrial volume index ($r = 0.48$; $ß_{nonstandardized} = 0.0003$; $p < 0.01$).

E/E' correlated with LV end-diastolic pressure at baseline ($r = 0.63$; $ß_{nonstandardized} = 0.87$; $p < 0.001$) and maximal exercise ($r = 0.48$; $ß_{nonstandardized} = 0.37$; $p < 0.01$), EDPVR at baseline ($r = 0.56$; $ß_{nonstandardized} = 75.2$; $p < 0.01$), and maximal exercise ($r = 0.52$; $ß_{nonstandardized} = 40.4$; $p < 0.01$).

On multivariate linear regression analyses including ECV, E/E', and left atrial volume index as the noninvasive imaging parameters potentially informing on LV stiffness, ECV emerged as the only

independent predictor for intrinsic LV stiffness ($ß_{standardized} = 0.75$; $ß_{nonstandardized} = 0.21$; $p < 0.01$).

ECV GROUPS IN HFpEF PATIENTS. When patients with HFpEF were grouped according to the median ECV (32.3%), no differences were observed in baseline characteristics, results of exercise testing, or noninvasive imaging parameters, but the group with ECV greater than the median showed higher ECV (35.4 ± 2.2% vs. 30.3 ± 1.4%; $p < 0.01$). Echocardiographic measures of diastolic function were comparable for ECV below or above the median: E/E' 15.0 ± 4.3 vs. 14.6 ± 4.1; $p = 0.80$; E deceleration time 200 ± 62 ms vs. 201 ± 39 ms; $p = 0.97$; E/A-ratio 1.0 (IQR: 0.8 to 1.5) vs. 1.0 (IQR: 0.8 to 1.6); $p = 0.59$; and Ar-A duration 38 ms (IQR: 28 to 51 ms) vs. 38 ms (IQR: 20 to 43 ms); $p = 0.66$, respectively.

Both groups had a pathological increase in EDPVR during exercise compared with control subjects with no between-group difference (Figure 2, Table 4). Although the group with ECV below the median showed a significantly higher beta, a lower-than-median ECV identified patients with a higher Ea, a hypertensive reaction to physical exercise with markedly elevated filling pressures, and prolonged active relaxation (Figures 2 and 3, Table 4).

REPRODUCIBILITY OF PV-LOOP MEASUREMENTS. Bland-Altman analysis demonstrated acceptable agreement with the following average differences between measurements: ESPVR −0.07 mm Hg/ml (upper limit of agreement [ULA]: 0.35 mm Hg/ml; lower limit of agreement [LLA]: −0.48 mm Hg/ml); EDPVR 0.0 mm Hg/ml (ULA: 0.05 mm Hg/ml; LLA: −0.05 mm Hg/ml); Ees 0.06 mm Hg/ml (ULA: 0.50 mm Hg/ml; LLA: −0.38 mm Hg/ml); Ea 0.13 mm Hg/ml (ULA: 0.78 mm Hg/ml; LLA: −0.53 mm Hg/ml); beta 0.002 (ULA: 0.011; LLA: −0.007); and tau −0.9 ms (ULA: 5.3 ms; LLA: −7.0 ms) (Online Figure 1). The reproducibility coefficients (given as percent of the average value of the measurements) were: 13% for ESPVR; 34% for EDPVR; 14% for Ees; 28% for Ea; 17% for tau; and 30% for beta. There was no significant proportional bias.

DISCUSSION

This is the first study comprehensively assessing the diagnostic performance of T_1 mapping and determination of ECV in patients with HFpEF. The main findings are: 1) the noninvasively obtainable ECV correlates highly with load-independent LV myocardial stiffness; 2) in patients with HFpEF and a near-normal ECV, predominant pathomechanisms other than myocardial stiffness must be assumed, with a predominant impairment of active relaxation; and 3) ECV assessment allowed for classification of HFpEF

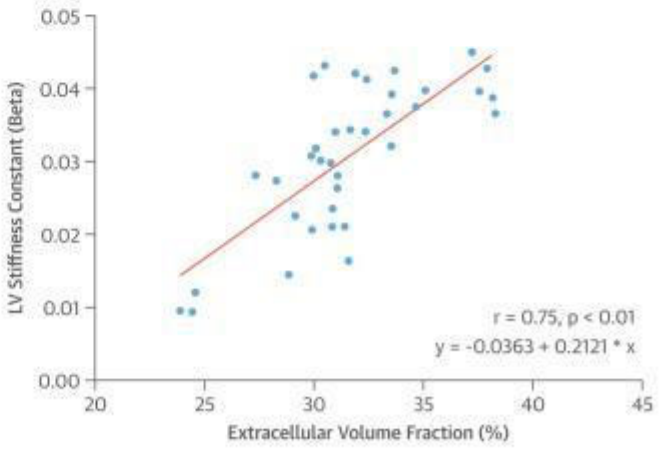
TABLE 3 Pressure Volume Loops

	HFpEF (n = 24)	Control (n = 12)	p Value
Baseline			
Heart rate, beats/min	68.4 ± 9.9	73.0 ± 7.8	0.16
LVESP, mm Hg	145 ± 21	135 ± 24	0.20
LVEDP, mm Hg	17.9 ± 4.3	13.5 ± 4.1	<0.01
Tau, ms	36.0 ± 8.9	30.8 ± 3.8	0.06
LVESPVR, mm Hg/ml	3.2 ± 1.3	2.8 ± 1.3	0.33
LVEDPVR, mm Hg/ml	0.11 ± 0.04	0.08 ± 0.02	0.04
Ees, mm Hg/ml	2.3 ± 0.8	2.9 ± 1.3	0.11
Ea, mm Hg/ml	1.5 ± 0.4	1.5 ± 0.3	0.55
Ea/Ees ratio	0.8 ± 0.4	0.6 ± 0.3	0.18
Exercise			
Heart rate, beats/min	87.9 ± 12.2	99.6 ± 7.6	<0.01
LVESP, mm Hg	196 ± 27	188 ± 30	0.42
LVEDP, mm Hg	26.4 ± 6.9	20.7 ± 3.9	0.01
Tau, ms	38.2 ± 5.2	33.4 ± 5.6	0.02
LVESPVR, mm Hg/ml	3.7 ± 2.0	3.2 ± 1.5	0.46
LVEDPVR, mm Hg/ml	0.21 ± 0.07	0.16 ± 0.03	0.05
Ees, mm Hg/ml	3.7 ± 2.0	3.2 ± 1.5	0.47
Ea, mm Hg/ml	2.7 ± 1.0	2.6 ± 0.9	0.88
Ea/Ees ratio	0.9 ± 0.4	1.0 ± 0.5	0.48
ΔEDPVR baseline-exercise, mm Hg/ml	0.10 ± 0.04	0.06 ± 0.02	<0.01
LV stiffness constant	0.037 (0.031–0.041)	0.021 (0.013–0.025)	<0.01

Values are mean ± SD or median (interquartile range).

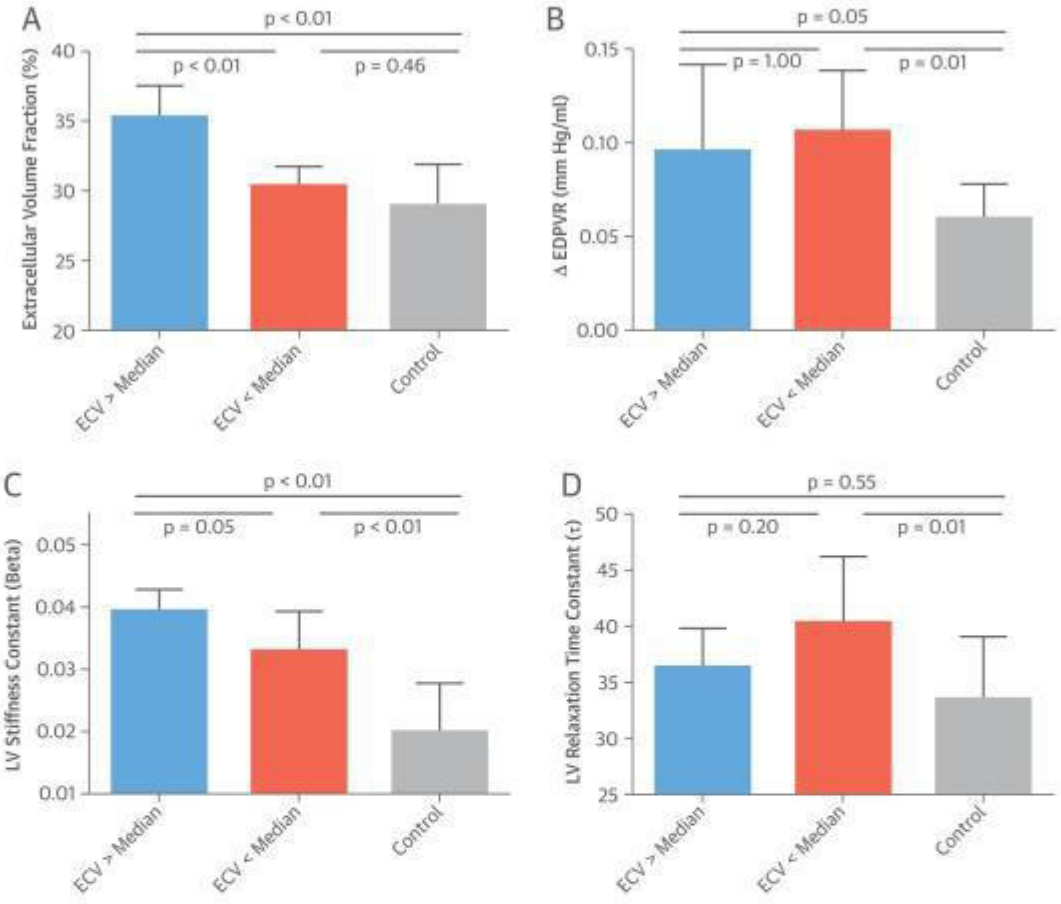
Ea = arterial elastance; EDP = end-diastolic pressure; ΔEDPVR = end-diastolic pressure-volume relation; Ees = end-systolic elastance; LVEDP = left ventricular end-diastolic pressure; LVEDPVR = left ventricular end-diastolic pressure-volume relation; LVESP = left ventricular end-systolic pressure; LVESPVR = left ventricular end-systolic pressure-volume relation; tau = time constant of relaxation; other abbreviations as in Table 2.

FIGURE 1 Correlation of LV Stiffness Constant and ECV



A significant positive correlation was observed between extracellular volume fraction (ECV) and left ventricular (LV) stiffness constant (beta).

FIGURE 2 Results According to ECV Group and Control Subjects



Differences in **(A)** extracellular volume fraction (ECV), **(B)** change in end-diastolic pressure-volume relation (ΔEDPVR) from baseline to exercise, **(C)** beta, and **(D)** time constant of active left ventricular relaxation (tau) are compared between control subjects and patients with heart failure with preserved ejection fraction (HFpEF) with ECV above and below the median. Values are mean ± SD.

patients into 2 groups demonstrating different underlying mechanisms for HFpEF and exercise intolerance.

The emerging clinical problem of patients with HF symptoms despite having a preserved LVEF has led to intensive research and diagnostic algorithms to better understand and ultimately treat these patients (20,27). Problems arise from the heterogeneity of the cohort classified as having HFpEF and the need to individualize possible treatment therapies.

Diastolic dysfunction is the hemodynamic consequence of many pathologies involved in HFpEF. Patients share a pathological upward shift of the EDPVR on exertion (28). Two main determinants of this scenario are an increase in intramyocardial stiffness and a prolongation of active myocardial relaxation (7). Whereas the former is thought to be a consequence of an increase in extracellular matrix (accumulation of collagen and abnormalities of the intramyocardial cytoskeleton), the latter is attributed to an impaired active process of muscular inactivation, asynchronous contraction, or pathological loading conditions (13). Both mechanisms have been demonstrated to play a major role in the development of HFpEF and possibly suggest different treatment targets (7).

Doppler echocardiography provides a foundation to noninvasively diagnose diastolic dysfunction. However, abnormalities found on echocardiographic evaluation are not specific to individuals with HFpEF and are highly load dependent; conclusions as to the underlying pathophysiological processes are limited (29).

The invasive recording of PV relations is the only way to directly assess the heart's diastolic properties. Therefore, the stiffness constant beta is related to a decreased ventricular compliance, consistent with intrinsic myocardial stiffening (12). Tau, or time

constant of isovolumetric relaxation, is a measure of the active relaxation process (25).

CMR T_1 mapping techniques have emerged as a noninvasive tool to quantify diffuse myocardial fibroses. Indeed, several studies have found a correlation between histologically proven fibrosis and T_1 mapping-derived estimated ECV, and its utility to characterize different cardiac conditions has been demonstrated (16,30–32). Compared with standard T_1 mapping techniques, ECV is not affected by many external patient-specific factors, permitting more accurate patient-to-patient comparisons (33). In a recent study, Ellims et al. (14) found that post-contrast T_1 times and ECV correlated with beta in heart transplant patients. In their patients, post-contrast T_1 time independently predicted beta, allowing them to establish a link between fibrosis and myocardial stiffness. However, their study predominantly examined male cardiac transplant patients with hardly any HF symptoms or signs of diastolic dysfunction and only mildly elevated filling pressures. Moreover, hemodynamic effects during exertion were not examined.

Our study comprehensively evaluated the diagnostic performance of T_1 mapping in HFpEF patients compared with control subjects. In line with previous studies, we found that HFpEF patients were predominantly female with multiple cardiovascular risk factors and reduced exercise capacities. Hemodynamically, this could be attributed to a pathological rise of the EDPVR through exercise caused by increased myocardial stiffness and prolongation of active relaxation. We also observed an increased ECV but only a trend toward lower post-contrast T_1 times in the HFpEF group. In line with Ellims et al. (14), we found a correlation with post-contrast T_1 times and beta. However, ECV was the only independent predictor for the myocardial stiffness constant in multivariate analysis. It should also be noted that, apart from extracellular fibrosis, myocardial wall thickness and alterations of the myocytoskeleton can contribute to myocardial stiffness, which may explain some degree of scatter within the correlation between ECV and beta.

The discrepancies between our study and the work by Ellims et al. (14) might further be explained by the differences in patient characteristics, with an overall higher ECV in our patients (31 ± 4% vs. 26 ± 9%) and different CMR mapping techniques. Our study added the observation that ECV might help differentiate between different aspects of exercise intolerance. When HFpEF patients were classified according to the ECV median, a group with near normal ECVs was generated and compared with a group with elevated ECV. Both groups showed a pathological upward shift of the EDPVR under exercise, which combines both increased intrinsic stiffening and impaired active relaxation. In patients with elevated ECV, the dominant pathomechanism was identified as an increase in passive stiffness. In the other group, patients had a significantly elevated Ea (i.e., arterial stiffness), marked hypertensive reaction to exercise, impaired active relaxation, and development of even higher LV pressures (**Figure 3, Central Illustration**). Active LV relaxation follows a biphasic course during afterload rise. Although small increases in afterload cause a shortening of tau, afterload excess, as observed in these patients, prolongs relaxation time leading to diastolic dysfunction (34). Although statistically significant differences in active relaxation and passive stiffness could be detected between groups, a relevant overlap between these mechanisms has to be assumed. In fact, patients in the group with ECV below the median showed a significantly higher LV stiffness constant than control subjects. Additionally, in patients with ECV greater than the median, the LV relaxation constant was numerically higher than in control subjects.

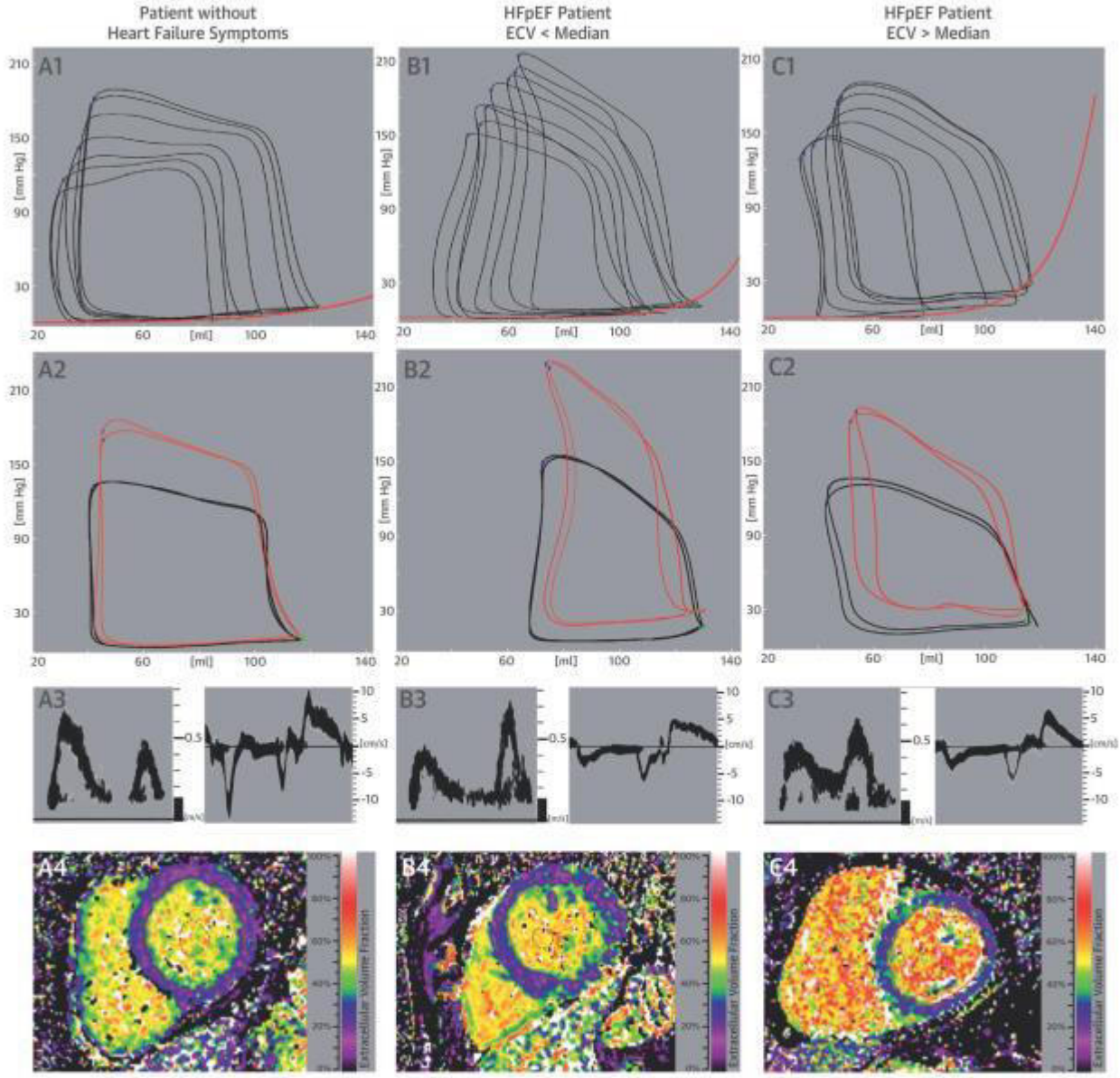
Importantly, both groups demonstrated similar echocardiographic findings and were only different when considering the CMR T_1 mapping results. These

TABLE 4 Pressure-Volume Loops by ECV Level

	HFpEF ECV < Median (n = 12)	HFpEF ECV > Median (n = 12)	p Value
Baseline			
Heart rate, beats/min	72.3 ± 4.7	69.4 ± 13.2	0.49
LVESP, mm Hg	150 ± 24	141 ± 18	0.27
LVEDP, mm Hg	17.8 ± 5.3	17.9 ± 3.2	0.96
Tau, ms	35.4 ± 6.2	35.8 ± 9.3	0.89
LVESPVR, mm Hg/ml	3.6 ± 1.3	2.8 ± 1.2	0.10
LVEDPVR, mm Hg/ml	0.12 ± 0.05	0.10 ± 0.03	0.18
Ees, mm Hg/ml	2.4 ± 0.7	2.1 ± 0.9	0.31
Ea, mm Hg/ml	1.7 ± 0.3	1.4 ± 0.4	0.04
Ea/Ees ratio	0.7 ± 0.2	0.8 ± 0.5	0.56
Exercise			
Heart rate, beats/min	87.5 ± 12.3	88.3 ± 12.7	0.88
LVESP, mm Hg	208 ± 21	185 ± 27	0.04
LVEDP, mm Hg	30.6 ± 5.8	22.5 ± 6.1	<0.01
Tau, ms	40.3 ± 5.9	36.3 ± 3.6	0.06
LVESPVR, mm Hg/ml	3.8 ± 1.5	3.7 ± 2.5	0.88
LVEDPVR, mm Hg/ml	0.24 ± 0.06	0.18 ± 0.08	0.03
Ees, mm Hg/ml	3.8 ± 1.5	3.6 ± 2.5	0.87
Ea, mm Hg/ml	2.9 ± 0.6	2.4 ± 1.1	0.14
Ea/Ees ratio	0.9 ± 0.4	0.8 ± 0.4	0.85
ΔEDPVR baseline-exercise, mm Hg/ml	0.11 ± 0.03	0.10 ± 0.05	0.55
LV stiffness constant	0.031 (0.028-0.040)	0.39 (0.037-0.042)	0.02

Values are mean ± SD or median (interquartile range).
Abbreviations as in Tables 2 and 3.

FIGURE 3 Pathomechanisms by ECV Group and Control Subjects



In patients without heart failure symptoms: **(A1)** Pressure-volume (PV) loops under transient pre-load reduction showed a shallow slope of the EDPVR line **(red line)**. **(A2)** PV loops at baseline **(black)** and throughout exercise **(red)** demonstrated a physiological response to exertion and a small change in EDPVR **(green points)**. **(A3)** Echocardiographic mitral valve (MV) inflow pattern **(left)** and septal MV annular velocities **(right)** showed no evidence of diastolic dysfunction. **(A4)** Cardiac magnetic resonance (CMR)–derived extracellular volume map demonstrated a low ECV of 25%. In HFpEF patients with ECV less than the median, **(B1)** PV loops under transient pre-load reduction showed an increased slope of the EDPVR line **(red line)**. **(B2)** PV loops at baseline **(black)** and throughout exercise **(red)** with elevated arterial elastance and marked hypertensive response to exertion resulted in significant changes in EDPVR **(green points)**. **(B3)** Echocardiographic MV inflow pattern **(left)** and septal MV annular velocities **(right)** showed diastolic dysfunction. **(B4)** CMR-derived extracellular volume map demonstrated a normal ECV of 28%. In HFpEF patients with ECV greater than the median: **(C1)** PV loops under transient pre-load reduction showed the steepest slope of the EDPVR line **(red line)**. **(C2)** PV loops at baseline **(black)** and throughout exercise **(red)** showed a significant change in EDPVR **(green points)**. **(C3)**: Echocardiographic MV inflow pattern **(left)** and septal MV annular velocities **(right)** show diastolic dysfunction without notable differences from the other ECV group. **(C4)** CMR-derived extracellular volume map demonstrated an elevated ECV of 36%. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **T_1 Mapping to Quantify LV Stiffness in Patients Without HF Symptoms and With HFpEF**

Assessments to characterize patient	No heart failure (HF) symptoms	HF with preserved ejection fraction (HFpEF)	
Symptoms:			
• Exercise capacity	↑	↓	
• Left ventricle (LV) filling pressures	↔	↑	
Cardiac Magnetic Resonance:		Near normal ECV	Elevated ECV
• Extracellular Volume Fraction (ECV)	Low ECV		
• Diffuse myocardial fibrosis	↓	↔	↑
Invasive assessment of diastolic function:			
• Intrinsic myocardial stiffness	↓	↑	↑↑
• Active LV relaxation	↔	↓↓	↓
• LV afterload under exercise	↑	↑↑	↑
• Arterial stiffness	↔	↑	↔

Rommel, K.-P. et al. J Am Coll Cardiol. 2016;67(15):1815–25.

Use of cardiac magnetic resonance T_1 mapping to quantify myocardial fibrosis as ECV independently predicted LV stiffness in patients with HFpEF, whereas degree of ECV helped distinguish among pathomechanisms in HFpEF. ECV = extracellular volume fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle.

data, therefore, suggest a valuable role of T_1 mapping in classifying patients with HFpEF in distinct groups that share the same symptoms and degree of exercise intolerance but exhibit different underlying pathophysiology. Because ECV was the only independent predictor for intrinsic ventricular stiffening, this parameter could be of tremendous value in estimating the contribution of intrinsic ventricular stiffness to HFpEF. Consequently, ECV evaluation might also be used to identify patients for whom an alternative mechanism of diastolic dysfunction is most likely, thus enhancing efforts to better tailor individual treatments.

STUDY LIMITATIONS. Given the invasiveness of applied conductance catheter methods, our sample was small, which importantly affects interpretation of the study results. Because multiple statistical testing in a small patient population is susceptible to a type I error, certainly possible in this study, interpretation of our results should be considered "hypothesis-generating" only. Presence of different comorbidities led to some heterogeneity of the small HFpEF patient population, hampering generalizability of our findings. Due to the control group's defined inclusion criteria (indication for invasive catheterization to exclude CAD), this group showed an extensive cardiovascular risk profile and should not be considered healthy subjects.

Importantly, a group of healthy control subjects may have yielded even clearer differences in hemodynamics and CMR parameters.

Exaggerated by the small sample size, HFpEF patients and control patients differed in age and sex distribution; both have a demonstrated effect on ECV. Although significant confounding of the correlation between CMR-derived ECV and load-independent myocardial stiffness appears unlikely, it cannot be excluded. Separation of patients per ECV exhibited 2 significantly different HFpEF phenotypes. However, relevant overlap between groups is to be expected. Furthermore, ECV might not reflect myocardial stiffening caused by other mechanisms such as myoskeletal alterations. These limitations, along with the small sample size, inhibited the general application of an ECV cutoff value for

characterization of HFpEF phenotypes. Echocardiographic diastolic stress was not part of the assessment, but it could have carried some additional diagnostic benefits (35) in this clinical scenario that remain to be determined.

Finally, optimal timing to assess T_1 post-contrast maps is disputed (36). It remains unclear whether earlier or later assessment (15-min post-contrast in this study) could improve diagnostic performance.

CONCLUSIONS

Diffuse myocardial fibrosis as assessed by CMR-derived T_1 mapping independently predicts invasively measured LV stiffness in HFpEF. Although a considerable overlap existed between groups, ECV emerged as a noninvasive way of distinguishing different pathomechanisms in HFpEF. Assessment of ECV could provide additional value in large-scale epidemiological, diagnostic, and therapeutic trials in this field, both in helping to establish certain ECV cutoff values and for subgroup analysis of treatment effects depending on baseline ECV.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Myocardial fibrosis, as assessed by CMR T_1-mapping derived measurement of ECV, correlates with myocardial stiffness and may be useful in identifying the mechanism of diastolic dysfunction in patients with HFpEF.

TRANSLATIONAL OUTLOOK: Further research is warranted to establish the utility of CMR T_1 mapping as a guide to clinical decision making in the evaluation and management of patients with HF.

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KEY WORDS diastolic dysfunction, heart failure with preserved ejection fraction, magnetic resonance imaging

APPENDIX For supplemental Methods and figures, please see the online version of this article.

2.1.2 Identifikation einer unabhängigen linksatrialen Kardiomyopathie als pathomechanistischer Faktor der Herzinsuffizienz mit erhaltener Pumpfunktion

Zitierweise:

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Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction

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Background—Although left atrial (LA) dysfunction is common in heart failure with preserved ejection fraction (HFpEF), its functional implications beyond the reflection of left ventricular (LV) pathology are not well understood. The aim of this study was to further characterize LA function in HFpEF patients.

Methods and Results—We performed cardiac magnetic resonance myocardial feature tracking in 22 patients with HFpEF and 12 patients without HFpEF. LA reservoir strain, LA conduit strain, and LA booster pump strain were quantified. Peak oxygen uptake (VO2max) was determined. Invasive pressure–volume loops were obtained to evaluate LV diastolic properties. LV early filling was determined from LV volume–time curves as derived from cardiac magnetic resonance. LA reservoir and conduit strain were significantly lower in HFpEF (LA reservoir strain, 22±7% versus 29±6%, P=0.04; LA conduit strain, −9±5% versus −15±4%, P<0.01). Patients with HFpEF showed lower oxygen uptake (17±6 versus 29±8 mL/(kg min); P<0.01). Strain measurement for LA conduit function was strongly associated with VO2max (r=0.80; P<0.01). On multivariable regression analysis, LA conduit strain emerged as strongest predictor for VO2max even after inclusion of LV stiffness and relaxation time (β=0.80; P<0.01). LA conduit strain correlated with the volume of early ventricular filling (r=0.67; P<0.01), but not LV stiffness constant β (−0.34; P=0.051) or relaxation constant τ (r=−0.33; P=0.06).

Conclusions—Cardiac magnetic resonance myocardial feature tracking–derived conduit strain is significantly impaired in HFpEF and associated with exercise intolerance. Impaired conduit function is associated with impaired early ventricular filling, as potential mechanism leading to impaired oxygen uptake. Our results propose that impaired LA conduit function represents a distinct feature of HFpEF, independent of LV stiffness and relaxation.

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Key Words: atrial function ■ exercise test ■ heart failure, diastolic ■ magnetic resonance imaging

Heart failure with preserved ejection fraction (HFpEF) is a syndrome with increasing significance because it accounts for morbidity, mortality, and impaired exercise capacity in a growing number of patients.[1,2] Different pathophysiological mechanisms are found to contribute to HFpEF, including left ventricular (LV) diastolic dysfunction, exercise-induced pulmonary hypertension, marked arterial hypertension on exertion, chronotropic incompetence, or right ventricular pathologies.[3–6]

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Left atrial (LA) remodeling and dysfunction are common in this population. In addition, LA dilatation and LA dysfunction were found to be independent risk factors for development and progression of HFpEF.[7–9] To date, the majority of studies on LA function in HFpEF have used echo-derived parameters, including deformation techniques such as tissue Doppler and speckle tracking for LA imaging.[10–12]

Magnetic resonance imaging is regarded as the most accurate technique for LA volume assessment, with its high spatial resolution and excellent myocardial border detection throughout the cardiac cycle. Cardiac magnetic resonance feature tracking (CMR-FT) is a novel tool to assess myocardial deformation directly from standard steady-state–free precession cine CMR images.[13] This allows for quantifying myocardial deformation without the need for complex tagging sequences.[14,15]

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LV diastolic function in HFpEF and LA dysfunction have been shown to be linked with each other.[16] However, it remains unclear whether the assessment of LA dysfunction can provide additional information, independent of active and passive LV diastolic function. Accordingly, the mechanisms involved and the impact of LA function on exercise capacity, independent of LV stiffness, are still poorly understood.

This study therefore aimed, first, to assess LA morphological and functional properties in HFpEF patients using CMR-FT–derived strain analysis; second, to assess the role of LA performance as a predictor for functional capacity when compared with other parameters of HFpEF pathology; and, third, to link LA performance to load-dependent and load-independent parameters of LV diastology and LV filling properties using CMR and invasive conductance catheters measurements.

Methods

Study Protocol

This study is a substudy of the STIFFMAP trial (Left Ventricular Stiffness vs. Fibrosis Quantification by T1 Mapping in Heart Failure With Preserved Ejection Fraction).[17] Patients with indication for coronary angiogram were prospectively recruited between July 2014 and January 2016 if they met the following criteria: HFpEF patients had to fulfill the following criteria (1) signs and symptoms of heart failure (New York Heart Association class ≥II) and (2) echocardiographic signs of diastolic dysfunction according to the consensus article of the European Society of Cardiology[18] (LV ejection fraction [LVEF] ≥50%, and E/E′ >15 or E/E′ 8–15 and an elevation in NT-proBNP [N-Terminal Pro-B-Type Natriuretic Peptide, Cobas; Elecsys NT-proBNP II, Roche, Basel, Switzerland; assay-specific elevations over 220 pg/mL]). Control patients had to be (1) free of heart failure symptoms (2) have an LVEF ≥50% and be free of echocardiographic signs of severe diastolic dysfunction (E/E′ <8). Patients with relevant coronary artery disease, contraindication to CMR imaging, acute coronary syndrome, more than mild valvular disease, or atrial fibrillation (AF) during CMR/cardiac catheterization were excluded from the study.

As part of the initial screening, echocardiographic studies were performed. Subsequently, eligible patients underwent cardiopulmonary exercise testing and magnetic resonance imaging and cardiac catheterization. To assure comparable levels of intravascular volumes, echocardiography, CMR, and invasive catheterization were performed consecutively and within a 5-hour time window.

The study was approved by the local ethics committee, and all patients gave written informed consent.

Exercise Testing

Cardiopulmonary exercise testing was performed on a supine bicycle ergometer (Ergoline, Germany). Work rate was started with 20 to 40 W. The patients were instructed to maintain a pedaling rate of 60 rotations per minute with stepwise workload increments of 10 to 20 W/min. Patients were encouraged to exercise until exhaustion. VO_2, CO2 production, and ventilation were measured on a breath-to-breath basis and calculated using established methodology (ZAN 600; ZAN, Steyr-Dietach, Austria). Peak VO_2 and respiratory exchange ratio were measured in the last 20 s at maximal exercise. A test with an respiratory exchange ratio ≥1.0 was considered sufficient. We defined peak VO_2 as the highest VO_2 obtained during an adequately performed test.[19]

Echocardiography

Transthoracic echocardiography was performed on Vivid E9 (GE Healthcare, Chalfont St. Giles, Great Britain). Analysis was performed offline using commercially available software (Echopac PC 6.1.0, GE Healthcare). LV size and LVEF were quantified according to current guidelines.[20] Diastolic properties were assessed by determining maximum early (E wave) and late (A wave) diastolic velocities on pulsed wave Doppler and by tissue Doppler peak diastolic velocities of the septal and lateral mitral annulus (E′). The E/E′ ratio was calculated.

CMR Protocol

CMR scans were performed on a 1.5-T scanner (Phillips Intera 1.5T, Best, The Netherlands). Electrocardiographic tracing and triggering were performed with the system's built-in patient monitoring unit. Initially, steady-state–free precession sequences were obtained in 2- and 4-chamber views and a short-axes cine stack covering the entirety of the heart (repetition time, 3.8 ms; echo time, 1.6 ms; flip angle, 60°; voxel size, 1.25×1.25×8 mm^2; 8–10 mm slice thickness).

Evaluation of volumes was performed offline on a remote workstation using commercially available software (cmr42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada). LVEF, LV end-diastolic volume, and LV end-systolic volume were assessed from the short-axis stack. Calculated volumes were normalized to body surface area. Semiautomated tracings of the LA area and length were performed in the 2- and 4-chamber views. LA volumes were calculated using the previously validated biplane area-length method.[21]

For assessment of LV filling properties, LV volumes throughout the cardiac cycle were calculated. Early LV filling, defined as the increase in LV volume during the first one third of diastole, was calculated. All volumes were indexed to body surface area.[22] T1-based extracellular volume fraction was assessed as previously described.[17] For further details see the Methods in the Data Supplement.

Feature Tracking

LA myocardial feature tracking was performed using dedicated software (2-dimensional cardiac performance analysis magnetic resonance, Version 1.1.2.36; TomTec Imaging Systems, Unterschleissheim, Germany) as previously described.[23] Temporal solution was 25 to 30 frames per cardiac cycle.

In brief, LA endocardial borders were manually traced in the 2- and 4-chamber views, and an automated tracking algorithm was applied (Figure 1A and 1B). In case of insufficient automated border tracking, manual adjustments were made to the initial contour, and the algorithm was reapplied. If the tracking quality was not sufficient, for example, because of the presence of pulmonary veins or LA appendage, the corresponding segment was excluded from the analysis. Tracking was repeated for 3× in both the 2- and 4- chamber views, and the respective averages of these repetitions were used for further analyses.

LA longitudinal strain (ε) and strain rate (SR) curves were generated from the averages of all 3 repetitions in both views. Three aspects of atrial strain were analyzed (Figure 1C): passive strain (εe, corresponding to atrial conduit function), active strain (εa, corresponding to atrial contractile booster pump function), and total strain (εs, corresponding to atrial reservoir function), the sum of passive and active strain. Accordingly, 3 SR parameters were evaluated (Figure 1D): peak positive strain rate (corresponding to atrial reservoir function), peak early negative strain rate (corresponding to atrial conduit function), and peak late negative strain rate (corresponding to atrial contractile booster pump function).[24] Negative values mean shortening. For description and statistical analysis, only the absolute values were used, and figures were edited accordingly. Thus, for example, better LA conduit strain means higher negative values.

Cardiac Catheterization Protocol

Standard invasive coronary angiography was performed via right femoral artery access to exclude significant coronary artery disease. Subsequently, a conductance catheter was introduced into the LV to simultaneously record pressures and volumes as previously described.[17] Briefly, using a 7F conductance catheter (CD Leycom, Zoetermeer, The Netherlands), continuous real-time LV pressure and volume signals were recorded for 10 s at baseline, with volume calibration performed using LV volumetric data from the preceding CMR scan. For reduction of preload, transient occlusion of the

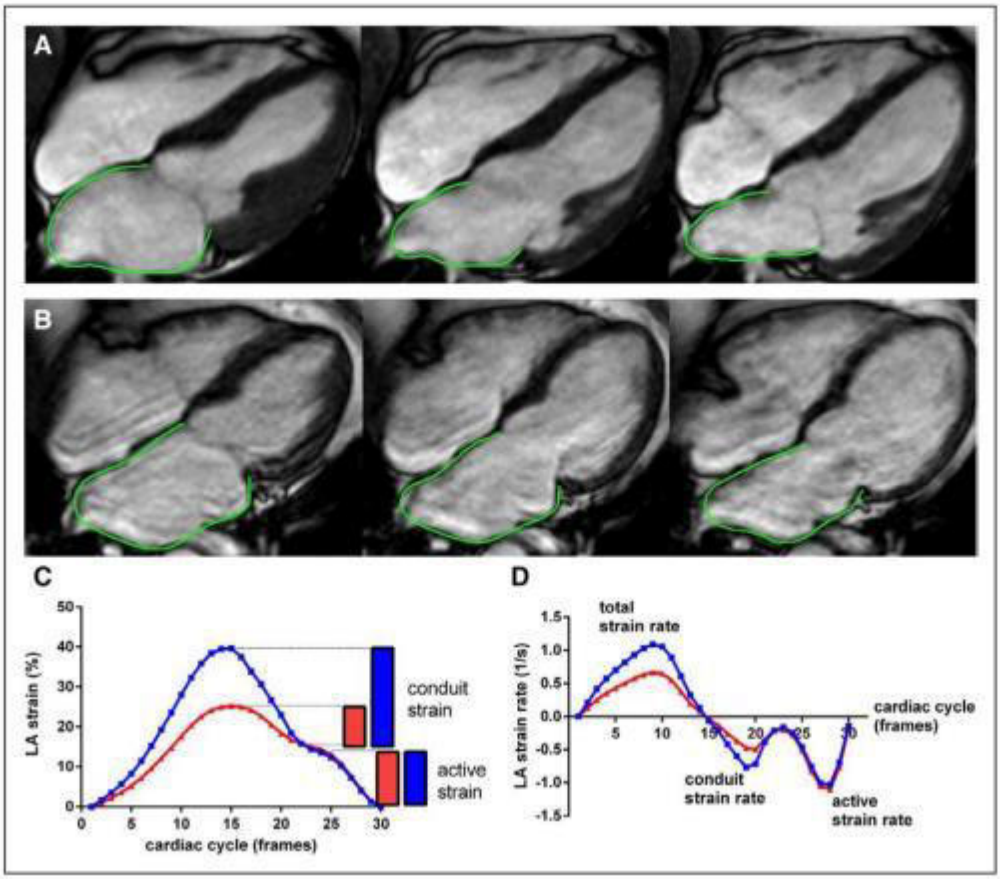

Figure 1. A and **B**, Left atrial (LA) tracking at maximal LA volume (**left**), atrial volume pre atrial contraction (**middle**), and minimal LA volume (**right**) with A showing better and B showing worse conduit function. **Bottom**, Corresponding strain curves. **C**, **bottom left**, LA strain showing better (blue) and worse (red) LA conduit strain and total strain with similar active strain; LA total strain=LA conduit strain+LA active strain. **D**, **bottom right**, corresponding LA strain rate.

inferior vena cava (VCO) was achieved by inflation of an Amplatzer sizing balloon (St. Jude Medical, Saint Paul, MN). On average, 12 pressure–volume loops were acquired during inflation and deflation of the balloon. The load-independent LV stiffness constant (ß) was extrapolated from the end-diastolic pressure–volume relations from the equation $EDP=C\times e^{\beta\times EDV}$, where EDP is LV end-diastolic pressure (LVEDP), C is a fitting constant, and EDV is LV end-diastolic volume. Loops were analyzed from the last heartbeat before the onset of volume/pressure decline for a minimum of 5 beats without increase in heart rate. Curve fitting was realized through Microsoft Excel (Version 14.0).

To increase afterload, patients were asked to perform handgrip exercise for 1 minute, and pressure–volume loops were acquired at baseline and throughout peak exercise.

The time constant of active relaxation (τ) was calculated after the method of Mirsky,[25] which evaluates the time needed for LV pressure to fall to one half of its value from peak rate of LV pressure fall (dP/dtmin).

Statistics

Data for continuous variables are presented as mean±SD, if normally distributed, or as median and interquartile range if non-normally distributed. Distribution was tested using Shapiro–Wilk test. Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using Fisher exact test for categorical variables. Continuous variables were compared with unpaired t tests or nonparametric Mann–Whitney U test where appropriate. HFpEF and controls were compared, and male controls were compared with age-matched female subjects from a previous study with regard to LA and LV function.[23,26]

Pearson (r) and Spearman (ρ) tests were used to find factors associated with VO2max. Univariate linear regression analysis and stepwise forward multivariable linear regression analysis were performed to search and control for influencing factors of VO2max in the whole cohort and partial correlation was analyzed. Different models were calculated, including the factors strongest correlated (with $P\leq0.005$) with VO2max. Standardized β coefficients are reported for multivariable regression analysis. To avoid possible multicollinearity between factors of LA dynamics, only 1 aspect of LA function at a time was included into analysis. Features of impaired LA function were searched using Pearson test, Spearman test, and univariate linear regression, including diastolic ventricular properties.

Results

Clinical and Demographic Data

A total of 44 patients were recruited, out of whom 10 patients were excluded in the course of the study: 2 because of incomplete CMR studies, 5 because of significant coronary artery disease, 2 because of AF, and 1 control subject with markedly younger age (34 years) when compared with the remaining population to reduce potential age-dependent confounding. For the final analyses, 34 patients were available, 22 patients with HFpEF and 12 control subjects. Baseline characteristics are displayed in Table 1.

All patients were stable patients without signs of decompensation. Referral for coronary angiogram was part of the diagnostic workup for HFpEF (mostly because of unexplained exertional dyspnea) and control patients (mostly because of

Table 1. Baseline Characteristics

	HFpEF (n=22)	Control (n=12)	*P* Value
Age, y	65±9	58±9	0.03*
Female, sex	19/22 (86%)	3/12 (25%)	0.001*
BMI, kg/m²	30.3±4.1	26.8±2.6	0.004*
NT-proBNP, ng/L	331 (IQR 205–456)	51 (IQR 28–78)	<0.0001*
NT-proBNP elevation	15/22 (68%)	0/12 (0%)	0.0001*
NYHA I	0/22 (0%)	12/12 (100%)	<0.0001*
NYHA II	19/22 (86%)	0/12 (0%)	
NYHA III	3/22 (14%)	0/12 (0%)	
Smoking	2/22 (9%)	7/12 (58%)	0.004*
Hypertension	21/22 (96%)	8/12 (67%)	0.04*
Hypercholesterolemia	18/22 (82%)	11/12 (92%)	0.63
Diabetes mellitus	3/22 (14%)	4/12 (3%)	0.21
COPD	2/22 (9%)	0/12 (0%)	0.53
Paroxysmal AF	5/22 (23%)	0/12 (0%)	0.14
OSA	3/22 (14%)	0/12 (0%)	0.54
β-blockers	10/22 (45%)	2/12 (17%)	0.14
ACE inhibitors/ARB	16/22 (73%)	5/12 (42%)	0.14
Ca^{2}+ antagonist	7/22 (32%)	3/12 (25%)	1.0
Aldosterone antagonists	0/22 (0%)	0/12 (0%)	n.a.
Statins	8/22 (36%)	4/12 (34%)	1.00
Diuretics	8/22 (36%)	1/12 (8%)	0.11

Values are presented as means±SD, medians+IQR or frequencies (percentages). ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive lung disease; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; n.a., not applicable; NYHA, New York Heart Association; and OSA, obstructive sleep apnea.
*P values below the significance level of 0.05.

atypical retrosternal pain without exertional symptoms) with onset of symptoms within 6 to 12 month before study inclusion.

HFpEF patients were older, more frequently female, had a higher body mass index, and more frequently arterial hypertension. Elevation of NT-proBNP was present in two thirds of HFpEF patients, who all reported exertional dyspnea, predominantly in New York Heart Association class II. Patients without heart failure symptoms presented with indication for coronary angiography because of chest pain and had a marked cardiovascular risk profile.

HFpEF patients showed significantly reduced functional capacity (97±33 versus 154±43 W; $P<0.001$) and maximal oxygen uptake (VO2max 17±6 versus 28±7 mL/(kg min); $P<0.001$) when compared with controls.

Echocardiography, CMR, and Invasive Parameters

No statistically significant differences on LVEF, LV dimensions, and LV stroke volume were found, whereas HFpEF patients had higher E-wave velocities and lower E′ velocities with resulting higher E/E′ ratios. HFpEF patients had higher LVEDPs at baseline and during exercise as shown in Table 2. Patients in the heart failure group showed a significantly higher intrinsic LV stiffness constant β and T1-based extracellular volume fraction.

LA Function

Results are shown in Figure 2. HFpEF patients had higher maximal LA volume (52±18 versus 34±8 mL/m²; $P=0.001$),

Table 2. CMR, TTE, and Invasive Measures Results

	HFpEF (n=22)	Control (n=12)	*P* Value
Echocardiography			
E–Vmax, m/s	0.9±0.2	0.7±0.1	0.001*
A–Vmax, m/s	0.8±0.3	0.7±0.1	0.21
E/A, ratio	1.0 (IQR 0.8–1.4)	0.9 (IQR 0.8–1.20)	0.58
E′ septal, m/s	0.06±0.02	0.08±0.01	0.006*
E′ lateral, m/s	0.07±0.02	0.12±0.03	0.0004*
E/E′ avg	14.6±4	7.2±1	<0.0001*
Mitral deceleration time, ms	197±43	213±281	0.23
CMR imaging			
LV EDV, mL/m²	69±12	70±13	0.66
LV ESV, mL/m²	23±8	27±9	0.25
LV EF, (%)	67±8	63±10	0.16
LV stroke volume, mL/m²	46±7	44±9	0.54
LV mass, g	131±40	125±30	0.62
LV mass index, g/m²	67±19	62±12	0.45
Extracellular volume fraction (%)	33±3.0	29±3	0.003*
Invasive measures			
Heart rate baseline, bpm	68±10	73±7	0.09
LV ESP baseline, mm Hg	156±22	147±20	0.23
LV EDP baseline, mm Hg	18±4	13±4	0.004*
PC wedge, mm Hg	12±5	8±3	0.03*
τ baseline, ms	37±9	31±4	0.04*
Heart rate exercise, bpm	89±12	100±7	0.005*
LV ESP exercise, mm Hg	181±29	186±27	0.65
LV EDP exercise, mm Hg	27±8	21±4	0.004*
τ exercise, ms	38±5	34±6	0.04*
LV stiffness (β)	0.036±0.006	0.022±0.008	<0.0001*

Values are presented as means±SD or medians+interquartile range. E′avg is calculated as (E′septal+E′lateral)/2. CMR indicates cardiac magnetic resonance; EDP, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; τ, time constant of relaxation; and TTE, transthoracic echocardiography.
*P values below the significance level of 0.05.

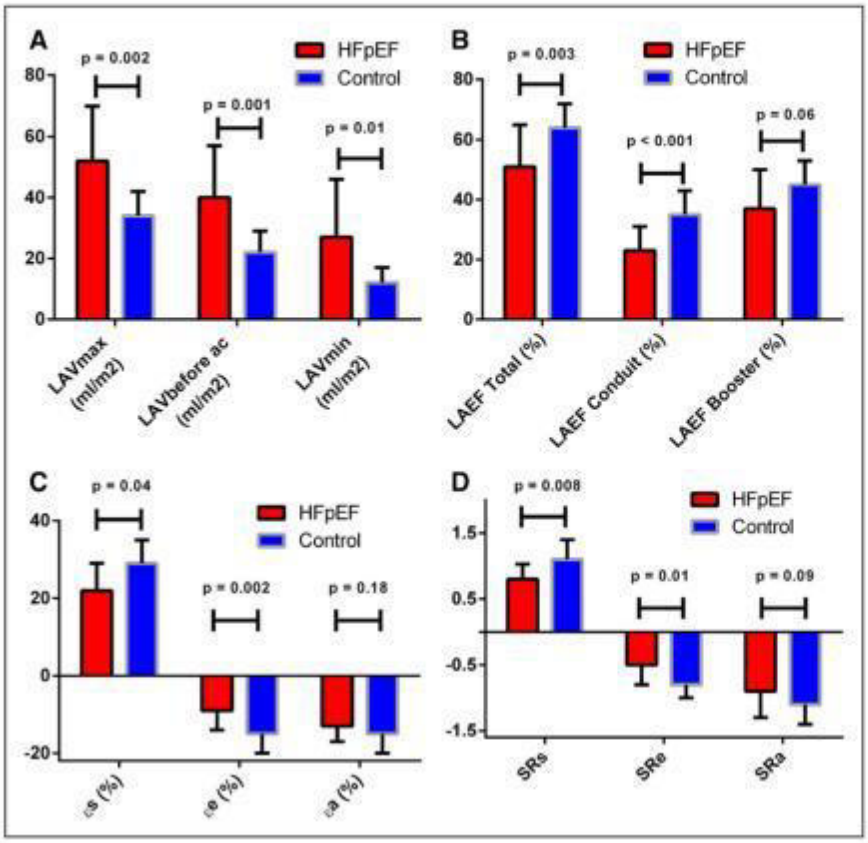

Figure 2. A, Left atrial volumes (LAV): maximal LA volume (LAVmax), LA volume before atrial contraction (LAVbefore ac), and minimal LA volume (LAVmin). **B**, LA function according to volumetric measurements: LA ejection fraction (LAEF). **C**, LA strain measurements: LA total strain (εs), LA conduit strain (εe), and LA active strain (εa). **D**, LA strain rate measurements: LA total strain rate (SRs), LA conduit strain rate (SRe), and LA active strain rate (SRa). HFpEF indicates heart failure with preserved ejection fraction.

higher LA volume before atrial contraction (40±17 versus 22±7 mL/m^2; P=0.001), and higher minimal LA volume (27±19 versus 12±5 mL/m^2; P=0.01). LA total EF and conduit EF were lower in HFpEF patients (LAEF total, 51±14% versus 64±8%, P=0.003; LAEF conduit, 23±8% versus 36±8%, P<0.001), whereas active LA contraction was not significantly different between both groups (LAEF booster, 37±13 versus 45±8%; P=0.06). Despite impaired volumetric LA reservoir and conduit function, similar LA stroke volumes (25±6 versus 21±5 mL/m^2; P=0.13) were observed in both groups, resulting from LA dilatation and higher LA active stroke volume in the HFpEF group (13±5 versus 10±3 mL/m^2; P=0.03). HFpEF patients had impaired LA total strain (εs, 22±7% versus 29±6%; P=0.04) and LA conduit strain (εe, 9±5% versus 15±4%; P=0.002) and a decreased peak positive strain rate (0.79±0.25 versus 1.1±0.3; P=0.008) and peak early negative strain rate (0.54±0.27 versus 0.77±0.20; P=0.014). No significant differences were found comparing markers of LA booster pump function (P=0.18 for strain and P=0.09 for strain rate). No significant difference on LA conduit function was found when comparing HFpEF patients with and without elevated NT-proBNP (εe, 8±4% versus 11±6%; P=0.08).

Factors Associated With Functional Capacity

Factors associated with maximal oxygen uptake are listed in Table 3. The strongest correlations with VO2max were present for LA conduit function (strain εe, r=0.8, P<0.001; conduit peak early negative strain rate, r=0.61, P<0.001; and LAEF conduit, r=0.58, P<0.001), E/E′ (r=−0.56; P=0.001), LA total strain (r=0.56; P=0.001), and age (r=−0.54; P=0.001). The univariate linear regression of εe with VO2max is shown in Figure 3.

Various multivariable linear models were tested: in a model including LA conduit strain and invasive markers of LV diastolic properties (stiffness constant ß and isovolumetric relaxation time τ), LA conduit strain remained the only independent predictor of VO2max (β=0.8; P<0.001). Another model, including conduit strain and the baseline characteristics, sex and age, showed a preserved strong influence of conduit strain (β=0.73; P<0.001) with a comparably weak influence of female sex (β=−0.27; P=0.01) on VO2max. When including E/E′ and εe, LA conduit strain remained the only independent predictor (P<0.001). Details of the multivariable models are shown in Table I in the Data Supplement.

Features of Impaired Conduit Function

To assess a potential link of LA conduit function and load-dependent and load-independent parameters of LV diastology, Pearson correlation was performed, including LV stiffness constant ß, E/E′, LVEDP, age, sex, and BMI. The factor strongest associated with LA conduit function was age (r=−0.59; P≤0.001). No relevant correlation with LV stiffness constant ß (r=−0.34; P=0.05), extracellular volume fraction (r=−0.34; P=0.05), relaxation constant τ (r=−0.3; P=0.09), or LVEDP (r=−0.3; P=0.08) at rest were present. Correlations with τ under maximal exercise (r=−0.46; P=0.007), NT-proBNP (r=−0.49; P=0.004), and E/E′ (r=−0.53; P=0.001) were observed.

Table 3. Univariate Correlation With Maximal Oxygen Uptake (mL/[kg min])

	Correlation Coefficient	*P* Value
Age, y	r=−0.54	0.001*
BMI, kg/m²	r=−0.40	0.02*
NT-proBNP, ng/L	ρ=−0.66	<0.0001*
E/E′ mean	r=−0.56	0.001*
εs (%)	r=0.56	0.001*
εe (−%)	r=0.80	<0.0001*
εa (−%)	r=0.03	0.87
SRs (%/s)	r=0.42	0.01*
SRe (−%/s)	r=0.61	0.0001*
SRa (−%/s)	r=0.11	0.52
LAVmax, mL/m²	r=−0.27	0.12
LAVmin, mL/m²	r=−0.32	0.065
LAVp-ac, mL/m²	r=−0.36	0.04*
LAEF total (%)	r=0.46	0.006*
LAEF conduit (%)	r=0.58	0.0003*
LAEF booster (%)	r=0.30	0.09
LV EDP baseline, mm Hg	r=−0.29	0.11
τ baseline, ms	r=−0.23	0.20
Heart rate exercise, bpm	r=0.31	0.08
LV ESP exercise, mm Hg	r=−0.02	0.92
LV EDP exercise, mm Hg	r=−0.16	0.40
τ exercise, ms	r=−0.25	0.16
LV stiffness (ß)	r=−0.41	0.02*
Extracellular volume fraction (%)	r=−0.35	0.049*

BMI indicates body mass index; EDP, end-diastolic pressure; ESP, end-systolic pressure; LAEF, left atrial ejection fraction; LAV, LA volume; LAVbefore ac, LA volume before atrial contraction; LAVmax, maximal LA volume; LAVmin, minimal LA volume; LAVp-ac, LA volume before atrial contraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; *r*, Pearson correlation; ρ, Spearman correlation; SRa, LA active strain rate; SRe, LA conduit strain rate; SRs, LA total strain rate; LV, left ventricular; τ, time constant of relaxation; εa, LA active strain; εe, LA conduit strain; and εs, LA total strain.

*P values below the significance level of 0.05.

Potential Mechanisms and Functional Implications of LA Conduit Function

The potential impact of LA conduit function on LV filling properties was assessed by analyzing time–volume curves of the LV (Figure 4A). On echocardiography, no patient had more than trace aortic regurgitation (as possible confounder for ventricular filling). Despite having similar stroke volumes, early ventricular filling was significantly lower in HFpEF (35±15 versus 53±11 as % of LV filling volume; P=0.001; Figure 4B). Early LV filling correlated significantly with LV conduit function (r=0.67; P<0.001) and age (r=−0.53; P=0.001), but not with LV stiffness (r=−0.32; P=0.07) or τ (r=−0.33; P=0.06). On bivariate linear regression analysis, including LA conduit function and age, conduit strain remained the only independent predictor of early LV filling (β=0.67; P<0.001). Figure 5 depicts the correlations of early LV filling with maximal oxygen uptake and LA conduit function, respectively.

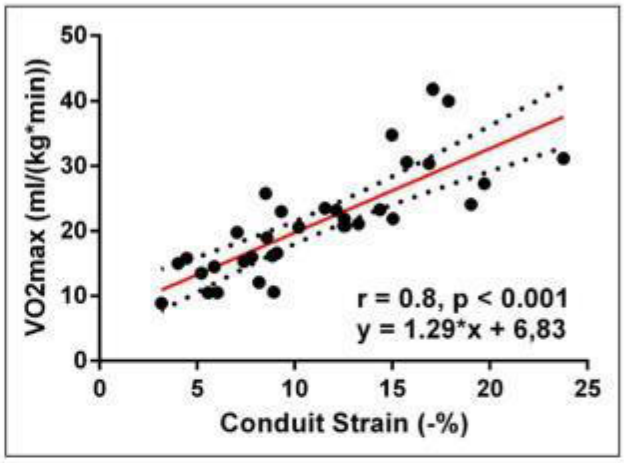

Figure 3. Univariate linear regression of conduit strain and VO2max.

Characteristics of the Control Group

Patients in the control group were more often male. When male control patients were compared with an age-matched female control group, no significant differences on LV and LA size and function were found. Table II in the Data Supplement shows the results.

Potential Influence of AF on LA Conduit Function

Within the HFpEF group, 5 patients had paroxysmal AF (PAF) with potential influence on LA function. During the time course of the study, all of them remained in sinus rhythm.

To detect potential confounders on AF and LA function, baseline, imaging, and invasive data from HFpEF patients with and without PAF were compared. The results are shown in Tables III through V in the Data Supplement. No differences with regard to baseline and invasive data were found. After excluding patients with PAF, correlation of LA conduit strain and VO2max remained highly significant (r=0.77; P<0.0001).

Discussion

This study comprehensively assessed LA and LV diastolic function using CMR-FT and LV pressure volume curves in HFpEF patients. The main findings are that (1) CMR-FT–derived LA conduit function is significantly impaired in HFpEF and a strong predictor of exercise intolerance; (2) impaired LA conduit function is associated with impaired early diastolic LV filling; (3) as such, LA conduit function seems as a distinct pathophysiological entity in HFpEF independent of load-independent LV stiffness or instantaneous LV relaxation.

Role of LA Dilatation and Dysfunction in HFpEF

For a longer period, HFpEF was thought to be primarily a diastolic LV filling problem with an increase in LVEDP and elevated LA pressure and dilatation. The dilated LA was primarily seen as a prognostic marker for disease progression, and indeed the prognostic relevance of LA dilatation is well established.[8,10] Recently, LA functional remodeling has been proposed as an independent prognostic marker in HFpEF patients.[12] Although

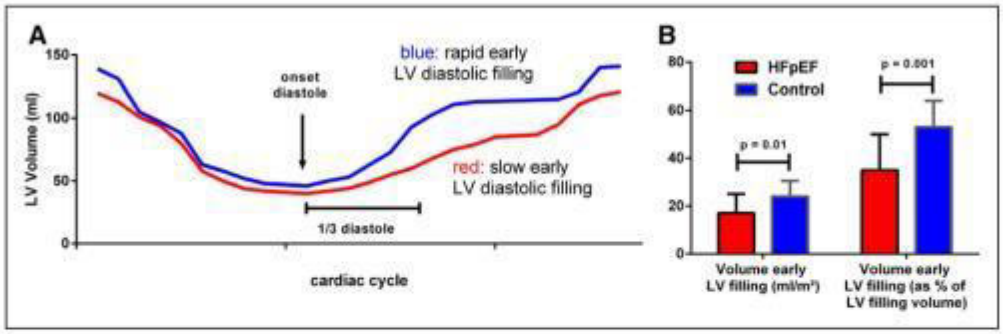

Figure 4. A, Left ventricular (LV) volume curves showing better (blue) and worse (red) early diastolic LV filling. **B**, LV filling volumes in heart failure with preserved ejection fraction (HFpEF) and controls.

LA remodeling is thought to be the consequence of LV diastolic dysfunction, little is known about the relations between LA functional parameters and individual aspects of LV diastolic function in HFpEF patients. Our study, therefore, sought to give insight into the pathophysiological role of LA function as measured by CMR-FT, given the advantages in myocardial border delineation and spatial resolution,[13,23] in relation to exercise capacity, invasively determined diastolic LV function and CMR-derived LV volume–time curves.

Time Course of LA Dysfunction

Consistent with previous reports, we demonstrated functional LA remodeling in HFpEF patients, who presented with higher filing pressures and increased LV stiffness. LA volumes were significantly increased at each point of the atrial cycle. LA reservoir and conduit function were decreased, whereas active LA function was comparable between HFpEF patients and controls. Importantly, active LA stroke volume was increased in HFpEF patients, allowing for compensation of impaired early LV filling as demonstrated in this population of HFpEF patients. This increase in active stroke volume at comparable booster pump function between groups can only be achieved with LA dilatation. Although cause and consequence remain speculative, LA dilatation might also be seen as a phenomenon known from the LV, which dilates with impaired systolic function and EF to maintain adequate stroke volumes. A biphasic time course of LA remodeling in response to LV remodeling has been described: although initially adaptive changes lead to an increased atrial contribution to LV filling, further LV stiffening is associated with a progressive decline in LA global and in particular booster function.[16] These variations in different aspects of LA function over time could explain the conflicting data on the role of different aspects of LA function in HFpEF, where many studies showed a predominant decline in LA total strain and LA active strain.[16,23] A recent echocardiographic speckle-tracking study found LA total strain (reservoir function) to be the most accurate predictor of VO2max. Whereas the influence of LA conduit function on oxygen uptake was not reported,[12] these differing results compared with our study might be explained by the course of LA remodeling over time and disease severity of the studied patient population. Our study included stable ambulatory patients only, without previous hospitalization for heart failure, exhibiting a higher maximal oxygen uptake when compared with the study population of Freed et al.[12] This suggests a less advanced stage of the disease. Nevertheless, most studies showed that LA conduit function is affected early and consistently in the course of LA remodeling and has therefore been proposed as an early marker of LA functional decline.[16] The fact that strain parameters were superior to volumetric assessment of LA function as a predictor for exercise capacity mirrors the results of previous studies.[12,27]

Influence of LA Function on Exercise Capacity

Parameters of LA function, especially LA conduit function, correlated closely with patients' exercise capacity. When adjusting for clinical, echocardiographic, and invasively measured clinical parameters, LA conduit strain emerged as best predictor of peak oxygen uptake. This suggests that LA dysfunction should not be considered as an innocent bystander of global cardiac pathology but is associated with functional limitations. In contrast to LA active (booster) function, which is thought to be mainly influenced by worsening of LV stiffness,[16] conduit function is predominantly modulated by passive LA parameters (elastance and stiffness)[9] and in our study to lesser degree by LV diastolic properties.[16] This suggests that conduit function might be a better reflect of early LA remodeling causing increased

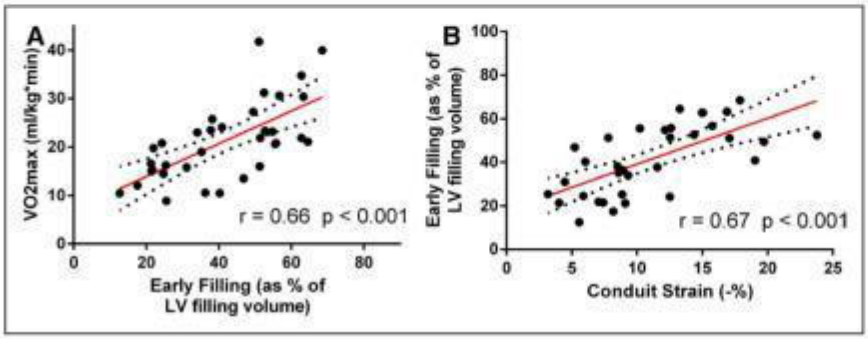

Figure 5. A, Correlation of early left ventricular (LV) filling with maximal oxygen uptake. **B**, Correlation of left atrial (LA) conduit strain and early LV filling.

stiffness and decreased elastance, whereas LA booster pump function reflects LV remodeling, causing stiffness and exacerbation of ventricular filling pressures. Another important finding of this study is the association of LA conduit function and early LV filling, which was not the case for LV stiffness or relaxation. This again points toward an important role of intrinsic LA function, which, if not independent, is at least only marginally explained by parameters of LV diastolic properties. Given the multifactorial modifiers of patients exercise capacity, the reproducible impact of LA function on peak oxygen uptake among different studies is intriguing.[12,28] Early diastolic filling has been shown to be a key determent of LV filling and thereby stroke volume during exercise. With shortening of diastole and partial fusion of passive and active filling phases,[29] alterations in LA conduit function governing early diastolic filling are likely to become even more relevant under exercise than at rest. In healthy subject, rise in stroke volume during exertion requires increased LA conduit emptying with consequent higher LV filling volumes. This emphasizes the physiological need for an increased early LV filling as an adaptation to exercise.[30] In HFpEF, limited conduit function at rest is likely to exaggerate during exercise and might no longer be compensated for by active LA contraction, impacting on LV early filling, LV stroke volume, cardiac output, and ultimately exercise capacity.

Determinants of LA Function

One of the strengths of our study is the ability to relate LA function to load-independent markers of LV stiffness and load-dependent markers of LV relaxation, both derived from pressure–volume loop analysis. This analysis showed that conduit function was not significantly associated with LV stiffness or relaxation, further supporting our discussion above that LA conduit function reflects intrinsic LA pathology, which cannot be sufficiently explained by ventricular pathology. The structural changes of the LA are also known to occur with aging. In our patients, LA conduit function showed a significant correlation to age. However, current data support the theory that LA dilation and impaired LA function reflect rather the clinical conditions that frequently accompany aging than the effects of physiological aging alone.[16] Data on the influence of known factors contributing to the HFpEF syndrome (eg, obesity, hypertension, diabetes mellitus, and age) and their specific influence on LA conduit function are currently lacking and might be of potential interest for analysis in future studies. Although the observed changes in LA function are closely related to disturbances in LV filling, the relative independence of other established markers of LV diastolic function and the strong relation between LA function and exercise capacity imply the ability to gain additional information on hemodynamic alterations in HFpEF patients by assessing LA function. Especially strain analyses seem to be of diagnostic value because they inform early and more specific on functional LA remodeling when compared with volumetric assessment only. Although LA dilatation could also be a physiological response to compensate for decreased LA function, LA strain analysis reveals intrinsic LA dysfunction and LA stiffness at an early stage. Our study confirms the hypothesis of the presence of an independent contribution of LA disease in HFpEF patients, although especially LA conduit function might be a promising diagnostic and therapeutic goal in future studies.

Limitations

Given the complexity and invasiveness, the acquisition of pressure–volume loops resulted in a limited sample size. To justify invasive catheterization in the control group, control subject had to have risk for coronary artery disease. This led to a wide variety of cardiovascular risk factors in these control subjects and to some differences in baseline characteristics between the control and the HFpEF group which could have introduced some confounding.

Importantly, recent data imply that many of the mechanistic abnormalities involved in HFpEF are noted with normal aging and are more pronounced in HFpEF.[31] Thus, progressive acquisition of cardiovascular risk factors and cardiovascular function abnormalities underlie the development of more symptomatic stages in patients at risk for HFpEF. We are therefore confident that our results and conclusions represent pathophysiological mechanisms contributing to the HFpEF syndrome, rather than resembling baseline group differences alone. We did not include imaging exercise testing using either stress echo or stress CMR imaging. This would have further clarified the influence of LA mechanics under exercise conditions. Five patients with PAF were included in the analysis. Because of the study protocol we did not acquire information on previous AF episodes. Although the inclusion of patients with PAF did not alter the results about the main results of this study, future research should clarify the impact of AF on atrial function in HFpEF.

Conclusions

CMR-FT–derived conduit strain is significantly impaired in HFpEF and associated with exercise intolerance. Impaired conduit function could lead to impaired early ventricular filling as a potential mechanism for decreased exercise capacity in HFpEF. LA conduit function emerges as a distinct feature of HFpEF, with functional implications independent of LV stiffness and relaxation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Accumulating evidence shows that heart failure with preserved ejection fraction is not an isolated diastolic heart disease but rather a syndrome of different intra- and extracardiac pathologies. This includes increased ventricular stiffness, increased systemic and pulmonary arterial stiffness, chronotropic incompetence, right ventricular disease, and left atrial disease. Quantifying the extend of each contributing factor permits a complete diagnostic workup. Measuring atrial function and especially left atrial conduit function allows explaining patients' decreased functional capacity. Especially in patients with poor echocardiographic image quality, cardiac magnetic resonance is an alternative with excellent image quality. Feature tracking is done from standard cine sequences without the need for gadolinium application and can also be done in patients with contraindication to contrast agents. Although cardiac magnetic resonance contrast is safe in most patients, this allows expanding the pool of new contrast-free imaging modalities.

2.1.3 Identifikation einer eingeschränkten rechtsventrikulären diastolischen Reservefunktion als Pathomechanismus der Herzinsuffizienz mit erhaltener Pumpfunktion

Zitierweise:

Rommel KP, von Roeder M, Oberueck C, Latuscynski K, Besler C, Blazek S, Stiermaier T, Fengler K, Adams V, Sandri M, Linke A, Schuler G, Thiele H, Lurz P. Load-Independent Systolic and Diastolic Right Ventricular Function in Heart Failure With Preserved Ejection Fraction as Assessed by Resting and Handgrip Exercise Pressure-Volume Loops**.**
Circ Heart Fail. 2018 Feb;11(2):e004121.

Load-Independent Systolic and Diastolic Right Ventricular Function in Heart Failure With Preserved Ejection Fraction as Assessed by Resting and Handgrip Exercise Pressure–Volume Loops

BACKGROUND: Although systolic right ventricular (RV) dysfunction has been shown to be a potent predictor for adverse outcomes in patients with heart failure with preserved ejection fraction (HFpEF), RV functional abnormalities in the course of the syndrome are not well characterized. We, therefore, sought to assess load-independent and load-dependent systolic and diastolic characteristics of RV function in stable outpatients with HFpEF.

METHODS AND RESULTS: We invasively obtained RV and left ventricular pressure–volume loops in 24 HFpEF patients and 9 patients without heart failure symptoms with a conductance catheter during basal conditions and handgrip exercise. Transient preload reduction was used to extrapolate the RV end-systolic elastance and diastolic stiffness constant. HFpEF patients and controls showed similar left ventricular and RV dimensions and ejection fractions with elevated left ventricular filling pressures. In HFpEF patients, invasively determined load-independent RV contractility (P=0.04) and load-independent passive RV stiffness constant β (P<0.01) were elevated. Although RV relaxation and cardiac output were similar at baseline, HFpEF patients demonstrated a blunted increase in cardiac output under exercise (P=0.01) associated with prolonged RV relaxation (P=0.01), decrease in stroke volume (P<0.01), higher RV-filling pressures (P<0.01), and a marked increase in the end-diastolic pressure–volume relationship (P<0.01).

CONCLUSIONS: In compensated stages of the HFpEF syndrome, systolic RV function is preserved, but diastolic abnormalities with intrinsic RV stiffness and prolonged RV relaxation are already present. Impaired diastolic RV reserve contributes to a blunted increase in cardiac output during exertion. Because impairments in diastolic function seem to be a biventricular phenomenon, RV diastolic dysfunction warrants further consideration when characterizing HFpEF patients.

CLINICAL TRIAL REGISTRATION: https://www.clinicaltrials.gov. Unique identifier: NCT02459626.

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Key Words: cardiac output ■ diastole ■ exercise ■ heart failure, diastolic ■ hemodynamics ■ right ventricle

WHAT IS NEW?

- Disturbances in right ventricular (RV) diastolic function occur during the course of heart failure with preserved ejection fraction (HFpEF) and cannot fully be explained by increased RV afterload.
- RV diastolic dysfunction leads to inappropriate RV filling with a blunted cardiac output reserve under handgrip exercise.

WHAT ARE THE CLINICAL IMPLICATIONS?

- HFpEF has to be considered a biventricular phenomenon with alterations of myocardial properties of right and left ventricle.
- RV diastolic dysfunction is part of the pathophysiology of the HFpEF syndrome, which needs to be considered when characterizing HFpEF patients.
- Further studies are warranted to clarify the impact of elevated pulmonary vascular load on RV myocardial remodeling in HFpEF and identify potential treatment targets specifically addressing the enhancement of RV function.

Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a complex syndrome. It can be secondary to multiple impairments in cardiac, vascular, and peripheral function, which coexist with one another, and eventually lead to heart failure (HF) symptoms. Left ventricular (LV) functional abnormalities in HFpEF patients are well characterized. LV diastolic dysfunction and impaired LV filling in conjunction with a subtle systolic dysfunction have been shown to lead to a blunted stroke volume response during physical endurance exercise.[1]

In contrast, right ventricular (RV) function has been underinvestigated in patients with HFpEF.[2] Recent studies reported a high prevalence of RV systolic dysfunction in this patient cohort and identified RV systolic dysfunction as a potent predictor of adverse outcomes.[3,4] RV diastolic dysfunction has also been implied in the setting of LV diastolic dysfunction.[3,5] Most recently, limited RV reserve capacity has been suggested in HFpEF patients because of unfavorable RV mechanics during exertion, as assessed by echocardiography.[6]

However, the role of RV diastolic dysfunction in hemodynamic adaption to various loading conditions in HFpEF patients is currently unclear. Up to now, studies investigating RV functional parameters were limited by the difficulty of differentiating between load-dependent and load-independent RV function. Given the high load dependence of various RV systolic and diastolic functional parameters, it remains unclear whether alterations in RV function in HFpEF patients are solely the consequence of altered RV load in this setting or reflecting truly impaired intrinsic RV function.

High-fidelity conductance catheters provide the opportunity to measure pressure and volume instantaneously and determine load-independent markers of diastolic and systolic RV function.[7,8]

We hypothesized that besides systolic abnormalities, also diastolic RV function abnormalities can be detected in HFpEF patients. This study, therefore, sought to determine load-dependent and load-independent markers of systolic and diastolic RV function and their role in hemodynamic adaption to handgrip exercise in HFpEF patients.

METHODS

Patients

This prospective study, conducted at the Heart-Center, Leipzig University, Germany, was a predefined substudy of the StiffMAP trial (Left Ventricular Stiffness vs. Fibrosis Quantification by T1 Mapping in Heart Failure With Preserved Ejection Fraction), which investigated the diagnostic value of cardiac magnetic resonance (CMR)-based fibrosis quantification in HFpEF.[9] Consecutive patients referred to our outpatient clinic for evaluation of dyspnea and suspected coronary artery diseases (CAD) were included, if they fulfilled the criteria for HFpEF diagnosis according to the consensus paper of the European Society of Cardiology[10]; specific inclusion criteria were LV ejection fraction (LV-EF) ≥50%, New York Heart Association class ≥II and E/E′ ≥15 or E/E′=8 to 15 combined with NT-proBNP (N-terminal pro-B-type natriuretic peptide) elevation >220 ng/L. Patients without HF symptoms served as controls; specific inclusion criteria were LV-EF ≥50%, E/E′ <8, and NT-proBNP values ≤220 ng/L. Patients with relevant CAD, any contraindication to CMR imaging including pacemaker or implantable cardioverter defibrillator implants, and an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, acute coronary syndrome, more than moderate valvular diseases, and persisting atrial fibrillation were excluded. Patients <40 years were also excluded from the analysis. NT-proBNP levels were analyzed centrally with a standard assay (Cobas, Elecsys NT-proBNP II; Roche).

To assure comparable levels of intravascular volumes, CMR and cardiac catheterization were preceded by an intravenous infusion of 500 mL isotonic buffered crystalloid solution. Oral medication was withheld on the day of diagnostic workup.

The study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

Echocardiographic Protocol

Echocardiographic studies were performed on a Vivid 9 system (General Electrics Healthcare). Mitral valve inflow pattern (E and A velocity) and septal and lateral mitral valve annular velocities (E′) were recorded in an apical 4-chamber view. The ratios of E/A, E/E′ septal, E/E′ lateral, and an averaged E/E′ were calculated as markers of diastolic function according to the recommendation of the American Society of Echocardiography

guidelines.[11] Data were analyzed from stored images by an experienced operator, unaware of other test results.

Spiroergometry

Cardiopulmonary exercise testing was performed on a bicycle ergometer before cardiac catheterization. Work rate was increased with a ramp protocol. Breath-by-breath respiratory gas exchange measurements were recorded throughout the test and averaged over a peak width of 20 seconds at the end of exercise to determine maximum values. Patients were encouraged to exercise until exhaustion.

CMR Protocol

CMR image acquisition was performed immediately before invasive catheterization. The detailed protocol has been described previously.[9] Evaluation of biventricular volumes was performed by manual delineation of the end-systolic and end-diastolic endocardial borders in every slice of the short-axis stack using a linked 4-chamber view as a navigator sequence. RV-EF <45% was considered abnormal.[12] Analyses were performed using certified CMR evaluation software (cmr42; Circle Cardiovascular Imaging, Inc). Data were interpreted by 2 readers blind to the subjects' clinical information and the results of other diagnostic tests.

Cardiac Catheterization Protocol

The detailed catheterization protocol is available in the supplemental material. In short, after exclusion of significant CAD, high-fidelity pressure tracings were realized using a retrograde approach for LV, as well as standard right heart catheterization for determination of pulmonary artery pressures (PAP) and pulmonary capillary wedge pressures. Pulmonary hypertension (PHT) was defined as mean PAP >25 mm Hg at rest and >30 mm Hg under exercise. A 7F conductance catheter(CD Leycom, Zoetermeer, the Netherlands) was used to obtain pressure–volume (PV) data for the LV as previously described.[9] Similarly, for RV assessment, a conductance catheter was advanced via the right femoral vein into the right ventricle under fluoroscopy and connected to a PV signal processor (Inca; CD Leycom). Real-time continuous RV pressure and volume signals were recorded for 10 seconds at baseline at resting expiratory level, using electrocardiographic determination of end systole and end diastole, as well as volume calibration using RV volumetric data from the preceding CMR scan. To examine load-independent properties of the RV, a family of PV loops was generated by preload reduction at rest via transient balloon occlusion of the inferior vena. To assess intrinsic contractility, the slope of the end-systolic elastance (RV-Ees) was determined as the linear relationship through the end-systolic PV relations during caval occlusion. Intrinsic RV stiffness was assessed by extrapolating the load-independent RV stiffness constant (β) from the end-diastolic PV relations (EDPVR), and the formula $EDP=C*\beta^{*EDV}$, where EDP is RV-end-diastolic pressure (RV-EDP), C is a fitting constant, and EDV is RV-end-diastolic volume (RV-EDV), applying the methods established for the LV.[7]

An afterload challenge was then realized through handgrip exercise. Patients were asked to perform handgrip exercise with a 2-handle tension-spring device (100 pounds resistance) for 1 minute at their maintainable, submaximal tolerated work rate. PV data were acquired from baseline throughout peak heart rate and afterload rise.

Following parameters were derived from the acquired PV data: RV end-systolic pressure (RV-ESP), RV-EDP, mean PAP, pulmonary capillary wedge pressure, LV-ESP, LV-EDP, RV end-diastolic volume (RV-EDV), RV end-systolic volume (RV-ESV), RV stroke volume (RV-SV), RV ejection fraction (RV-EF), preload adjusted maximal change in pressure over time (PAdp/dt) as instantaneous contractility marker,[13] cardiac index (Heartrate*SV/body surface area), the time constant of active RV relaxation (τ), calculated after the method of Mirsky[14], and RV end-diastolic PV relation (RV-EDPVR), and RV end-systolic PV relation (RV-ESPVR). RV systolic load was quantified as pulmonary vascular elastance (RV-Ea=RV-ESP/RV-SV). The ventricular pulmonary vascular coupling was assed as RV-Ea/Ees=RV-ESV/RV-SV. Similarly, LV PV relations were assessed at rest and under afterload challenge using a femoral retrograde approach. Volumes were indexed to body surface area.

Statistics

Data for continuous variables was tested for normality using Shapiro–Wilk tests and are presented as mean±SD or median with interquartile range where appropriate. Continuous variables were compared using repeated-measures ANOVAs with Bonferroni corrections for differences between values at baseline and under afterload challenge as well as between group differences and the interaction of group assignment and afterload challenge.

For the comparisons of characteristics at baseline and exercise between groups, as well as the comparisons of the absolute change of hemodynamic variables from baseline to maximal afterload challenge between groups unpaired *t* tests or single-factor ANOVAs were applied where appropriate. Categorical variables are presented as frequencies and percentages and were compared between groups using Fisher exact tests.

Additional analysis with adjustments for age and sex where performed using ANCOVAs and adjusted repeated-measures ANOVAs.

A 2-tailed *P* value of <0.05 was considered statistically significant. SPSS version 20.0 was used for statistical analyses.

RESULTS

Clinical and Demographic Data

Out of 46 patients screened for eligibility, significant CAD was seen in 5 patients, 2 patients had atrial fibrillation during catheterization, and in 5 patients RV-PV data were found to be of insufficient quality. One patient was excluded from the control group because of age (34 years). Therefore, 9 patients serving as controls and 24 patients with HFpEF were included within the final analyses.

Baseline characteristics are presented in Table 1. HFpEF patients were more frequently female, had a higher body mass index with a comparable body surface area, and had higher rates of arterial hypertension and diuretic intake. An elevation of NT-proBNP was present in two thirds of HFpEF patients, who all reported exer-

Table 1. Baseline Characteristics

	HFpEF (n=24)	Control (n=9)	*P* Value
Age, y	66.2±8.5	59.5±8.2	0.05
Female sex	22 (92)	3 (33)	<0.01
BMI, kg/m²	29.8±4.4	27.2±2.1	0.03
Body surface area, m²	1.93±0.19	2.01±0.18	0.25
Abdominal girth, cm	98±12	98±9	0.87
Systolic BP baseline, mm Hg	155±13	154±18	0.82
Diastolic BP baseline, mm Hg	80±9	80±9	0.93
Heart rate baseline, beats per min	68±8	74±10	0.13
GFR, mL/min per 1.73 m²	73.8±18.0	82.2±11.6	0.26
Fasting glucose, mmol/L	5.3 (IQR 5.0–6.0)	5.5 (IQR 5.1–14.7)	0.32
NT-proBNP, ng/L	331 (IQR 187–614)	52 (IQR 33–76)	<0.01
NT-proBNP elevation	16 (67)	0 (0)	<0.01
NYHA I	0 (0)	9 (100)	<0.01
NYHA II	19 (79)	0 (0)	<0.01
NYHA III	5 (21)	0 (0)	0.16
Smoking	2 (8)	6 (66)	<0.01
Hypertension	23 (96)	6 (67)	0.02
Hypercholesterolemia	22 (92)	8 (89)	0.81
Diabetes mellitus	5 (21)	3 (33)	0.41
COPD	2 (8)	0 (0)	0.38
Paroxysmal AF	6 (25)	0 (0)	0.10
OSA	2 (8)	0 (0)	0.38
β-Blockers	10 (42)	1 (11)	0.10
ACE inhibitors/ARB	17 (71)	4 (44)	0.17
Ca^{2+} antagonist	8 (33)	1 (11)	0.21
Statins	10 (42)	3 (33)	0.67
Diuretics	8 (33)	0 (0)	0.05

Values are presented as mean±SD or frequencies (percentages). ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive lung disease; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; and OSA, obstructive sleep apnea.

tional dyspnea, predominantly in New York Heart Association class II. Patients without HF symptoms presented with indication for coronary angiography because of chest pain and had a significant cardiovascular risk profile with a high prevalence of smoking, arterial hypertension, hypercholesterolemia, and diabetes mellitus. Two patients in the HFpEF group and none in the control group had previous diagnosis of chronic obstructive pulmonary diseases. Six patients in the HFpEF group and none in the control group had a history of paroxysmal atrial fibrillation, whereas all patients were in sinus rhythm during diagnostic workup.

Exercise Capacity

Patients with HFpEF had an impaired exercise capacity in comparison to the control group (workload: 93±34 versus 151±42 W; $P<0.01$, maximal oxygen uptake: 16 [interquartile range, 13–20] versus 24 [interquartile range, 22–31] mL/kg*min; $P<0.01$).

CMR and Echocardiography Data

Noninvasively assed ventricular volumes were comparable between groups for RV-EDV (66±14 versus 69±11 mL/m²; $P=0.66$) and RV-ESV (25±10 versus 29±6 mL/m²; $P=0.19$). Similarly, LV-EDV (71±14 versus 69±14 mL/m²; $P=0.75$) and LV-ESV (28±9 versus 29±11 mL/m²; $P=0.75$) did not differ between HFpEF patients and controls. Although HFpEF patients demonstrated a slightly higher RV-EF (64±10% versus 57±4%; $P=0.03$), LV-EF (63±7% versus 63±5%; $P=0.87$) was similar between groups. LV mass was only numerically higher in HFpEF patients (104±33 versus 82±16 g/m²; $P=0.08$).

On echocardiography, patients with HFpEF demonstrated larger left atrial volumes (41±15 versus 25±9 mL/m²; $P<0.01$), higher E-wave velocities (0.9±0.2 versus 0.7±0.1 m/s; $P<0.01$), lower septal myocardial velocity (0.06±0.02 versus 0.08±0.02 m/s; $P<0.01$), lower lateral myocardial velocity (0.07±0.02 versus 0.11±0.03 m/s; $P<0.01$), and, therefore, higher E/E′ ratios (15±4 versus 7±1; $P<0.01$).

Hemodynamics at Rest

Hemodynamic data at rest and during afterload challenge are displayed in Table 2 and Figure 1. At baseline, resting heart rate, RV and LV ESV and EDVs, and RV-SV were comparable between groups. Consequently, RV cardiac index was similar. However, HFpEF patients showed higher systolic and diastolic RV pressures, end-diastolic LV pressures, and higher pulmonary artery pressures. Nine HFpEF patients (38%) and none of the control patients (0%) were found to have PHT at rest (mean PAP >25 mm Hg; $P=0.03$). LV systolic pressures were similar between groups, but LV-EDP and pulmonary capillary wedge pressures were elevated in HFpEF patients.

Only 1 patient in the HFpEF group (4%) was found to have a reduced RV-EF (42%), who also demonstrated elevated pulmonary arterial pressures (mean pulmonary artery pressure 31 mm Hg).

Active relaxation (τ) of RV and LV was prolonged in HFpEF patients ($P<0.01$ and $P=0.03$), who also showed higher RV- and LV-EDPVRs, indicating decreased chamber distensibility. RV-ESPVR (indicating increased systolic stiffness), RV-Ees, and pulmonary vascular load (RV-Ea) were increased in HFpEF patients. PAdp/dt+ was comparable between groups (2.5±1.6 versus 2.5±0.8 mm Hg/s*mL; $P=0.95$). The ratio of RV-Ea/Ees, reflecting ventricular–vascular coupling, was lower in

Table 2. Hemodynamic Data

	HFpEF (n=24)		Control (n=9)		Δ Baseline Exercise	RM-ANOVA		
	Baseline	Exercise	Baseline	Exercise	HFpEF vs Control	Baseline vs Exercise	HFpEF vs Control	Interaction
Heart rate, beats per min	70.9±10.6	91.8±14.1	73.6±12.3	100.1±8.8	0.18	<0.01	0.26	0.21
Cardiac index, mL/min per m²	3.0±0.8	3.4±1.0	2.9±0.8	4.0±0.8	<0.01	<0.01	0.56	<0.01
RV ESP, mm Hg	32.5±9.2*	46.9±11.7*	27.1±2.3	37.7±4.6	0.14	<0.01	0.04	0.19
RV EDP, mm Hg	7.2±1.8*	12.4±4.1*	4.1±1.3	5.6±1.9	<0.01	<0.01	<0.01	<0.01
RV EDV index, mL/m²	66.4±13.9	63.6±12.4	68.4±10.9	70.9±14.4	0.01	0.99	0.51	0.01
RV ESV index, mL/m²	24.6±10.0	26.6±10.8	29.4±6.0	30.9±10.8	0.99	0.13	0.35	0.84
RV SV index, mL/m²	41.7±8.3	36.9±7.7	39.1±6.2	40.0±6.9	<0.01	0.04	0.92	<0.01
RV EF, %	63.7±9.8*	59.0±11.4	57.2±4.1	57.1±7.4	0.06	0.07	0.33	0.08
RV τ, ms	36.7±8.3†	41.0±10.5*	29.8±8.4	27.0±8.1	0.02	0.70	<0.01	0.02
RV EDPVR, mm Hg/mL	0.06±0.02*	0.10±0.04*	0.03±0.01	0.04±0.02	<0.01	<0.01	<0.01	<0.01
RV ESPVR, mm Hg/mL	0.83±0.55*	1.1±0.55*	0.47±0.08	0.65±0.16	0.20	<0.01	0.08	0.36
RV Ea, mm Hg/mL	0.42±0.15†	0.71±0.30*	0.35±0.04	0.48±0.11	<0.01	<0.01	0.08	0.03
RV Ea/Ees ratio	0.61±0.26†	0.76±0.35	0.76±0.14	0.78±0.24	0.27	0.05	0.47	0.19
PA systolic, mm Hg	34.7±8.5*	48.4±9.9*	27.8±4.4	39.5±4.9	0.49	<0.01	0.03	0.57
PA diastolic, mm Hg	15.2±4.1*	25.6±5.9*	9.1±2.8	15.8±4.6	0.13	<0.01	<0.01	0.06
PA mean, mm Hg	24.7±5.5*	37.1±6.7*	17.1±3.5	26.9±4.4	0.23	<0.01	<0.01	0.20
PCWP, mm Hg	13.3±3.6*	24.4±6.7*	7.9±2.8	14.1±4.8	0.01	<0.01	<0.01	<0.01
LV ESP, mm Hg	154.4±22.2	191.2±25.5	148.0±18.1	189.2±19.9	0.50	<0.01	0.66	0.64
LV EDP, mm Hg	18.9±3.3*	29.0±6.0*	13.0±2.6	20.1±2.7	0.07	<0.01	<0.01	0.16
LV EDV index, mL/m²	71.0±13.6	70.5±16.9	69.3±14.3	70.5±13.2	0.46	0.85	0.91	0.41
LV ESV index, mL/m²	27.9±9.1	33.9±15.2	28.8±10.8	30.0±9.6	0.13	0.07	0.94	0.25
LV SV index, mL/m²	43.1±8.5	36.6±8.2	40.4±5.3	40.5±6.1	<0.01	<0.01	0.92	<0.01
LV EF, %	61.2±8.2	53.3±12.2	59.5±8.4	58.2±7.9	0.03	<0.01	0.94	0.08
LV τ, ms	35.8±9.1	38.0±5.2†	30.8±4.3	33.6±4.8	0.82	0.22	0.08	0.84
LV EDPVR, mm Hg/mL	0.14±0.04*	0.23±0.07*	0.09±0.01	0.15±0.02	0.03	<0.01	<0.01	0.08
LV ESPVR, mm Hg/mL	3.20±1.16	3.56±1.73	2.89±1.10	3.35±1.2	0.53	0.04	0.50	0.98
LV Ea, mm Hg/mL	1.94±0.47	2.90±0.90†	1.85±0.30	2.38±0.43	<0.01	<0.01	0.25	0.03
LV Ea/Ees ratio	0.66±0.22	0.99±0.45†	0.71±0.23	0.74±0.22	<0.01	<0.01	0.60	0.04

Values are presented as mean±SD. Significant p-values for comparison at baseline and exercise between groups are indicated. Ea indicates vascular load; Ea/Ees, ventricular vascular coupling; EDP, end-diastolic pressure; EDPVR, end-diastolic pressure–volume relation; EDV, end-diastolic volume; EF, ejection fraction; ESP, end-systolic pressure; ESPVR, end-systolic pressure–volume relation; ESV, end-systolic volume; LV, left ventricular; PA, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RM, repeated measures; RV, right ventricular; and SV, stroke volume.

*$P \leq 0.01$.

†$P < 0.05$.

HFpEF patients, indicating a systolic overcompensation of arterial load.

Invasive Measures of Load-Independent Function

During caval balloon obstruction, sufficient preload reduction with acquisition of a series of PV loops could be achieved in 23 HFpEF and 9 control patients. The determined slope RV-Ees as load-independent marker of intrinsic contractility did not show depressed systolic RV function; on the contrary, HFpEF patients showed an increased RV-Ees (0.49±0.16 versus 0.69±0.27 mm Hg/mL; $P=0.04$) with comparable x-axis intercepts at V0 (8.8±19.0 versus 16.3±17.2 mL; $P=0.35$). Patients in the HFpEF group demonstrated a higher end-diastolic RV stiffness, as assessed by β (0.018±0.003 versus 0.012±0.003; $P<0.01$; Figure 2).

Hemodynamics Under Afterload Challenge

Hemodynamic data at rest and during afterload challenge are displayed in Table 2 and Figure 1. During

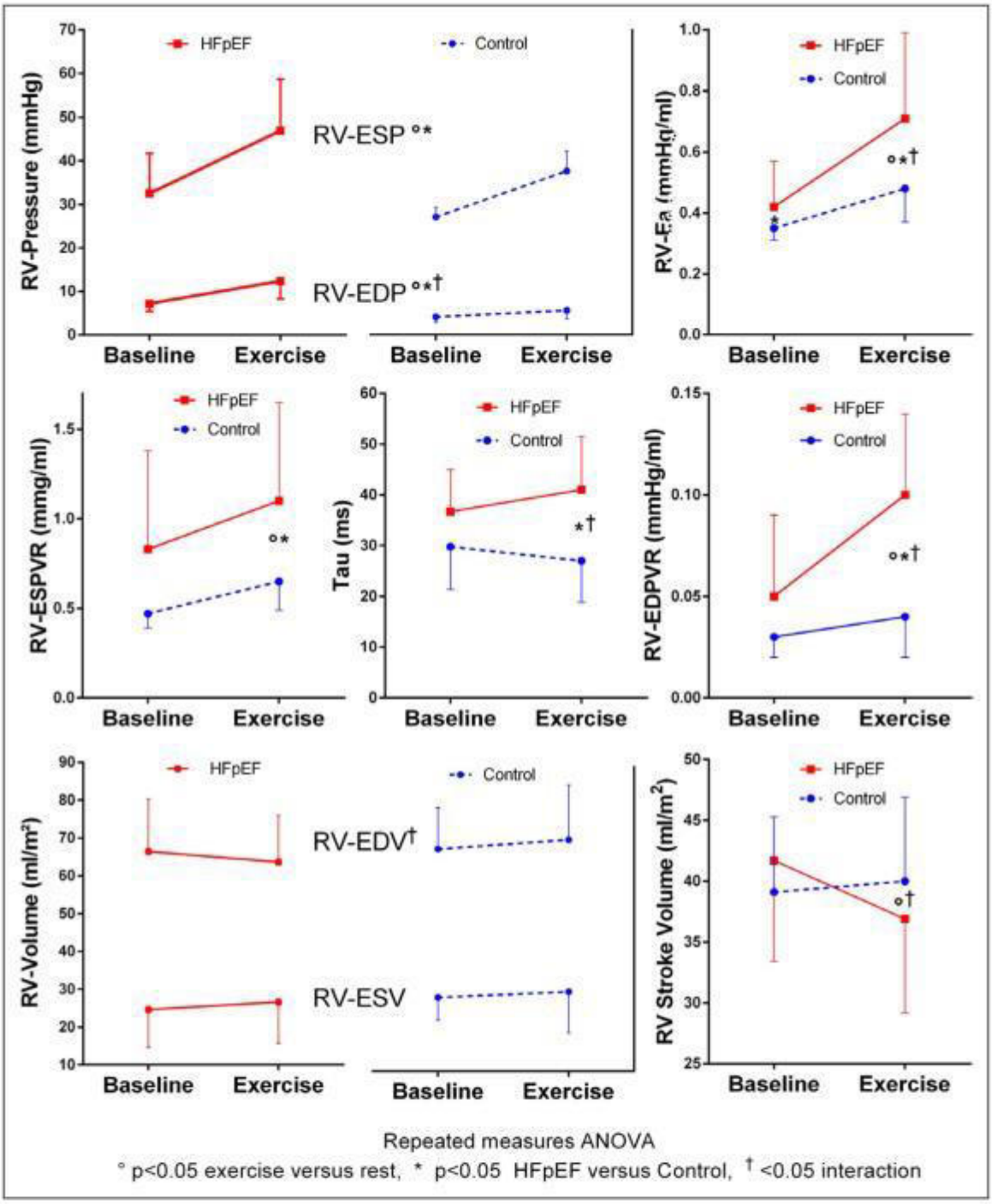

Figure 1. Hemodynamic changes from baseline to handgrip exercise in heart failure with preserved ejection fraction (HFpEF; red) and controls (blue).

EDP indicates end-diastolic pressure; EDV, end-diastolic volume; EDPVR, end-diastolic pressure–volume relation; ESP, end-systolic pressure; ESPVR, end systolic pressure volume relation; ESV, end-systolic volume; RV, right ventricular; and RV-EA, pulmonary elastance.

handgrip exercise, LV-EDP, RV-EDP, LV-ESP, RV-ESP, and pulmonary arterial pressures rose in both groups, whereas the absolute changes for RV-EDP and pulmonary capillary wedge pressures were significantly greater in HFpEF patients. Eighteen patients (75%) with HFpEF and 3 controls (33%) demonstrated PHT (mean pulmonary artery pressure >30 mm Hg; *P*=0.01).

LV-Ea and RV-Ea increased in both groups, whereas a greater change from baseline was noted in HFpEF patients. RV-ESPVR and LV-ESPVR increased similarly in both groups with significantly elevated RV-ESPVR levels in HFpEF patients. Similarly, PAdp/dt+ increased in both groups with a greater increase in HFpPEF patients (4.3±1.7 versus 3.4±0.6 mm Hg/s*mL; *P*=0.04). Con-

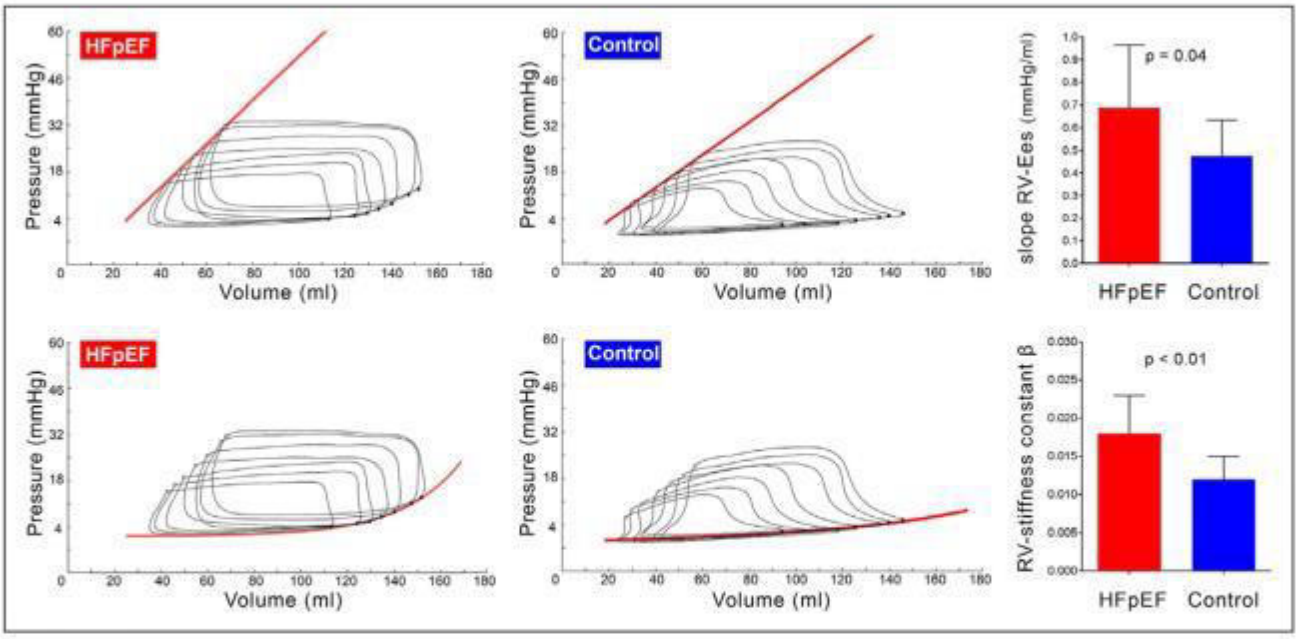

Figure 2. Reduction of preload in heart failure with preserved ejection fraction (HFpEF; left column) and controls (middle column) to determine load-independent markers of contractility (Ees slope) and stiffness (β; right column). Ees indicates endsystolic elastance; and RV, right ventricular.

sequently, RV-Ea/Ees ratio increased in HFpEF patients close to the values of the control patients, in whom RV-Ea/Ees ratio was kept constant.

Under handgrip exercise, RV-τ was shortened in control patients, whereas HFpEF patients showed a prolongation of RV-τ, with a significant difference of the absolute within-group changes and group–exercise interaction. LV-τ rose only modestly during handgrip exercise, with overall LV-τ prolongation in HFpEF patients.

The RV-EDPVR and the LV-EDPVR increased significantly during exercise in HFpEF patients with the change from baseline to exercise being greater in HFpEF than in controls.

RV-ESV similarly increased in both groups. Although in controls RV-EDV increased with elevated RV-EDP under afterload challenge, HFpEF patients failed to increase their RV-EDV with a significant group–exercise interaction. Consequently, RV-SV was maintained from baseline to exercise in controls but decreased in HFpEF patients. Similarly, RV-EF decreased in the HFpEF group, whereas control patients maintained their RV-EF on the same level.

Although LV-EDV was nearly unchanged with afterload intervention in HFpEF and in control patients, the HF cohort showed a numerically higher increase in LV-ESV, leading to changes of LV-SV and EFs comparable to those of the RV.

Heart rate during exercise increased in both groups with no significant differences.

As a result, in the HFpEF group, cardiac index increased slightly from baseline to exercise with the heart rate increase compensating for the decrease in stoke volumes but increased significantly more in control patients during the afterload intervention (Figure 1; Table 2).

Above-described adaptions to handgrip exercise in HFpEF patients resulted in a shift of the PV relation upward at maximal exertion (Figure 3).

Analyzing only HFpEF patients with and without PHT at rest (Tables I and II in the Data Supplement) or with and without PHT at exercise (Tables III and IV in the Data Supplement) did not alter the results significantly.

Similarly, considering only patients between the age of 50 and 70 years for the analysis and adjusting for age and sex yielded comparable results (Tables V through VIII in the Data Supplement).

DISCUSSION

The present study builds on the recent evidence of RV contribution to the HFpEF syndrome[3,4,6,15,16] and is the first to characterize RV systolic and diastolic properties using a comprehensive approach with acquisition of invasive PV tracings. This approach allowed differentiating between load-independent systolic function (RV-Ees slope), load-independent diastolic function (RV-stiffness constant β), and load-dependent parameters of RV functionality (RV-EF, RV relaxation time constant τ, and change of RV-EDPVR).

The main findings are (1) at a compensated stage of the HFpEF syndrome, intrinsic systolic RV contractility was not impaired compared with controls; (2) abnormalities of RV diastolic function mirror those of

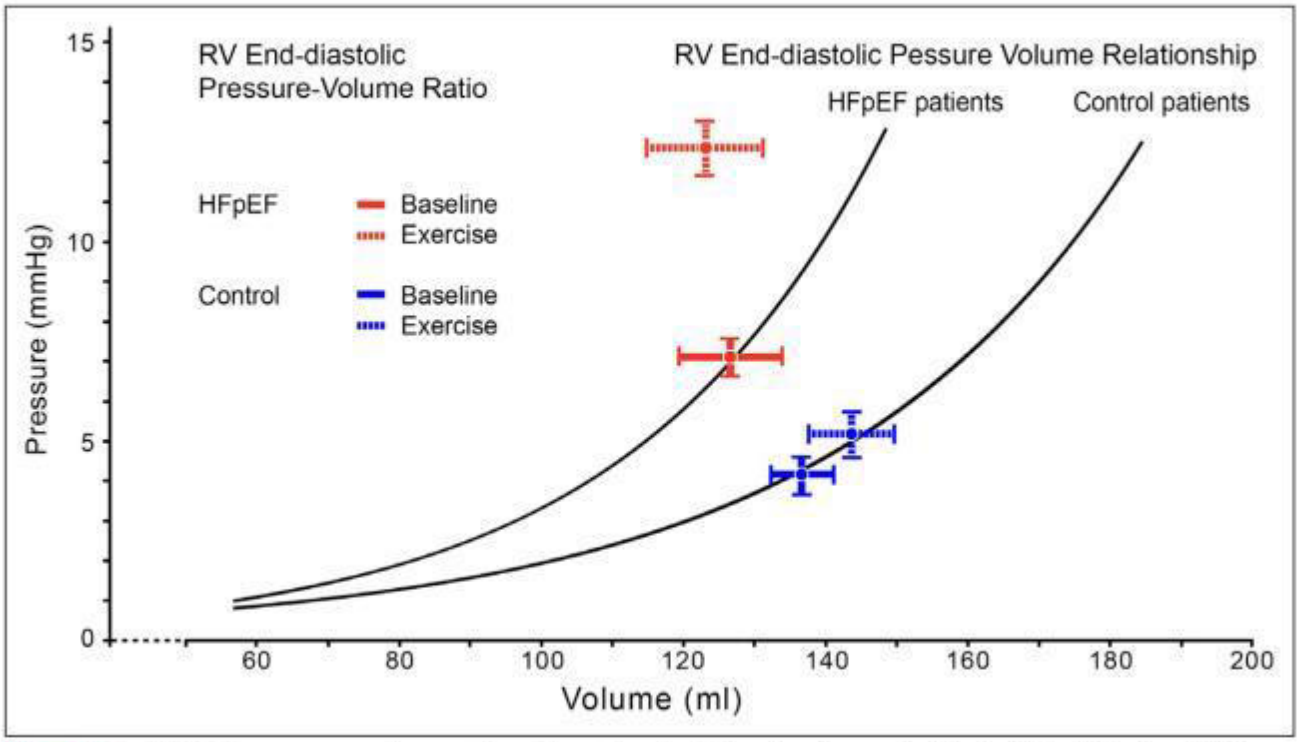

Figure 3. End-diastolic pressure–volume ratios at baseline (solid lines) and exercise (dashed lines) for heart failure with preserved ejection fraction (HFpEF; red) and control (blue).
Black curves represent the end-diastolic pressure–volume relationships determined by caval occlusion. Crosses indicate the mean end-diastolic volume (with horizontal error bars indicating the SEM) and pressure (vertical error bars indicating SEM) during baseline conditions (solid lines) and during handgrip exercise (dashed lines). RV indicates right ventricular.

the LV in our HFpEF cohort and can be summarized as follows: increased load-independent RV stiffness and impaired RV active relaxation; (3) pathological RV diastolic function was associated with inappropriate RV filling, consequentially leading to the inability to augment biventricular stroke volumes and cardiac output during handgrip exercise.

RV Load–Independent Systolic Function

Previously, it has been demonstrated that a significant proportion of HFpEF patients exhibits RV systolic dysfunction at rest[3] and during exercise[6] and that its presence is accompanied by an unfavorable prognosis. In our study, RV-EF and PAdp/dt at rest were not impaired in HFpEF patients compared with controls. End-systolic stiffness, as reflected by RV-ESPVR, and load-independent contractility, as reflected by RV-Ees, were even elevated in our HFpEF cohort.

Several reasons might account for these findings. We exclusively included compensated outpatients in our study with no history of hospitalization for HF decompensation and of younger age than patients in previous HFpEF studies. Patients with atrial fibrillation and RV pacemakers, who were found to have a high prevalence of RV systolic dysfunction in previous studies,[3,4] were excluded from the present analysis. Moreover, patients were recruited on the basis of the echocardiographic and proBNP level–based European Society of Cardiology consensus criteria[10] rather than Framingham criteria, which largely rely on clinical findings reflecting right heart dysfunction. In summary, our HFpEF patients were less diseased and younger than those of other studies.[3,4] As such, our HF patients likely represent a compensated stage of HFpEF, at which enhanced ventricular contractility and systolic stiffening allow the ventricles to compensate for chronic and acute afterload increases.[1,17]

RV Intrinsic Stiffness

In contrast, HFpEF patients showed increased intrinsic, load-independent RV stiffness, mirroring the results of the LV. For the LV, these functional abnormalities are known to be secondary to diffuse interstitial fibrosis (extracellular stiffness), as well as alterations of the cytoskeleton such as titin (intracellular stiffness).[9,18]

Mechanisms of increased RV stiffness in our HFpEF patients remain speculative. So far, a single study in PHT patients demonstrated increased extra- and intracellular stiffness of the chronically pressure overloaded RV, comparable to changes found in the LV of HFpEF patients.[19] The increase in stiffness has been linked to a high degree of chronic pressure overload.[3,20]

HFpEF patients in our study exhibited only a mild degree of RV pressure overload. The finding of increased RV stiffness in this young HFpEF cohort without overt RV pressure overload is even more intriguing and proposes the following: (1) RV stiffness represents an independent pathological entity of the HFpEF syndrome; (2) RV stiffening cannot solely be explained by RV pressure overload.

Alternatively, it is plausible to reason that the same pathways responsible for increased LV myofibril stiffness, namely, exposure of the myocardium to a systemic proinflammatory state, limited NO bioavailability, and decrease in protein kinase G–mediated cellular processes, might play a major role in RV stiffening,[18] although a considerable degree of overlap is likely.

Ventricular Relaxation and Adaptation to Handgrip Exercise

Acute afterload challenge led to an upward, rather than rightward, shift of the PV relation as seen in controls and considered as physiological adaptation to dynamic exercise.[1] Somewhat counterintuitively, RV filling pressures rose even in the absence of enhanced RV preload. However, similar findings have been demonstrated for the LV in response to handgrip,[17] as well as dynamic exercise.[21]

Elevated intrinsic RV stiffness, determined via the preload reduction maneuver, cannot fully explain the unproportional rise in RV-EDP in our HFpEF patients in absence of increased preload, as it represents a nondynamic component of stiffness, which remains unaffected by afterload.

Alternatively, changes in relaxation patterns are likely to contribute to higher filling pressures with afterload increases. As mild afterload increases reduce ventricular relaxation time, more pronounced or late systolic afterload increases lead to premature onset and slowing of active relaxation.[22,23] Here, we present data implying that these concepts can also be applied to the RV, with impairments in RV relaxation with increased RV afterload during handgrip exercise. This phenomenon is further exaggerated with higher heart rates and shortening of diastole, which eventually leads to incomplete relaxation and unproportional elevation of filling pressures.[24,25] Pathophysiologically, abnormal intracardiac calcium handling or altered β-adrenergic downstream signaling may relate to this heightened diastolic afterload sensitivity in HFpEF patients.[26,27]

Intrathoracic pressure levels can also influence PV measurements. However, their confounding effects were minimized by deriving parameters at resting expiratory level at baseline and as the mean of inspiration and expiration under handgrip exercise. Also, care was taken to avoid Valsalva maneuvers under handgripping.

Furthermore, interactions of the ventricles have to be considered given the shared myofiber anatomy and their spatial relations relative to the common septum and pericardial space. Indeed, parallel upward shifting of the RV and LV PV relations has been demonstrated with handgrip exercise. This has been thought to be mediated in part by pericardial constraint, as determined by exclusion and experimental setups showing RV distension under afterload challenges at constant heart rates.[28] In our study, total biventricular volume was not increased with the exercise maneuver. Thus, pericardial restraint must be considered a rather unlikely explanation for the observed biventricular PV changes. However, as total intracardiac volume was not assessed under handgrip exercise, a contribution of pericardial–ventricular interaction cannot fully be excluded.

Importantly, load-independent and load-dependent RV diastolic dysfunction was associated with limited RV filling during handgrip exercise and a lack of cardiac output reserve in our study. Direct causality and discrimination of different contributions to RV filling restrictions is obviously difficult. RV filling depends not only on RV diastolic function but also on LV forward flow. The inextricably linked functions of both ventricles in the structurally normal and abnormal heart prohibit an approach of focusing on one ventricle more than on the other. On the basis our findings, we would argue that alterations in RV filling represent an important factor in the complex hemodynamic pathophysiology of HFpEF patients, equally important as LV abnormalities.

RV filling is also influenced by the ability to recruit unstressed volume during exercise.[29] This might be limited by a handgrip exercise protocol, given the predominant pressure work rather than volume work,[30] the recumbent position, the shortness of the intervention, and the rather small muscle mass involved in the intervention. However, because exercise RV filling was increased in controls, these confounding effects should be considered as minor.

Together, our findings imply that pathological findings known to affect LV function in HFpEF also apply to the opposite ventricle, even at a compensated stage and in absence of overt pressure overload. RV diastolic abnormalities most likely contribute substantially to cardiac maladaptation to exercise and thereby to the clinical syndrome of HFpEF. Well-designed studies are warranted to clarify the natural course of PHT in HFpEF and the impact of elevated pulmonary vascular load on RV myocardial remodeling in HFpEF and identify potential treatment targets specifically addressing the enhancement of RV function.

Limitations

Our study is limited by the small sample size, as a result of the highly invasive study protocol. This renders the

results susceptible to a type I error, which cannot be excluded in this study. Interpretation of results and conclusions should, therefore, be considered as hypothesis generating only.

Baseline characteristics of HFpEF patients and control patients differed in sex and body mass index, which are known to have an impact on RV function.[31]

The control group showed an extensive cardiovascular risk profile, as they were to have an indication for invasive catheterization for exclusion of CAD and consequently should not be referred to as healthy subjects. However, comparing our HFpEF cohort with a truly healthy population would have even aggravated the observed differences between groups.

The study protocol included an afterload challenge using handgrip exercise, which is known to elicit predominantly cardiac pressure rather than volume work. Although we think that this method facilitated new insights in RV pathology, mechanisms of intolerance to dynamic exercise in HFpEF patients are likely to be manifold and cannot be explained by RV dysfunction alone.

Finally, given the low percentage of patients with PHT compared with previous reports on RV function in HFpEF,[3,4,32] results might not be applicable to patients with significant pulmonary vascular disease. Similarly, patients with atrial fibrillation and pacemaker implants were excluded, although it is known that this HFpEF cohort is associated with RV dysfunction and PHT.[4] Nevertheless, mean PAP was comparable to previous HFpEF trials,[33] and the evidence of RV pathology in the absence of relevant RV pressure overload emphasizes an independent role of intrinsic RV changes in the HFpEF syndrome.

Conclusions

RV intrinsic stiffening is part of HFpEF pathophysiology already at a compensated disease stage, presumably proceeding RV systolic dysfunction. Alterations in RV diastolic function are associated with limitations in RV filling and are likely to contribute to exercise intolerance. RV dysfunctional diastology should be added to the numerous entities associated with the clinical syndrome of HFpEF, which warrants consideration when characterizing HFpEF patients.

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DISCLOSURES

None.

AFFILIATIONS

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FOOTNOTES

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2.1.4 Identifikation einer unabhängigen rechtsatrialen Kardiomyopathie als pathomechanistischer Faktor der Herzinsuffizienz mit erhaltener Pumpfunktion

Zitierweise:

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ORIGINAL PAPER

Right atrial–right ventricular coupling in heart failure with preserved ejection fraction

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Abstract

Background Right ventricular (RV) function is prognostically relevant in heart failure with preserved ejection fraction (HFpEF) but data on profound assessment of RV and right atrial (RA) interaction in HFpEF are lacking. The current study characterizes RV and RA interaction using invasive pressure–volume-loop analysis and cardiac magnetic resonance imaging (CMR) data.

Methods and results We performed CMR and myocardial feature-tracking in 24 HFpEF patients and 12 patients without HFpEF. Invasive pressure–volume-loops were obtained to evaluate systolic and diastolic RV properties. RV early filling was determined from CMR RV volume–time curves. RV systolic function was slightly increased in HFpEF (RV EF 68 ± 8 vs. 60 ± 9%, $p = 0.01$), while no differences in RV stroke volume were found (45 ± 7 vs 42 ± 9 ml/m^2, $p = 0.32$). RV early filling was decreased in HFpEF (21 ± 11 vs. 40 ± 11% of RV filling volume, $p < 0.01$) and RV early filling was the strongest predictor for VO_{2max} even after inclusion of invasively derived RV stiffness and relaxation constant (Beta 0.63, $p < 0.01$). RA conduit-function was lower in HFpEF (RA conduit-strain − 11 ± 5 vs. − 16 ± 4%, $p < 0.01$) while RA booster-pump-function was increased (RA active-strain − 18 ± 6 vs. − 12 ± 6%, $p = 0.01$) as a compensation. RV filling was associated with RA conduit-function ($r = -0.55$, $p < 0.01$) but not with invasively derived RV relaxation constant.

Conclusion In compensated HFpEF patients RV early filling was impaired and compensated by increased RA booster pump function, while RV systolic function was preserved. Impaired RV diastology and RA–RV interaction were linked to impaired exercise tolerance and RA–RV-coupling seems to be independent of RV relaxation, suggestive of an independent pathophysiological contribution of RA dysfunction in HFpEF.

Clinical-Trial-Registration NCT02459626 (www.clinicaltrials.gov).

Keywords Heart failure · Preserved ejection fraction · Right heart · Magnetic resonance imaging · Feature tracking · Pressure–volume-loops · Right atrium

Introduction

Growing evidence suggests an important functional and prognostic role of right heart dysfunction in heart failure with preserved ejection fraction (HFpEF) [1–4]. Pathophysiological mechanisms include exercise-induced pulmonary hypertension (PH), impaired right ventricular–pulmonary arterial coupling and right ventricular dysfunction (RVD) [1–6]. Large-size studies show prognostic importance of RVD [2, 3] and right atrial (RA) mechanics [7], but pathophysiological understanding of RV and RA function, RA–RV interaction and their relation to exercise intolerance remains low in HFpEF. Earlier research proposed RV diastolic dysfunction as a consequence of impaired RV systolic function [8], but only recently we could demonstrate that already in compensated stages of the HFpEF syndrome with preserved systolic RV function, RV diastolic dysfunction is present and associated with impaired RV filling and a

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blunted increase in cardiac output during handgrip exercise [6].

The assessment of RH chamber interplay is hampered given the complexity of RH geometry and cardiac magnetic resonance imaging (CMR) is considered the reference standard for imaging of the RH [9]. CMR feature tracking (CMR-FT) allows for quantification of myocardial deformation from standard steady-state free precession sequences without the need for myocardial tagging [10].

RV systolic and diastolic functional parameters are highly load-dependent and pressure–volume-loop (PVL) analysis using high-fidelity conductance catheters under altered loading conditions gives the opportunity to study load-independent markers of RV function [11].

The present study, therefore, investigated RA and RV function in HFpEF patients and controls without prior heart failure related hospital admissions using CMR, CMR-FT and high-fidelity PVL analysis. We sought to identify systolic and diastolic RV and RA properties, RA–RV-interaction and clarify their influence on impaired exercise tolerance in compensated HFpEF patients.

Methods

Study protocol

The current study is a substudy of the STIFFMAP-trial (NCT02459626) [12] and patient selection is described elsewhere [12, 13]. In brief, outpatients referred for coronary angiogram at the University of Leipzig Heart Center for diagnostic work up of exertional dyspnea and/or suspected coronary artery disease were prospectively recruited. As part of the initial screening, echocardiography was performed. Patients were stratified as HFpEF or controls according to the following criteria:

HFpEF: (1) signs and symptoms of heart failure (New York Heart Association class (NYHA) ≥ II) AND (2) echocardiographic signs of diastolic dysfunction according to the consensus paper of the European Society of Cardiology [14] (LV-EF ≥ 50%, and $E/E' > 15$ OR $E/E' = 8–15$ and an elevation in NT-proBNP (Cobas, Elecsys NT-proBNP II, Roche, Basel, Switzerland; assay-specific elevations over 220 pg/mL).

Controls: (1) be free of heart failure symptoms (2) have an LV-EF ≥ 50% and be free of echocardiographic signs of severe diastolic dysfunction ($E/E' < 8$). Exclusion criteria from the study were relevant coronary artery disease, contraindication to CMR imaging, acute coronary syndrome, more than mild valvular disease or atrial fibrillation during CMR/cardiac catheterization.

Subsequently, eligible patients underwent the study procedures: on day 1 cardiopulmonary exercise testing and on day 2 CMR and invasive catheterization (CC) were performed consecutively and within a 5 h time window. To ensure comparable levels of intravascular volumes in a fasting state and to improve invasive RV measurements, 500 ml Ringer's lactate solution were infused intravenously 1–2 h prior to CMR and CC. The study was approved by the local ethics committee and all patients gave written informed consent.

Echocardiography

Transthoracic echocardiography was performed on Vivid E9 (GE Healthcare, Chalfont St. Giles, Great Britain) and analysis was performed offline using commercially available software (Echopac PC 6.1.0, GE Healthcare). LV size and function were quantified according to current guidelines [15]. Diastolic properties were assessed according to guidelines [14] by determining transmitral early (*E*-wave) and late (*A*-wave) flow velocities on pulsed wave Doppler and by tissue Doppler peak diastolic velocities of the septal and lateral mitral annulus (*E'*). The *E*/*E'* ratio was calculated.

Exercise testing

Spiroergometry was performed on a supine bicycle ergometer (Ergoline, Germany). Work rate was started with 20–40 W with stepwise increased workload of 10–20 W/min. Patients were instructed to maintain a pedaling rate of 60 rotations/min and encouraged to exercise until exhaustion. VO_2 and CO_2 production were measured on a breath-to-breath basis and calculated using established methodology (ZAN 600, ZAN, Steyr-Dietach, Austria). Peak VO_2 and respiratory exchange ratio (RER) were measured in the last 20 s at maximal exercise defining peak VO_2 as the highest VO_2 obtained during an adequately performed test [16].

CMR protocol

A 1.5-T scanner (Philips Intera, Phillips, Best, The Netherlands) was used for CMR-scans. Steady-state free precession (SSFP) sequences were obtained in two and four chamber views, as well as a short axes cine stack covering the left and right ventricle (repetition time 3.8 ms, echo time 1.6 ms, flip angle 60°, voxel size $1.25 \times 1.25 \times 8$ mm^2, 8–10 mm slice thickness). Volumetric assessment was performed offline using commercially available software (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Right- and left-ventricular (RV/LV) end-diastolic and end-systolic volumes (EDV, ESV) and ejection fraction (EF) were measured from the short axis stack. All volumes were normalized to body surface area (BSA). RA area and length were measured in the four-chamber view. RA volumes were measured

at maximal volume, before atrial contraction and minimal volume using the area-length method.

For assessment of RV filling properties, RV volumes throughout the cardiac cycle were measured in RV short axis stack. Duration of RV diastole was measured and early diastole was defined as first 1/3 and late diastole as last 2/3 [17]. RV mass was calculated using a commercially available post-processing software (QMass®, Version 3.1.16.0, Medis Medical Imaging Systems, Leiden, Netherlands) [18].

Feature tracking

RA and RV CMR-FT was performed using dedicated software (TomTec Imaging Systems, 2D CPA MR, Version 1.1.2.36, Unterschleissheim, Germany) as previously described [19, 20]. Temporal solution was 30 frames/cardiac cycle. RA and RV endocardial borders were manually traced in the four-chamber view at end-diastole with subsequent application of an automated tracking algorithm (Fig. 1). In case of insufficient automated border tracking, manual adjustments were made to the initial contour and the algorithm was reapplied. If the tracking quality was not sufficient, e.g., due to the presence of Eustachian valve or right atrial appendage, the corresponding segment was excluded from the analysis. Tracking was repeated for three times and the respective averages of these repetitions were used for further analyses [19, 20]. RA and RV longitudinal strain curves were generated and three aspects were analyzed: RA: total strain, conduit strain and active strain. RV: systolic strain, early diastolic strain and RV strain at atrial contraction. Figure 1 shows exemplary strain curves of a control patient and explanations. Negative values mean shortening, accordingly better RV systolic strain means higher negative values.

Cardiac catheterization protocol

Standard invasive coronary angiography was performed via right femoral artery access to exclude significant CAD; patients with indication for the treatment of epicardial stenosis were excluded. Pulmonary artery pressures (PAP) as well as pulmonary capillary wedge pressures (PCWP) were determined via standard right heart catheterization and all pressures were measured at end-expiration and represent the mean of ≥ 3 beats. LV-EDP and PCWP were verified based on characteristic waveforms and appearance on fluoroscopy. Via right femoral venous access a seven-French conductance catheter (CC,CD Leycom, Zoetermeer, Netherlands) was advanced into the right ventricle under fluoroscopy. Correct catheter position was determined by angiographic evidence of a centered position in the ventricle and by monitoring individual segmental pressure–volume loops. Signals were analyzed on a pressure–volume (PV) signal processor (Inca, CD Leycom). Real-time continuous RV pressure and volume signals were recorded for 10 s at baseline at resting expiratory level, with volume calibration performed using RV volumetric data from the preceding CMR scan. To examine load-independent properties of the RV a family of P–V-loops was generated by preload reduction. This was realized performing a transient occlusion of the inferior vena cava by inflation of an Amplatzer sizing balloon (St. Jude Medical,

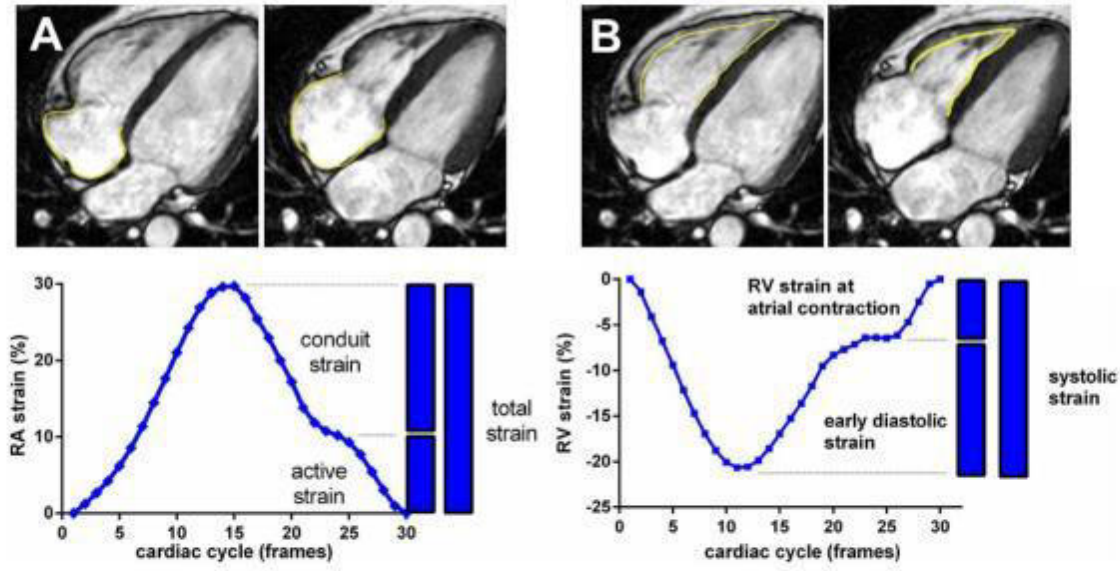

Fig. 1 Strain curves of a control patient: **a** (left): RA strain curve showing RA total, conduit and active strain ("booster pump"). **b** (Right): RV strain curve showing RV systolic, early diastolic and RV strain at atrial contraction

Saint Paul, USA). Care was taken to record data under resting expiratory level and the maneuver was repeated in case the investigators detected abrupt and unproportional changes in pressure or volumes. To assess intrinsic contractility the slope of the endsystolic elastance (Ees) was determined as the linear relationship through the endsystolic-pressure–volume-relations during preload reduction. Hereby right-ventricular end-systolic pressure (RVESP) and its corresponding volume were determined using electrocardiographic triggering to ensure pressure readings at end-systole as opposed to maximal ejection/pressure. End-systolic volume at end-systolic pressure of 0 (V0) and 30 mmHg (V30) were derived from the linear Ees curve. Intrinsic RV stiffness was assessed by extrapolating the load-independent RV stiffness constant (Beta) from the enddiastolic-pressure–volume relations (EDPVR) and the formula $EDP = C*eBeta*EDV$, where EDP is RV-enddiastolic pressure (RV-EDP), C is a fitting constant and EDV is RV-enddiastolic volume (RV-EDV), applying the methods established for the LV [11]. End-diastolic volume at end-diastolic pressure of 10 mmHg was derived from the extrapolated stiffness curve. Loops were analyzed from the last heartbeat before the onset of volume/pressure decline for a minimum of five beats without increase in heart rate. Curve-fitting was realized through Microsoft Excel (version 14.0). The time constant of active relaxation (τ) was calculated after the method of Mirsky [21], which evaluates the time needed for RV-pressure to fall to one half of its value from peak rate of RV pressure fall (dP/dtmin).

Statistics

Data for continuous variables are presented as mean ± standard deviation (SD), if normally distributed, or as median and interquartile range (IQR) if non-normally distributed. Distribution was tested using Shapiro–Wilk test. Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using Fisher's exact test for categorical variables. Continuous variables were compared with unpaired *t* tests or nonparametric Mann–Whitney *U* test where appropriate.

Pearson's (r) and Spearman's (ρ) test were used as appropriate to find factors associated with VO_{2max} and early RV filling. Univariate linear regression analysis and stepwise forward multivariable linear regression analysis were performed to search and control for influencing factors of VO_{2max} in the whole cohort and partial correlation was analyzed. Different models were calculated including the factors which were strongest correlated (with $p \leq 0.005$) with VO_{2max}. Standardized beta coefficients (Beta) are reported for multivariable regression analysis.

Results

Clinical and demographic data

A total of 46 patients were recruited and underwent CMR and cardiac catheterization (CC). Out of them, ten patients were excluded in the course of the study: two patients had atrial fibrillation during CC, two had incomplete CMR studies and in five patients significant CAD was found. One considerably younger control subject (34 years) than the remaining population was also excluded from the analysis. Finally, 24 HFpEF patients and 12 control subjects were analyzed. All patients were stable outpatients without prior hospitalization for heart failure. Baseline characteristics are shown in Table 1.

HFpEF patients were older, more often female, had a higher body mass index and were more often hypertensive. CC in control patients was indicated to exclude CAD in case of chest pain and/or an increased cardiovascular risk profile with high prevalence of diabetes, HLP and smoking. No significant differences were found with regard to medication. Elevation of NT-proBNP was present in 2/3rds of HFpEF patients, who all reported exertional dyspnea, predominantly in NYHA class II.

Functional capacity and maximal oxygen uptake were reduced in HFpEF patients (94 ± 33 vs. 154 ± 43 W, $p < 0.0001$; VO_{2max} 17 ± 5 vs. 28 ± 8 ml/(kg*min), $p = 0.001$).

Echocardiography and CMR

While no differences with regard to LV-size (LV-EDV 72 ± 14 vs. 71 ± 15 ml/m^2, $p = 0.74$) and—function (LVEF 60 ± 7 vs. $60 \pm 8\%$, $p = 0.91$) were found, HFpEF patients showed typical echocardiographic features of diastolic dysfunction with higher transmitral *E*-wave velocities (0.9 ± 0.2 vs. 0.7 ± 0.1 m/s, $p = 0.001$) and decreased septal and lateral *E'*-velocities (septal 0.06 ± 0.02 vs. 0.08 ± 0.01 m/s, $p = 0.0002$; lateral 0.07 ± 0.02 vs. 0.12 ± 0.03 m/s, $p = 0.00003$), resulting in higher E/E' ratios [14.5 (IQR 11.3–16.2) vs. 7.4 (IQR 6.7–7.7), $p \leq 0.00001$]. No signs of RV hypertrophy were present in HFpEF patients (RV mass 53.6 ± 10.6 g in HFpEF and 60.9 ± 8.9 g in controls, $p = 0.051$). Results are shown in Table 2.

Invasive hemodynamic and pressure–volume loop measurements

Results are shown in Table 2. Right ventricular pressure–volume loops were of sufficient quality in 23 patients in the HFpEF group and in nine controls. HFpEF patients

Table 1 Baseline characteristics

	HFpEF ($n=24$)	Control ($n=12$)	p
Age (years)	69 (IQR 63–71)	56 (IQR 54–67)	**0.02**
Female sex	21/24 (88%)	3/9 (25%)	**<0.0001**
BMI (kg/m^2)	30 ± 4	27 ± 3	**0.02**
NT-proBNP-elevation	16/24 (67%)	0/12 (0%)	**<0.0001**
NT-proBNP (pg/ml)	331 (IQR 187–496)	51 (IQR 28–79)	**<0.0001**
NYHA I	0/24 (0%)	12/12 (100%)	**<0.0001**
NYHA II	19/24 (79%)	0/9 (0%)	
NYHA III	5/24 (21%)	0/9 (0%)	
Systolic BP (mmHg)	156 ± 13	153 ± 16	0.54
Diastolic BP (mmHg)	80 ± 9	80 ± 9	0.95
Hypertension	23/24 (96%)	8/12 (67%)	**0.03**
Hypercholesterolemia	21/24 (88%)	11/12 (92%)	1.0
Diabetes mellitus	5/24 (21%)	4/12 (33%)	0.44
Smoking	2/24 (8%)	8/12 (80%)	**0.001**
COPD	2/24 (8%)	0/12 (0%)	0.54
Paroxysmal atrial fibrillation	6/24 (25%)	0/12 (0%)	0.08
ß-blockers	10/24 (42%)	2/12 (17%)	0.26
ACE-inhibitors/ARB	17/24 (71%)	5/12 (42%)	0.15
Ca^{2+}-antagonist	9/24 (38%)	3/12 (25%)	0.71
Aldosterone antagonists	0/24 (0%)	0/12 (0%)	n.a.
Statins	10/24 (42%)	4/12 (33%)	0.73
Diuretics	9/24 (38%)	1/12 (9%)	0.07
ECG PQ duration (ms)	177 ± 27	170 ± 18	0.41
ECG QRS duration (ms)	99 ± 25	92 ± 22	0.39

Values are presented as mean ± standard deviation, medians + interquartile range or frequencies (percentages), p values below the significance level of 0.05 are highlighted in bold

BMI body mass index, *BP* blood pressure, *nt-pro-BNP* n-terminal propeptide brain-natriuretic-peptide, *NYHA* New York heart association class, *COPD* chronic obstructive lung disease, *OSA* obstructive sleep apnea, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blocker

had higher left ventricular end-diastolic pressure (19 ± 3 vs. 13 ± 3 mmHg, $p=0.00008$) and higher PCWP (13 ± 4 vs. 8 ± 3 mmHg, $p=0.0006$), while left ventricular end-systolic pressure was similar in both groups. Systolic pulmonary artery pressure (sPAP, 35 ± 8 vs. 28 ± 4 mmHg, $p=0.01$) and mean pulmonary artery pressure (mPAP, 24 ± 6 vs. 17 ± 3 mmHg, $p=0.001$) were higher in HFpEF patients. One-third ($n=8$) of HFpEF patients was found to have postcapillary PH at rest (mPAP > 25 mmHg), while none of the control patients showed PH ($p=0.02$). RV end-systolic elastance was slightly higher in HFpEFs [RV-Ees, 0.65 (IQR 0.56–0.85) vs. 0.51 (IQR 0.42–0.53), $p=0.009$] with no difference in end-systolic volume at an end-systolic pressure of 30 mmHg ($p=0.48$). No statistically significant differences were found in pulmonary arterial elastance ($p=0.21$) or RV to PA coupling ($p=0.29$). RV intrinsic stiffness constant β was significantly higher in HFpEF (0.019 ± 0.003 vs. 0.012 ± 0.003, $p<0.0001$), as well as relaxation constant Tau (38 ± 8 vs. 30 ± 8 ms, $p=0.02$).

Right ventricular systolic function

While no significant differences between HFpEF and controls with regard to RV stroke volume (45 ± 7 vs 42 ± 9 ml/m^2, $p=0.32$) or RV end-diastolic volume (66 ± 12 vs. 70 ± 13 ml/m^2, $p=0.41$) were found, RV end-systolic volume (21 ± 8 vs 28 ± 8 ml/m^2, $p=0.03$) was significantly lower in HFpEF, resulting in a higher RVEF (68 ± 8 vs. 60 ± 9, $p=0.01$). RV systolic strain was also higher in HFpEF [− 23 (IQR − 22 to − 27) vs. − 21 (IQR − 19 to − 23) %, $p=0.04$) showing preserved or slightly increased RV function as compared to controls.

Right ventricular diastolic function

Investigating diastolic function, strain analysis revealed no differences in RV early diastolic strain (12 ± 5 vs. 13 ± 3%, $p=0.56$) but RV strain at atrial contraction was significantly higher in HFpEF as compared to controls (13 ± 4 vs 8 ± 3%, $p=0.001$). Filling volume at early diastole was significantly lower in HFpEF patients (21 ± 11 vs.

Table 2 CMR

CMR	HFpEF ($n=24$)	Control ($n=12$)	p
LV-EDV (ml/m^2)	72 ± 14	71 ± 15	0.74
LV-ESV (m/m^2 l)	29 ± 9	29 ± 10	0.94
LV-EF (%)	60 ± 7	60 ± 8	0.91
LV-stroke volume (ml/m^2)	43 ± 9	42 ± 9	0.69
Echocardiography			
Transmitral E–V_{max} (m/s)	0.9 ± 0.2	0.7 ± 0.1	**0.001**
Transmitral A–V_{max} (m/s)	0.8 ± 0.2	0.7 ± 0.1	0.16
E/A, (ratio)	1.02 (IQR 0.82–1.56)	0.91 (IQR 0.78–1.16)	0.46
E' septal (m/s)	0.06 ± 0.02	0.08 ± 0.01	**0.0002**
E' lateral (m/s)	0.07 ± 0.02	0.12 ± 0.03	**0.00003**
E/*E*' (mean)	14.5 (IQR 11.3–16.2)	7.4 (IQR 6.7–7.7)	**< 0.00001**
Tricuspid regurgitation			
Trace/mild	24/24 (100%)	12/12 (100%)	n.a.
Moderate/severe	0/24 (0%)	0/12 (0%)	
Invasive measures			
Heart rate (/min)	69 ± 11	72 ± 7	0.45
LV-ESP (mmHg)	155 ± 22	146 ± 17	0.19
LV-EDP (mmHg)	19 ± 3	13 ± 3	**0.00008**
PCWP (mmHg)	13 ± 4	8 ± 3	**0.0006**
RV-ESP (mmHg)	33 ± 9	27 ± 2	**0.01**
RV-EDP (mmHg)	7 ± 2	4 ± 1	**< 0.001**
Systolic PA pressure (mmHg)	35 ± 8	28 ± 4	**0.01**
Mean PA pressure (mmHg)	24 ± 6	17 ± 3	**0.001**
Mean PA pressure > 25 mmHg	8/24 (33%)	0/12 (0%)	**0.02**
	$n=23$	$n=9$	
RV end-systolic pressure volume relation *mmHg/ml*	0.59 (IQR 0.41–0.75)	0.38 (IQR 0.30–0.44)	**0.009**
RV-capacity at ESP 0 mmHg (V0, ml/m^2)	−0.8 ± 13.0	2.2 ± 9.8	0.49
RV-capacity at ESP 30 mmHg (V30, ml/m^2)	26 ± 14	29 ± 6	0.48
RV end-systolic elastance (Ees) (mmHg/ml)	0.65 (IQR 0.56–0.85)	0.51 (IQR 0.42-0.53)	**0.009**
Pulmonary arterial elastance (Ea) (mmHg/ml)	0.35 (IQR 0.21–0.47)	0.29 (IQR 0.23–0.32)	0.21
RV-Ea/Ees ratio	0.62 (IQR 0.44–0.62)	0.73 (IQR 0.56–0.82)	0.29
RV-Tau (ms)	38 ± 8	30 ± 8	**0.02**
RV end-diastolic pressure–volume-relationship fitting constant (C)	0.75 ± 0.47	0.93 ± 0.53	0.39
RV-capacity at EDP 10 mmHg (ml/m^2)	82 ± 26	113 ± 25	**0.008**
RV-stiffness (ß)	0.019 ± 0.003	0.012 ± 0.003	**< 0.0001**

Values are presented as mean ± standard deviation or medians + interquartile range, p values below the significance level of 0.05 are highlighted in bold

E/E'avg E' avg is calculated as (*E'*septal + *E'*lateral)/2, *LV* left-ventricular, *RV* right-ventricular, *PCWP* pulmonary capillary wedge pressure, *PA* pulmonary artery, *ESP* endsystolic pressure, *EDP* enddiastolic pressure, *Tau* time constant of relaxation

40 ± 11% of RV filling volume, $p \leq 0.0001$) and significantly higher at filling during last 2/3 of diastole (79 ± 11 vs. 60 ± 11% of RV filling volume, $p \leq 0.0001$), thus strain and volumetric assessment together revealed a pattern of impaired early ventricular filling with compensatory filling during right atrial contraction. Results of RV volumetric and strain analysis are shown in Fig. 2.

Right atrial function

Volumetric assessment showed no differences with respect to maximal RA volume (36 ± 11 vs. 34 ± 10 ml/m^2, $p=0.5$) and RA total EF (54 ± 10 vs. 50 ± 8%, $p=0.26$), but RA passive EF—during early ventricular filling—was significantly lower in HFpEF (17 ± 8 vs 24 ± 9%, $p=0.02$) while

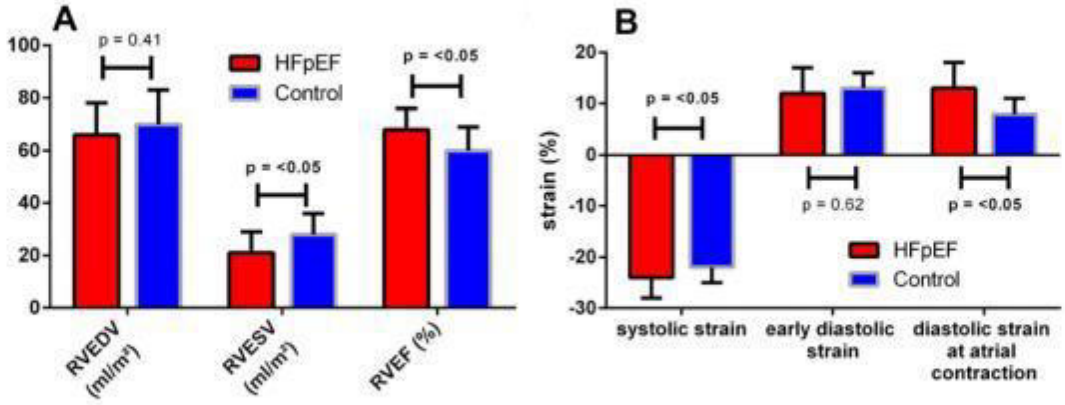

Fig. 2 **a** (Left): right ventricular volumes: *RVEDV* right ventricular end diastolic volume, *RVESV* right ventricular end systolic volume, *RVEF* right ventricular ejection fraction. **b** (Right): right ventricular systolic strain, early diastolic strain and strain at atrial contraction

RA active EF (booster pump function) was higher (45 ± 10 vs 34 ± 8%, $p = 0.005$). Strain measurements revealed similar patterns with RA total strain being comparable between both groups (29 ± 7 vs. 28 ± 5%, $p = 0.68$) in contrast to RA conduit strain, which was significantly lower in HFpEF (− 11 ± 5 vs. − 16 ± 4%, $p = 0.002$) and which was compensated by higher RA active strain (− 18 ± 6 vs. − 12 ± 6%, $p = 0.01$, Fig. 3).

RA–RV interaction

RA and RV function were closely related throughout the cardiac cycle with special emphasis on diastology: RV early diastolic strain was inversely related to RA conduit strain ($r = -0.72$, $p \leq 0.0001$) and RV diastolic strain at atrial contraction was inversely related to RA active strain ($r = -0.72$, $p \leq 0.0001$). Inverse correlation in this case describes the amount of atrial contraction during ventricular relaxation. Figure 4b shows atrial and ventricular strain curves of one representative HFpEF and control patient.

Association with maximal oxygen uptake

Features associated with maximal oxygen uptake are shown in Table 3. Factors with strongest positive association were early RV filling ($r = 0.61$, $p = 0.0008$), RA conduit strain ($r = -0.54$, $p = 0.001$, negative strain means contraction and stronger atrial contraction is associated with increased VO_{2max}) and RV early diastolic strain ($r = 0.36$, $p = 0.03$). Negatively associated with VO_{2max} were RV strain at atrial contraction ($r = -0.54$, $p = 0.001$), NT-proBNP-elevation ($\rho = -0.53$, $p = 0.001$), age ($\rho = -0.49$, $p = 0.003$) and female sex ($\rho = -0.42$, $p = 0.01$). Multivariable stepwise regression analysis including early ventricular filling,

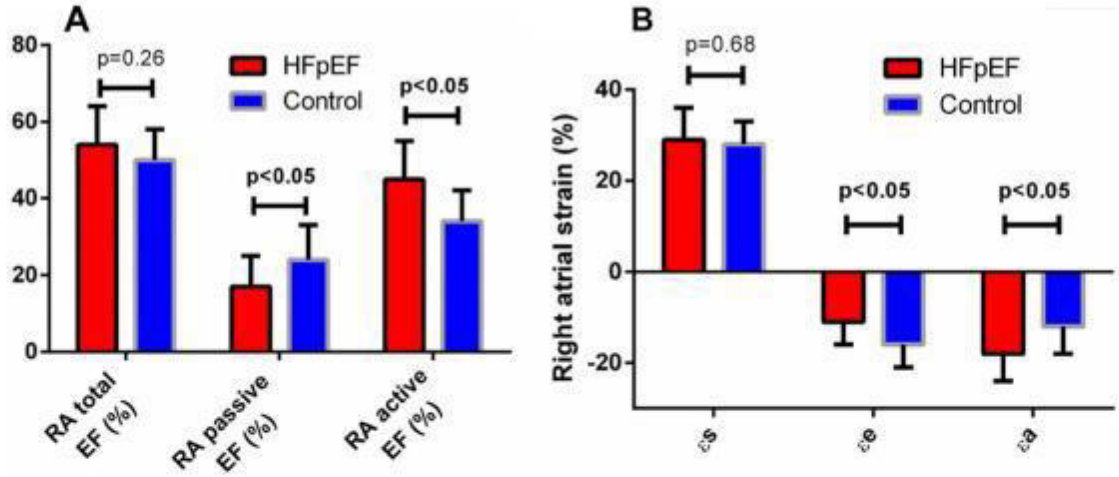

Fig. 3 **a** (Left): RA function according to volumetric measurements: *RAEF* RA ejection fraction. **b** (Right): RA strain measurements: *εs* RA total strain, *εe* RA conduit strain, *εa* RA active strain ("booster pump")

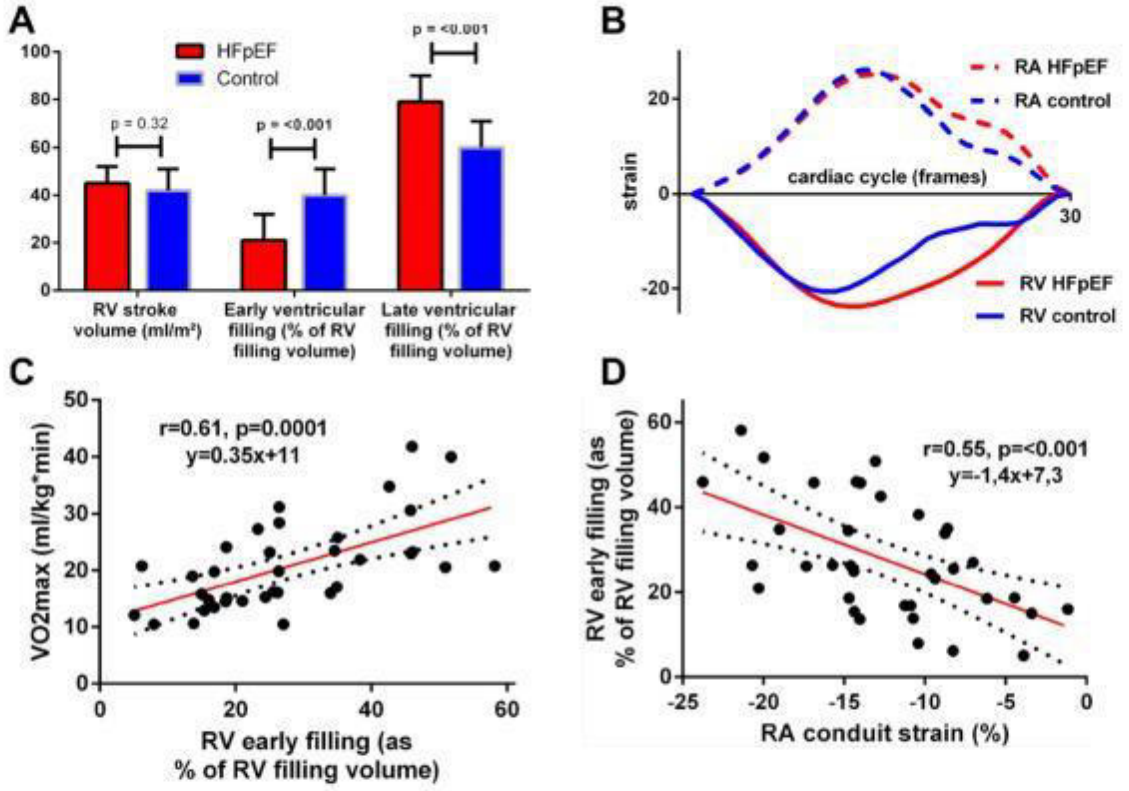

Fig. 4 **a** (Top left): RV stroke volume and RV filling as percentage of RV filling volume in HFpEF and controls. **b** (Top right): representative RA (dotted line) and RV (straight line) strain curves of one HFpEF (red) and one control (blue) patient; RA conduit strain is impaired and RA active strain increased in HFpEF with corresponding ventricular motion. **c** (Bottom left): correlation of early RV filling with maximal oxygen uptake. **d** (Bottom right): correlation of RA conduit strain and early RV filling

NT-proBNP-elevation and age revealed a standardized Beta for early ventricular filling of 0.39 ($p=0.007$), highlighting the preserved importance of early RV filling in the context of strong baseline characteristics with regard to VO_{2max}. When including early ventricular filling, invasively derived RV relaxation constant Tau and stiffness constant β into multivariable regression analysis, RV early filling remained the only independent predictor of VO_{2max} (standardized β 0.63, $p=0.0003$). In different models including early ventricular filling and markers of vascular load (pulmonary arterial elastance, sPAP or mPAP), early ventricular filling remained the only independent predictor of VO_{2max}. Figure 4 depicts the association of right ventricular early filling and VO_{2max}.

Right ventricular early filling and diastolic function

Better RV early filling was associated with a pattern of higher RA conduit strain ($r=-0.55$, $p=0.0005$) and RV early diastolic strain ($r=0.43$, $p=0.01$). Markers of higher RV systolic contraction [end-systolic elastance ($\rho=-0.54$, $p=0.003$), RV EF ($r=-0.47$, $p=0.004$)] and increased active RA contraction [RA active strain ($r=0.55$, $p=0.0005$), RV strain during atrial contraction ($r=-0.59$, $p=0.0002$)] were associated with impaired early ventricular filling. No significant correlations with relaxation constant Tau or RV stiffness constant β were found, suggesting a mechanism of early RV filling independent of RV relaxation and stiffness and related to RA conduit function. Results are shown in Table 4 and Fig. 4c, d.

Discussion

The current study investigated systolic and diastolic RV and RA properties in HFpEF using CMR, CMR-FT and invasive PVL analysis.

The main findings can be summarized as follows:

1. At a compensated stage of HFpEF, early RV filling is disturbed and linked to exercise intolerance. Ventricular filling at rest is compensated by increased RA booster pump function and correspondingly increased RV filling in late diastole.
2. Although RV diastology is characterized by increased RV stiffness and myocardial relaxation, functional impairments are associated with RA conduit function,

Table 3 Univariate correlation with maximal oxygen uptake [ml/(kg*min)]

	Correlation coefficient	*p*
RV early filling (% of RV stroke volume)	$r=0.61$	**0.00008**
RA conduit strain εe (− %)	$r=0.54$	**0.001**
RV diastolic strain at atrial contraction (%)	$r=-0.54$	**0.001**
NT-proBNP elevation	$\rho=-0.53$	**0.001**
Age (years)	$\rho=-0.49$	**0.003**
Sex (female)	$\rho=-0.42$	**0.01**
Pulmonary arterial elastance (Ea, mmHg/ml)	$\rho=-0.40$	**0.03**
BMI (kg/m^2)	$r=-0.38$	**0.02**
RV early diastolic strain (%)	$r=0.36$	**0.03**
RA active strain εa (− %)	$r=-0.35$	**0.04**
RV end-systolic elastance (Ees, mmHg/ml)	$\rho=-0.36$	0.06
RV-Stiffness (ß)	$r=-0.34$	0.07
RV-Tau (ms)	$r=-0.29$	0.11
RV EF Total (%)	$r=-0.27$	0.12
Systolic PA pressure (mmHg)	$r=-0.25$	0.14
RV systolic strain (− %)	$\rho=-0.21$	0.22
RV-Ea/Ees ratio	$\rho=0.15$	0.41
Paroxysmal atrial fibrillation	$\rho=-0.15$	0.37
RV stroke volume (ml/m^2)	$r=0.12$	0.49
RA total strain εs (%)	$r=0.05$	0.79

p values below the significance level of 0.05 are highlighted in bold

r Pearson's and ρ = Spearman's correlation coefficient, *Tau* time constant of relaxation

Table 4 Univariate correlation with RV early filling (% of RV stroke volume)

	Correlation coefficient	P
RV diastolic strain at atrial contraction (%)	$r=-0.59$	**0.0002**
RA conduit strain εe (− %)	$r=0.55$	**0.0005**
RA active strain εa (− %)	$r=-0.55$	**0.001**
RV end-systolic elastance (Ees, mmHg/ml)	$\rho=-0.54$	**0.003**
RV EF Total (%)	$r=-0.47$	**0.004**
Sex (female)	$\rho=-0.47$	**0.004**
NT-proBNP elevation	$\rho=-0.43$	**0.01**
RV early diastolic strain (%)	$r=0.43$	**0.009**
Pulmonary arterial elastance (Ea, mmHg/ml)	$\rho=-0.39$	**0.03**
Mean PA pressure (mmHg)	$r=-0.35$	**0.04**
BMI (kg/m^2)	$r=-0.34$	**0.04**
Age (years)	$\rho=-0.33$	**0.046**
RV-Stiffness (ß)	$r=-0.3$	0.12
Systolic PA pressure (mmHg)	$r=-0.29$	0.09
RA total strain εs (%)	$r=-0.09$	0.63
RV stroke volume (ml/m^2)	$r=-0.09$	0.59
RV systolic strain (− %)	$\rho=0.1$	0.56
Paroxysmal atrial fibrillation	$\rho=-0.15$	0.38
RV-Ea/Ees ratio	$\rho=0.15$	0.40
RV-Tau (ms)	$r=-0.04$	0.85

p values below the significance level of 0.05 are highlighted in bold

r Pearson's and ρ Spearman's correlation coefficient, *Tau* time constant of relaxation

suggesting an independent disease entity of impaired RA function and disturbed RA–RV coupling in the HFpEF syndrome.

RV diastology in HFpEF

To the best of our knowledge, this is the first study evaluating CMR-derived RV filling and diastolic RV strain in combination with invasive pressure–volume-loops in HFpEF. Our study expands the understanding of RV diastolic function in compensated HFpEF. RV diastolic dysfunction (RVDD) is a known consequence of increased arterial load and results in impaired relaxation [22] and increased stiffness in more advanced stages of the disease [23]. If myocardial disease is present, RVDD is also caused as a consequence of RV systolic dysfunction (RVSD) [24, 25].

In a recent profound analysis of 50 patients with HFpEF, Borlaug et al. [2] found evidence of exercise-induced RVDD with blunted cardiac output and impaired exercise tolerance as compared to controls. RVDD and RVSD were assessed using lateral tricuspid tissue-Doppler velocities and no significant baseline differences were found between HFpEF and controls at rest. Exercise testing revealed a tremendous increase in left- and right-sided filling pressures, suggestive of afterload-induced RVDD and indeed, while pulmonary resistance dropped in controls, it remained unchanged in HFpEF patients. As compared to our cohort, resting PCWP and mPAP were higher in the cohort investigated by Borlaug et al. [26] and might reflect a more decompensated stage or a distinct obese phenotype of the disease with markedly reduced VO_{2max} as compared to our cohort.

Our results demonstrate RVDD at a compensated stage of the disease without significant PH. Importantly, early ventricular filling was the only independent predictor of VO_{2max} on multivariable regression analysis when including markers of pulmonary vascular load. In the study conducted by Borlaug, RVDD significantly correlated with RVSD and HFpEF patients already had RV dilatation, raising the question, whether RVDD might be the consequence of RVSD, which is found in about 20–25% of HFpEF patients [27]. Instead, we found slightly increased load-dependent (RVEF, RV longitudinal strain) and load-independent (RV Es slope) measures of RV contractility in our cohort of HFpEF patients without prior HF hospitalizations and without RV dilatation, again suggestive of a compensated stage or distinct phenotype of the disease. Pulmonary artery (PA) pressure in our cohort was rather low as compared to other HFpEF studies with only 33% of HFpEF patients exceeding an

mPAP of 25 mmHg at rest [28, 29]. Given the ability of the RV to increase its contractility by factor 4–5 in response to increased afterload [30], mildly increased RV elastance in our cohort seems to be an effective mechanism to preserve RV–PA coupling.

RA function and RA–RV coupling

Atrial function improves ventricular filling by (1) storing blood as a reservoir during ventricular systole while atrioventricular (AV) valves are closed (reservoir function) (2) serving as a conduit and passive emptying during early ventricular filling (conduit function) and (3) providing additional ventricular filling with active contraction before AV valve closure (booster pump function). Recently, the additional functional and prognostic information from functional atrial analysis was examined, giving the opportunity to reveal atrial dysfunction and disturbance in cardiac mechanics before overt failure is present. In HFpEF LA dysfunction emerged as a strong and independent predictor of death, heart failure hospitalization and exercise intolerance [13, 31, 32], and recently RA reservoir and conduit function—in the absence of RA dilatation—were also identified as prognostic parameters [7]. Impaired ventricular diastology and chronic atrial pressure overload lead to atrial dilatation in an advanced stage of left and right heart disease and eventually cause atrial dysfunction with inappropriate ventricular filling [33]. In PAH without left heart disease—a model of isolated pressure overload—RA reservoir and conduit function decline in the presence of concomitant RA dilatation, while booster pump function is preserved to maintain ventricular filling [33]. Melenovsky et al. [2] found RA dilatation and impaired RA reservoir function in patients with HFpEF with advanced RV dysfunction, moderate–severe tricuspid regurgitation (TR), pulmonary hypertension (PH) and high mortality rates (56% mortality at 2 years). Given the decompensated stage of the disease and presence of volume (TR) and pressure (PH) overload, several confounders are present when comparing RA function with our cohort. While RA function (RA EF) was a predictor of mortality on univariate analysis, this effect vanished on multivariable adjustment and only RA size remained an independent predictor of mortality—most likely as a marker of chronic RA pressure and/or volume overload. In our cohort, no significant differences regarding RA size were found, but RA conduit function was reduced and compensated by increased booster pump function. This was not assessed in the study by Melenovsky et al. [2] presumably due to the high prevalence of atrial fibrillation, but the association of RA conduit function with VO_{2max} in our cohort emphasizes the functional implication of disturbed RA mechanics in a compensated stage of the disease without prior heart failure hospitalization. Importantly, early RV filling—the strongest predictor of VO_{2max} in our cohort—was associated with RA conduit function and not with invasively derived RV relaxation, suggestive of a contribution of RA dysfunction and RA–RV coupling to exercise intolerance in HFpEF independent of instantaneous RV relaxation. Pathophysiological evidence regarding this mechanism exists for the left sided heart chambers: in an animal model of early hypertensive HFpEF impaired left atrial (LA) conduit function was compensated by increased booster pump function (a potential mechanism to preserve LA–LV coupling). Despite this compensatory mechanism overall LA–LV coupling was impaired due to an even more severe increase in ventricular elastance and impaired coupling was associated with lower LV stroke volume in hypertensive HFpEF dogs. On autopsy LA cardiomyocyte cross-sectional area was greater in HFpEF, as was titin phosphorylation and posterior LA fibrosis [34].

We recently demonstrated an impaired diastolic RV reserve capacity with RV filling limiting cardiac output under handgrip exercise, suggesting that impaired RV diastology can occur even in the absence of RV systolic dysfunction [6]. We now extend these observations and demonstrate the importance of the RA–RV interaction in HFpEF pathophysiology. Disturbed filling might be aggravated during physiologic exercise, when shortening of diastole leads to partial fusion of passive and active ventricular filling phases with increasing importance of passive RA restoring forces to maintain adequate ventricular filling [35]. Assessing RA function might play a role when planning volume-shifting interventions in HFpEF patients with interatrial shunt devices [36]. Volume shifts from the left to the right atrium for relief of left atrial pressure might come at the cost of further deterioration of RA function. In contrast, counteracting decreased RV afterload due to improved LA pressure and consecutive PA pressure with improved RV relaxation might compensate for RA volume overload. Results of ongoing trials will help to answer this question (NCT03088033).

Limitations

Our study results are acquired during resting conditions and some pathophysiological mechanisms in HFpEF can only be revealed during exercise. We assessed exercise capacity and maximal oxygen uptake and found significant associations with markers of RA mechanics and RV filling altogether suggesting disturbed RV diastology and RA–RV coupling in HFpEF. Adding an exercise imaging test might have truly revealed those disturbances under physiological conditions.

Due to invasiveness, complexity and cost of pressure–volume loop acquisition our study group consists of a limited sample size, making the results susceptible to a type I error and should be regarded as "hypothesis generating" only.

The baseline characteristics differ between HFpEF and control patients, with HFpEF patients being more often female and older. Although this is known from previous and contemporary HFpEF cohorts [37, 38] age and sex have a significant influence on RA and RV function in healthy people [39] and we cannot exclude a certain amount of selection bias in our cohort. A large number of cardiovascular and heart failure risk factors are present in the control group, justifying cardiac catheterization in the first place, making our control group different from a healthy control group. However, we were able to detect disturbances in cardiac mechanics associated with impaired exercise tolerance besides the presence of risk factors in the control group obviously marking the transition from prevalent risk factors to overt disease.

Conclusion

While RV systolic function is preserved in compensated HFpEF without prior heart failure hospitalization, early RV filling and early RA–RV coupling are disturbed and associated with impaired exercise tolerance. RA dysfunction seems to be independent of invasively derived RV relaxation and should be considered when characterizing the various pathophysiological entities of the HFpEF syndrome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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2.2 ENTWICKLUNG EINES THERAPEUTISCHEN KONZEPTES FÜR PATIENTEN MIT HERZINSUFFIZIENZ UND ERHALTENER PUMPFUNKTION UND TRIKUSPIDALKLAPPENINSUFFIZIENZ

2.2.1 Biventrikuläre hämodynamische Effekte einer katheterbasierten Trikuspidalklappenrekonstruktion

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Physiological and Clinical Consequences of Right Ventricular Volume Overload Reduction After Transcatheter Treatment for Tricuspid Regurgitation

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ABSTRACT

OBJECTIVES This study sought to examine the impact of chronic right ventricular (RV) volume overload and implications of tricuspid regurgitation (TR) reduction on biventricular function.

BACKGROUND Severe TR is a major determinant of adverse outcomes in advanced heart failure patients. The understanding of TR pathophysiology and implications of correction is still limited. Transcatheter tricuspid edge-to-edge repair (TTVR) is a new treatment option in patients at high surgical risk and provides a unique pathophysiological model without confounding effects of cardiac surgery.

METHODS Twenty-nine patients (78 ± 4 years of age) with severe isolated TR and high surgical risk underwent TTVR using the MitraClip system, and of these 18 underwent repeated cardiac magnetic resonance. Clinical follow-up was realized at 1 and 6 months after the intervention.

RESULTS TR fraction was reduced from 41% to 21% ($p < 0.01$) without increase in RV afterload ($p = 0.52$) and RV end-diastolic volume ($p < 0.01$), and RV stroke volume decreased ($p = 0.03$), whereas RV effective forward flow increased ($p = 0.03$). Left ventricular (LV) filling improved with an increase in LV end-diastolic volume ($p = 0.01$) and LV stroke volume ($p = 0.02$), leading to an augmentation of cardiac indices (2.2 ± 0.6 l/min/m^2 vs. 2.7 ± 0.6 l/min/m^2; $p < 0.01$) with similar results at 6 months follow-up. After TTVR, New York Heart Association functional class significantly improved ($p < 0.01$), peripheral edema decreased ($p = 0.01$), and 6-min walk distance increased by 20% and 22% after 1 and 6 months, respectively ($p < 0.01$).

CONCLUSIONS TTVR reduces chronic RV volume overload without increase in RV afterload, improves RV performance and LV filling, and enhances cardiac output. These changes translate into symptomatic and functional improvement. These implications for biventricular physiology and clinical status are maintained at 6 months follow-up. (J Am Coll Cardiol Intv 2019;12:1423–34) © 2019 by the American College of Cardiology Foundation.

Severe tricuspid regurgitation (TR) is associated with exercise intolerance and increased risk of heart failure (HF) hospitalizations and cardiovascular mortality (1–3).

Functional TR is the most common form and occurs mainly from annular dilation and right ventricular (RV) enlargement, which is often secondary to left heart failure from myocardial or valvular causes, RV volume and pressure overload, and dilation of cardiac chambers. Importantly, TR might develop also as a standalone vitium or late after successful correction of left-sided valvular

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

EROA = effective regurgitation orifice area

HF = heart failure

LV = left ventricle/ventricular

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RA = right atrium/atrial

RV = right ventricle/ventricular

SV = stroke volume

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

TTVR = transcatheter tricuspid edge-to-edge repair

TV = tricuspid valve

disease (isolated TR), and independently predicts worse outcomes also in this group of patients (2,3).

Therapeutic options for severe TR are limited, as patients often present late during the natural history of the disease, when they are at prohibitive risk for open heart surgery. Furthermore, surgical correction is associated with substantial perioperative mortality and is therefore infrequently performed (4–6).

Recently, new transcatheter treatment options for TR have emerged, among them the most widely used being the transcatheter tricuspid edge-to-edge repair (TTVR) technique (MitraClip, Abbott Vascular, Abbott Park, Illinois) (7). This technique has been demonstrated to be feasible and to be associated with an improvement in New York Heart Association (NYHA) functional class and 6-min walk distance (8,9). Further preliminary data from a mixed cohort of patients in which two-thirds were concomitantly treated with percutaneous edge-to-edge mitral valve repair showed that successful TTVR was associated with a reduction in mortality and heart failure hospitalization (10).

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Performed on patients with isolated TR, this technique provides a unique model to study the impact of reduction in chronic RV volume overload without the confounding effects of cardiac surgery (e.g., cardiopulmonary bypass) and concomitant left-sided interventions.

The understanding of TR pathophysiology and implications of correction is still limited. Research in this field has been hampered by the complex RV anatomy and the associated difficulties of echocardiography to assess RV physiology in a quantitative manner.

Cardiac magnetic resonance (CMR) has emerged as the reference standard for biventricular dimension and function analysis, especially overcoming echocardiographic limitations in assessing the right-sided heart chambers and allowing for direct quantification of valvular regurgitations (11).

The aim of the present study was to investigate the physiological effects and clinical consequences of isolated TTVR during short-term and midterm follow-up with the help of a multimodal imaging approach, including CMR.

METHODS

PATIENTS. The study was conducted at the Heart Center Leipzig at the University of Leipzig, Germany. Twenty-nine consecutive patients treated successfully with TTVR for isolated TR between July 2016 and April 2018 were included. All patients were referred with symptoms of right-sided HF and were in NYHA functional classes II to IV despite guideline-directed medical therapy. Pre-procedural assessment included a comprehensive transthoracic and transesophageal echocardiography, evaluation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (Cobas, Elecsys NT-proBNP II, Roche, Basel, Switzerland) and a 6-min walk test. Patients were discussed at the local heart team meeting and considered to be at prohibitive risk for surgery. Therefore, an interventional approach for TR treatment on a compassionate use basis was suggested. Considerations for patient selection were previously reported (7,10). All patients gave written informed consent, and this analysis was approved by the local ethics committee.

ECHOCARDIOGRAPHY. All echocardiograms were performed on a GE Vivid E9 (GE Healthcare, Chicago, Illinois) according to current guidelines by the European Association of Cardiovascular Imaging and American Society of Echocardiography and analyzed from stored images by an experienced operator blinded to procedural details (12). The detailed imaging protocol has been described previously (7). In brief, grading of TR severity was based on the assessment of vena contracta, effective regurgitation orifice area (EROA), and estimated regurgitant volume, and TR severity grades of mild, moderate, and severe were extended by a grade IV (massive or torrential according to previous publications (8,13). For post-procedural assessment of TR EROA, the largest flow convergence zone was used for calculation, whereas post-procedural venae contractae is given as the sum of all visualized venae contractae.

RV function was assessed using tricuspid annular plane systolic excursion (TAPSE) and fractional area change. In patients with evaluable tissue Doppler imaging parameters at all 3 time points (n = 18), additionally peak myocardial velocity at the lateral tricuspid annulus, the load-independent parameter of RV isovolumic acceleration (i.e., isovolumic peak velocity divided by isovolumic acceleration time), and RV ejection time were assessed as previously described (14). Additionally, tissue Doppler-based

myocardial velocities during ventricular inflow at the lateral TV annulus (n = 18) and the septal and lateral mitral valve annulus (n = 20) were assessed. Mitral valve and TV inflow velocities were recorded using pulsed wave Doppler imaging in the 4-chamber view. To assess interventricular interaction, left ventricular (LV) eccentricity index, defined as the ratio of the LV anteroposterior to septolateral diameters in a short-axis view, were measured at end-systole and end-diastole, with values >1 indicating leftward bowing of the interventricular septum (14). RV to right atrial (RA) pressure gradient was calculated from the continuous wave Doppler profile of the TR jet, and RV systolic pressures were assessed by adding estimated RA pressure from imaging the inferior vena cava as recently suggested (12). Measurements were performed on 3 consecutive cardiac cycles, and the average of these values was calculated.

CARDIAC MAGNETIC RESONANCE. CMR was performed after a standardized protocol as described previously (15). Patients with pacemaker or implantable cardioverter-defibrillator devices (n = 10) were excluded from CMR. In brief, patients were examined with a 1.5-T scanner (Intera, Philips Healthcare, Eindhoven, the Netherlands). Retrospective gated steady-state free-precession cine images were acquired in the vertical long-axis view, 4-chamber view, and short-axis views covering the entirety of both ventricles. Aortic and pulmonary flow data were acquired with a flow-sensitive gradient echo sequence during free breathing. Assessment of LV and RV volumes was performed by manually defining the endocardial outline at end-diastole and end-systole in each of the short-axis cine images (cmr42, Circle Cardiovascular Imaging, Calgary, Canada). LV and RV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using the slice summation method. The stroke volume (SV) was the difference between EDV and ESV, and ejection fraction (EF) was SV divided by EDV expressed as a proportion. An effective LVSV was calculated to reflect the net forward blood flow into the aorta as follows: effective LVSV = total aortic forward flow − aortic backward flow. Effective RVSV was calculated accordingly: effective RVSV = total pulmonary forward flow - pulmonary backward flow. Mitral regurgitation fraction was calculated as follows: (total LVSV − total aortic forward flow / total LVSV) · 100. Tricuspid regurgitation was calculated as: ([total RVSV − total pulmonary forward flow]/total RVSV) · 100. The cardiac index was calculated from effective stroke volumes and heart rates. All volumes and flow measurements were indexed for body surface area and expressed in ml/m^2.

TTVR USING THE MitraClip SYSTEM. Procedural details haven been described previously (7). TTVR was performed under general anesthesia with interventional guidance by transesophageal echocardiography and fluoroscopy via the right femoral vein, the inferior vena cava, and the RA. The clip delivery system was aligned perpendicular to the targeted commissure. Transesophageal echocardiography multiplane imaging, including trans-gastric views, was used to confirm correct clip and leaflet grasping. More than 1 clip was used if satisfactory reduction of TR was not achieved after implantation of the first clip. Invasive RA and systemic pressures were recorded before and after the procedure while under general anesthesia.

FOLLOW-UP EXAMINATIONS. Patients were seen for follow-up visits at our hospital at 1 and 6 months after the procedure. On each visit, symptoms were recorded and a physical examination was performed. All patients underwent repeated 6-min walk test, transthoracic echocardiography, laboratory analysis, and CMR in absence of contraindications.

STATISTICAL ANALYSIS. Data for continuous variables are presented as mean ± SD or median (interquartile range [IQR]). Categorical variables are presented as frequencies and proportions. Comparisons before and after TTVR were made with Friedman 2-way analysis of variance by ranks. Between-group differences were compared with Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. Correlations between parametric variables was assessed by Spearman's rho. Assuming a baseline cardiac output of 2.2 l/min/m^2 (10), an increase of 15% with a SD of 0.6 l/min/m^2 at a power of 80% required 18 patients (2-sided Student's *t*-test). Statistical significance was inferred when $p < 0.05$.

RESULTS

BASELINE CHARACTERISTICS. We studied 29 patients (55% men, mean age 78 ± 4 years) with isolated TR. Baseline data are summarized in Table 1. Patients had multiple comorbidities and were at high surgical risk (mean European System for Cardiac Operative Risk Evaluation II 10.6%). Etiology of the TV disease was functional in 93% and mixed in 7% of cases. Eight patients presented with HF with reduced EF and 5 patients who presented with preserved LVEF (i.e., >50%) had prior valve interventions as potential cause for TR. Thirteen patients had invasively

TABLE 1 Baseline Characteristics

	All Patients (N = 29)	CMR+ Patients (n = 18)	CMR- Patients (n = 11)	p Value
Age, yrs	78.4 ± 4.0	78.3 ± 4.2	78.5 ± 4.0	0.71
Female	13 (45)	9 (50)	4 (36)	0.70
BMI, kg/m²	26.4 ± 4.3	26.7 ± 4.1	25.9 ± 4.8	0.62
EuroSCORE II, %	10.6 ± 10.5	10.7 ± 12.6	10.4 ± 6.0	0.39
Chronic dialysis	1 (3)	1 (6)	0 (0)	0.99
Coronary artery disease	14 (48)	8 (44)	6 (55)	0.71
Previous MI	3 (10)	3 (17)	0 (0)	0.27
Previous PCI	8 (28)	5 (28)	2 (27)	0.99
Previous CABG	6 (21)	4 (22)	2 (18)	0.99
Previous valve intervention	6 (21)	4 (22)	2 (18)	0.99
Atrial fibrillation	27 (93)	16 (89)	11 (100)	0.51
Arterial hypertension	28 (97)	18 (100)	10 (91)	0.38
Previous/current smoking	11 (38)	5 (28)	6 (55)	0.24
Diabetes mellitus	14 (48)	9 (50)	5 (46)	0.99
Chronic lung disease	8 (28)	4 (22)	4 (36)	0.43
RV lead present	10 (35)	0 (0)	10 (91)	<0.01
HFrEF	8 (28)	3 (17)	5 (46)	0.20
HFpEF	13 (45)	9 (50)	4 (36)	0.70
RV FAC <35%	11 (38)	7 (39)	4 (36)	0.60
TAPSE <17 mm	19 (66)	6 (55)	13 (72)	0.43
PAP systolic >50 mm Hg	14 (48)	10 (56)	4 (36)	0.45
PAP mean >25 mm Hg	20 (69)	12 (67)	8 (73)	0.99
Symptom duration, months	17.3 ± 13.2	15.1 ± 12.1	22.3 ± 14.9	0.29
HF hospitalization previous 6 months	24 (83)	15 (83)	11 (82)	0.99
NYHA functional class II NYHA functional class III NYHA functional class IV	6 (21) 16 (55) 7 (24)	4 (22) 11 (61) 3 (17)	2 (18) 5 (46) 4 (36)	0.48
Peripheral edema	22 (76)	13 (72)	9 (82)	0.68
Ascites	9 (31)	4 (22)	5 (45)	0.24
NT-proBNP, ng/l	7,480 ± 12,083	8,774 ± 14,946	5,363 ± 4,595	0.84
6-min walk distance, m	268.5 ± 131.1	270.7 ± 132.7	264.4 ± 135.1	0.81
ACE inhibitor/ARB	29 (100)	18 (100)	11 (100)	0.99
Beta-blocker	28 (97)	17 (94)	11 (100)	0.99
Loop diuretic agents	29 (100)	18 (100)	11 (100)	0.99
Furosemide equivalent dose, mg	71.4 ± 55.8	66.7 ± 50.0	79.1 ± 67.3	0.57
Thiazide diuretic agent	7 (24)	5 (28)	2 (18)	0.68
Aldosterone antagonist	7 (24)	2 (11)	5 (46)	0.07

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; CMR = cardiac magnetic resonance; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FAC = fractional area change; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PCI = percutaneous coronary intervention; RV = right ventricular; TAPSE = tricuspid annular peak systolic excursion.

diagnosed HF with preserved EF and the 3 remaining patients showed tricuspid annular dilatation in the context of long-standing atrial fibrillation.

Patients were highly symptomatic, predominantly in NYHA functional classes III and IV, a markedly reduced 6-min walk test and highly elevated NT-proBNP levels (Table 1). A significant proportion of patients had peripheral edema, pleural effusion, or ascites, and all patients were on diuretic therapy. Neither baseline characteristics nor echocardiographic parameters differed significantly between patients with and without serial CMR assessment (Table 1).

Clinical assessment and imaging were realized in median 4 (IQR: 2 to 20) days before the intervention and 27 (IQR: 11 to 90) days and 118 (IQR: 83 to 186) days after the procedure.

PROCEDURAL RESULTS. All patients underwent successful clip deployment in the TV, and thereby a total of 59 clips were implanted (1 clip in 14%, 2 clips in 69%, 3 clips in 17% of patients). All patients but 1 were clipped between the anterior and septal leaflet. An additional posterior septal leaflet clipping was realized in 5 patients and 1 patient received 2 clips exclusively to the septal posterior commissure. Acutely, mean RA pressures were reduced from 13.9 ± 7.7 mm Hg to 11.6 ± 6.7 mm Hg ($p = 0.01$) with significant increases in systemic blood pressures (systolic from 121.8 ± 16.2 mm Hg to 127.6 ± 15.2 mm Hg; $p = 0.01$; diastolic from 82.8 ± 12.3 mm Hg to 86.5 ± 11.0 mm Hg; $p = 0.01$).

ECHOCARDIOGRAPHY. TR grade could be reduced to at least moderate in all but 1 patient. In this patient, clip deployment lead to a reduction of TR severity in terms of EROA (from 1.1 cm^2 to 0.6 cm^2) and estimated regurgitant volume (from 56 ml to 42 ml); however, this fell still within the diagnostic limits of severe TR. Overall, TR was reduced with a decrease in vena contracta from 9.8 ± 2.7 mm to 5.6 ± 1.5 mm, EROA from 0.6 ± 0.3 cm^2 to 0.2 ± 0.1 cm^2, and estimated regurgitant volume from 51 ± 17 ml to 21 ± 9 ml (Table 2). Estimated RV systolic pressure remained unchanged (50 ± 15 mm Hg vs. 51 ± 12 mm Hg; $p = 0.52$).

RV inflow velocity increased, as did the mean TV gradient without significant stenosis in any patient. Mitral inflow velocities increased as a result of improved LV filling (105 ± 35 cm/s vs. 120 ± 41 cm/s; $p < 0.01$). At the same time, diastolic LV myocardial tissue velocities did not change proportionally, which led to an increase of the ratio between inflow velocity and myocardial velocity during ventricular inflow (E/e': 14.3 ± 6.2 vs. 16.7 ± 6.2; $p < 0.01$). Biventricular function (as assessed by LVEF, RV fractional area change, TAPSE, RV peak systolic myocardial velocity at the lateral tricuspid annulus, and RV isovolumic acceleration) remained unchanged, whereas normalized RV ejection time decreased (422 ± 81 ms vs. 389 ± 80 ms; $p = 0.01$). LV eccentricity index showed

TABLE 2 Echocardiographic Results

	Baseline (n = 18)	1 Month (n = 18)	6 Months (n = 18)	p Value	Baseline vs. 1M	Baseline vs. 6M	1M vs. 6M
Heart rate, beats/min	72.1 ± 12.8	71.8 ± 10.1	72.3 ± 11.8	0.57			
LVEF, %	52.0 ± 12.6	53.2 ± 10.7	52.4 ± 10.8	0.60	0.42	0.80	0.44
LV eccentricity index diastole ratio	1.32 ± 0.20	1.12 ± 0.09	1.14 ± 0.11	<0.01	<0.01	<0.01	0.68
LV eccentricity index systole ratio	1.04 ± 0.07	1.05 ± 0.08	1.04 ± 0.05	0.72	0.54	0.82	0.45
RV FAC, %	39.7 ± 8.8	38.7 ± 7.7	36.8 ± 8.2	0.07	0.45	0.07	0.06
TAPSE, mm	16.1 ± 4.8	15.9 ± 4.3	16.5 ± 4.5	0.68	0.82	0.68	0.38
RA area, cm^2	40.4 ± 9.1	36.1 ± 9.2	36.2 ± 9.5	<0.01	<0.01	<0.01	0.94
RA-RV pressure gradient maximum, mm Hg	38.1 ± 16.0	41.9 ± 12.8	38.9 ± 13.0	0.17	0.11	0.77	0.16
Estimated RV systolic pressure, mm Hg	49.8 ± 14.7	51.1 ± 12.2	48.1 ± 12.3	0.37	0.52	0.49	0.16
TR vena contracta, mm	9.8 ± 2.7	5.6 ± 1.5	5.7 ± 1.9	<0.01	<0.01	<0.01	0.44
TR EROA PISA, cm^2	0.6 ± 0.3	0.2 ± 0.1	0.3 ± 0.3	<0.01	<0.01	<0.01	0.20
TV regurgitant volume, ml	51.1 ± 16.5	20.6 ± 9.3	23.4 ± 7.9	<0.01	<0.01	<0.01	0.09
TV Pmean, mm Hg	1.0 ± 0.5	1.9 ± 0.5	2.1 ± 0.8	<0.01	<0.01	<0.01	0.06
TV S'-wave velocity, cm/s	9.7 ± 3.4	9.0 ± 3.2	8.8 ± 3.2	0.33	0.14	0.13	0.32
TV e'-wave velocity, cm/s	10.3 ± 3.4	9.2 ± 3.4	9.3 ± 3.5	0.33	0.13	0.19	0.81
TV E-wave velocity, cm/s	98.7 ± 35.4	117.4 ± 31.6	113.3 ± 34.6	<0.01	<0.01	<0.01	0.83
RV isovolumic acceleration, m/s^2	1.43 ± 0.48	1.39 ± 0.35	1.42 ± 0.35	0.46	0.38	0.90	0.53
RV ejection time, normalized, ms	422 ± 81	389 ± 80	374 ± 53	0.01	0.04	0.01	0.30
MV E-wave velocity, cm/s	105.4 ± 34.8	120.4 ± 40.7	117.0 ± 42.1	<0.01	<0.01	<0.01	0.18
MV e' septal velocity, cm/s	5.4 ± 1.8	5.0 ± 1.3	5.3 ± 1.2	0.40	0.25	0.55	0.36
MV e' lateral velocity, cm/s	9.4 ± 3.1	9.2 ± 2.8	9.2 ± 2.7	0.84	0.58	0.63	0.99
MV E/e' septal ratio	19.6 ± 8.6	23.3 ± 7.7	21.9 ± 8.5	0.05	0.01	0.10	0.31
MV E/e' lateral ratio	11.4 ± 5.0	13.3 ± 5.6	13.0 ± 6.3	0.01	0.01	0.03	0.69
MV E/e' mean ratio	14.3 ± 6.2	16.7 ± 6.2	16.1 ± 6.7	0.01	<0.01	0.03	0.46
Mitral regurgitation							
Grade 0	3 (10)	2 (7)	2 (7)	0.16	0.99	0.16	0.16
Grade 1	21 (72)	21 (75)	19 (68)				
Grade 2	5 (17)	5 (18)	7 (25)				
TR							
Grade 1	0 (0)	9 (32)	9 (32)	<0.01	<0.01	<0.01	0.49
Grade 2	0 (0)	18 (64)	16 (57)				
Grade 3	26 (90)	1 (4)	3 (11)				
Grade 4	3 (10)	0 (0)	0 (0)				

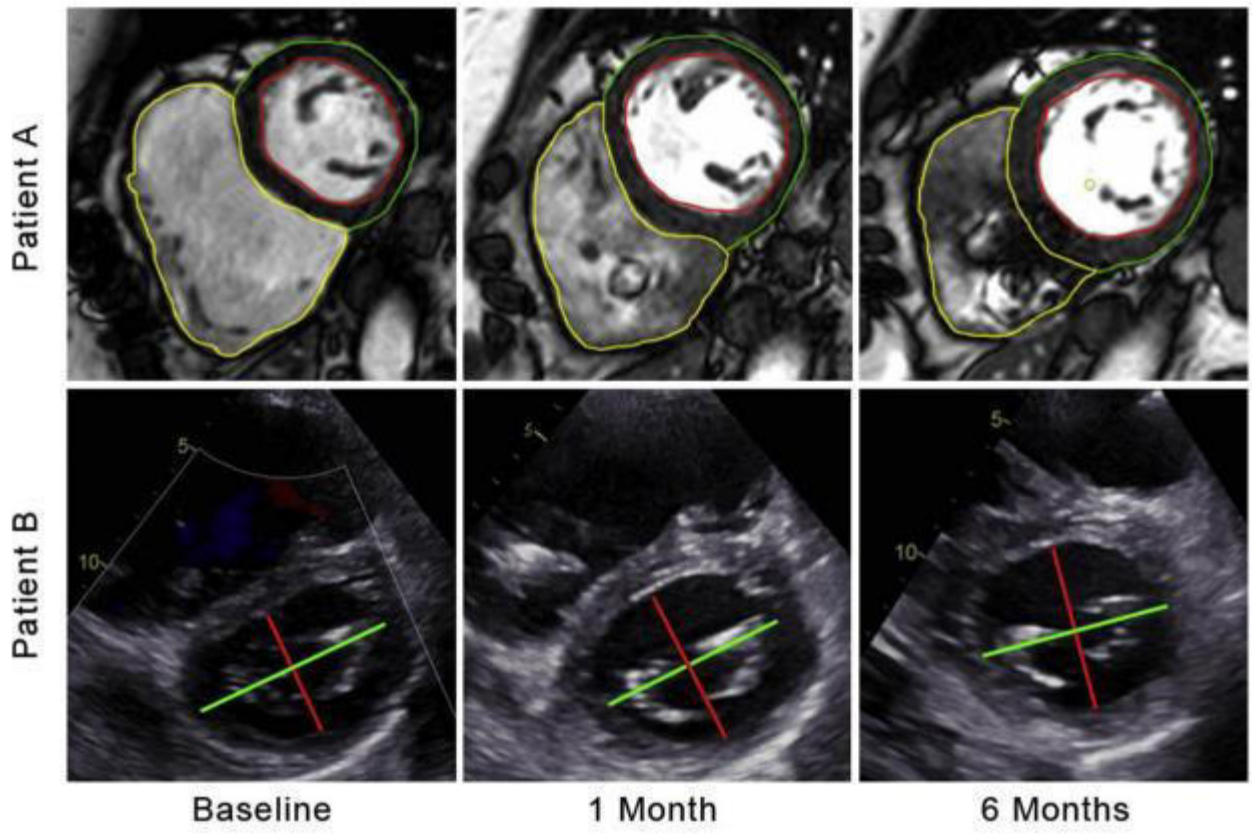
Values are mean ± SD or n (%).

1M = 1 month; 6M = 6 months; e' = diastolic myocardial tissue velocity; E/e' = ratio of inflow velocity and diastolic myocardial tissue velocity; EF = ejection fraction; EROA = effective regurgitation orifice area; LV = left ventricular; MV = mitral valve; Pmean = mean pressure gradient; PISA = proximal isovelocity surface area; RA = right atrium; S' = peak systolic myocardial velocity; TR = tricuspid regurgitation; TV = tricuspid valve; other abbreviations as in Table 1.

diastolic leftward deviation of the interventricular septum, which was reduced after TTVR (Figure 1, Table 2). LV systolic eccentricity index was altered neither at baseline nor during follow-up visits. Echocardiographic results remained stable at 6-month follow-up (Table 2).

CARDIAC MAGNETIC RESONANCE. Ten patients presented with RV lead and were excluded from CMR. Additionally, 1 female patient without RV lead died before the first follow-up visit, also precluding her from repeated CMR. Therefore, eighteen patients underwent serial CMR assessments at 3 time points. Results are displayed in Table 3 and Figures 1 and 2. Repeated CMR revealed a marked reduction in TR fraction with sustained effect over time (41 ± 9% vs. 21 ± 5% vs. 21 ± 7%; $p < 0.01$). RV end-diastolic volumes (126 ± 29 ml/m^2 vs. 112 ± 32 ml/m^2 vs. 112 ± 34 ml/m^2; $p < 0.01$) and RV stroke volumes (57 ± 13 ml/m^2 vs. 51 ± 13 ml/m^2 vs. 49 ± 13 ml/m^2; $p = 0.02$) decreased, whereas effective forward flow in the pulmonary artery increased (33 ± 10 ml/m^2 vs. 36 ± 9 ml/m^2 vs. 37 ± 9 ml/m^2; $p = 0.03$). The change in effective RVSV was inversely correlated with the change in TR fraction ($r = -0.72$; $p = 0.01$) (Figure 3). The enhanced RV forward flow was accompanied by a volume shift to the left as LVEDV increased

FIGURE 1 Changes in End-Diastolic Biventricular Volumes and Ventricular Interaction



(Top row) Cardiac magnetic resonance steady-state free precession imaging short-axis imaging (end-diastole) demonstrating reduction in right ventricular (RV) size and more physiological septal curvature during follow-up; the **yellow line** indicates RV endocardial borders, the **green line** indicates left ventricular (LV) epicardial borders, and the **red line** indicates RV endocardial borders. **(Bottom row)** Transthoracic echocardiographic short-axis images of the LV below the mitral valve (end-diastole) demonstrating a decrease in LV eccentricity during follow-up as visible by a relative increase of septolateral diameter **(red)** to the anteroposterior diameter **(green)**.

(79.7 ± 25.2 ml/m² vs. 85.8 ± 29.5 ml/m² vs. 86.0 ± 31.4 ml/m²; p = 0.01). Mitral regurgitant fraction was unchanged (18 ± 7% vs. 17 ± 8% vs. 16 ± 7%; p = 0.20). RA volumes decreased numerically without reaching statistical significance (103.0 ± 41.6 ml/m² vs. 99.1 ± 43.0 ml/m² vs. 92.8 ± 36.9 ml/m²; p = 0.38) and LA volumes were unchanged (95 ± 47 ml/m² vs. 96 ± 45 ml/m² vs. 95 ± 49 ml/m²; p = 0.89).

The changes in cardiac output were comparable between patients with pulmonary artery pressures ≤50 mm Hg (n = 10; 2.2 ± 0.7 mm Hg vs. 2.7 ± 0.7 mm Hg vs. 2.6 ± 0.7 mm Hg) and those >50 mm Hg (n = 8; 2.3 ± 0.5 mm Hg vs. 2.6 ± 0.5 mm Hg vs. 2.6 ± 0.5 mm Hg).

The increase in effective LVSV (33 ± 9 ml/m² vs. 38 ± 10 ml/m² vs. 37 ± 9 ml/m²; p = 0.02) resulted in an augmentation of cardiac index at short-term and at 6-month follow-up (2.2 ± 0.6 l/m²/min vs. 2.7 ± 0.6 l/m²/min vs. 2.6 ± 0.6 l/m²/min; p < 0.01) at comparable heart rates (70 ± 16 beats/min vs. 72 ± 11 beats/min vs. 71 ± 10 beats/min; p = 0.82). Biventricular EFs remained stable (LVEF: 55 ± 12% vs. 56 ± 7% vs. 55 ± 10%; p = 0.51; RVEF: 46 ± 9% vs. 46 ± 10% vs. 43 ± 8%; p = 0.40).

CLINICAL FOLLOW-UP. Follow-up for clinical events was completed for all patients. Overall, there were 10 (35%) patients experiencing a clinical event during 6 months after TTVR. Two (7%) patients died. One patient experienced a malignant stroke 7 days after successful isolated TTVR, and another patient, who was on chronic dialysis and who showed a good interventional result after 1 month, was admitted to the hospital because of inflammatory signs and

TABLE 3 CMR Results

	Baseline (n = 18)	1M (n = 18)	6M (n = 18)	p Value	Baseline vs. 1M	Baseline vs. 6M	1M vs. 6M
Heart rate, beats/min	69.8 ± 15.8	72.0 ± 10.8	71.4 ± 9.7	0.82	0.57	0.71	0.77
LA index, ml/m²	94.8 ± 47.3	95.9 ± 44.5	95.3 ± 49.1	0.89	0.61	0.77	0.84
RA index, ml/m²	103.0 ± 41.6	99.1 ± 43.0	92.8 ± 36.9	0.38	0.60	0.17	0.35
LV mass index, g/m²	115.4 ± 34.1	116.2 ± 30.5	116.1 ± 34.8	0.90	0.69	0.73	0.96
RVEDV index, ml/m²	125.6 ± 28.9	112.4 ± 32.0	112.3 ± 33.9	<0.01	<0.01	0.01	0.98
RVESV index, ml/m²	68.5 ± 24.6	64.2 ± 25.6	65.5 ± 28.0	0.28	0.15	0.48	0.61
RVSV index, ml/m²	57.0 ± 13.4	51.4 ± 12.5	49.2 ± 12.8	0.02	0.04	0.01	0.24
RVEF, %	45.9 ± 8.7	45.8 ± 10.2	43.1 ± 8.0	0.40	0.95	0.25	0.26
RVSV effective index, ml/m²	33.4 ± 9.9	37.5 ± 9.3	36.8 ± 8.9	0.03	0.01	0.05	0.67
LVEDV index, ml/m²	79.7 ± 25.2	85.8 ± 29.5	86.0 ± 31.4	0.01	<0.01	0.01	0.88
LVESV index, ml/m²	37.0 ± 20.1	38.5 ± 20.5	40.5 ± 27.7	0.42	0.23	0.20	0.32
LVSV index, ml/m²	42.7 ± 12.0	47.3 ± 12.1	45.5 ± 10.1	0.05	0.01	0.13	0.24
LVEF, %	54.8 ± 12.3	56.4 ± 7.2	55.4 ± 10.0	0.51	0.39	0.77	0.43
LVSV effective index, ml/m²	33.4 ± 9.1	37.5 ± 9.8	36.8 ± 8.6	0.02	0.01	0.05	0.66
Aortic regurgitant fraction, %	4.1 ± 4.7	4.2 ± 4.2	3.2 ± 5.2	0.53	0.92	0.26	0.32
Pulmonary regurgitant fraction, %	2.8 ± 3.7	1.8 ± 1.6	1.0 ± 1.6	0.18	0.25	0.10	0.10
Mitral regurgitant fraction, %	18.1 ± 6.5	17.0 ± 7.6	16.2 ± 7.0	0.20	0.17	0.16	0.56
Tricuspid regurgitant fraction, %	40.7 ± 9.1	21.1 ± 5.2	21.7 ± 6.7	<0.01	<0.01	<0.01	0.73
Qp/Qs ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.96	0.83	0.99	0.81
Cardiac index, ml/min/m²	2.2 ± 0.6	2.7 ± 0.6	2.6 ± 0.6	<0.01	<0.01	<0.01	0.52

Values are mean ± SD.
EDV = end-diastolic volume; ESV = end-systolic volume; LA = left atrial; SV = stroke volume; other abbreviations as in Tables 1 and 2.

decompensation 53 days after TTVR. Fluid overload was managed successfully and the patient was treated for suspected endocarditis (new vegetations on mitral and aortic valves). Although no microbiological evidence of bacteremia could be achieved and broad-spectrum antibiotic treatment was initiated in a timely fashion, the patient died 78 days after TTVR. Another patient experienced a nonfatal stroke 104 days after tricuspid clipping despite being on oral anticoagulation for persisting atrial fibrillation. Eight (28%) patients were admitted for HF decompensation, whereas, in the same time before TTVR, 24 (83%) of patients had been admitted for decompensated HF.

Although 80% of patients were predominantly in NYHA functional classes III and IV before the intervention, NYHA functional class improved in all but 5 patients (who stayed in class III) with 72% of patients in functional class I and II. At 6 months, subjective dyspnea further improved in 7 patients and deteriorated in 5 patients, with overall 80% of patients being in NYHA functional classes I and II (Central Illustration).

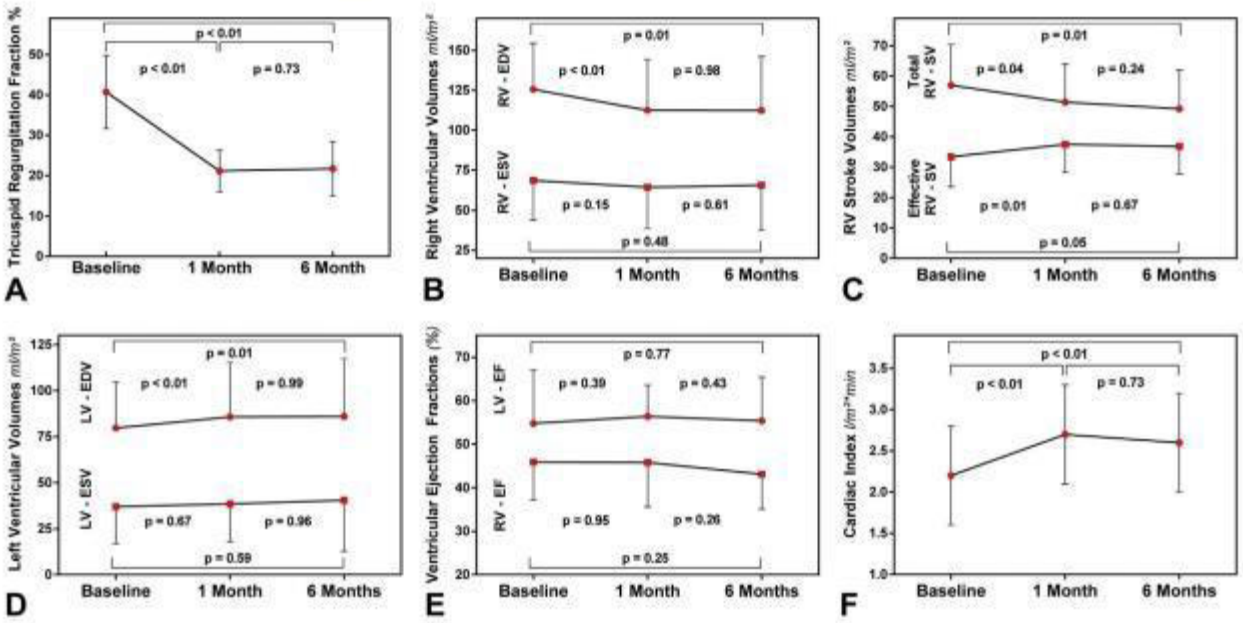
Six-min walk distance increased by 20% and 22% at 1 and 6 months, respectively. The number of patients reporting peripheral edema and the finding of ascites on physical examination decreased accordingly (edema: from 76% to 57% to 44%; $p < 0.01$; ascites: from 31% to 18% to 16%; $p = 0.04$). Median NT-proBNP values declined numerically without reaching statistical significance (Central Illustration). This was true regardless of RV function. In fact, the NT-proBNP reduction was more pronounced in patients with an impaired TAPSE (TAPSE ≥17 mm, n = 7: 2,150 [IQR: 1,312 to 3,466] ng/l vs. 2,508 [IQR: 1,417 to 5,013] ng/l vs. 1,880 [IQR: 1,775 to 4,592] ng/l; $p = 0.87$; and TAPSE <17 mm, n = 15: 5,951 [IQR: 3,037 to 7,507] ng/l vs. 2,229 [IQR: 951 to 8,863] ng/l vs. 2,153 [IQR: 845 to 7,082] ng/l; $p = 0.16$ for baseline, 1-month, and 6-month assessment, respectively).

Median loop diuretic dosage numerically declined (furosemide equivalent dose: 60 [IQR: 33 to 100] mg vs. 50 [IQR: 25 to 100] mg vs. 40 [IQR: 20 to 75] mg; $p = 0.09$) with reduction in dosage in 9 patients at 1 month and 6 months and increases in dosages in 5 and 6 patients at 1 month and 6 months, respectively.

DISCUSSION

The present study investigated physiological adaptations and clinical results of the relatively novel

FIGURE 2 Cardiac Magnetic Resonance Imaging Results



Results for **(A)** Tricuspid regurgitant fraction, **(B)** RV volume, **(C)** RV stroke volume (SV), **(D)** LV volumes **(E)** biventricular ejection fraction (EF), and **(F)** cardiac index. EDV = end-diastolic volume; ESV = end-systolic volume; other abbreviations as Figure 1.

treatment strategy of TTVR in patients with isolated TR at high surgical risk and right heart failure.

The main findings are: 1) TTVR is effective in reducing TR severity using a multimodal imaging approach; 2) reduction of TR regurgitant volume reduces RV volume overload with a reduction in RV diastolic dimensions and total RVSV at preserved RV function; 3) the reduction in TR regurgitant volume leads to an augmentation of pulmonary forward flow with subsequent enhanced LV filling and improvements in cardiac index; and 4) improved physiology is associated with better functional status up to 6 months in a high-risk patient cohort.

CLINICAL PROBLEM OF SEVERE TR. Recently, the cardiovascular community has shifted its focus toward the TV as data are accumulating that patients with isolated TR or residual TR following treatment of left-sided valvular pathologies face a poor prognosis (1-3,16). A high prevalence in combination with the low incidence of surgery for severe TR and a stagnant, but relevant operative mortality (4-6) has created a large population of patients in need of percutaneous, innovative therapies to improve clinical outcome of TR.

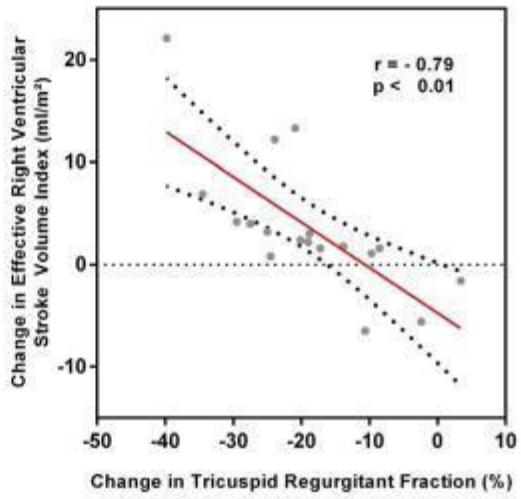
HEMODYNAMIC AND CLINICAL EFFECTS OF TTVR. The hemodynamic and to a lesser extent the morphological impact of TR correction have been hard to study because of the confounding effects of cardiac surgery (e.g., cardiopulmonary bypass, left-sided interventions) and the limitations of echocardiography in reliably quantifying RV dimensions and function.

The use of TTVR in patients with isolated TR and CMR assessment before and after the procedure in our study permits, for the first time, investigation of the direct effects of reduction in chronic RV volume overload on cardiac function and clinical status.

In keeping with previous reports on patients undergoing TTVR (8,10), patients in the present study were at an advanced age, were highly symptomatic despite optimal medical therapy, and presented with many comorbidities and a high perioperative risk profile. Almost one-half of the patients demonstrated pulmonary hypertension and right heart chamber dilatation, which can be seen as a compensatory mechanism in the presence of volume overload to maintain forward SV. However, and despite the fact that over two-thirds of patients had normal LV function, cardiac index was markedly reduced.

TTVR led to reduced RVEDV, whereas RVESV remained unchanged. These observations can be explained by reduced RV volume overload on the one hand and unchanged RV afterload on the other hand (17,18). Although total RVSV fell due to reduced regurgitant volume, the effective forward flow increased. With enhanced forward flow and despite presence of pulmonary hypertension in two-thirds of patients, RA to RV pressure gradients and estimated RV systolic pressures did not increase significantly and load-dependent and load-independent markers of RV performance did not deteriorate. In this context, it is important to note that the intervention did not eliminate TR completely, while leaving all patients with at least mild-to-moderate TR. The reduction in RVSV and RV ejection duration at maintained low pressures indicates a reduction in external work of the RV. At the same time effective RVSV increased, leading to a more efficient RV performance, which in turn should reduce myocardial oxygen consumption. Together, these findings imply a shift of the RV from a decompensated state to a more compensated limb of the Frank-Starling curve by the decrement in TV regurgitant volume.

FIGURE 3 **Relationship between Change in Tricuspid Regurgitant Fraction and Change in Effective Right Ventricular Stroke Volume**



Data are presented as regression line **(red)** with 95% confidence interval **(black dots)**. **Grey dots** indicate data for each individual patient.

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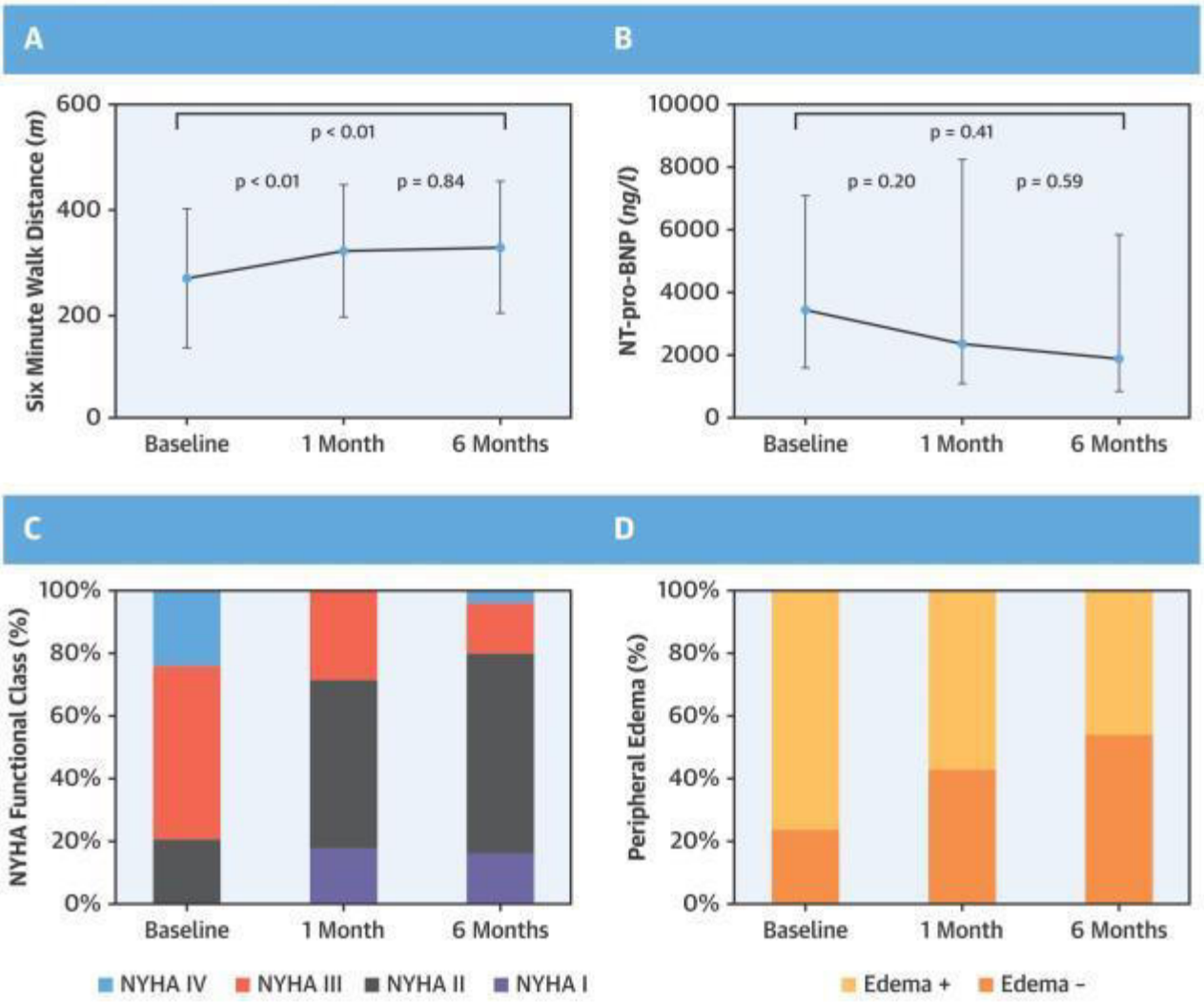
The benefits of the reduction of RV volume overload could also be noted in the LV: there was an increase in LVEDV and LVSV. Consequently, cardiac output at rest increased after 1 month with no further improvements after 6 months. We interpret these findings as enhancement of LV preload through augmented pulmonary flow after TTVR in the context of chronic "latent LV under filling" (19) and improvements in ventricular interaction as suggested from less leftward deviation of the septum during diastole (as a result of lower diastolic RV volumes and pressures and improvements in interventricular mechanical delay) (20). The preload augmentation leads to an increase in myocardial stretch and thus SV. LVEF did not change with increased ratio of LV inflow velocity and diastolic myocardial velocity during ventricular inflow, as a marker of LV filling pressures, indicating that an augmentation of cardiac index comes at the price of elevated LV filling pressures in this old and comorbid patient cohort. However, given the fact that the changes in RV and LV function were accompanied by improvements in both subjective and objective measures of symptoms and exercise performance, the increase in filling pressures should be less clinically relevant than RV volume overload.

Overall, the described short-term changes are a consequence of altered RV preload and mirror those of surgical TR reduction (21) and those of percutaneous pulmonary valve implantation (17,18) as a different model of short-term reduction in RV volume overload.

Although not compared with a control condition, the observation of symptomatic and functional improvement in our patients bares the hope that TTVR is not only effective in reducing TR, but could also have an effect on patients' clinical course during follow-up. Especially the increase in patients' walking distance is encouraging. Exercise intolerance is one of the clinical cornerstones of TR and is related to low cardiac output reserve and low LV preload (19). As demonstrated, TTVR improves both cardiac output and LV filling, explaining the patients' improved functional status.

Interestingly, there is no evidence for further structural or functional improvement during the 6-month follow-up beyond short-term changes. Conceptually, short-term changes should be a consequence of altered RV preload and are likely to occur immediately after intervention (22). This is supported by the lack of changes in isovolumic acceleration as an estimate for load-independent contractility (14). Later changes should reflect the potential for positive reverse remodeling, which did not occur during the first 6 months in our cohort. Factors that could have limited positive remodeling at 6 months in the present study are multifactorial and could include: 1) insufficient TR reduction to allow for positive remodeling; 2) TTVR being

CENTRAL ILLUSTRATION Clinical and Functional Outcomes



Rommel, K.-P. et al. J Am Coll Cardiol Intv. 2019;12(15):1423-34.

Development of **(A)** 6-min walk distance, **(B)** N-terminal pro-B-type natriuretic peptide (NT-proBNP), **(C)** New York Heart Association (NYHA) functional class, and **(D)** frequency of peripheral edema from baseline to follow-up. Data are presented as mean ± SD in **A**, median with interquartile range in **B**, and frequency in **C and D**.

performed too late when consequences of chronic RV volume overload might have become irreversible; and 3) patients not being followed up for long enough, with adverse RV remodeling in these chronically ill patients being reversible only in the long term. Either way, the initial RV load depended improvements were well maintained at 6 months.

STUDY LIMITATIONS. First, the sample size is clearly limited and one-third of patients were not assessed by CMR. Given the relatively young field of TTVR, the applied methods and the echocardiographic and clinical improvements in all patients, we believe that our results are suitable to give insights into physiological consequences of the procedure. Second, the follow-up period was only 6 months, which precludes definitive conclusions on reverse remodeling and the evaluation of hard clinical endpoints. Third, the study lacks a control group. However, as all patients were on diuretic agents before the intervention, it seems unlikely that further hemodynamic improvements could have been achieved by conservative therapy alone. TTVR produces multiple TR jets. In this scenario, no echocardiographic quantitative estimation of TR has been validated up to

date. In the future, a head-to-head comparison of CMR and echocardiography-based TR quantification in a larger cohort of patients could help to establish reliable echocardiographic TR quantification after TTVR.

The comparable improvements in cardiac output on CMR in patients without and with overt pulmonary hypertension is encouraging for the latter cohort. However, the limited number of patients prohibits any conclusions and potential differing implications of TTVR in patients with and without pulmonary hypertension, which need assessment in larger trials.

Last, metal-induced magnetic field inhomogeneity may impede CMR evaluation. However, biventricular endocardial borders could be delineated in all patients.

CONCLUSIONS

TTVR, for the first time, provides a pure model with which to study the effects of chronic RV volume overload in patients with severe TR. A biventricular assessment should enhance our present limited understanding of RV performance under unfavorable loading condition, inform on how to judge procedural success and suggest that focusing on effective SV rather than EF permits better interpretation of the physiology.

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PERSPECTIVES

WHAT IS KNOWN? Recent evidence suggests that TTVR is safe and feasible in patients with symptomatic TR at high surgical risk and associated with functional improvement early after the procedure.

WHAT IS NEW? The present analysis suggests that TTVR is associated with favorable biventricular physiology and demonstrates that effective stroke volumes and consequently cardiac output can be enhanced by percutaneously treating isolated TR. These changes explain clinical and functional improvements in patients undergoing TTVR.

WHAT IS NEXT? The present findings will serve as a reference on how to interpret changes in biventricular physiology and how to measure procedural success following transcatheter TR reduction. The ability of TTVR to reduce hard clinical outcomes in this high-risk patient group will have to be investigated in the light of achieved physiological improvements in larger prospective studies.

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KEY WORDS heart failure, MitraClip edge-to-edge repair, right ventricle, transcatheter therapy, tricuspid regurgitation

2.2.2 Effekt einer katheterbasierten Trikuspidalklappenrekonstruktion auf die Hospitalisierungsrate von Herzinsuffizienzpatienten

Zitierweise:

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CLINICAL RESEARCH

Transcatheter Edge-to-Edge Tricuspid Repair for Severe Tricuspid Regurgitation Reduces Hospitalizations for Heart Failure

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ABSTRACT

OBJECTIVES The goal of this study was to evaluate the effect of transcatheter edge-to-edge tricuspid valve repair (TTVR) for severe tricuspid regurgitation (TR) on hospitalization for heart failure (HHF) and HF-related endpoints.

BACKGROUND Patients with severe TR need effective therapies beyond conservative treatment. The impact of TTVR on HHF and HF-related endpoints is unknown.

METHODS Isolated TTVR was performed in 119 patients. Assessments were conducted of New York Heart Association functional class, 6-min walk distance, Minnesota Living with Heart Failure Questionnaire scores, N-terminal pro-B-type natriuretic peptide level, and medication. HHFs were analyzed in the preceding 12 months before and until the longest available follow-up after TTVR. Results were compared with those of 114 patients who underwent combined mitral and tricuspid valve repair.

RESULTS Procedural success with a reduction to moderate or less TR and no in-hospital death was achieved in 82% of patients. With a median follow-up of 360 days (interquartile range: 187 to 408 days), a durable TR reduction to moderate or less was achieved in 72% of patients ($p < 0.001$). TTVR reduced the annual rate of HHF by 22% (1.21 to 0.95 HHF/patient-year; $p = 0.02$), with concomitant clinical improvement in New York Heart Association functional class (patients in class II or lower: 9% to 67%; $p < 0.001$), 6-min walk distance (+39 m; $p = 0.001$), and Minnesota Living with Heart Failure Questionnaire score (−6 points; $p = 0.02$). N-terminal pro-B-type natriuretic peptide level decreased numerically by 783 pg/ml. Diuretic dose before TTVR was increased, but HF medication did not change after TTVR. Procedural success was associated with improved 1-year survival (79% vs. 60%; $p = 0.04$) and event-free-survival (death + first HHF: 67% vs. 40%; $p = 0.001$). Transcatheter mitral and tricuspid valve repair–treated patients had comparable outcomes.

CONCLUSIONS TTVR for severe TR is associated with a reduction of HHF and improved clinical outcomes.
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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

HF = heart failure

HHF = hospitalization for heart failure

MLHFQ = Minnesota Living with Heart Failure Questionnaire

MR = mitral regurgitation

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

RV = right ventricular

TMTVR = transcatheter mitral and tricuspid valve repair

TMVR = transcatheter mitral valve repair

TR = tricuspid regurgitation

TTVR = transcatheter edge-to-edge tricuspid valve repair

Severe tricuspid regurgitation (TR) is an unsolved clinical challenge in patients at prohibitive or high surgical risk and is associated with poor prognosis (1–4). The mutuality of secondary TR, tricuspid valve annular dilatation, and right ventricular (RV) dysfunction causes right-sided heart failure (HF) with repeat hospitalizations (5). Beyond limited symptomatic medical therapy with diuretic agents, tricuspid valve repair or replacement is a guideline-recommended technique in surgical candidates unless operative mortality risk related to RV dysfunction and other significant comorbidities have become limiting factors (6,7). Recent developments in valve therapy have made percutaneous tricuspid valve repair feasible in patients with prohibitive surgical risk. The first reports of transcatheter edge-to-edge tricuspid valve repair (TTVR) showed promising short- and mid-term results, with effective TR reduction and symptomatic improvement (8–13). Long-term improvement in HF-related symptoms and relevant endpoints such as hospitalization for HF (HHF) is unknown.

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The purpose of the current observational analysis was to investigate the impact of isolated TTVR on HHF. We hypothesized that HHFs would be reduced after TTVR as a consequence of TR reduction, RV unloading, and stabilization of fluid balance. In addition, we sought to assess the impact of TTVR on HF symptoms, exercise capacity, RV size and function, diuretic and HF medication, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels up to 12 months after the intervention. Furthermore, a second group of patients undergoing combined transcatheter mitral and tricuspid valve repair (TMTVR) was analyzed and compared versus patients with isolated TTVR.

METHODS

STUDY POPULATION. Patients with isolated TTVR procedures for severe TR, performed between December 1, 2015, and December 3, 2018, were included in this analysis. Patients were treated within compassionate use programs in 4 academic centers: St. Michael's Hospital, Toronto, Ontario, Canada; University Hospital of Zurich, Zurich, Switzerland; University Hospital of Ludwig-Maximilians University, Munich, Germany; and Heart Center Leipzig at the University of Leipzig, Leipzig, Germany. Clinical and anatomic inclusion and exclusion criteria were previously described (10,14). All patients were symptomatic with signs of right-sided HF as peripheral edema, ascites, pleural effusion, jugular vein distension, congestive renal failure, or shortness of breath as expressed by New York Heart Association (NYHA) functional class. All patients were deemed at prohibitive surgical risk by an interdisciplinary heart team and provided written informed consent. The local ethics committees at each institution approved the data analysis of patients treated with TTVR. As a comparison group, patients who received combined TMTVR for mitral regurgitation (MR) and TR over the same period were analyzed.

ECHOCARDIOGRAPHY. TR was graded as mild (1+), moderate (2+), or severe (3+) according to current recommendations, taking into account vena contracta width and effective regurgitant orifice area according to the proximal isovelocity surface area method (15). The RV systolic function was estimated with tricuspid annular plane systolic excursion and fractional area change. Cardiac chamber quantification followed current recommendations (16).

PROCEDURE. A transcatheter edge-to-edge repair system (MitraClip [Abbott, Santa Clara, California] or PASCAL [Edwards Lifesciences, Irvine, California])

Zurich, Zurich, Switzerland. *Drs. Orban, Rommel, and Ho contributed equally to this work. †Drs. Fam, Lurz, and Hausleiter contributed equally to this work as senior authors. Klinikum der Universität München has received grant support from Abbott Vascular. Dr. Connelly has received honoraria from Abbott. Drs. Braun and Nabauer have received speaker honoraria from Abbott Vascular. Dr. Miura has served as a consultant for Japan Lifeline. Dr. Zuber has received research support from VISCARDIA; and honoraria and consultation fees from Abbott, Cardiovalve, SwissVortex, Pfizer, Canon, and Edwards Lifesciences SA. Dr. Martin Orban has received speaker honoraria from Sedana Medical and AstraZeneca. Dr. Nabauer has received lecture fees from Abbott Laboratories and Edwards Lifesciences. Dr. Maisano has served as a consultant for Abbott Vascular, Edwards Lifesciences, Cardiovalve, Valtech, and Medtronic; and is cofounder of 4Tech. Dr. Taramasso is a consultant for Abbott Vascular, Boston Scientific, 4Tech, and CoreMedic; and has received speaker honoraria from Edwards Lifesciences. Dr. Fam is a consultant for Edwards; and received speaker honoraria from Abbott Vascular. Dr. Lurz has received speaker honoraria from Abbott Vascular. Dr. Hausleiter has received speaker honoraria from Abbott Vascular and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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was introduced transfemorally under general anesthesia. Image guidance was provided by two- and three-dimensional transesophageal echocardiography with additional fluoroscopy. The number of implanted devices was left to the discretion of the treating interventionalist to accomplish a significant reduction of TR. Technical success was defined as placement of at least 1 device in the tricuspid valve. Procedural success was defined as a successful implantation of the device and a post-procedural grade of ≤TR2+ (13).

OUTCOMES. The primary objective of this study was to determine the effect of TTVR on the rate of HHF in the follow-up period compared with the period 1 year before TTVR. Unplanned hospitalizations for more than 24 h within a time period of 12 months before (retrospectively) and after (prospectively) the procedure were categorized as being caused by decompensated HF or other causes. Decompensated HF was defined as recurrence or worsening of peripheral edemas or ascites, weight gain through fluid overload, increased dyspnea, radiographic signs of pulmonary congestion or pleural effusion, or need for intravenous diuretic agents. Secondary endpoints included mortality, the combined endpoint of freedom from death and first HHF after TTVR, and improvements in HF-related clinical symptoms, exercise capacity, diuretic dose, and NT-proBNP levels. The symptomatic outcome was assessed up to 12 months after TTVR compared with the pre-procedural baseline status. If patients were not able to visit the outpatient service, telephone interviews were performed.

Peri-procedural safety outcomes during the hospitalization for the repair procedure included all-cause mortality, new-onset atrial fibrillation, stroke, myocardial infarction, infection, low cardiac output syndrome (post-procedural need for intravenous inotropic support for >24 h), pericardial effusion, acute kidney injury (rise of serum creatinine by ≥0.3 mg/dl or increase to ≥1.5 times within 48 h after intervention), transfusion, and conversion to open heart surgery. Symptomatic outcome was assessed with NYHA functional class, quality of life with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, and physical capacity with the 6-min walk distance (6MWD) test. If patients were not able to walk due to critical condition or a neurologic or orthopedic cause, 6MWD was not applicable. Changes in HF medication and diuretic dose of furosemide equivalent from a pre-interventional time point to baseline and follow-up were recorded. We chose a conservative estimation of loop diuretic

TABLE 1 Baseline Patient Characteristics

	TTVR (n = 119)	TMTVR (n = 114)	p Value
Device for tricuspid valve repair			**0.007**
MitraClip	111 (93)	114 (100)	
PASCAL	8 (7)	0 (0)	
Age, yrs	75.2 ± 10.8	77.0 ± 8.4	0.2
Female	61 (51)	63 (55)	0.59
Atrial fibrillation	104 (87)	99 (87)	1.00
Transtricuspid lead	32 (27)	49 (43)	**0.013**
TR severity			
Mild	0	0	
Moderate	0	7 (6)	
Severe	119 (100)	107 (94)	**0.006**
TR etiology			
Primary	5 (4)	3 (3)	
Secondary	105 (88)	108 (94)	0.18
Mixed/other	9 (8)	3 (3)	
TR jet origin			
Antero-septal	20 (17)	11 (10)	
Antero-posterior	1 (1)	5 (4)	
Postero-septal	2 (2)	11 (10)	
Central	96 (81)	87 (76)	
Central or antero-septal	116 (97)	98 (86)	**0.001**
MR severity			
Mild or trace	85 (71)	3 (3)	
Mild to moderate	26 (22)	7 (6)	
Moderate to severe	6 (5)	74 (65)	
Severe	2 (2)	30 (26)	
Moderate to severe or worse	7 (6)	104 (91)	**<0.001**
NYHA functional class			
I	1 (1)	0 (0)	
II	9 (8)	2 (2)	
III	79 (66)	70 (61)	
IV	30 (25)	42 (37)	
III or higher	109 (92)	112 (98)	**0.034**
Ascites	35 (29)	28 (25)	0.46
Pleural effusion	27 (23)	50 (44)	**<0.001**
Jugular vein distension	49 (41)	38 (33)	0.22
Peripheral edema	95 (80)	79 (69)	0.07
Previous left-sided valve intervention			
Surgical	25 (21)	9 (8)	**0.005**
Transcatheter	18 (15)	8 (7)	0.06
Total	42 (35)*	17 (15)	**<0.001**
Renal failure, eGFR <60 ml/min	90 (76)	95 (83)	0.19
eGFR, ml/min	47.6 ± 21.7	44.0 ± 19.0	0.24
NT-proBNP, pg/ml	2,978 (1,298–5,304)	3,929 (2,109–7,939)	**0.002**
6MWD, m	227 ± 120	205 ± 111	0.24
MLHFQ score, arbitrary units	39 ± 20	39 ± 18	0.91
LVEF, %	53.3 ± 12.9	45.8 ± 16.3	**<0.001**
RV FAC, %	38.7 ± 9.9	35.3 ± 8.0	**0.013**
Echo-SPAP, mm Hg	43.4 ± 14.2	48.7 ± 15.8	**0.009**

Values are n (%), mean ± SD, or median (interquartile range). *1 patient underwent both surgical and transcatheter left-sided valve intervention. **Bold** values indicate $p < 0.05$.

6MWD = 6-min walk distance; Echo-SPAP = echocardiographic systolic pulmonary artery pressure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RV-FAC = right ventricular fractional area change; TMTVR = transcatheter edge-to-edge mitral and tricuspid valve repair; TR = tricuspid regurgitation; TTVR = transcatheter edge-to-edge tricuspid valve repair.

TABLE 2 Procedural Outcomes After TTVR and TMTVR

	TTVR	TMTVR	p Value TTVR vs. TMTVR
Number of tricuspid devices per patient	2.2 ± 0.8	1.8 ± 0.8	**<0.001**
Technical success	117 (98)	110 (96)	0.44
Procedural success	98 (82)	89 (78)	0.51
Postprocedural TR severity			0.39
Mild	47 (39)	54 (47)	
Moderate	51 (43)	38 (33)	
Severe	21 (18)	22 (19)	
Device location			
No device placement	2 (2)	4 (4)	
Only antero-septal	62 (52)	68 (60)	0.25
Only postero-septal	10 (8)	7 (6)	
Only antero-posterior	1 (1)	0 (0)	
Combined antero-septal + antero-posterior	2 (2)	2 (2)	
Combined antero-septal + postero-septal	41 (34)	33 (29)	0.37
Combined antero-septal + postero-septal + antero-posterior	1 (1)	0 (0)	
Hospital length of stay (95% CI), days	8.6 (6.6–10.7)	9.5 (7.9–11.1)	**0.028**
ICU length of stay (95% CI), days	1.9 (1.1–2.6)	2.6 (1.7–3.6)	**0.019**

Values are mean ± SD or n (%), unless otherwise indicated. **Bold** values indicate $p < 0.05$.
CI = confidence interval; ICU = intensive care unit; other abbreviations as in Table 1.

equivalence, with 10 mg of oral torsemide considered equivalent to 20 mg of oral furosemide (17). Notably, we aimed for maintaining the baseline diuretic dose during the first 6 months after the procedure to allow for RV reverse remodeling (18). NT-proBNP level was determined as an objective, standardized laboratory parameter for HF.

STATISTICAL METHODS. Continuous variables are expressed as mean ± SD or 95% confidence interval (CI); otherwise, the median (interquartile range [IQR]) is shown. Categorical variables are expressed as absolute numbers and proportions. Statistical testing of continuous variables was done with either the paired Student's *t*-test (normal distribution, paired), the Wilcoxon test (non-normal distribution, paired), or the Mann-Whitney *U* test (non-normal distribution, unpaired). For categorical variables, the Fisher exact test was applied. The estimated annual rate of HHF was calculated by dividing the individual number of HF admissions by the longest available follow-up or death interval in years. The annual rate before and after intervention was compared by using a Poisson regression model. Kaplan-Meier estimates were applied for death and time to first HHF after TTVR. The log-rank (Mantel-Cox) test was used for curve comparison. A p value <0.05 was considered statistically significant. Statistical analyses were performed by using R statistical software version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Prism 8 software version 8.0.1 (GraphPad Software, Inc., San Diego, California).

RESULTS

PATIENT CHARACTERISTICS. The analysis included 119 TTVR-treated patients, among them 1 patient who had a combined TTVR and left atrial appendage occlusion procedure (Supplemental Figure 1). Patients undergoing isolated TTVR had a mean age of 75 ± 11 years, and 61 (51%) were female. All patients had severe TR at baseline (Table 1). The majority of patients (92%) were in NYHA functional class III or IV despite optimal medical therapy (Supplemental Table 1). The etiology of TR was secondary in 105 (88%) patients. Etiologic background of secondary TR in patients with TTVR was as follows: 5 (5%) were receiving dialysis, 2 (2%) had severe MR, 50 (48%) had pulmonary hypertension, 45 (43%) had chronic atrial fibrillation, and 3 (3%) had an undetermined cause (Supplemental Figure 2). A total of 116 (97%) patients had central or antero-septal jets. RV systolic function was reduced with a tricuspid annular plane systolic excursion of 16 ± 4 mm (Supplemental Table 2). Overall, the left ventricular ejection fraction was preserved with 53 ± 13%.

TMTVR-treated patients had higher grades of MR (91% vs. 6% moderate to severe or severe MR; $p < 0.001$), a higher proportion of NYHA functional class III or higher (98% vs. 92%; $p = 0.03$), a reduced left ventricular ejection fraction (46% vs. 53%; $p < 0.001$), more often trans-tricuspid leads (43% vs. 27%; $p = 0.013$), and more often pleural effusion (44% vs. 23%; $p < 0.001$). In contrast, TTVR-treated patients had a higher proportion of severe TR grade (100% vs. 94%; $p = 0.006$), more often central or antero-septal jet origins (97% vs. 86%; $p = 0.001$), had undergone more previous left-sided valve surgery/interventions (35% vs. 15%; $p < 0.001$), and had a lower baseline NT-proBNP level (2,978 vs. 3,929 pg/ml; $p = 0.002$).

PROCEDURAL RESULTS. A total of 111 (93%) patients were treated with the MitraClip system and 8 (7%) with the PASCAL system. Technical success in isolated TTVR was possible in 117 (98%) patients. In 2 patients, device implantation failed, and thus TR remained severe. A total of 258 devices (mean 2.2 ± 0.8 per patient) were implanted into the tricuspid valve (Table 2). Leaflet position of the devices was antero-septal in 62 (52%) patients, postero-septal in 10 (8%) patients, antero-posterior in 1 (1%) patient, combined antero-septal and antero-posterior in 2 (2%) patients, and combined antero-septal and

postero-septal in 41 (34%) patients; 1 (1%) patient had all 3 commissures. After device placement, 98 (82%) patients had ≤TR2+ (Supplemental Figure 3).

All patients in the TMTVR group were treated with MitraClip devices. Patients undergoing TMTVR had fewer devices per patient implanted in the tricuspid valve (1.8 ± 0.8; $p < 0.001$). Furthermore, TMTVR-treated patients stayed longer in the hospital (9.5 vs. 8.6 days; $p = 0.028$) and on the intensive care unit (2.6 vs. 1.9 days; $p = 0.019$) during the index hospitalization.

PROCEDURAL SAFETY AND IN-HOSPITAL COMPLICATIONS. Two patients died during the index hospitalization after TTVR (Supplemental Table 3). Safety events comprised intrahospital conversion to open heart surgery (n = 1), infection (n = 6), low cardiac output syndrome (n = 6), myocardial infarction (n = 1), acute kidney injury (n = 7), and transfusions (n = 10). No cases of stroke or pericardial effusion were observed. There were no statistically significant differences between the TTVR- and TMTVR-treated patients in terms of intrahospital safety events.

MORTALITY AFTER TTVR AND TMTVR. The follow-up rates on mortality and HHF data after TTVR were 100% and 98%, respectively, with a median follow-up of 360 days (IQR: 187 to 408 days). Four patients with recurrence of severe TR within 4 months after the index procedure underwent another TTVR procedure. One patient underwent heart transplantation. Kaplan-Meier estimates for survival at 30 days, 6 months, and 12 months were 97%, 89%, and 76%, respectively (Supplemental Figure 4). The follow-up rates on mortality and HHF data after TMTVR were 99% and 99%, with a median follow-up of 368 days (IQR: 274 to 472 days). The survival rate did not differ between TTVR- and TMTVR-treated patients ($p = 0.92$).

HHF AFTER TTVR AND TMTVR. Eighty-one (69%) patients had at least 1 HHF within 12 months before TTVR, and 42 (36%) patients had >1 HHF before TTVR (Table 3, Supplemental Figure 5). The mean annual rate of HHF before TTVR was 1.21 (95% CI: 1.00 to 1.41) HHF/patient-year (Figure 1, Central Illustration). During follow-up, 37 (32%) patients had at least 1 HHF after TTVR ($p < 0.001$). The estimated annual rate of HHF after TTVR was significantly reduced to 0.95 (95% CI: 0.56 to 1.35) HHF/patient-year ($p = 0.02$). This finding translates into a 22% reduction in the annual rate of HHF.

In patients scheduled for TMTVR, 89 (78%) had at least 1 HHF and 47 (41%) had >1 HHF before TMTVR. The mean annual rate of HHF was 1.56 (95% CI: 1.28 to 1.84) HHF/patient-year before TMTVR. After TMTVR, 36 (32%) patients had at least 1 HHF ($p < 0.001$). The estimated annual rate of HHF after TMTVR was 0.53 (95% CI: 0.34 to 0.72) HHF/patient-year; thus, there was a 66% reduction in the annual

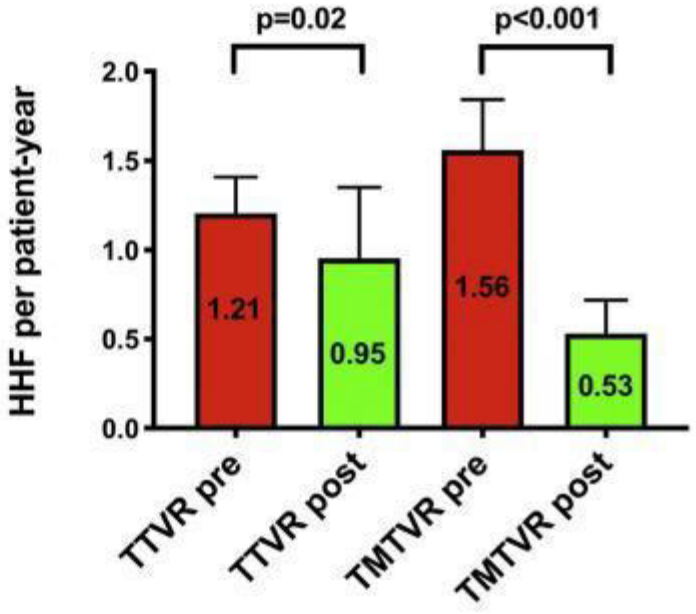
TABLE 3 Rates of HHF Before and After TTVR and TMTVR

	Pre-Procedure	Post-Procedure	p Value*
TTVR†			
Follow-up, days	NA	360 (187-408)	
Patients with HHF	81 (69)	37 (32)	**<0.001**
Number of HHF	142	59	
Sum of patient-yrs	119	116	
Rate of HHF/patient-yr (95% CI)	1.21 (1.00-1.41)	0.95 (0.56-1.35)	**0.02**
TMTVR‡			
Follow-up, days	NA	368 (274-472)	
Patients with HHF	89 (78)	36 (32)	**<0.001**
Number of HHF	178	45	
Sum of patient-yrs	114	126	
Rate of HHF/patient-yr (95% CI)	1.56 (1.28-1.84)	0.53 (0.34-0.72)	**<0.001**

Values are n (%), n, or median (interquartile range), unless otherwise indicated. *The Fisher exact test for comparison of proportion of patients with hospitalization for heart failure (HHF) before and after the procedure; Poisson regression analysis for comparison of rates of HHF before and after the procedure. †In 1 patient before and 2 patients after TTVR, data on hospitalization after the procedure were not obtainable. ‡In 1 patient after TMTVR, data on hospitalization were not obtainable. **Bold** values indicate $p < 0.05$.

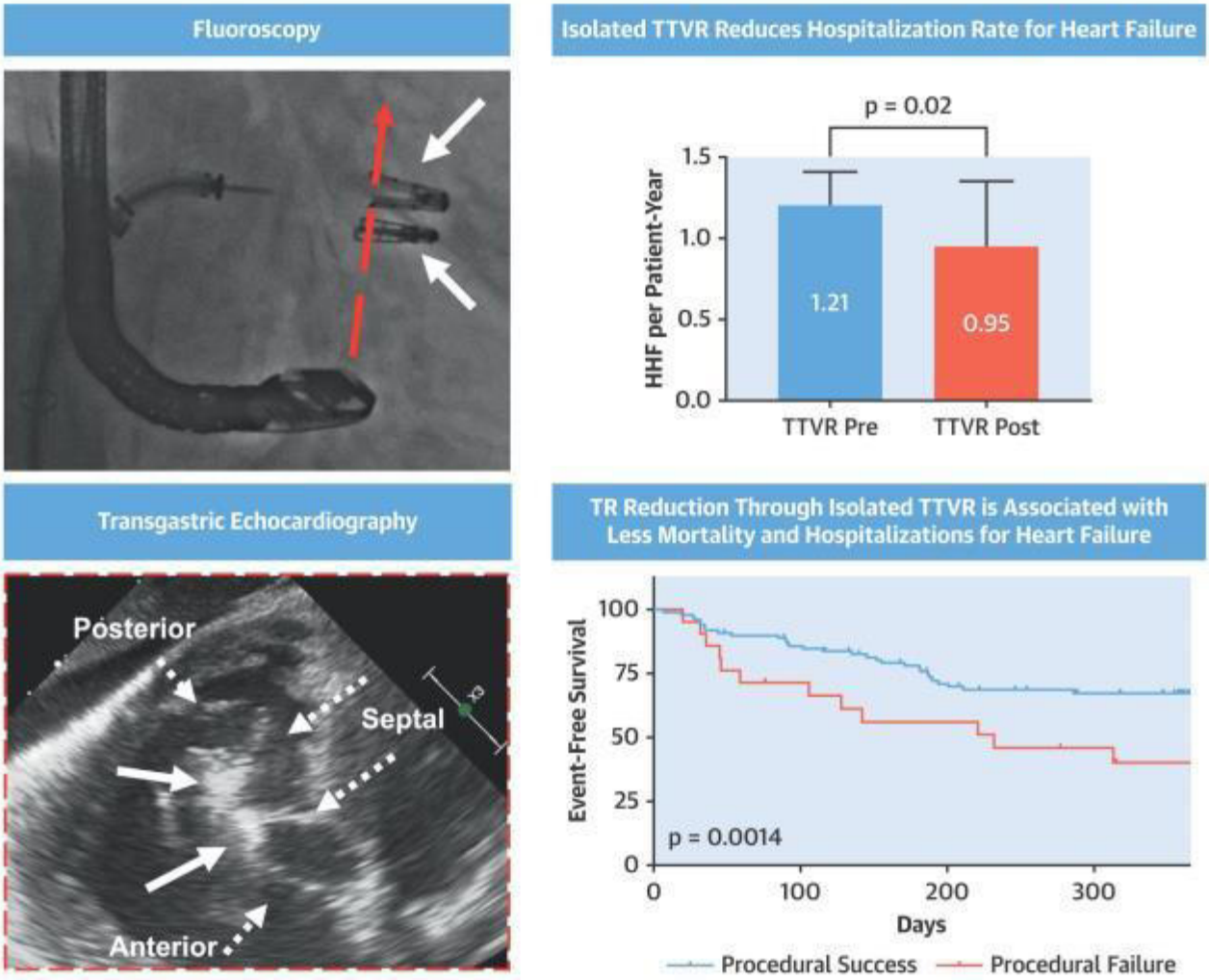
NA = not available; other abbreviations as in Tables 1 and 2.

FIGURE 1 Estimated Annual Rate of HHF Before and After TTVR and TMTVR



The estimated annual rate of hospitalization for heart failure (HHF) after transcatheter edge-to-edge tricuspid valve repair (TTVR) or combined transcatheter mitral and tricuspid valve repair (TMTVR) was calculated by dividing the number of HHF by the longest available follow-up period in years. Values are given as mean with 95% confidence interval.

CENTRAL ILLUSTRATION **Transcatheter Edge-to-Edge Tricuspid Valve Repair Is a Novel Treatment Option for Severe Tricuspid Regurgitation With the Potential to Reduce Heart Failure Hospitalization Rate and Improve Outcome if Procedural Success Is Achieved**



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Patients with severe tricuspid regurgitation (TR) and right-sided heart failure experience frequent hospitalizations for decompensated heart failure. Transcatheter tricuspid edge-to-edge repair is a novel method to reduce severe TR. The procedure is guided by fluoroscopy **(top left)** and echocardiography (transgastric view, **bottom left**) to grasp and approximate the tricuspid leaflets by the device to reduce the regurgitant orifice (**red arrow** depicts echocardiographic plane, **solid arrows** show 2 devices in place; **white dashed arrows** depict tricuspid leaflets). Isolated transcatheter edge-to-edge tricuspid valve repair (TTVR) potentially leads to fewer hospitalizations **(top right)**. If TR reduction is successful after isolated TTVR, patients have fewer combined endpoints of death and hospitalization for heart failure **(bottom right)**.

rate of HHF ($p < 0.001$). Comparing freedom from first HHF after the procedure, TTVR- and TMTVR-treated patients exhibited no difference, with Kaplan-Meier estimates of 76% and 76% after 6 months and 67% and 71% after 12 months, respectively ($p = 0.68$) (Supplemental Figure 6).

RELATIONSHIP OF TR REDUCTION TO MORTALITY AND HHF. Regarding the single and combined endpoints, an association with procedural success was observed in TTVR-treated patients. At the 1-year follow-up, 79% of patients with procedural success survived compared with 60% without procedural

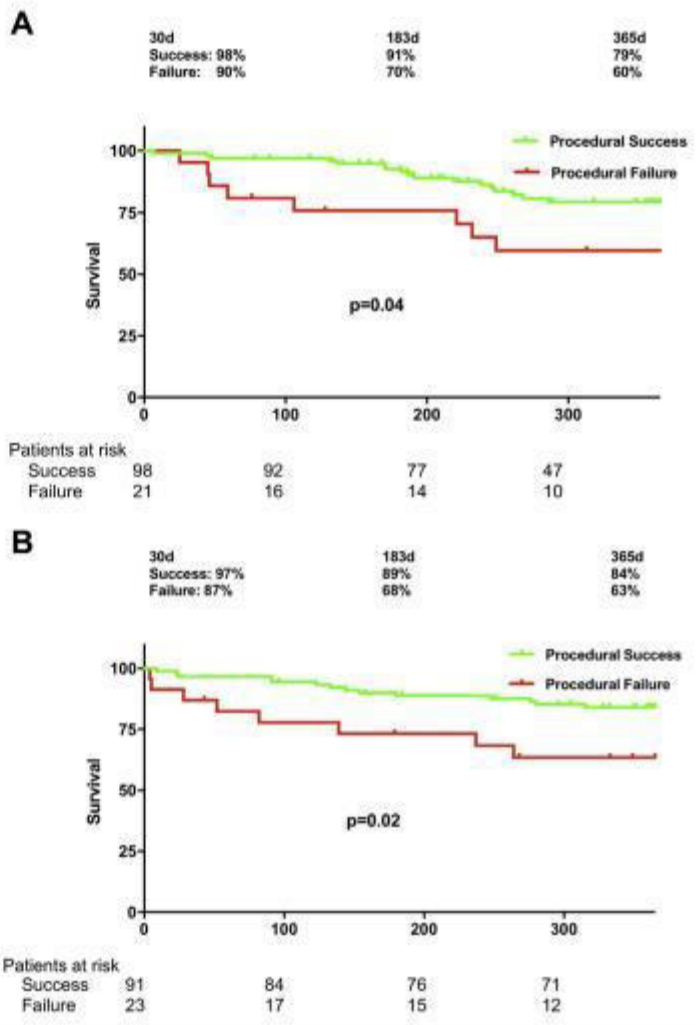
success (p = 0.04) (Figure 2A). Furthermore, 67% of TTVR-treated patients with procedural success were free of the combined endpoint compared with 40% with procedural failure (p = 0.001) (Figure 3A). Procedural failure was a predictor for hospitalization after TTVR (Supplemental Table 4). At baseline, patients with procedural failure were younger, had more severe TR as expressed by larger vena contracta and effective regurgitant orifice area, a higher loop diuretic dose, less intake of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and a lower echocardiographically determined systolic pulmonary pressure (Supplemental Table 5).

Patients undergoing TMTVR also had better survival if procedural success was achieved (84% vs. 63% alive at 1-year follow-up; p = 0.02) (Figure 2B) and a nonsignificant trend toward freedom of the combined endpoint if procedural success for TR was achieved (68% vs. 55% event-free at follow-up; p = 0.16) (Figure 3B).

CLINICAL OUTCOMES. In patients with clinical follow-up assessment, reduction of TR persisted after 12 months, with 72% of TTVR-treated patients and 77% of TMTVR-treated patients having moderate or less TR (p < 0.001) (Figure 4A). We observed significant reductions in both vena contracta and effective regurgitant orifice area as quantitative measurements of TR severity and decreases in RV mid-diameter at follow-up (Supplemental Figure 7). RV function by tricuspid annular plane systolic excursion did not change. The proportion of patients in NYHA functional class III or higher could be reduced from 92% to 33% in the TTVR group and from 98% to 30% in the TMTVR group (p < 0.001) (Figure 4B). The 6MWD increased significantly both in the TTVR group (from 234 ± 122 m to 273 ± 130 m; p = 0.001) and in the TMTVR group (from 212 ± 111 m to 256 ± 141 m; p = 0.001) (Figure 4C). As expressed by a reduction in MLHFQ score, the quality of life improved in TTVR-treated patients from 40 ± 20 to 34 ± 19 (p = 0.02) and in TMTVR-treated patients from 39 ± 18 to 32 ± 20 (p = 0.006). In the TTVR group, the NT-proBNP level decreased numerically from 2,900 pg/ml (IQR: 1,307 to 5,407 pg/ml) to 2,117 pg/ml (IQR: 1,222 to 4,853 pg/ml) (p = 0.36). In the TMTVR group, the NT-proBNP level decreased significantly from 4,833 pg/ml (IQR: 2,250 to 6,835 pg/ml) to 3,496 pg/ml (IQR: 1,888 to 5,827 pg/ml) (p = 0.007). The furosemide-equivalent dose was significantly increased from the year before TTVR to baseline but remained stable from the intervention to follow-up: 70 mg (95% CI: 54 to 87 mg) to 85 mg (95% CI: 67 to 104 mg) to 83 mg (95% CI: 58 to 109 mg; p = 0.03) (Supplemental Table 1, Supplemental Figure 8A).

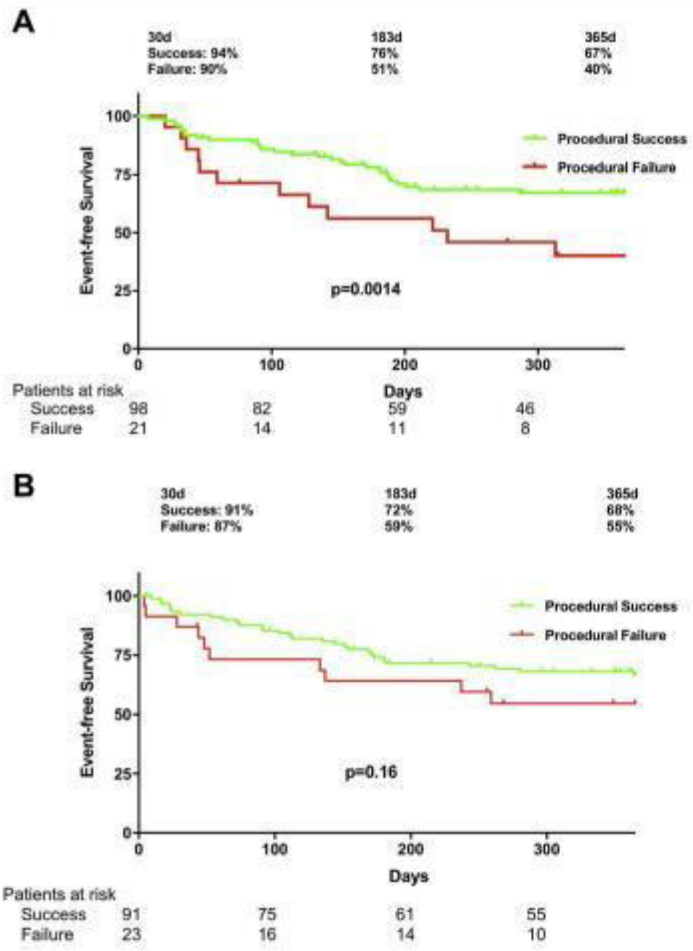
Twenty-nine percent of isolated TTVR-treated patients had an increase in loop diuretic dose (mean +74 mg). In TMTVR-treated patients, the loop diuretic dose did not change significantly over the observation period (Supplemental Figure 8B). At baseline, 57% of isolated TTVR-treated patients took angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, 78% took beta-blockers, and 42% took aldosterone antagonists, with no significant difference versus TMTVR-treated patients

FIGURE 2 Relationship of Procedural Success to Mortality After TTVR and TMTVR



Freedom from death in patients undergoing TTVR **(A)** and TMTVR **(B)** stratified according to the procedural success. Patients at risk are shown below the graph; Kaplan-Meier estimates of freedom from death after 30 days, 183 days, and 356 days are shown at the top. Abbreviations as in Figure 1.

FIGURE 3 Relationship of Procedural Success to Mortality and First HHF After TTVR and TMTVR



Freedom from death or first HHF in patients undergoing TTVR **(A)** and TMTVR **(B)** stratified according to the procedural success. Patients at risk are shown below the graph; Kaplan-Meier estimates of freedom from death or first HHF after 30 days, 183 days, and 356 days are shown at the top. Abbreviations as in Figure 1.

(Table 4, Supplemental Table 1). There was no significant difference in these proportions compared with pre-interventional and follow-up time points (Supplemental Table 1). Furthermore, relevant changes in dosage, initiation, or discontinuation of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, or aldosterone antagonists did not differ before and after TTVR (Supplemental Table 6).

DISCUSSION

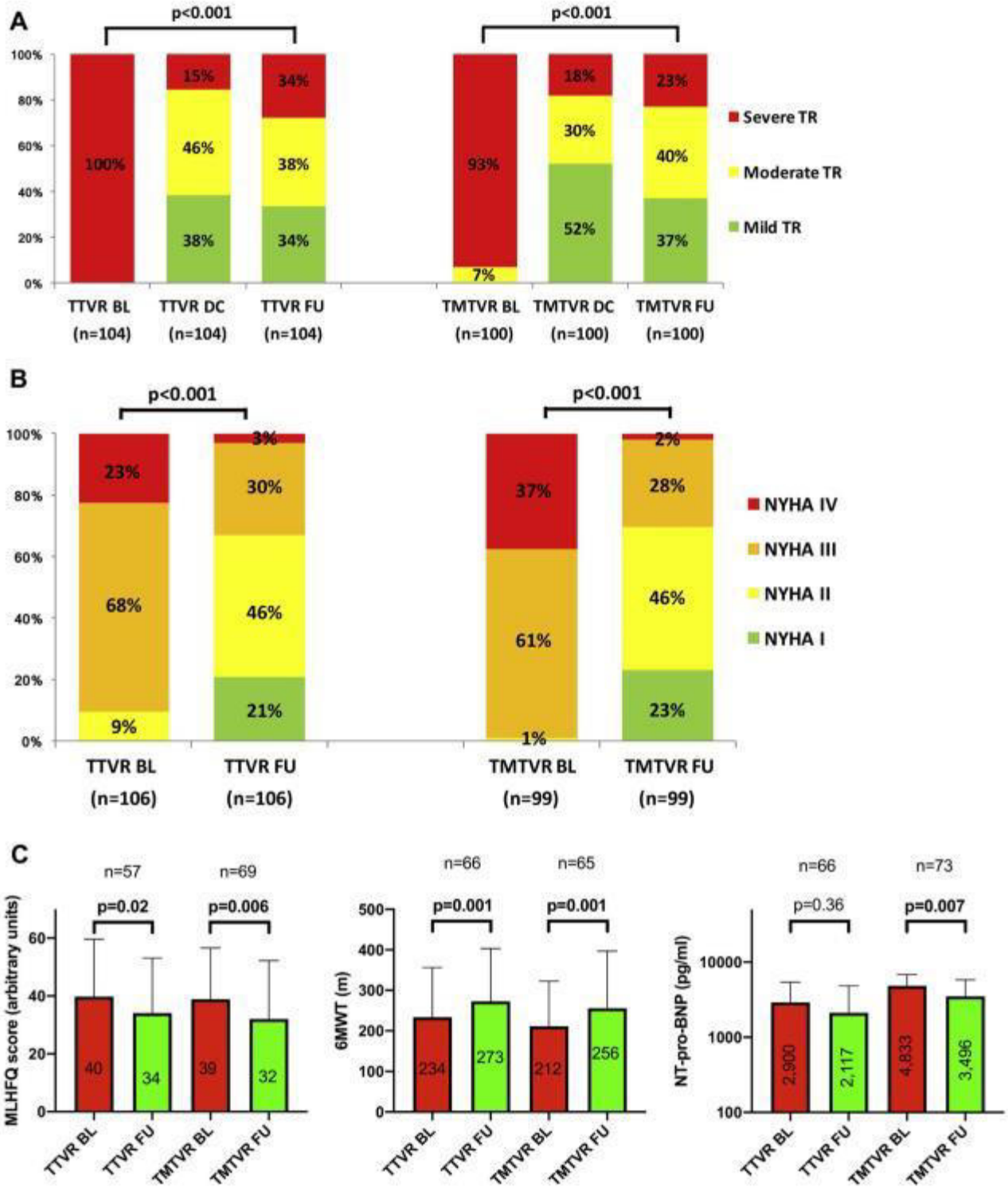
This analysis is, to date, the first and largest multicenter study to evaluate the effect of isolated TTVR on relevant HF-related clinical endpoints and HHF in high-risk patients with severe TR at 1-year follow-up. The most relevant finding of this study is the significant decrease in annual HHF rate after isolated TTVR. Furthermore, patients treated with isolated TTVR had a significant symptomatic benefit as seen with improvements in NYHA functional class, 6MWD, and MLHFQ score (Table 5). In contrast to rising loop diuretic doses until the intervention, no further escalation after TTVR was observed, which indicates a stabilization of fluid balance in these patients with a history of repeat decompensations. The rise in loop diuretic dose before TTVR could have potentially affected the clinical results, but optimal doses in patients with isolated TR and RV dysfunction are not well defined in the published data.

This registry confirms the favorable safety profile of TTVR with low procedure-related complication rates. The procedural success rate was 82% and thus higher than in previous reports, which could reflect the growing experience with TTVR (13). In addition, an association of procedural success with survival and freedom from the combined endpoint of death and HHF was observed. Both aspects implicate that TTVR may exert its potential benefit on outcome directly through TR reduction.

HHF is a relevant endpoint in cardiovascular disease studies and leads to major health care costs (19). High-risk or inoperable patients with significant valvular heart disease are particularly affected by repeat HHF, due also to the lack of effective treatment options or undertreatment (20,21). In patients with severe MR and prohibitive surgical risk, transcatheter mitral valve repair (TMVR) is an established therapy that showed potential benefit in terms of HHF in registries and randomized trials of high-risk patients (22–24). In fact, the reported annual HHF rates before TMVR of up to 0.83 HHF/patient-year with secondary MR (25) and 0.67 HHF/patient-year with primary MR (22) are much lower compared with the rate of 1.56 HHF/patient-year before TMTVR and 1.21 HHF/patient-year before TTVR in the current study patients. This difference highlights the clinical relevance of tricuspid valve disease and the frailty of patients with significant TR alone or in conjunction with severe MR and impaired left ventricular function.

The relatively high HHF rate in the current study patients before intervention could be explained by a progressive disease state of the tricuspid valve apparatus and possibly the right ventricle, as shown by impaired RV systolic function and RV dilatation. Therefore, the question arises from our results of when to perform TTVR. Recent studies have shown that treatment of large coaptation gaps of >7.2 mm is associated with procedural failure, which itself will

FIGURE 4 Development of TR- and HF-Related Endpoints Before and After TTVR and TMTVR



Development of tricuspid regurgitation (TR) grade **(A)**, New York Heart Association (NYHA) functional class **(B)**, quality of life, 6-min walk test (6MWT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels **(C)** before and after TTVR and TMTVR in patients with clinical follow-up data only. The p values for paired comparison between patients with baseline (BL) and follow-up (FU) data only. 6MWT and Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores are shown as mean with standard deviation; NT-proBNP levels are shown as median with interquartile range. Abbreviations as in Figure 1.

TABLE 4 Heart Failure Medication at Baseline and Follow-Up

	TTVR (n = 119)		TMTVR (n = 114)	
	Baseline*	Follow-Up*	Baseline*	Follow-Up*
ACE inhibitor/ARB	68 (57)	54 (65)	74 (65)	68 (77)
Aldosterone antagonist	49 (42)	53 (50)	42 (38)	31 (32)
Beta-blocker	91 (78)	85 (89)	98 (87)	80 (89)
Loop diuretic†	107 (94)	91 (94)	105 (95)	83 (93)

Values are n (%). *Only patients with available data. †Patients on chronic dialysis were excluded from the loop diuretic agents analysis.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; other abbreviations as in Table 1.

lead to poor outcome after TTVR (13,26). These results illustrate that a late-stage disease with an increasingly distorted valve anatomy impairs edge-to-edge device implantation and consequently procedural and clinical long-term success. The influence of RV dilatation and dysfunction on TTVR and vice versa is less clear, although recent data suggest that successful TTVR is associated with improvement in RV performance and reverse remodeling, which itself correlates with improved outcome after TTVR (18). The notion that TR reduction is directly linked to improved HF endpoints is further supported by a recent study showing that successful TTVR elicits favorable biventricular hemodynamic effects that ultimately enhance cardiac output (27). Other challenges of this investigational approach include refining the device design to bridge large gaps, the combination with different tricuspid valve repair techniques such as transcatheter annuloplasty, and its appropriate use in different tricuspid pathologies and clinical settings (28).

The recent COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial has reported the effect of transcatheter edge-to-edge valve repair (TMVR) on outcome in high-risk patients with severe mitral regurgitation and the importance of HHF as a major endpoint in randomized transcatheter device studies (24). This landmark investigation by Stone et al. proved that TMVR reduces HF admissions in high-risk patients with secondary severe MR in addition to guideline-directed medical therapy. Whether TTVR proves to be equally effective in reducing hospitalization for right-sided HF in patients with isolated severe TR must be shown in a comparable randomized controlled trial.

Applying appropriate patient selection criteria, standardized echocardiographic assessment protocols, procedures in experienced heart valve and HF centers, and adequate clinical HF endpoints for future clinical trials will be critical to clearly understand the potential impact of new tricuspid transcatheter devices on morbidity and mortality (29).

TABLE 5 Novel Findings From the Current Study

Isolated TTVR and combined TMTVR reduce HHF
Isolated TTVR and combined TMTVR improve heart failure-related symptoms up to 12 months (assessed by NYHA functional class, 6MWD, and heart failure–related QoL)
Isolated TTVR has the potential to stabilize diuretic doses
Isolated TTVR leads to right ventricular reverse remodeling at midterm

6MWD = 6-min walk distance; HHF = hospitalization for heart failure; QoL = quality of life; other abbreviations as in Tables 1 to 3.

STUDY LIMITATIONS. This analysis was an observational, nonrandomized, noncontrolled study. Although we gathered clinical data after TTVR prospectively, pre-intervention HHF rates were retrospectively assessed. We cannot rule out a regression to the mean or selection bias, as treating physicians selected patients for TTVR at their discretion. A centrally adjudicated, predefined run-in period for maximal uptitration of diuretic dose and HF medication with a sufficient interval between last uptitration and TTVR would have further strengthened the conclusion of our findings. We cannot rule out a contributory effect of a recently increased preinterventional diuretic dose. There was no prespecified clinical follow-up protocol in terms of observation intervals and parameters measured across the different centers. In addition, we cannot provide core laboratory–controlled echocardiographic data for the TR and cardiac chamber assessment. Finally, due to the small sample sizes, no comparisons can be made between the devices used.

CONCLUSIONS

This study found that isolated TTVR results in a significant and durable TR reduction that decreased HHF. Accordingly, successful TR reduction might be associated with improved survival. Based on these results, further randomized studies comparing TTVR with guideline-directed medical therapy will be needed to prove the clinical and prognostic benefit of TTVR for severe TR in patients with right-sided HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This international multicenter study provides the first comprehensive HF-related assessment with the longest follow-up in patients with severe TR and right-sided HF treated with interventional edge-to-edge repair of the tricuspid valve. In addition to durable improvements in NYHA functional class, exercise capacity, quality of life, and RV reverse remodeling, this novel technique is associated with a reduction in HHF and potentially mortality that was related to TR reduction. Interventional tricuspid repair is safe and seems to be a reasonable treatment option for patients with severe TR and right-sided HF to reduce the burden of hospitalization for decompensated HF.

TRANSLATIONAL OUTLOOK: Interventional tricuspid valve repair is a promising therapeutic option in patients with severe TR. With growing experience and adapted device design, long-term success could be further improved. Randomized trials comparing interventional tricuspid valve repair versus optimal medical therapy in patients ineligible or at high risk for surgery should be performed to confirm this finding.

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KEY WORDS heart failure, MitraClip, PASCAL, percutaneous edge-to-edge repair, right heart, transcatheter tricuspid valve repair, tricuspid regurgitation, tricuspid valve

APPENDIX For supplemental figures and tables, please see the online version of this paper.

2.2.3 Bedeutung der pulmonalen Hypertonie für die katheterbasierte Trikuspidalklappenrekonstruktion

Zitierweise:

Lurz P, Orban M, Besler C, Braun D, Schlotter F, Noack T, Desch S, Karam N, Kresoja KP, Hagl C, Borger M, Nabauer M, Massberg S, Thiele H, Hausleiter J*, **Rommel KP***.

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*equal contribution

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CLINICAL RESEARCH
Valvular heart disease

Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair

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Aims Patients with pulmonary hypertension (PHT) are often excluded from surgical therapies for tricuspid regurgitation (TR). Transcatheter tricuspid valve repair (TTVR) with the MitraClip™ technique is a novel treatment option for these patients. We aimed to assess the role of PHT in severe TR and its implications for TTVR.

Methods and results A total of 243 patients underwent TTVR at two centres. One hundred twenty-one patients were grouped as iPHT+ [invasive systolic pulmonary artery pressures (PAPs) ≥50 mmHg]. Patients were similarly stratified according to echocardiographic PAPs (ePHT). The occurrence of the combined clinical endpoint (death, heart failure hospitalization, and reintervention) was investigated during a follow-up of 330 (interquartile range 175–402) days. iPHT+ patients were at higher preoperative risk ($P < 0.01$), had more severe symptoms ($P = 0.01$), higher N-terminal pro-B-type natriuretic peptide levels ($P < 0.01$), more impaired right ventricular (RV) function ($P < 0.01$), and afterload corrected RV function ($P < 0.01$). Procedural TTVR success was similar in iPHT+ and iPHT- patients (84 vs. 84%, $P = 0.99$). The echocardiographic diagnostic accuracy to detect iPHT was only 55%. During follow-up, 35% of patients reached the combined clinical endpoint. The discordant diagnosis of iPHT+/ePHT- carried the highest risk for the combined clinical endpoint [HR 3.76 (CI 2.25–6.37), $P < 0.01$], while iPHT+/ePHT+ patients had a similar survival-free time from the combined endpoint compared to iPHT- patients ($P = 0.48$). In patients with isolated tricuspid procedure ($n = 131$) a discordant iPHT+/ePHT- diagnosis and an impaired afterload corrected RV function ($P < 0.01$ for both) were independent predictors for the occurrence of the combined endpoint.

Conclusion The discordant echocardiographic and invasive diagnosis of PHT in severe TR predicts outcomes after TTVR.

Keywords Tricuspid regurgitation • Pulmonary hypertension • MitraClip™ • edge-to-edge repair • Transcatheter therapy • Right ventricle • Heart failure

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Introduction

Severe tricuspid regurgitation (TR) poses a significant medical challenge in ageing societies and is associated with poor functional outcomes and poor prognosis.[1–3]

Functional TR is the most common form and occurs mainly in the setting of annular dilation and right ventricular (RV) enlargement. These morphological alterations may occur idiopathically or secondary to other pathologies such as heart failure (HF) from myocardial or valvular causes. In particular, pulmonary hypertension (PHT) is thought to contribute to the development of severe TR by inducing RV elongation and spherical deformation with subsequent valve deformation.[4] In addition, PHT has been shown to portend adverse outcomes in multiple HF populations[5] and patients undergoing tricuspid surgery.[6] In fact, current guidelines discourage surgical tricuspid interventions in patients with significant PHT.[7]

Recently, new transcatheter treatment options for TR have been developed, specifically addressing the large number of patients deemed at prohibitive surgical risk. Transcatheter tricuspid valve edge-to-edge repair (transcatheter tricuspid valve repair, TTVR, MitraClip™, Abbott Vascular, IL, USA) is currently the most widely used approach, either off-label or in compassionate use programmes.[8,9] This technique has been demonstrated to be feasible and to be associated with improvement in functional outcomes.[8,10,11] In the search for appropriate patient selection criteria, several morphological TR characteristics have been proposed as predictors of procedural success, which itself predicts favourable clinical outcomes.[12] Although debated as a potential marker for adverse outcomes in this patient group, the specific role of PHT has not been studied so far.

We therefore aimed to investigate the clinical characteristics, diagnosis, and risk stratification of PHT in patients with severe TR and its impact on outcomes after TTVR.

Methods

Patients

The study was conducted in patients with symptomatic moderate to severe TR treated by TTVR at two tertiary care centres in Germany (Heart Center Leipzig at University of Leipzig, Leipzig, Germany, and the University Hospital of the Ludwig-Maximilians Universität, Munich, Germany) between March 2016 and March 2019. Details of patient selection and assessment have been described previously[12] and are detailed in the Supplementary material online. Invasive systolic pulmonary artery pressure (PAP) ≥50mmHg (iPHT) was defined as invasive systolic pulmonary artery pressure (PAPs ≥50 mmHg) on standard right heart catheterization (RHC).[4,8]

Echocardiography

All echocardiograms were performed on and analysed according to current European and American guidelines with the addition of a 4th TR grade for torrential TR.[13,14] The imaging protocol has been described previously[8] and is detailed in the Supplementary material online. Right ventricular to right atrial pressure (RAP) gradient was estimated from the continuous wave Doppler profile of the TR jet and echocardiographic PAPs was assessed by adding estimated RAP from imaging the inferior vena cava as recently suggested.[13] Echocardiographic PAP ≥ 50 mmHg (ePHT+) was defined as echocardiographic PAPs ≥50 mmHg.[4,15,16] For prognostic evaluation, a discordant iPHT/ePHT diagnosis was considered when estimated PAPs differed by >10 mmHg from iPAPs. As an estimate of RV function after correction for afterload, we calculated the tricuspid annular plane systolic excursion (TAPSE)/iPAPs ratio as previously described.[5]

Transcatheter tricuspid valve repair

Procedural details have been described previously[8] and are further described in the Supplementary material online. Transcatheter tricuspid valve repair was performed under general anaesthesia with interventional guidance by transoesophageal echocardiography and fluoroscopy via the right femoral vein, the inferior vena cava, and the right atrium using the MitraClip™ System. More than one clip was used if satisfactory reduction of TR was not achieved after implantation of the first clip. Procedural success was defined as successful clip deployment and reduction to a TR grade of ≤2. Procedural failure was defined as a residual TR grade ≥3.

Follow-up examinations

Patients were followed-up for symptoms, N-terminal pro-B-type natriuretic peptide (NT-proBNP), 6-min walk test (6MWT), and the occurrence of clinical events. The primary study endpoint was defined as a composite of all-cause mortality, need for repeat hospitalization for HF, and reintervention during follow-up. Secondary endpoints included the singular components of the combined endpoint as well as changes in New York Heart Association (NYHA) class, 6MWT distance, and NT-pro-BNP levels.

Statistical analysis

Continuous data are presented as mean ± standard deviation and mean difference with 95% confidence interval (CI) or median with interquartile range (IQR) and Hodges–Lehmann estimators with CI. Categorical data are presented as frequencies and percentages. Paired data were analysed with Wilcoxon rank or paired *t*-tests. Between-group differences were compared with Kruskal–Wallis tests, Student's *t*-test, or χ^2 tests. Correlations were assessed by Spearman's rho. Logistic regression was applied for predictor analysis. Odds ratios (ORs) and CI are reported. The Kaplan–Meier method was used for survival time analyses. Cox regression analyses were carried out to identify predictors for the occurrence of the combined endpoint. Hazard ratios (HRs) with CI are reported. The underlying assumptions of the statistical tests were evaluated. Statistical significance was inferred when $P < 0.05$.

For further details of methodology please refer to the Supplementary material online.

Results

Clinical characteristics

Baseline characteristics of the 243 patients enrolled within the present analysis are presented in *Table 1*. Completeness of data for patient characterization is illustrated in the Supplementary material online, *Table S6*. Mean age in the population was 77 ± 9 years and the sex ratio was balanced. Invasive systolic PAPs ranged from 19 to 117 mmHg, with 121 patients (50%) demonstrating a PAPs ≥50 mmHg, further referred to as the iPHT+ group. Compared to the 122 patients (50%) with PAPs <50 mmHg (iPHT- group), these patients were at higher preoperative risk (EUROscore II: $P < 0.01$; STS predicted mortality: $P = 0.01$), had more often been hospitalized for HF within the prior year ($P = 0.01$), a longer symptom duration

Table I Patient characteristics according to PHT groups

Baseline characteristics PHT groups	All patients ($n = 243$)	iPHT− patients ($n = 122$)	iPHT+ patients ($n = 121$)	Mean difference/Hodges–Lehmann estimator[a] (CI)	P-value
Age (years)	77 ± 9	78 ± 8	76 ± 9	-1.9 (-4.1 to 0.23)	0.08
Female sex, *n* (%)	121 (50)	66 (54)	55 (46)	—	0.20
BMI (kg/m^2)	27 ± 5	26 ± 5	28 ± 5	2.2 (0.6–0.9)	<0.01
EUROscore II (%)	7.7 ± 7.0	6.6 ± 6.0	8.9 ± 7.3	2.4 (0.6–4.1)	<0.01
STS predicted mortality (%)	5.4 ± 5.1	4.2 ± 2.9	6.6 ± 6.0	2.4 (1.1–3.8)	<0.01
eGFR (mL/min/1.73 m^2)	48 ± 22	52 ± 21	43 ± 22	-9 (-15 to -4)	<0.01
eGFR <30 mL/min/1.73 m^2, *n* (%)	52 (21)	17 (14)	35 (29)	—	0.01
Chronic dialysis, *n* (%)	14 (6)	4 (3)	10 (8)	—	0.11
Previous PCI, *n* (%)	56 (23)	30 (25)	26 (22)	—	0.65
Previous CABG, n (%)	30 (12)	15 (12)	15 (12)	—	0.99
Previous valve intervention, n (%)	31 (13)	14 (12)	17 (14)	—	0.57
Atrial fibrillation, n (%)	214 (88)	104 (85)	110 (91)	—	0.24
Chronic lung disease, *n* (%)	57 (24)	20 (16)	37 (31)	—	0.01
Right ventricular lead present, n (%)	67 (28)	30 (25)	37 (31)	—	0.32
HF hospitalization prior year, *n* (%)	175 (76)	79 (69)	96 (84)	—	0.01
Symptomduration (months)	8 (4–17)	8 (3–12)	10 (5–20)	2 (0–4)[a]	0.01
NYHA II, *n* (%)	18 (7)	11 (9)	7 (6)	—	<0.01
NYHA III, *n* (%)	159 (65)	92 (75)	67 (55)	—	
NYHA IV, *n* (%)	66 (27)	19 (16)	47 (39)	—	
NT-pro-BNP (ng/L)	3110 (1678–6276)	2614 (1315–4407)	4634 (2099–8016)	1513 (814–2410)[a]	<0.01
6-min walk distance (m)	234 ± 119	263 ± 119	202 ± 101	-61 (-92 to -30)	<0.01
Right heart catheter—PHT groups					
PAP systolic (mmHg)	49 ± 15	38 ± 7	61 ± 12	23 (21–26)	<0.01
PAP mean (mmHg)	32 ± 10	24 ± 6	39 ± 8	15 (14–17)	<0.01
PAP mean >25 mmHg, *n* (%)	163 (68)	65 (46)	98 (98)		<0.01
RAP mean (mmHg)	15 ± 7	12 ± 5	18 ± 7	6 (5–8)	<0.01
PCWP or LAP mean (mmHg)	20 ± 7	16 ± 5	24 ± 6	8 (7–10)	<0.01
Pulmonary vascular resistance (WU)	3.4 ± 2.1	2.5 ± 1.3	4.2 ± 2.4	1.7 (1.2–2.2)	<0.01
Transpulmonary gradient (mmHg)	12 ± 7	8 ± 5	16 ± 7	8 (6–9)	<0.01
TAPSE/PAPs ratio (mm/mmHG)	0.38 ± 0.17	0.49 ± 0.17	0.27 ± 0.10	-0.21 (-0.25 to -0.18)	<0.01
Echo variables—PHT groups					
LV ejection fraction (%)	51 ± 14	52 ± 13	49 ± 16	-3 (-6 to 1)	0.08
LV EDD (mm)	51 ± 9	50 ± 8	53 ± 9	3.3 (1.1–5.4)	<0.01
TAPSE (mm)	17 ± 5	18 ± 5	16 ± 5	-1.7 (-2.9 to -0.6)	<0.01
RA area (cm^2)	37 ± 12	38 ± 12	36 ± 12	-1.7 (-4.9 to 1.4)	0.28
RV midventricular diameter (mm)	43 ± 8	42 ± 8	43 ± 8	1.0 (-1.1 to 3.1)	0.36
TV annulus diameter (ml/m^2)	48 ± 7	48 ± 8	47 ± 6	-0.65 (-2.5 to 1.2)	0.50
Estimated PAPs (mmHg)	49 ± 15	43 ± 9	54 ± 17	11 (8–15)	<0.01
TR vena contracta (mm)	10 ± 3	10 ± 3	9 ± 3	-0.6 (-1.5 to 0.3)	0.18
TR EROA PISA (cm^2)	0.57 ± 0.32	0.62 ± 0.32	0.52 ± 0.32	-0.13 (-0.22 to -0.03)	0.02
TR coaptation gap (mm)	5 ± 3	6 ± 3	5 ± 3	-0.8 (-1.6 to 0.1)	0.06
TR tenting height (mm)	9 ± 4	9 ± 4	9 ± 3	-0.2 (-1.2 to 0.9)	0.73
TR tenting area (cm^2)	2.2 ± 1.1	2.4 ± 1.2	2.1 ± 1.0	-0.2 (-1.3 to 0.9)	0.19
Mitral regurgitation					
Grade 0–1	95 (39)	55 (45)	40 (33)	—	0.18
Grade 2	49 (20)	25 (21)	24 (20)	—	
Grade 3	86 (35)	38 (31)	48 (40)	—	
Grade 4	13 (5)	4 (3)	9 (7)	—	

Continued

Table 1 *Continued*

Baseline characteristics PHT groups	All patients ($n = 243$)	iPHT− patients ($n = 122$)	iPHT+ patients ($n = 121$)	Mean difference/Hodges–Lehmann estimator[a] (CI)	*P*-value
Tricuspid regurgitation					
Grade 2	13 (5)	2 (2)	11 (9)	—	0.10
Grade 3	163 (67)	85 (70)	78 (65)	—	
Grade 4	67 (28)	35 (28)	32 (26)	—	

For completeness of data please refer to Supplementary material online, *Table S6*.
[a]Symptomduration (months) = duration of heart failure symptoms prior to TTVR NT-proBNP.
BMI, body mass index; CABG, coronary artery bypass grafting; CI, 95% confidence interval; EDD, end-diastolic dimension; EROA, effective regurgitation orifice area; HF, heart failure; iPHT-, invasive PAP < 50 mmHg; iPHT+, invasive PAP ≥ 50 mmHg; LAP, left atrial pressure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PAPs, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; PISA, proximal isovelocity surface area; RA, right atrial; RAP, RA pressure; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve; WU, Wood units.

($P = 0.01$), had more severe symptoms (NYHA Class IV: 39 vs. 16%, $P < 0.01$), higher NT-pro-BNP levels ($P < 0.01$), more impaired renal function ($P < 0.01$), a higher rate of chronic lung diseases ($P = 0.01$), and more impaired functional capacity (6MWT: $P < 0.01$). iPHT+ patients demonstrated higher invasive mean PAP, higher pulmonary capillary wedge pressures (PCWP) and RAPs, higher pulmonary vascular resistances (PVR), and higher transpulmonary gradients (TPG) and impaired afterload corrected RV function ($P < 0.01$ for all, *Table 1*). Similar results were observed when considering only patients with isolated TTVR and patients with a combined mitral-tricuspid procedure (Supplementary material online, *Tables S1a* and *S1b*).

Overall, iPHT+ patients demonstrated more severe RV dysfunction and left ventricular (LV) dilatation as well as higher non-invasively determined PAPs. Afterload corrected RV function (TAPSE/iPAPs ratio) was significantly impaired in iPHT+ patients. Mitral regurgitation (MR) and TR grades were similar between iPHT groups, although iPHT+ patients demonstrated a slightly smaller effective regurgitation orifice area (EROA; $P = 0.01$) but similar coaptation gaps and tenting parameters (*Table 1*). Similar results were obtained in isolated TTVR patients and patients undergoing a concomitant mitral procedure (Supplementary material online, *Tables S1a* and *S1b*).

Impact of pulmonary hypertension on procedural outcomes

Concomitant transcatheter treatment of the mitral valve repair (TMTVR) was performed in 46% of patients ($n = 111$). In 96% of these patients, the MR could be reduced to MR ≤ 2, without any differences between iPHT+ groups (Supplementary material online, *Table S2b*).

Overall, in the tricuspid position, a median of 2 (IQR 2–2) clips were implanted predominantly in the anteroseptal (92%) and posteroseptal commissure (39% of patients). Procedural success was documented in 84% of patients with no differences between iPHT+ and iPHT- group (*Table 2*, *Figure 1*). This was true also when considering patient with isolated TTVR and patients with a concomitant mitral procedure separately (Supplementary material online, *Tables S2a* and *S2b*).

Correlation of invasive and echocardiographic pressures

Median time from echocardiography to right heart catheter was 6 (IQR 2–17) days and comparable within all subgroups. Overall, we observed a moderate correlation between invasive and echocardiographic PAPs ($r = 0.47$, $P < 0.01$). However, the sensitivity for echocardiography to detect iPHT+ was only 55% with a specificity of 74% (*Figure 2*). Accordingly, 45% of iPHT+ patients were not diagnosed as having PHT by echocardiographic assessment (iPHT+/ePHT- group, 55 patients). Invasively determined RAP correlated weakly with echocardiographically determined RAP ($r = 0.28$, $P < 0.01$) and showed higher absolute values (15 ± 7 mmHg vs. 12 ± 4 mmHg, $P < 0.01$). The underestimation was most pronounced in iPHT+/ePHT- patients and was mainly due to the systematic underestimation of invasive RAP values over 15 mmHg. Echocardiographic mean PAP and PVR estimates correlated moderately with invasive assessments (TR flow integral-derived mean PAP: $r = 0.48$, $P < 0.01$; TR velocity-derived mean PAP: $r = 0.33$, $P < 0.01$, RV outflow tract flow acceleration time derived mean PAP: $r = 0.40$, $P < 0.01$, RV outflow tract flow integral and TR velocity derived PVR: $r = 0.47$, $P < 0.01$) and demonstrated low specificity in identifying iPHT. While invasive mean PAP correlated significantly with invasive PAPs ($r = 0.91$, $P < 0.01$), an invasive mean PAP >25 mmHg demonstrated low specificity (62%) in identifying iPHT.

Clinical outcomes

Patients were followed for a median of 330 (IQR 175–402) days. Over the follow-up time, 35% of patients ($n = 85$) reached the combined endpoint. While 45 patients (19%) died, 67 patients (28%) were hospitalized for HF and 9 patients (4%) underwent a reintervention (6 × TTVR, 2 × tricuspid surgery, 1 × heart transplantation).

The presence of iPHT was predictive of the occurrence of the combined endpoint on univariate Cox regression [HR 2.11 (CI 1.35–3.29], $P = 0.01$, *Table 3*). Time free of the occurrence of the combined endpoint, of death and hospitalization for HF were longer in the iPHT- as compared to the iPHT+ group (log rank: $P < 0.01$, $P < 0.01$, and $P = 0.01$, respectively). The same was true when considering only patients with isolated TTVR [HR 3.10 (CI 1.69–5.70), $P < 0.01$; log rank: $P < 0.01$ for all] but not patients with a concomitant mitral

Table 2 Procedural details according to PHT groups

Procedural detailsPHT groups	All patients (n = 243)	iPHT− patients (n = 122)	iPHT+ patients (n = 121)	P-value
Concomitant mitral procedure, *n* (%)	111 (46)	51 (42)	60 (50)	0.25
Number of tricuspid clips (*n*)	2 (2–2)	2 (2–2)	2 (2–2)	0.62
Anteroseptal clip placement, *n* (%)	224 (92)	110 (90)	114 (94)	0.34
Posteroseptal clip placement, *n* (%)	95 (39)	51 (42)	44 (36)	0.43
Anteroposterior clip placement, *n* (%)	10 (4)	4 (4)	6 (5)	0.54
Procedural success, *n* (%)	205 (84)	103 (84)	102 (84)	0.99

Hodges–Lehmann estimators with 95% confidence interval 0 (0–0) for number of tricuspid clips between iPHT groups.
iPHT+, invasive PAPs ≥ 50 mmHg; iPHT-, invasive PAPs < 50 mmHg.

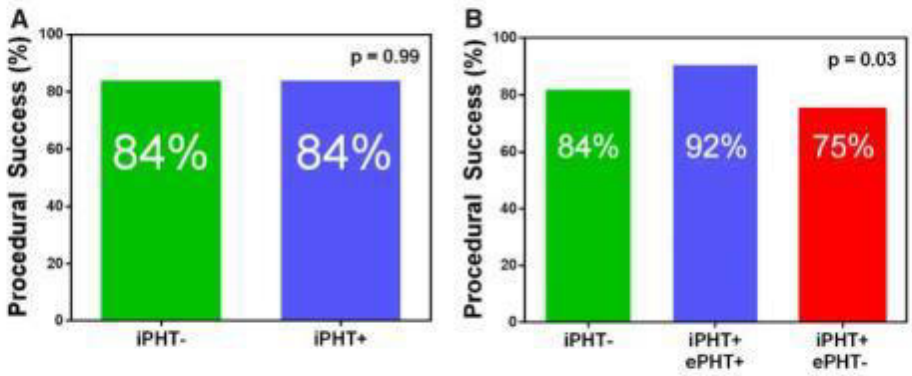


Figure 1 Distribution of procedural success rates across patient groups. (*A*) Patient groups according to invasive assessment is shown. (*B*) Patients according to invasive and echocardiographic groups is shown. ePHT-, echocardiographic PAPs <50 mmHg; ePHT+, echocardiographic PAPs ≥50 mmHg; iPHT-, invasive PAPs <50 mmHg; iPHT+, invasive PAPs ≥50 mmHg.

procedure [HR 1.36 (CI 0.70–2.65), $P = 0.02$; log rank $P = 0.35$, $P = 0.46$ and $P = 0.78$; *Figure 3* and Supplementary material online, *Figure S1*]. Times free of the occurrence of the combined endpoint were numerically but not significantly longer in TMTVR patients (log rank: $P = 0.11$).

Assessment according to invasive and echocardiographic pulmonary hypertension

Compared to 66 patients with iPHT+/ePHT+, the 55 iPHT+/ePHT- patients had numerically higher preoperative risk scores, more severe dyspnoea and worse 6MWT results (*Table 4*). A V-wave cut-off sign, defined as an early peaking and a triangular CW Doppler signal, indicative of high right atrial 'C–V' waves,[17] was more common in iPHT+/ePHT- patients (38%) compared to iPHT+/ePHT (12%, $P < 0.01$, *Figure 5*) but was not predictive of outcomes. An echocardiographic false negative diagnosis of PHT (iPHT+/ePHT- group) was associated with higher RAPs, more impaired LV function, the lowest echocardiographically determined PAPs and a more severe TR (EROA: $P = 0.01$, TR grade: $P < 0.01$, *Table 4*). Similar results were observed when considering patients with or without concomitant

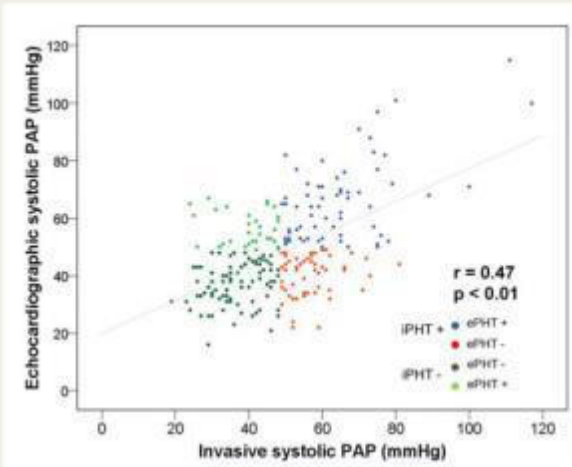


Figure 2 Correlation between invasively and echocardiographically determined systolic pulmonary artery pressures. ePHT-, echocardiographic PAPs <50 mmHg; ePHT+, echocardiographic PAPs ≥50 mmHg; iPHT-, invasive PAPs <50 mmHg; iPHT+, invasive PAPs ≥50 mmHg.

Table 3 Cox regression analysis for combined endpoint

	Univariate		Multivariable stepwise	
	HR (CI)	P-value	HR (CI)	P-value
Overall cohort				
Symptomduration >12 months	1.72 (1.12–2.65)	0.02	—	—
6 MWD (per 20 m decrease)	1.07 (1.02–1.11)	<0.01	—	—
TAPSE/iPAPs <0.29 mm/mmHG	2.27 (1.47–3.50)	<0.01	—	—
Procedural failure (binary)	2.18 (1.23–3.84)	0.01	—	—
TPG >12 mmHg (binary)	1.86 (1.18–2.95)	0.01	—	—
iPHT+/ePHT- (binary)	3.35 (2.17–5.19)	<0.01	3.76 (2.25–6.27)	<0.01
iPHT+ (binary)	2.07 (1.33–3.23)	<0.01		
ePHT+ (binary)	0.54 (0.34–0.87)	0.01		
Isolated TTVR				
6 MWD (per 20 m decrease)	1.05 (1.00–1.11)	0.05	—	—
TAPSE/iPAPs <0.29 mm/mmHG	3.52 (1.97–6.30)	<0.01	2.57 (1.20–5.51)	0.02
Procedural failure (binary)	2.29 (1.19–4.40)	0.01	—	—
TPG >12 mmHg (binary)	1.91 (1.05–3.50)	0.04	—	—
iPHT+/ePHT- (binary)	3.97 (2.25–6.98)	<0.01	3.66 (1.71–7.83)	<0.01
iPHT+ (binary)	2.98 (1.62–5.48)	<0.01		

CI, 95% confidence interval; ePHT+, echocardiographic PAPs ≥ 50 mmHg; HR, hazard ratio; iPAPs, invasive systolic pulmonary pressure; iPHT+, invasive PAPs ≥ 50 mmHg; TAPSE, tricuspid annular plane systolic.

mitral procedure separately (Supplementary material online, *Tables S3a* and *S3b*).

The iPHT+/ePHT- group demonstrated the least favourable procedural TTVR success rates in all patient groups, reaching statistical significance in the overall cohort (*Figure 1*).

The worst clinical outcomes with the shortest event-free time for the combined endpoint was found in the iPHT+/ePHT- group ($P < 0.01$, *Figure 3*). Event-free survival time between iPHT- and iPHT+/ePHT+ did not significantly differ (log rank: $P = 0.48$). The same was true for isolated TTVR procedures and those combined with mitral interventions (Supplementary material online, *Figure S1*).

On univariate Cox regression analysis, a poorer functional capacity, longer symptom duration, a low afterload corrected RV function, an unsuccessful TTVR-procedure, and an elevated TGP (but not an elevated PVR) were predictive of the occurrence of the combined endpoint. In a model with iPHT/ePHT information, the assignment to the iPHT+/ePHT- group emerged as independent predictor for the combined clinical endpoint (*Table 3*). In patients with isolated TTVR, a worse TAPSE/PAPs ratio and an iPHT+/ePHT- diagnosis were independent predictors in a multivariable model (*Table 3*). Neither concomitant mitral clipping [HR 0.70 (CI 0.45–1.10), $P = 0.10$], nor procedural mitral clipping success [96% of patients, HR 0.63 (CI 0.15–2.63), $P = 0.53$] were predictors for the combined endpoint. The independent predictive value of a discordant PHT diagnosis remained significant even after adjustment for baseline heterogeneities between subgroups.

Echocardiographic predictors of a discordant diagnosis were LV ejection fraction (EF) <50% [OR 2.2 (CI 1.2–4.0), $P = 0.01$], TAPSE <17 mm [OR 2.8 (1.5–5.5), $P < 0.01$], V-wave cut-off sign [OR 2.8 (1.5–5.4), $P < 0.01$], and TR-grade > 3 [OR 2.9 (1.5–5.4), $P < 0.01$]. The presence of neither of these parameters or the presence of all parameters excluded or verified a discordant PHT diagnosis with high diagnostic certainty (24% of patients).

Clinical and echocardiographic implications of transcatheter tricuspid valve repair

Clinically, 75% of patients demonstrated improvement in NYHA class during follow-up comparably in all groups ($P = 0.81$ for between-group comparisons, *Figure 4*). Overall, 6-min walk distance increased [+49 (CI 35–62) m, $P < 0.01$] and NT-pro-BNP levels were reduced [-455 (CI -733 to -219) ng/L, $P < 0.01$], with a non-significant improvements in the iPHT+/ePHT- group (*Figure 4*).

Echocardiographically, tricuspid valve EROA [-0.27 (CI -0.32 to -0.22) cm^2, $P < 0.01$], and vena contracta [-4.1 (CI -4.6 to -3.6) mm, $P < 0.01$] were similarly reduced in all groups (*Figure 4*). Tricuspid annular plane systolic excursion did not change significantly after TTVR [-0.5 (CI -1.3 to 0.35) mm, $P = 0.27$]. Overall, echocardiographically determined PAPs declined after TTVR [-3.6 (CI -5.5 to -1.7) mmHg, $P < 0.01$]. While echo PAPs was unchanged in iPHT- ($P = 0.13$) and decreased in iPHT+/ePHT+ ($P < 0.01$) patients, it increased in iPHT+/ePHT- patients ($P < 0.01$; *Figure 5*). Similar results were obtained when considering isolated TTVR or combined TMTVR patient separately.

In isolated TTVR, NYHA class improved in 66% of patients as compared to 86% in patients with combined TMTVR ($P < 0.01$), without differences between iPHT/ePHT groups within both patient cohorts. Six-min walk distance, NT-pro-BNP, and echocardiographic changes in these two subgroups mirrored those of the overall cohort (data not shown).

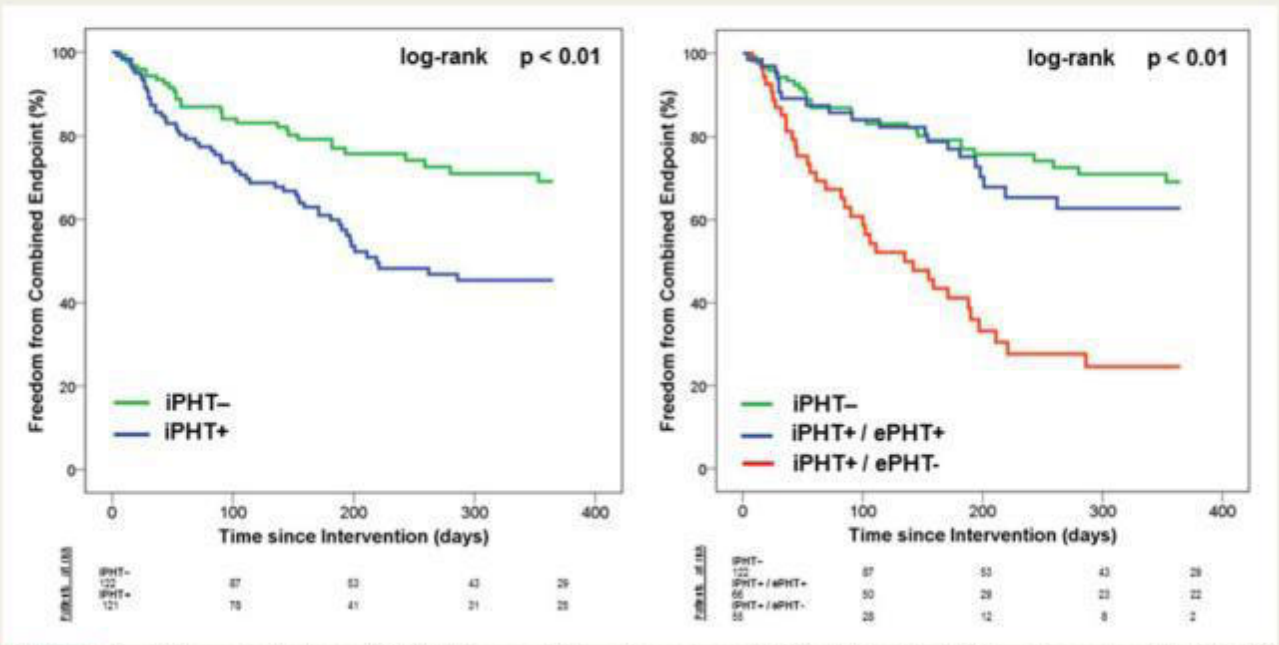


Figure 3 Event free survival between iPHT/ePHT groups.ePHT-, echocardiographic PAPs <50 mmHg; ePHT+, echocardiographic PAPs ≥50 mmHg; iPHT-, invasive PAPs <50 mmHg; iPHT+, invasive PAPs ≥50 mmHg.

The use of 60 mmHg as cut-off to define iPHT and ePHT yielded similar overall results to the analyses using a cut-off of 50 mmHg (Supplementary material online, *Figure S2*, *Tables S4* and *S5*).

Discussion

This is the first study comprehensively assessing the role of PHT in patients with severe TR at high surgical risk undergoing TTVR. The main findings can be summarized as follows:

(1) PHT frequently coexists with severe TR and is associated with more severe right and LV HF and a higher preoperative risk.
(2) Echocardiographic assessment of PAPs is of limited diagnostic value for the presence of PHT. In fact, sensitivity and specificity to accurately detect invasively confirmed PHT in patients with severe TR was only 55% and 74%, respectively.
(3) Patients with both iPHT and ePHT had similar outcomes as patients without iPHT in terms of hard clinical endpoints, whereas iPHT and a false negative echocardiographic PHT diagnosis had the worst outcomes.
(4) RV–PA coupling is independently associated with event-free survival in patients undergoing isolated TTVR.

Pulmonary hypertension often coexists with TR and TV dysfunction by RV pressure overload and subsequent remodelling.[4] The combined presence of TR and PHT indicates a poor prognosis and high operative risk[4,18] in a population traditionally underserved by surgical therapies.[19] Current guidelines exclude patients with PHT from surgical interventions[7] and the potential implications of PHT for TR treatment are yet unknown. For the first time, TTVR represents a potential treatment option for TR in patients with PHT, and serves as an opportunity to enhance our understanding of PHT in TR.

Our patient cohort is 10–20 years older and at higher estimated preoperative risk than cohorts reported to have undergone tricuspid surgery.[20–22] Data on the frequency of PHT in patients considered to undergo treatment are rare. Kundi *et al.* reported that only 17% of Medicare beneficiaries undergoing either TV repair or replacement were diagnosed with PHT. We found that a much higher percentage of patients with TR (50%) exhibit PHT at this later presentation age and accompanying risk, and that PHT is associated with more severe RV systolic dysfunction.[20]

Although echocardiography is the non-invasive reference standard to assess TR severity and PHT by estimation of PAPs, it has been recognized that the determination of PAPs might be limited in severe TR patients.[14,23]

Uniquely, our study included both invasive and echocardiographic approaches to diagnose PHT. Although a positive linear correlation was evident between invasive and echocardiographic PAPs, the sensitivity to adequately identify patients with PHT by echo was only 55%. Doppler echocardiography can underestimate PAP in severe TR[14] due to: (i) rapid pressure equalization between RA and RV with an effective loss of a RV–RA pressure gradient and (ii) the underestimation of RAP in the setting of severe TR. Indeed, patients with a false negative echocardiographic PHT diagnosis showed the most severe TR grades. Furthermore, echocardiography significantly underestimated invasively assessed RAP.

During follow-up, event rates were substantially elevated at an overall mortality rate of 19% at roughly 11 months of follow-up. However, considering the high-risk cohort in this study, these numbers seem to compare favourably to tricuspid surgery series and studies investigating the natural history of TR.[1,21] Pulmonary hypertension has been shown to be associated with unfavourable outcomes after a number of surgical and percutaneous valvular

Table 4 Patient characteristics according to iPHT/ePHT groups

Baseline iPHT/ePHT groups	iPHT+/ePHT− (*n* = 55)	iPHT+/ePHT+ (*n* = 66)	Mean difference/Hodges–Lehmann estimator[a] (CI)	*P*-value
Age (years)	75 ± 10	76 ± 8	-1 (-5 to 2)	0.38
Female sex, *n* (%)	27 (49)	28 (42)	—	0.47
BMI (kg/m^2)	28 ± 5	27 ± 5	0 (-1 to 2)	0.65
EUROscore II (%)	10.5 ± 9.2	7.6 ± 4.8	2.9 (0.4 to 5.5)	0.03
STS predicted mortality (%)	7.6 ± 8.1	5.7 ± 5.9	1.9 (-0.6 to 4.4)	0.14
eGFR (mL/min/1.73 m^2)	44 ± 26	42 ± 17	2 (-6 to 10)	0.60
eGFR <30 mL/min/1.73 m^2, *n* (%)	17 (31)	18 (27)	—	0.69
Chronic dialysis, *n* (%)	7 (13)	3 (5)	—	0.10
Previous PCI, *n* (%)	14 (26)	12 (18)	—	0.38
Previous CABG, *n* (%)	10 (18)	5 (8)	—	0.10
Previous valve intervention, *n* (%)	10 (18)	7 (11)	—	0.30
Atrial fibrillation, *n* (%)	46 (84)	64 (97)	—	0.02
Chronic lung disease, *n* (%)	15 (27)	22 (33)	—	0.55
Right ventricular lead present, *n* (%)	17 (31)	20 (30)	—	0.94
HF hospitalization prior year, *n* (%)	43 (84)	53 (83)	—	0.83
Symptomduration (months)	9 (4–25)	12 (6–17)	0 (-3 to 3)[a]	0.99
NYHA II, *n* (%)	0 (0)	7 (11)	—	0.01
NYHA III, *n* (%)	28 (51)	39 (59)		
NYHA IV, *n* (%)	27 (49)	20 (30)		
NT-pro-BNP (ng/L)	5 084 (2438–8201)	3757 (1857–6805)	-548 (-1938 to 665)[a]	0.33
6-min walk distance (m)	175 ± 93	221 ± 120	-46 (-89 to -3)	0.04
Right heart catheter—PHT groups				
PAP systolic (mmHg)	60 ± 11	62 ± 13	-2 (-6 to 3)	0.46
PAP mean (mmHg)	40 ± 7	39 ± 8	0 (-2 to 3)	0.74
PAP mean >25 mmHg, *n* (%)	53 (98)	64 (99)	—	0.90
RAP mean (mmHg)	20 ± 7	16 ± 6	4 (1–6)	<0.01
PCWP or LAP mean (mmHg)	24 ± 5	24 ± 7	0 (-2 to 3)	0.76
Pulmonary vascular resistance (WU	3.8 ± 2.1	4.6 ± 2.6	-0.8 (-1.7 to 0.1)	0.09
Transpulmonary gradient (mmHg)	16 ± 6	16 ± 8	0 (-3 to 3)	0.92
TAPSE/PAPs ratio (mm/mmHG)	0.27 ± 0.09	0.28 ± 0.09	-0.01 (-0.04 to 0.03)	0.63
Echo variables—PHT groups				
LV ejection fraction (%)	46 ± 15	52 ± 15	-5 (-11 to 0)	0.05
LV EDD (mm)	52 ± 9	53 ± 9	-1 (-4 to 3)	0.62
TAPSE (mm)	15 ± 5	16 ± 4	-1 (-2 to 1)	0.34
RA area (cm^2)	36 ± 13	37 ± 10	-1 (-5 to 3)	0.64
RV midventricular diameter (mm)	43 ± 8	44 ± 8	-1 (-4 to 2)	0.56
TV annulus diameter (mL/m^2)	46 ± 6	48 ± 6	-2 (-4 to 0)	0.07
Estimated PAPs (mmHg)	42 ± 10	65 ± 15	-23 (-28 to -19)	<0.01
TR vena contracta (mm)	10 ± 3	9 ± 3	1 (0–2)	0.15
TR EROA PISA (cm^2)	0.60 ± 0.41	0.45 ± 0.20	0.16 (0.04–0.27)	0.01
TR coaptation gap (mm)	6 ± 3	5 ± 2	1 (0–2)	0.07
TR tenting height (mm)	9 ± 4	9 ± 3	0 (-2 to 1)	0.76
TR tenting area (cm^2)	2.0 ± 1.0	2.2 ± 0.9	-0.2 (-0.6 to 0.2)	0.31
Mitral regurgitation				
Grade 0–1	20 (36)	20 (30)	—	0.68
Grade 2	12 (23)	12 (18)		
Grade 3	19 (34)	29 (44)		
Grade 4	4 (8)	5 (8)		

Continued

Table 4 *Continued*

Baseline iPHT/ePHT groups	iPHT+/ePHT− (*n* = 55)	iPHT+/ePHT+ (*n* = 66)	Mean difference/Hodges–Lehmann estimator[a] (CI)	*P*-value
Tricuspid regurgitation				
Grade 2	3 (6)	8 (12)	—	<0.01
Grade 3	27 (49)	51 (77)		
Grade 4	25 (46)	7 (11)		

For completeness of data please refer to Supplementary material online, Table S6.
[a]Symptomduration (months) = duration of heart failure symptoms prior to TTVR NT-proBNP.
BMI, body mass index; CABG, coronary artery bypass grafting; CI, 95% confidence interval; EDD, end-diastolic dimension; ePHT-, echocardiographic PAP < 50 mmHg; ePHT+, echocardiographic PAP ≥ 50 mmHg; EROA, effective regurgitation orifice area; HF, heart failure; iPHT-, invasive PAP < 50 mmHg; iPHT+, invasive PAP ≥ 50 mmHg; LAP, left atrial pressure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PAPs, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; PISA, proximal isovelocity surface area; RA, right atrial; RAP, right atrial pressure; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve; WU, Wood units.

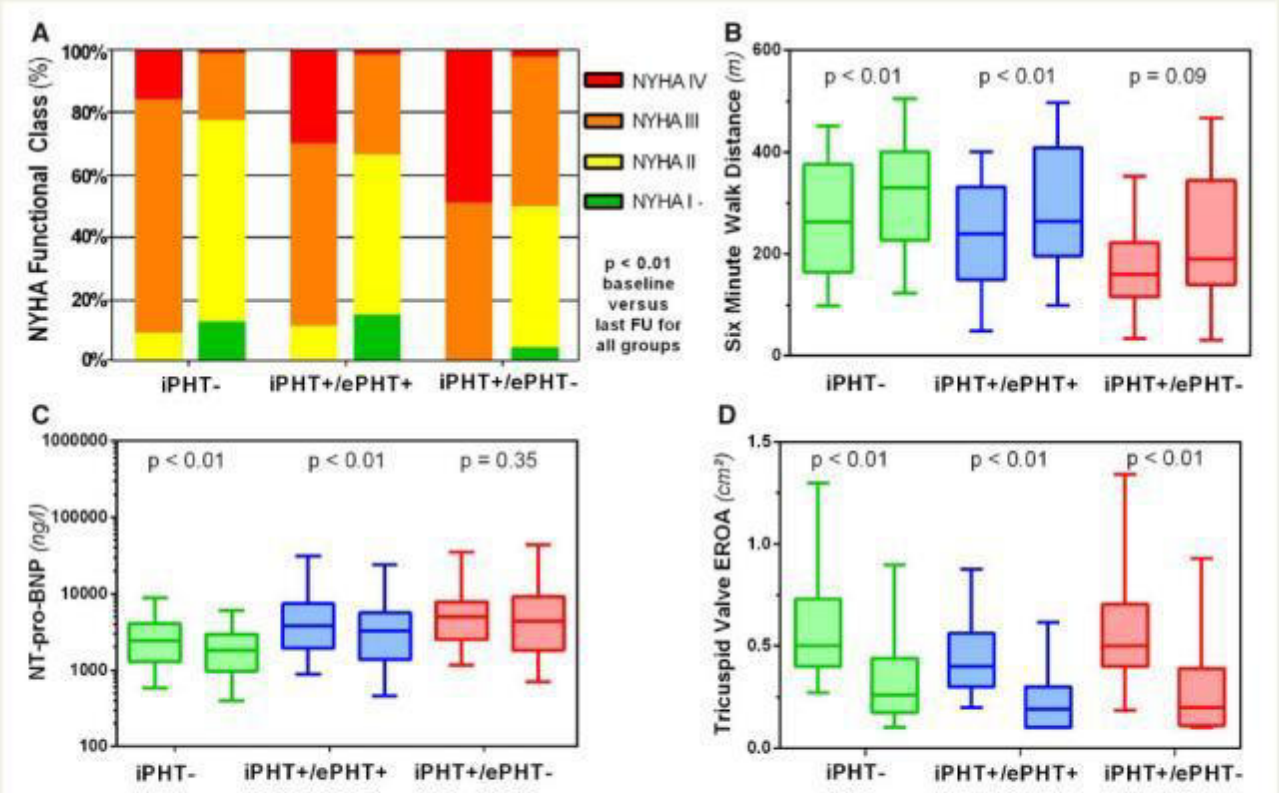


Figure 4 Clinical and echocardiographic changes according to iPHT/ePHT groups. Development of (*A*) New York Heart Association functional class, (*B*) 6-min walk distance, (*C*) N-terminal pro-B-type natriuretic peptide, and (*D*) tricuspid valve effective regurgitation orifice area from baseline (left plot for each group) to last follow-up (right plot for each group). Data are presented as frequencies bars (*A*) and box plots (25th centile, median, and 75th centile) and whisker (5th and 95th centiles) (*B–D*). ePHT-, echocardiographic PAPs<50 mmHg; ePHT+, echocardiographic PAPs≥50 mmHg; iPHT-, invasive PAPs<50 mmHg; iPHT+, invasive PAPs ≥50 mmHg.

interventions including aortic valve replacement,[24] percutaneous mitral valve edge-to-edge repair,[25] and mitral- and/or tricuspid surgery.[20,26] However, conflicting data exist in tricuspid surgery, while Di Mauro *et al.*[20] clearly demonstrate that the presence of PHT is associated with mortality, Kundi *et al.*[21] report an HR of 0.82 for secondary PHT to predict 1-year mortality after tricuspid surgery, suggesting that the presence of PHT is rather protective. Although the authors do not comment on their technique to assess PHT or further interpret this finding in their manuscript, our data might contribute to reconcile these conflicting data.

Although echocardiography underestimates pulmonary pressures in a significant number of patients with TR, this diagnostic limitation

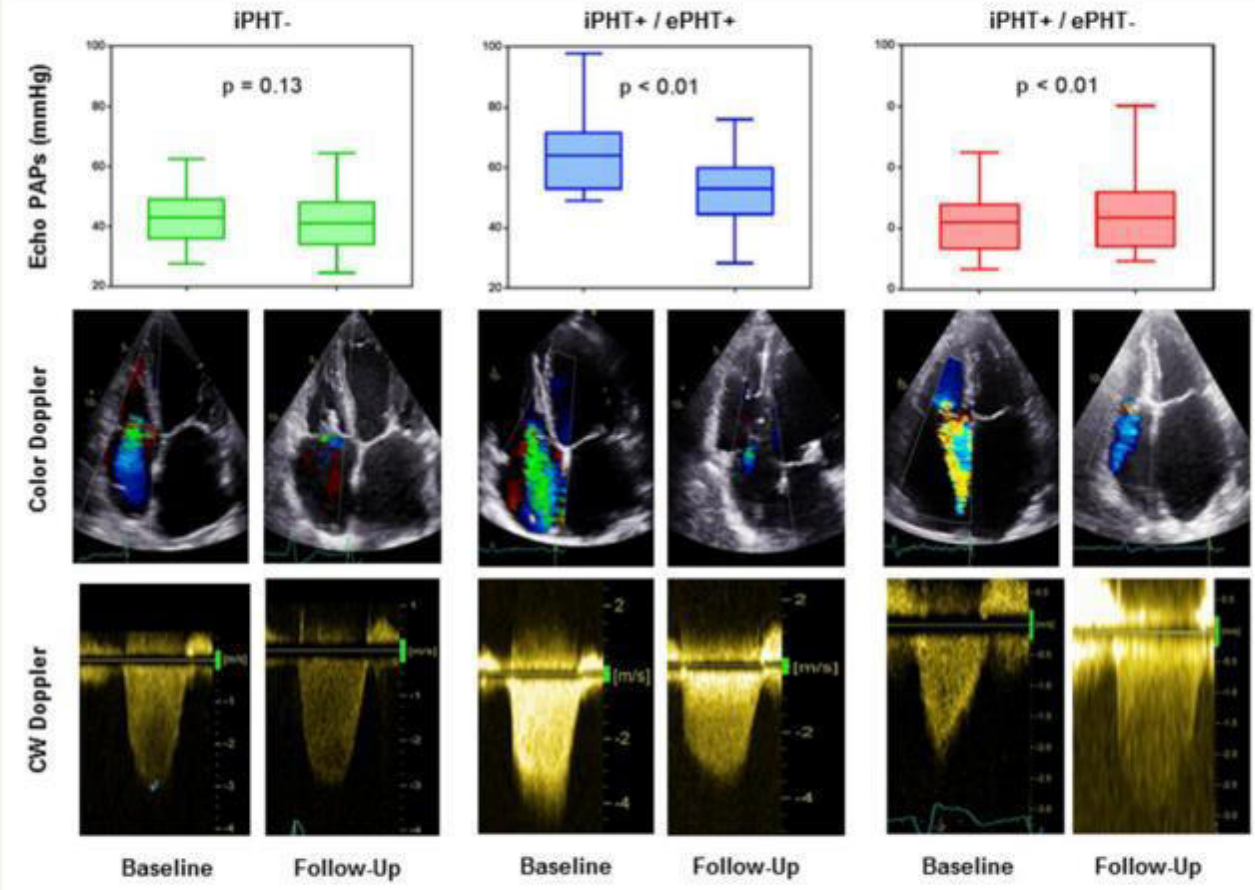
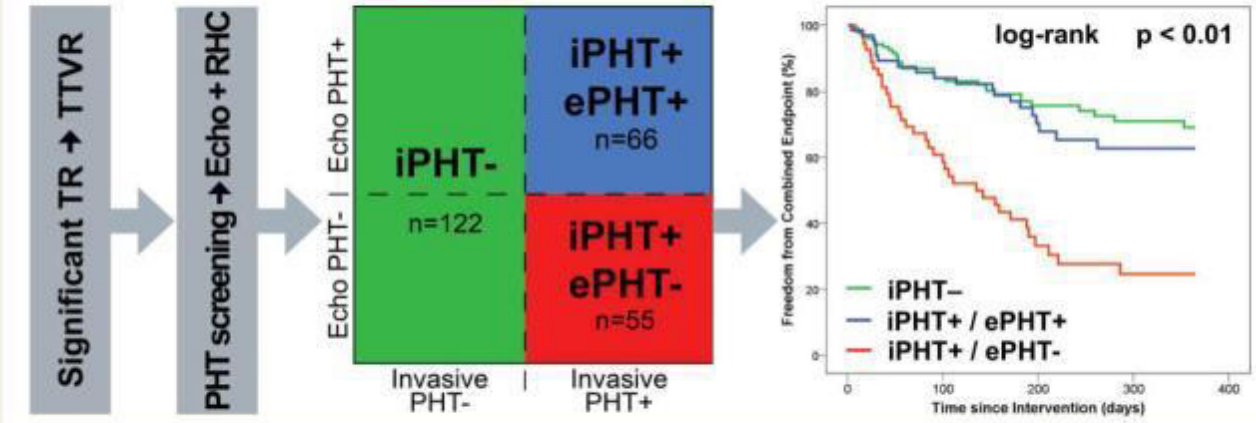


Figure 5 Evolution of echocardiographic systolic pulmonary artery pressure after transcatheter tricuspid valve repair according to iPHT/ePHT groups. Data are presented as box plots (25th centile, median, and 75th centile) and whisker (5th and 95th centiles). Note the V-wave cut-off sign at baseline in iPHT+/ePHT- group. ePHT-, echocardiographic PAPs <50 mmHg; ePHT+, echocardiographic PAPs ≥50 mmHg; iPHT-, invasive PAPs <50 mmHg; iPHT+, invasive PAPs ≥50 mmHg. iPHT- (n = 110); iPHT+/ePHT- (n = 44); iPH+/ePHT+ (n = 65).

conveys additional prognostic information. The combination of echocardiographic and invasive assessment of pulmonary pressures reveals two distinct patient cohorts: patients with a concordant PHT diagnosis (iPHT+/ePHT+) with a similar outcome as patients without PHT; and patients with a discordant diagnosis (iPHT+/ePHT- patients), who have the worst outcome. The inferior outcome of a discordant diagnosis might be explained by more severe baseline symptoms, a lower LV-EF and more severe TR. In addition, procedural success was less frequent in patients with a discordant diagnosis, which itself is a predictor of outcome[12] and is probably explained by the presence of more severe TR. Interestingly, there were no significant differences in TASPE between the two cohorts. However, TAPSE in patients with a discordant diagnosis and more severe TR might be overestimated and not reflecting true RV contractility. The finding of a discordant PHT diagnosis as an independent predictor for outcome suggests that this feature is not explained by conventional risk factors but represents a novel and easily applicable marker for outcome prediction in TTVR.

Echocardiographically estimated PAPs decreased during follow-up in the overall cohort as well as in the iPHT+/ePHT+ group. This is most likely explained by concomitant treatment of MR. In fact, iPHT+ was not predictive of the occurrence of the combined endpoint on Cox regression analysis in the combined TMTVR group, suggesting that MR treatment also ameliorates PHT. In addition, reduction in RV volume overload improves septal interaction and thereby facilitates LV filling following TTVR with consequently lower LV filling pressures, which could explain the PAPs decrease in the isolated TTVR concordant PHT group.[27,28] Conversely, estimated PAPs increased in iPHT+/ePHT- patients. We argue that TTVR restores the RA–RV gradient and thereby the validity of echocardiographic PAP estimation, rather than representing a true rise in PA pressures. However, given the missing invasive follow-up data, it cannot be excluded that a true rise in PAPs might have occurred in iPHT+/ePHT- patients. These findings illustrate the complexity of PAP estimation before and after TR treatment. If potential induction of RV afterload by TTVR is found to be detrimental, this certainly will have to be assessed invasively in future trials.

Our data imply that echocardiography as a singular technique is not sufficient to screen for or follow-up on the development of PHT in the majority of patients undergoing TTVR. However, a combined



Take home figure Flow for risk assessment of patients with tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve repair (TTVR) according to pulmonary hypertension (PHT) using echocardiography (Echo, *e*) and right heart catheter (RHC, invasive, *i*).

diagnostic approach with invasive assessment and echocardiography offers incremental value for prognostication of TR patients. In fact, patients with a concordant iPHT and ePHT diagnosis had a similar outcome to patients without PHT, suggesting TTVR as a useful therapeutic approach also in selected PHT patients. Importantly, previous and ongoing trials in the field of TTVR exclude patients with estimated PAP > 60 mmHg,[29,30] clinicaltrials.gov NCT02981953). The results of this study do not support the exclusion of patients with ePHT in clinical trials and further highlight the importance of incorporating invasive PHT assessment in the work-up of patients with severe TR and TTVR trial protocols to allow for optimal haemodynamic and prognostic stratification. As such, a discordant invasive and echocardiographic PHT diagnosis might serve a better exclusion criterion than the presence of ePHT in future TTVR trials.

A number of limitations have to be considered when interpreting the findings. Although the present cohort of patients undergoing TTVR with comprehensive assessment of PHT is the largest published thus far, the number of patients is still limited. Given the availability of echocardiographic and invasive PAPs in all patients with TR and the good comparability of invasive and non-invasive assessments, we used PAPs ≥50 mmHg as criterion to define PHT in our study. However, guideline recommended PHT definitions are based on PAPm ≥ 25 mmHg. Future studies are needed to establish the optimal echocardiographic parameters for the assessment of PHT probability in TR patients given the apparent shortcomings in standard imaging. Echocardiographic and hemodynamic data were analysed by experienced institutional cardiologists, but there were no echocardiographic or hemodynamic core lab analyses performed. Although comparable to previous studies investigating the role of echo and invasive PAP assessment, the time interval between echocardiographic and invasive assessment might have introduced some confounding. A significant proportion of patients underwent concomitant treatment for MR. This was well-balanced between iPHT+/ePHT+ and iPHT+/ePHT- patients, thereby unlikely to explain the major divide in clinical outcomes of these two cohorts. Nevertheless, some confounding is likely and needs consideration. Finally, TTVR produces multiple TR jets. In this scenario, no echocardiographic quantitative estimation of TR has been validated up to date. In the future, a head to head comparison of cardio magnetic resonance imaging and echo based TR quantification could help to establish reliable echo TR quantification after TTVR.

In conclusion, PHT is a frequent finding in patients scheduled for TTVR and associated with more severe HF and a predisposition to worse hard clinical outcomes, although clinical improvement can be achieved by TTVR irrespective of PHT status. Combining invasive and echocardiographic assessment of PHT is essential for risk stratification and patient selection. TTVR poses a promising therapeutic option also in patients with TR and PHT, especially if invasive and echocardiographic PHT diagnosis is concordant.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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2.2.4 Klinische Effektivität einer katheterbasierten Trikuspidalklappenrekonstruktion bei Patienten mit Herzinsuffizienz und erhaltener Pumpfunktion

Zitierweise:

Kresoja KP, Lauten A, Orban M, **Rommel KP**, Alushi B, Besler C, Braun D, Unterhuber M, Stangl K, Landmesser U, Massberg S, Thiele H, Hausleiter J, Lurz P. Transcatheter tricuspid valve repair in the setting of heart failure with preserved or reduced left ventricular ejection fraction.
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RESEARCH ARTICLE

Transcatheter tricuspid valve repair in the setting of heart failure with preserved or reduced left ventricular ejection fraction

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Aims Severe tricuspid regurgitation (TR) impairs prognosis in patients with left-sided heart failure (HF) with preserved (≥50%, HFpEF) and reduced ejection fraction (<50%, HFrEF). Transcatheter tricuspid valve edge-to-edge repair (TTVR) potentially improves prognosis among patients with severe TR. We sought to assess the impact of left-sided HF types on outcomes of TTVR.

Methods and results In this retrospective study, 71 HFpEF and 40 HFrEF patients, defined according to the European Society of Cardiology criteria, with isolated TR treated by TTVR in two tertiary care centres between 2016 and 2019 were analysed. The primary outcome was a composite outcome of all-cause mortality and HF hospitalization at 12 months [median follow-up 238 (interquartile range 175–365) days]. Additionally, a propensity score matching with a conservatively treated cohort of 914 patients with severe TR was performed. Procedural success did not differ between HFpEF (mean age 75.9 ± 9.3 years) or HFrEF (mean age 74.7 ± 9.1 years) patients (86% vs. 78%, $P = 0.299$). The primary endpoint occurred more frequently in patients with HFrEF as compared to HFpEF (50% vs. 30%, $P = 0.016$). Procedural success was associated with a reduced occurrence of the primary endpoint among patients with HFpEF ($P < 0.001$) but not HFrEF ($P = 0.813$), while both groups showed improvement in New York Heart Association functional class (both $P < 0.001$). After matching for age, EuroSCORE II, presence of a right ventricular lead and systolic pulmonary artery pressure, successful TTVR was associated with lower mortality as compared to conservative therapy in HFpEF patients ($P = 0.020$), but not in HFrEF patients ($P = 0.274$).

Conclusion Transcatheter tricuspid valve edge-to-edge repair might be a treatment option in patients with severe TR and HFpEF compared to conservative therapy.

Keywords Tricuspid regurgitation • Heart failure • Heart failure with preserved ejection fraction • Heart failure with reduced ejection fraction • Heart valve disease • Transcatheter heart valve therapies

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Introduction

The natural history of patients with left-sided heart failure (HF) is frequently characterized by the development of significant tricuspid regurgitation (TR).[1–4] Severe TR is associated with a dismal prognosis in HF patients irrespective of left ventricular (LV) function.[5,6] However, while severe TR has been shown to be associated with impaired outcomes in patients with left-sided HF and preserved ejection fraction (HFpEF),[6,7] its role in patients with HF and mid-range/reduced ejection fraction (HFmrEF/HFrEF) is more controversial.[5,8] Distinguishing the type of left-sided HF might be crucial in patients with severe TR as, on the one hand, the development and progression of TR has been proposed as a key mechanism and prognostic factor in the heterogeneous syndrome of HFpEF.[3,8,9] On the other hand, the prognostic significance of severe TR in HFrEF patients has been discussed controversially as the condition itself might serve as competing risk.[5,10]

Isolated severe TR is often undertreated surgically, given the late presentation of patients at high perioperative risks and a substantial perioperative mortality.[11–13] Recently, new transcatheter treatment options, on a compassionate use basis, have emerged,[12–14] amongst them the most widely performed leaflet edge-to-edge repair technique with the MitraClip, providing a treatment option also for patients at high or prohibitive surgical risk.[15] Successful transcatheter tricuspid valve edge-to-edge repair (TTVR) has been suggested to reduce symptom burden[16–18] and even to reduce mortality and HF hospitalizations when compared to a conservatively treated propensity-matched cohort of patients.[19] However, it remains unclear whether this holds true for patients with different types of concomitant left-sided HF. Additionally, most previous analyses also included patients undergoing combined interventional treatment for severe mitral regurgitation, which hampers conclusions on the benefit of interventional TR treatment in left-sided HF.

We therefore sought to assess the clinical effects and outcomes of successful TTVR in patients with isolated TR and left-sided HF stratified according to the guideline-based definitions of HF with reduced and preserved ejection fraction. Furthermore, we aimed to investigate the prognostic role and effect size of TTVR in HFpEF and HFrEF patients as compared to a conservatively treated cohort of patients with relevant TR.

Methods

Study population

For this analysis, 147 consecutive patients undergoing isolated TTVR using the MitraClip device for symptomatic, at least moderate to severe TR in two high-volume tertiary care centres between July 2016 and April 2019 were included. All patients had symptoms of HF and were in New York Heart Association (NYHA) functional class II to IV despite guideline-directed medical therapy (GDMT). Pre-procedural assessment included a comprehensive transthoracic (TTE) and transoesophageal echocardiography (TOE), evaluation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (Cobas, Elecsys NT-proBNP II, Roche, Basel, Switzerland) and a 6-min walk test. Echocardiographic assessment was performed as described before.[17,18,20] In brief, grading of TR severity was based on the assessment of vena contracta, effective regurgitant orifice area, and estimated regurgitant volume, and TR severity grades of mild, moderate, and severe were extended by a grade IV (massive or torrential according to previous publications).[21,22] LV ejection fraction (LVEF) was assessed on baseline TTE and in cases of uncertainties additional three-dimensional TTE was performed. Patients were discussed at the local heart team meeting and considered to be at high or prohibitive risk for surgery. Therefore, an interventional approach for treatment of TR on a compassionate use basis was suggested. Patients with poor echocardiographic visualization of the tricuspid valve on screening TOE, with pacemaker lead induced TR, with any degree of tricuspid valve stenosis, with severe aortic stenosis and with tricuspid anatomy deemed unsuitable for edge-to-edge repair were excluded from TTVR. HFpEF was defined according to current European Society of Cardiology HF guidelines,[23] as LVEF ≥50%, NT-proBNP elevation, HF symptoms and evidence of elevated filling pressures on echocardiography. HFrEF was defined by a LVEF ≤49% and elevated NT-proBNP, as well as signs or symptoms of HF (HFmrEF the subgroup of HFrEF patients with an LVEF 40–49%).[23]

Patients with evidence of pre-capillary pulmonary hypertension [medical history or invasive evidence defined as pulmonary capillary wedge pressure (PCWP) <15 mmHg and invasive mean pulmonary artery pressure (mPAP) ≥25 mmHg] and patients with missing data precluding stratification in left- or right-sided HF were excluded from the current study.

Follow-up examinations

Patients underwent TTE assessment at discharge, and at 1-,6- and 12-month follow-up visits. On each visit, symptoms and quality of life were recorded, a physical examination and a 6-min walk test were performed. Patients were regularly contacted by telephone if no further outpatient appointments were scheduled.

Outcomes

Procedural success of TTVR was defined as successful clip placement and reduction of TR of at least one grade assessed on TTE at discharge, as described before.[15,17,22]

The primary outcome was a combined endpoint of all-cause mortality and rehospitalization for HF within 1 year after the index procedure.

Secondary outcomes included changes in NYHA functional class, quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), NT-proBNP level and 6-min walk test at last available follow-up.

Matched control cohort

Consecutive patients evaluated at Charité Medical University, Campus Charité Mitte and Benjamin Franklin formed the control cohort of patients with at least moderate to severe functional TR between 2010 and 2017. Patients were retrospectively identified on the basis of the presence of at least moderate to severe TR with functional aetiology. A local institutional review board for the collection of retrospective data approved the inclusion of patients in this study. All patients were medically treated according to GDMT. All patients underwent comprehensive TTE with grading of TR severity, as well as stratification into type of left-sided HF as described above. Follow-up was obtained

by contacting the local registration offices. The primary outcome of this cohort was all-cause mortality. Both study cohorts and the investigation conform with the principles outlined in the Declaration of Helsinki.[24]

Statistical analysis and matching

In case of normal distribution (Kolmogorov–Smirnov test), data are given as the mean and corresponding standard deviation (±), if data did not follow normal distribution they are given as median and corresponding interquartile range (IQR). The number of missing data is given in the corresponding tables. Continuous variables were compared with Student's *t*-test and Mann–Whitney U test where appropriate. Categorical variables were compared using the Fisher's exact test.

Kaplan–Meier analyses were used to compare the survival in different subgroups; the log-rank test was used to test for differences. Cox regression analyses were performed to test the prognostic relevance of dichotomous/dichotomized and continuous variables with regard to the primary outcome; results are presented as hazard ratios (HR) with corresponding 95% confidence interval (CI).

Patients in the TTVR cohort were matched with the control cohort using propensity score matching with the R-package 'PSMATCHING3.04'. Propensity scores were calculated using age, EuroSCORE II, presence of a right ventricular (RV) lead and echocardiographically estimated pulmonary artery systolic pressure (Echo-sPAP) for HFpEF patients, and using age, EuroSCORE II, presence of an RV lead, Echo-sPAP as well as LVEF for HFrEF patients. For each case, one control patient was randomly selected from the potential pool of candidates defined by the parameters using the nearest neighbour rule of ±0.20 standard deviation. A two-sided significance level of α 0.05 was defined appropriate to indicate statistical significance. Statistical analyses were performed using the SPSS software (IBM Corp. released 2017; IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA) and matching was performed using R version 3.3.0 (R Core Team 2016;, R Foundation for Statistical Computing, Vienna, Austria).

Results

Study cohort and baseline characteristics

Overall, 147 patients underwent isolated TTVR between 2016 and 2019 at our two tertiary care centres. Eight patients were excluded due to either history or invasive evidence of pre-capillary pulmonary hypertension and 28 patients were excluded due to missing data precluding clear stratification into left- or right-sided HF. The final analysis comprised 71 patients with HFpEF and 40 patients with HFrEF (19/40 with mid-range ejection fraction). Of note, all of the HFpEF patients who had invasive filling pressures measured (n = 61), had elevated PCWP or LV end-diastolic pressure (LVEDP) ≥15 mmHg.

Baseline characteristics are shown in *Table 1*. There was no difference in age, sex or body mass index between patients with HFpEF and HFrEF. The perioperative risk was elevated in both groups, with a higher EuroSCORE II in HFrEF patients. NT-proBNP levels were higher in HFrEF patients. HF medication was not different between HFpEF and HFrEF patients.

Echocardiographic and haemodynamic characteristics

All patients demonstrated at least moderate to severe TR with sole functional aetiology in all, but in five cases were a mixed morphological and functional aetiology was present. Echocardiographically patients presented with both RV and atrial dilatation. LV dilatation, as indicated by an increased LV end-diastolic diameter (53 ± 9 vs. 49 ± 7 mm; P = 0.004) and impaired RV function (RV fractional area change 36 ± 11% vs. 43 ± 9%; P = 0.001) were more pronounced in HFrEF patients. There were no differences in qualitative or quantitative parameters of TR grading (online supplementary *Table S1*).

On invasive haemodynamic assessment, there were no differences in PCWP/LVEDP (21.2 ± 4.8/62 vs. 21.6 ± 8.1/31 mmHg, P = 0.737) and mPAP (32 ± 9/66 vs. 34 ± 13 mmHg, P = 0.854) between HFpEF and HFrEF patients.

Procedural results

Procedural success did not differ between HFpEF and HFrEF (86% vs. 78%, P = 0.299). The median number of clips deployed did not differ between groups [median 2 (IQR 2–3) clips per patient, P = 0.442], with the predominant position being anteroseptal (online supplementary *Table S2*).

At last available follow-up, both vena contracta [HFpEFΔ median −4 (IQR −6 to −2) mm; HFrEFΔ −4 (IQR −5 to −2) mm; both P < 0.001] and effective regurgitant orifice area [HFpEFΔ median −0.28 (IQR −0.40 to −0.11) cm^2; HFrEFΔ −0.24 (−0.31 to −0.07) cm^2; P < 0.001 and 0.004, respectively] improved significantly, irrespective of the type of left-sided HF (*Figure 1*).

Outcomes after transcatheter tricuspid valve repair

At last available follow-up, both HFpEF and HFrEF patients showed symptomatic benefit after TTVR in terms of NYHA functional class (*Figure 1C*), with 71% of HFpEF patients improving at least one NYHA class vs. 57% of HFrEF patients (P = 0.168 for between-group difference). The 6-min walk distance improved significantly in HFpEF patients but did only show borderline significance in HFrEF patients (P < 0.001 and P = 0.059, respectively; *Figure 1D*). There was no change in NT-proBNP at last available follow-up in either HFpEF [−29 (−437 to 332); P = 0.665] or HFrEF patients [−118 (−1949 to 1501); P = 0.970]. The MLHFQ was reduced in HFpEF patients, indicating favourable quality of life [median Δ −7 (IQR −19 to 1), n = 28; P = 0.008] but not HFrEF patients [Δ −2 (−15 to 18), n = 17; P = 0.758].

During a median follow-up of 238 (IQR 175–367) days (HFpEF median 287, IQR 183–371 vs. HFrEF 201, IQR 153–327 days; P = 0.012), the composite endpoint occurred in 21 (30%) HFpEF patients and 20 (50%) HFrEF patients (P = 0.016) (online supplementary *Figure S1A*). The lower incidence of the composite outcome in HFpEF patients was mainly driven by a lower number of hospitalizations for HF (23% vs. 45%; log-rank P = 0.019), while there were no differences in mortality (online supplementary *Figure S1*). Accordingly, an increase of LVEF per 10% was associated

Table 1 Baseline characteristics

Variable	HFpEF ($n = 71$)	HFrEF ($n = 40$)	P-value
Age, years	75.9 ± 9.3	74.7 ± 9.1	0.500
Female sex, *n* (%)	38 (54)	19 (48)	0.691
BMI, kg/m^2	26.9 ± 5.3	26.8 ± 4.7 ($n = 39$)	0.982
EuroSCORE II, %	6.9 ± 5.2	10.8 ± 12.4	**0.020**
STS score, %	5.1 ± 4.2	5.4 ± 5.2	0.767
Symptoms			
NYHA functional class, *n* (%)			0.520
II	9 (13)	5 (13)	
III	45 (63)	22 (54)	
IV	17 (24)	13 (33)	
6MWD, m	252 ± 132 ($n = 64$)	255 ± 122 ($n = 36$)	0.910
MLHFQ	40 ± 17 ($n = 38$)	45 ± 21 ($n = 21$)	0.303
Past medical history, *n* (%)			
Previous PCI	15 (21)	9 (23)	0.814
Previous CABG	13 (18)	9 (23)	0.621
Previous valvular intervention	14 (20)	8 (20)	1.000
Lung disease	18 (25)	9 (23)	1.000
Current dialysis	3 (4)	4 (10)	0.242
Atrial fibrillation	64 (90)	32 (80)	0.244
RV lead	16 (23)	18 (45)	**0.017**
Medication			
Beta-blocker, *n* (%)	64 (89)	36 (90)	0.744
ACEi/ARB, *n* (%)	51 (71)	29 (73)	0.825
Diuretics, *n* (%)	66 (93)	38 (95)	0.420
Loop diuretic furosemide dose, mg/day	45 (21–100) ($n = 70$)	60 (40–150)	0.165
Lab chart			
NT-proBNP, pg/mL	2150 (1205–4108) ($n = 68$)	4947 (2726–7507)	**0.001**
eGFR, mL/min/1.73 m^2	47 (32–65)	43 (28–58)	0.198
Bilirubin, mg/dL	0.9 (0.61.3) ($n = 69$)	1.0 (0.6–1.5) ($n = 38$)	0.359
AST, U/L	29 (24–38)	30 (24–38) ($n = 38$)	0.970
ALT, U/L	20 (15–26)	23 (14–30) ($n = 36$)	0.229
Albumin, g/L	44 (40–45) ($n = 39$)	45 (41–47) ($n = 17$)	0.260

6MWD, 6-min walk distance; ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MLHFQ, Minnesota Living with Heart Failure questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RV, right ventricular; STS, Society of Thoracic Surgeons.

with a decreased HR for the occurrence of the composite endpoint (HR 0.77; 95% CI 0.63–0.94).

Outcome according to procedural success

Successful TTVR was associated with a significant longer composite event-free survival in HFpEF ($P < 0.001$) but not in HFrEF patients ($P = 0.813$) (*Figure 2*). HFpEF patients with procedural success had less HF hospitalizations (log-rank $P < 0.001$) and all-cause mortality (log-rank $P = 0.001$) with no differences in HFrEF patients (online supplementary *Figure S2*). Procedural success predicted a beneficial 12-month composite outcome in HFpEF patients, also after adjustment for factors that were more frequent in HFrEF patients (i.e. EuroSCORE II, NT-proBNP, or presence of an RV lead, respectively; online supplementary *Table S3*).

Propensity-matched cohort

Of the 914 patients in the conservative cohort, 307 patients were classified as having HFpEF (34%), and 360 (39%) as HFrEF. Furthermore, 247 could not be clearly classified as left- or right-sided HF due to missing data (27%).

After matching with the TTVR cohort, 61 pairs of HFpEF patients and 33 pairs of HFrEF patients were identified. Standardized mean differences are displayed in online supplementary *Figure S3*. Baseline characteristics before and after matching are displayed in online supplementary *Table S4* and *Table 2*, respectively. At baseline, TTVR HFpEF patients more frequently exhibited NYHA functional class III or IV at admission ($P = 0.011$) and had higher RV midventricular diameter ($P = 0.038$). In HFrEF patients, there were no differences in baseline characteristics except for a slightly lower body mass index in the conservative group.

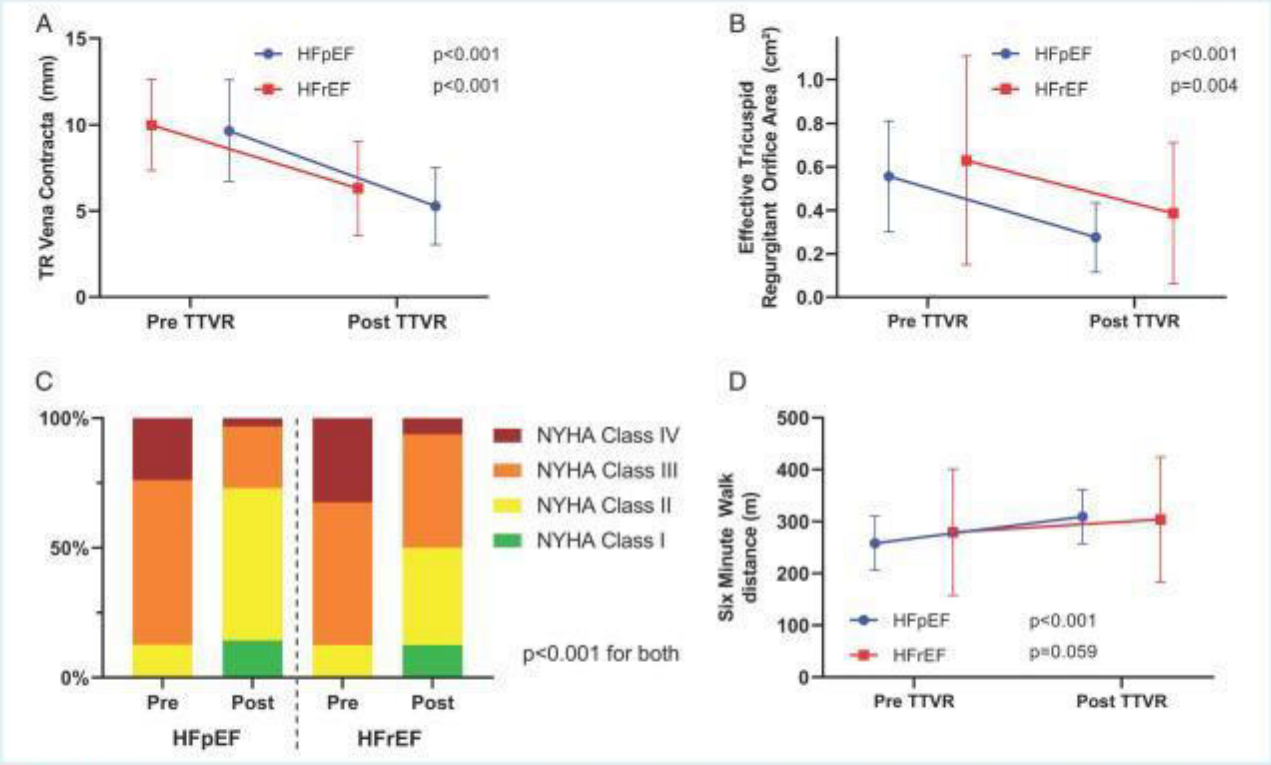

Figure 1 Changes in (*A*) vena contracta, (*B*) effective tricuspid regurgitant orifice area, (*C*) New York Heart Association (NYHA) functional class, and (*D*) 6-min walk test at last available follow-up. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve edge-to-edge repair.

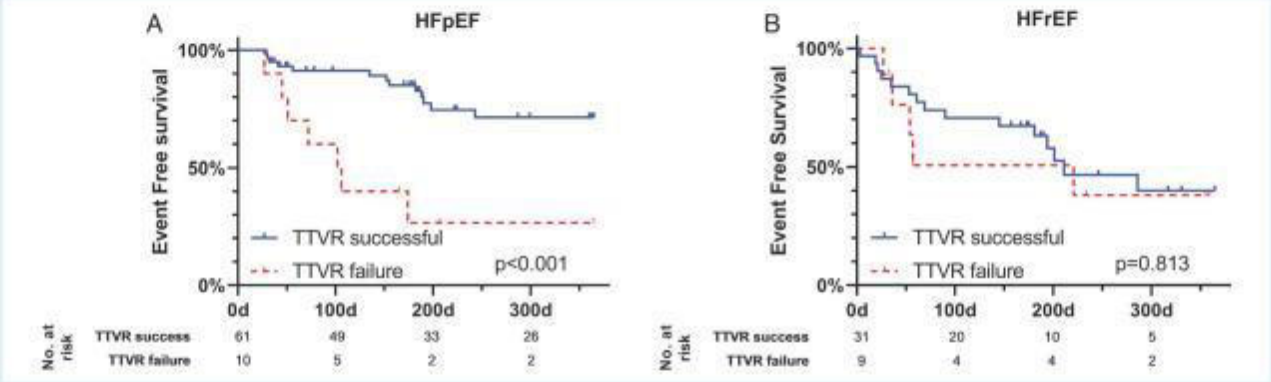

Figure 2 Survival free from the composite endpoint (all-cause mortality and heart failure hospitalization) according to successful transcatheter tricuspid valve edge-to-edge repair (TTVR) in (*A*) heart failure with preserved ejection fraction (HFpEF) patients and (*B*) heart failure with reduced ejection fraction (HFrEF) patients.

Survival of heart failure with preserved or reduced ejection fraction patients: transcatheter tricuspid valve repair vs. matched cohort

Within the HFpEF population, 18 matched control patients (30%) and 6 of the successfully treated TTVR patients (9.8%) died within 12 months. Patients with successful TTVR had a lower all-cause mortality at 12 months when compared to only conservatively treated patients (HR 0.35, 95% CI 0.14–0.89; $P = 0.027$) (*Figure 3A*). However, when patients with procedural failure were included in the analysis TTVR was only borderline significantly associated with improved survival (log-rank $P = 0.056$).

Table 2 Comparison of baseline characteristics in the matched heart failure with preserved and reduced ejection fraction cohorts

	HFpEF			HFrEF		
	TTVR ($n = 61$)	Conservative ($n = 61$)	*P*-value	TTVR ($n = 33$)	Conservative ($n = 33$)	*P*-value
Age, years	77.3 (73.6–81.0)	78.0 (73.0–82.5)	0.674	77.0 (72.6–81)	77.0 (67.5–82.5)	0.878
Female sex, *n* (%)	32 (53)	39 (64)	0.271	16 (49)	15 (46)	1.000
BMI, kg/m^2	25.2 (23.0–30.3)	25.1 (22.0–27.8) ($n = 39$)	0.502	26.0 (23.5–29.9)	25.8 (22–8-26.2) ($n = 30$)	0.128
EuroSCORE II, %	4.4 (2.7–6.4)	4.1 (2.2–6.7)	0.376	6.0 (3.8–8.6)	5.6 (3.3–10.4)	0.748
Comorbidities, *n* (%)						
Coronary artery disease	14 (23)	8 (13)	0.239	12 (36)	12 (36)	1.000
Previous CABG	8 (13)	5 (8)	0.395	6 (18)	6 (18)	1.000
Atrial fibrillation	55 (92)	48 (79)	0.072	27 (82)	23 (70)	0.389
Chronic lung disease	14 (23)	18 (30)	0.537	7 (21)	12 (36)	0.277
RV lead	11 (18)	14 (23)	0.654	14 (42)	11 (33)	0.612
Dialysis	2 (3)	6 (10)	0.272	4 (12)	3 (9)	1.000
NYHA class III/IV at admission	52 (85)	38 (64)	**0.011**	28 (85)	28 (85)	1.000
Lab chart						
NT-proBNP, pg/mL	3336 ± 5126 ($n = 58$)	4754 ± 4429 ($n = 41$)	0.155	8888 ± 13 966	8751 ± 13 924 ($n = 21$)	0.972
Creatinine, mg/dL	1.2 (1.0–1.5)	1.3 (0.9–1.7)	0.859	1.5 (1.2–2.1)	1.4 (1.1–1.9)	0.335
eGFR, mL/min/1.73 m^2	50 (35–68)	50 (32–69)	0.916	40 (27–58)	46 (31–61)	0.493
<45 mL/min/1.73 m^2	20 (33)	25 (41)	0.453	18 (55)	16 (49)	0.806
Echocardiography						
LVEF, %	60 ± 7	60 ± 8	0.879	37 ± 9	36 ± 9	0.787
<40%, *n* (%)	0	0		18 (55)	19 (58)	1.000
TAPSE, mm	17 ± 5	18 ± 5	0.325	15 ± 5	16 ± 4	0.968
<17 mm, *n* (%)	27 (46)	23 (38)	0.459	22 (69)	21 (64)	0.794
Echo-sPAP, mmHg	48 ± 17	50 ± 18	0.559	46 ± 15	43 ± 12	0.361
TAPSE/Echo-sPAP, mm/mmHg	0.40 ± 0.19	0.41 ± 0.19	0.734	0.38 ± 0.17	0.39 ± 0.15	0.850
RV midventricular diameter, mm	43 ± 7 ($n = 54$)	39 ± 9 ($n = 59$)	**0.038**	45 ± 8	41 ± 10	0.104
TR grade, *n* (%)			0.105			0.184
II–III	4 (7)	4 (7)		0	1 (3)	
III	41 (67)	50 (82)		29 (88)	31 (94)	
IV	16 (26)	7 (12)		4 (12)	1 (3)	
TR vena contracta, mm	9.5 ± 3.2 ($n = 54$)	9.7 ± 2.8	0.814	9.9 ± 2.7 ($n = 31$)	9.0 ± 2.4 ($n = 32$)	0.120
TR EROA, cm^2	0.59 ± 0.30	0.56 ± 0.20 ($n = 58$)	0.531	0.58 ± 0.43	0.59 ± 0.17 ($n = 28$)	0.922
Medication						
ACEi/ARB, *n* (%)	44 (72)	35/44 (77)	0.493	26 (81)	19/22 (86)	0.723
Beta-blockers, *n* (%)	54 (89)	36/44 (82)	0.401	29 (91)	21/22 (96)	0.638
MRA, *n* (%)	15 (25)	11/44 (25)	1.000	18 (56)	8/22 (36)	0.176
Diuretics, *n* (%)	56 (93)	37/44 (84)	0.196	97 (31)	21/22 (96)	1.000
Furosemide equivalent dose[a], mg/day	45 (26–95)	25 (18–43) ($n = 44$)	**0.004**	60 (40–100)	25 (25–50) ($n = 22$)	0.140
Thiazide diuretics, *n* (%)	20 (34)	9/44 (21)	0.189	5 (16)	2/22 (9)	0.686
MRA dose, mg/day	25 (25–50)	50 (25–50) ($n = 44$)	0.144	25 (25–50)	25 (22–50) ($n = 22$)	0.539

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant office area; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve edge-to-edge repair.

[a] Assumption that 1 mg torasemide equals 2 mg furosemide.

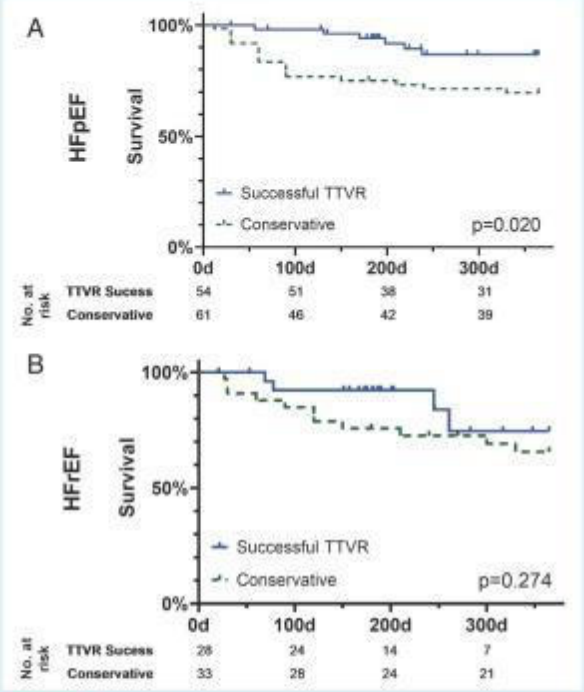

Figure 3 Kaplan–Meier estimates comparing transcatheter tricuspid valve edge-to-edge repair (TTVR) to a matched control cohort according to 12-month survival stratified by (*A*) heart failure with preserved ejection fraction (HFpEF) and (*B*) heart failure with reduced ejection fraction (HFrEF).

In the HFrEF population, 11 matched control patients (33%) and four of the successfully treated TTVR patients (12%) died within 12 months. Successful TTVR was not associated with lower mortality at 12 months compared to the conservative cohort (HR 0.53, 95% CI 0.17–1.69) (*Figure 3B*).

Discussion

This is the first study analysing the impact of TTVR in patients stratified according to left-sided HF types. The main findings are as follows: (i) TTVR was associated with a symptomatic improvement irrespective of left-sided HF type; (ii) the composite outcome of all-cause mortality and hospitalization for HF occurred more frequently in HFrEF patients than in HFpEF patients 12 months after TTVR; (iii) successful TTVR was associated with a reduction of the composite outcome, as well as all-cause mortality and hospitalization for HF in HFpEF patients but not in HFrEF patients at 12 months; (iv) when propensity score matched to a conservatively treated cohort of patients with significant TR, HFpEF patients treated successfully by TTVR showed a higher survival at 1-year follow-up.

Clinically significant TR is a heterogeneous condition comprising a variety of different clinical scenarios such as primary valve pathologies, pulmonary hypertension, atrial fibrillation and other comorbidities, but most often it is secondary to left-sided HF.[1,3–5,8,25] Left-sided HF causes increased LV filling pressures and therefore reduction in pulmonary arterial compliance,[3,26] and sequentially a pressure overload in the right ventricle. This leads to the development of right heart and tricuspid annulus dilatation and the development of TR. Furthermore, atrial fibrillation, which is common among patients with HFpEF and might be induced by increased filling pressures, might by itself cause further dilatation of the tricuspid annulus confined to its portion along the RV free wall.[27] As soon as TR worsens due to RV dilatation, volume overload adds to the pre-existing pressure overload, thereby promoting a vicious circle of RV failure in patients with relevant TR and left-sided HF.[3]

Transcatheter tricuspid valve repair has been shown to improve symptoms,[17,18] induces RV reverse remodelling,[18] reduces hospitalization for HF, and potentially even prolongs survival in a heterogeneous cohort of patients with TR.[19,28] However, overall event rates remain high following TTVR,[17–20] which highlights the disease severity and the need to refine patient selection for tricuspid valve interventions. The aim of this study was to assess the implications of TTVR by stratifying patients according to left-sided HF type, thereby potentially informing on patient selection and trial design in the future.

Our data confirm that in patients with isolated relevant TR the symptomatic burden in HFpEF and HFrEF patients is similar at presentation and might be reduced by successful TTVR. However, prognostic effects of TTVR seem to be confined to HFpEF patients, as TTVR success was associated with better outcomes in HFpEF than in HFrEF patients. These observations made within our TTVR cohort were corroborated within propensity score-matched cohorts of conservatively treated TR patients. Successful TTVR was associated with a reduction in mortality at 12 months in HFpEF but not in HFrEF patients as compared to controls.

While there is clear evidence that significant TR is a contributor to mortality and morbidity in HFpEF patients, this relationship is less clear in HFrEF.[5,6,8,25,29] Competing risks other than TR in HFrEF might have precluded prognostic effects of TTVR in these patients. In our cohort, HFrEF patients were characterized by higher EuroSCORE II, higher rate of previous HF hospitalizations, more progressive LV dilatation and higher NT-proBNP levels. Notwithstanding, the current study cannot fully assess the role of TTVR in patients with HFrEF due to the limited sample size. In addition, TTVR might not reduce mortality but rates of rehospitalization for HF in HFrEF, which was not available in the control group of the propensity matched comparison and therefore could not have been detected in this analysis.

However, the prognostic effect of successful TTVR in HFpEF patients remained significant even after adjusting for differences in baseline characteristics between HFpEF and HFrEF patients. In fact, in patients with HFpEF, a favourable outcome was uniform and consistent when either comparing successful TTVR to failure or conservatively treated patients. As the highest effect was observed for hospitalization for HF within the TTVR cohort, the treatment effect observed in the propensity-matched analysis might even have been underestimated, with only mortality being assessed.

The clinical impact of successful TTVR might reflect an altered specific pathophysiology of TR in HFpEF. At rest and even more

so during exercise, TR causes RV volume overload with LV compression and thereby restrictions in LV filling due to pericardial constraints.[9,26] This pathological ventricular interaction exaggerates diastolic dysfunction in HFpEF patients with a further rise in LV filling pressures.[9,30,31] We recently showed that successful TTVR reduces RV end-diastolic volume, improves RV forward stroke volume and increases LV end-diastolic volumes.[18] The reduction in RV volume overload by TTVR should result in more favourable ventricular interaction with decompression of the left ventricle and improved LV filling secondary to more pulmonary artery forward flow and hence more pulmonary venous return at maintained or even reduced LV filling pressure due to less pericardial constraints.[9] These haemodynamic effects of TTVR might explain the effect on both symptoms and survival in HFpEF patients. In HFrEF patients, these mechanisms might not have a similar impact on a pathologic remodelled left ventricle with impaired systolic function.

The findings of better survival in HFpEF patients undergoing TTVR support the concept of TR as a causal driver of disease progression in HFpEF (rather than a mere surrogate for more advanced disease) and promotes TTVR as a promising interventional therapy to improve survival in this group of patients with limited treatment options.

Within the growing evidence of beneficial effect of TTVR,[19] this analysis is the first focusing on different HF types, suggesting that the distinction between left-sided HF with either preserved or reduced ejection fraction should be included in the future endeavour to refine patient selection for TTVR.

Limitations

Despite comparable patient numbers to recently published studies in the field of TTVR, the overall sample size remains limited. This is in particular the case for HFrEF as opposed to HFpEF patients. Although a propensity score matching generated comparable cohorts, our data are hypothesis generating only and need to be verified in a prospective, randomized controlled setting. Following the propensity score matching differences in diuretic dose, RV midventricular diameter and proportion of patients in NYHA class III/IV at baseline remained in disadvantage to the treatment group in patients with HFpEF. The matched analysis considered mortality only, and results might have differed for rate of HF hospitalization. Given the lack of longitudinal data prior to TTVR in our study, it is not possible to fully ascertain that HFpEF was the cause of severe TR, rather than TR being the cause of elevated filling pressures. Finally, TTVR failure seemed to have a worse outcome than conservatively treated patients; a selection bias towards a more progressed disease stage in patients referred for TTVR cannot be excluded. Another possible explanation is that failed TTVR might be harmful to patients impairing prognosis even further.

Conclusion

In highly selected patients with severe TR, successful TTVR was associated with improved outcomes in patients with HFpEF but not HFrEF. A propensity score matched analysis indicated a clinically relevant survival impact in HFpEF patients. Successful TTVR might therefore pose an effective therapy in haemodynamically proven HFpEF with severe TR.

Supplementary Information

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

Conflict of interest: A.L.: speaker and proctor fees from Abbott, Edwards Lifesciences and Medtronic, as well as consultant for P&F TricValve. K.S.: speaker and proctor fees from Abbott, Edwards Lifesciences and Medtronic. J.H.: speaker honoraria and research support from Abbott Vascular and Edwards Lifesciences. P.L.: consultant to Abbott, Medtronic, Edwards, ReCor, RoxMedical. All other authors have nothing to disclose.

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2.3 ENTWICKLUNG EINES THERAPEUTISCHEN KONZEPTES FÜR PATIENTEN MIT HERZINSUFFIZIENZ UND ERHALTENER PUMPFUNKTION UND RESISTENTER ARTERIELLER HYPERTONIE

2.3.1 Übersicht über physiologische Effekte einer katheterbasierten Modulation des renalen Sympathikotonus

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REVIEW

Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success

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Abstract

Many forms of human hypertension are associated with an increased systemic sympathetic activity. Especially the renal sympathetic nervous system has been found to play a prominent role in this context. Therefore, catheter-interventional renal sympathetic denervation (RDN) has been established as a treatment for patients suffering from therapy resistant hypertension in the past decade. The initial enthusiasm for this treatment was markedly dampened by the results of the Symplicity-HTN-3 trial, although the transferability of the results into clinical practice to date appears to be questionable. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, its effects on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Effects of RDN have been described on many levels in human trials: From altered systemic sympathetic activity across cardiac and metabolic alterations down to changes in renal function. Most of these changes could sustainably change long-term morbidity and mortality of the treated patients, even if blood pressure remains unchanged. Furthermore, a number of promising predictors for a successful treatment with RDN have been identified recently and further trials are ongoing. This will certainly help to improve the preselection of potential candidates for RDN and thereby optimize treatment outcomes. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

Key words: Renal sympathetic denervation; Sympathetic nervous system; Predictors; Hypertension; Renal hypertension

Core tip: The initial enthusiasm for renal sympathetic denervation (RDN) has disappeared. However, the detailed effects of RDN on the complex pathophysiological

mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Moreover, a number of promising predictors for successful RDN treatment have been identified recently which could help to improve future trial design. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

Fengler K, Rommel KP, Okon T, Schuler G, Lurz P. Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success. *World J Cardiol* 2016; 8(8): 436-446 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/436.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.436

BACKGROUND

Many forms of human hypertension are associated with an increased systemic sympathetic activity[1]. Especially the sympathetic nervous system of the kidney plays a key role in the pathogenesis and perpetuation of hypertension. An activation of efferent renal nerve fibers leads to salt and water retention *via* stimulation of α_{1B}-adrenoceptors, activation of the renin-angiotensin-aldosterone system *via* β_1-adrenoceptors causing thereby an increased systemic blood pressure (BP)[1,2]. The release of vasoactive peptides present in renal nerve fibers is also controlled by efferent sympathetic fibers[3,4]. *Via* afferent fibers, the kidney itself affects systemic sympathetic activity[1].

One option to reduce the systemic sympathetic activity is renal sympathetic denervation (RDN). Once introduced as a surgical treatment for hypertension in the past century[5,6], this interesting therapeutic approach lost clinical relevance since medical antihypertensive treatment was introduced to practice. As the burden of cardiovascular diseases associated with hypertension increased over the last decades, RDN experienced a renaissance, now as a catheter-based interventional treatment option[7]. After the first promising trial results, the initial enthusiasm for this therapy strategy was markedly dampened, when the results of the sham-controlled randomized Symplicity-HTN-3 trial did not show any significant effect on BP of RDN-treated *vs* sham-treated patients[8]. The results of this particular trial are part of an ongoing debate and further trials to allow definite conclusion on the effect of RDN on BP are on the way[9]. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, the detailed effects of RDN on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood.

In the following review we present a short overview of the manifold effects described for RDN so far (Table 1).

EFFECTS OF RDN

BP

The main indication for RDN in the past decade and in the past century has been therapy resistant hypertension. Therefore, BP as an end point has been included in nearly every single trial regarding RDN. In almost any trial, controlled, uncontrolled or sham-controlled, a significant BP reduction was found after RDN[7,10-14] (Table 2). However, the largest randomized sham-controlled trial to date, the Symplicity-HTN-3 trial, failed to show any superiority of RDN over sham-control, mostly through an unexpected drop in BP in the sham-treated arm of the trial[8].

Another sham-controlled randomized approach, excluding most of the confounding factors which might have blurred the results of Symplicity-HTN-3 by careful patient selection, the ongoing SPYRAL-HTN trial (NCT02439775), will hopefully give a definite answer to this issue soon.

It is of particular interest, that many of the effects attributed to RDN result in a reduced BP: A diminished systemic vascular tone leading to a reduced afterload, sympathetic mediated alterations in cardiac output, altered sodium- and volume-state or (*via* the renin-angiotensin-aldosterone axis) humoral-mediated changes. Which and how much these effects contribute to a RDN-induced BP drop and how they are counter-regulated remains an unresolved issue that needs to be clarified in future RDN-trials.

Besides other confounders, a constant observation in clinical trials is that a proportion of patients does not respond to RDN, which might in part contribute to the negative results in Symplicity-HTN3. Interestingly, the problem of non-responsiveness to renal denervation seems to be as old as the procedure itself: Even for surgical sympathectomy a high proportion of non-responders (ranging between 55% and 68%) has been described[5,6]. Despite that, a strong positive effect on long-term mortality was found in a large series of 1200 patients[5]. This leads to the question which other beneficial effects besides BP reduction RDN might have in humans, which might explain this discrepancy.

Renal function and sodium excretion

A potential deterioration of renal function - either by renal artery stenosis or by changes in intrarenal hemodynamics - is an often raised concern regarding RDN. On the contrary, as renal blood flow and salt/water retention is influenced by sympathetic activity[2], RDN might have nephroprotective effects.

Two larger non-randomized analyses found glomerular filtration rates (GFR) to be unchanged after RDN[15,16]. Interestingly, one trial could even show a decrease in albuminuria, consistent with an improvement of hypertension-induced end-organ damage[16]. In another study, examining the effects of RDN in patients with impaired renal function, the authors were able to show that the hypertension-related deterioration of renal

Table 1 Effects of renal sympathetic denervation

Ref.	Year	*n* (RDN/control)	Effector	Effect	Control
Ott *et al*[15]	2013	19/-	Renal blood flow	None	None
Pöss *et al*[19]	2015	137/-	Renal sodium excretion	Increased sodium excretion, less pronounced in responders	None
Mahfoud *et al*[24]	2014	55/17	Left ventricular mass	Reduced left ventricular mass after RDN	Medical therapy
Doltra *et al*[25]	2014	5/23			Medical therapy
McLellan *et al*[26]	2015	14/-			None
Lu *et al*[27]	2016	139/-			Meta-analysis
McLellan *et al*[26]	2015	14/-	Atrial conduction	Improved atrial conduction after RDN	None
Qiu *et al*[71]	2016	21/-	Persistent atrial fibrillation	Reduced heart rate after RDN	None
Armaganijan *et al*[96]	2015	10/-	Ventricular arrhythmia	Reduced frequency of ventricular arrhythmia episodes	None
Ott *et al*[15]	2013	19/-	Central hemodynamics	Reduced central BP and augmentation index after RDN	None
Brandt *et al*[98]	2012	110/10		Reduced aortic pulse pressure, pulse wave velocity and augmentation index	Medical
Mortensen *et al*[99]	2012	21/-			None
Hering *et al*[100]	2013	40/10		Reduced augmentation index	Medical
Okon *et al*[101]	2016	23/-		Unchanged invasive pulse wave velocity after RDN	None
Donazzan *et al*[91]	2015	11/-	Sympathetic activity	Reduced cardiac sympathetic activity after RDN	None
van Brussel *et al*[92]	2016	21/-		Unchanged cardiac sympathetic activity after RDN	None
Tsioufis *et al*[93]	2014	14/-		Reduced heart rate and arrhythmia burden and improved heart rate variability after RDN	None
Vink *et al*[95]	2014	13/-			None
Brinkmann *et al*[56]	2012	12/-		Unchanged muscle sympathetic nervous activity after RDN	None
Hering *et al*[57]	2013	10/25		Reduced muscle sympathetic nervous activity after RDN	Medical
Dörr *et al*[58,59]	2015	150/-		Reduced Neuropeptide Y and transiently reduced brain derived neutrophic factor after RDN	None
	2015	100/-			
Dörr *et al*[65]	2015	60/-	Inflammation	Reduced systemic inflammation after RDN	None
Mahfoud *et al*[85]	2011	37/13	Insulin sensitivity	Improved insulin sensitivity after RDN	Medical
Verloop *et al*[86]	2015	29/-		Unchanged insulin sensitivity	None
Ewen *et al*[71]	2014	50/10	Exercise testing	Reduced Exercise BP after RDN	Medical
Ukena *et al*[69]	2011	37/9			Medical
Fengler *et al*[70]	2016	22/26			Sham
Lenski *et al*[72]	2013	36	Orthostatic reaction	None	None

BP: Blood pressure; RDN: Renal sympathetic denervation.

function could be halted with RDN over a follow up of three years[17]. This suggests overall beneficial effects of RDN on renal function, especially in these patients who already suffer from hypertension-induced end-organ damage, which will clearly improve long-term mortality.

Despite the known vasoconstrictive effects of systemic sympathetic activity on the arterial vasculature[2] and significant alterations in an animal study[18], RDN does neither seem to improve nor deteriorate renal blood flow in humans[15]. Presumably, this can be explained by the auto-regulative capacities of the renal vessels outweighing any RDN-induced changes.

The putative effect of RDN on renal sodium excretion is a promising therapeutic goal. The only human trial investigating this hard-to-assess endpoint however showed mixed results, as patients with stronger BP response after RDN showed a diminished effect on sodium excretion compared to those with less BP changes[19]. To some extent this might be explained by a compensatory dietary sodium intake which was not assessed in the study. Therefore, this interesting aspect of RDN needs to be investigated thoroughly by additional rigorous assessment of dietary sodium intake. An additional MRI-based quantification of tissue sodium and water might be helpful here as elevated concentrations are observed in patients with essential hypertension. Sodium and water tissue content might therefore represent an interesting diagnostic and therapeutic goal[20,21].

Cardiac and hemodynamic changes

Left-ventricular-mass and fibrosis: An elevated left-ventricular mass is a frequent finding in hypertensive subjects[22]. Its presence and its regression through therapeutic interventions significantly affects patients' outcomes[22,23]. Therefore, it is a worthwhile therapeutic target in the treatment of human hypertension.

Several smaller studies and one recent meta-analysis describe a reduction of left-ventricular mass after RDN[24-27]. In one of them an additional improvement in left-ventricular strain and ejection fraction was observed in patients with reduced values at baseline[24]. Besides reversal of myocyte hypertrophy left-ventricular fibrosis might be altered by renal denervation, as the absolute extracellular volume was found to be reduced

Table 2 Blood pressure effects of renal sympathetic denervation

Ref.	Year	Control	*n* (RDN/control)	Systolic office BP (mmHg)	P-value	Systolic ambulatory BP (mmHg)	*P*-value
Krum *et al*[7]	2009	None	50	-22	< 0.001[a]	NA	NA
Esler *et al*[11]	2010	RDN *vs* medical	106 (52/54)	-32 *vs* 1	< 0.00001[b]	-11/-7 *vs* -3/-1	NA
Bhatt *et al*[9]	2014	RDN *vs* sham	535 (364/171)	-14 *vs* -12	0.26[b]	-6.8 *vs* -4.8	0.98[b]
Desch *et al*[10]	2015	RDN *vs* sham	71 (35/36, intention to treat)	NA	NA	-8.5 *vs* -4.7	0.06[b]
			63 (29/34, per protocol)	NA	NA	-8.3 *vs* -3.5	0.04[b]
Rosa *et al*[13]	2015	RDN *vs* intensified medical treatment	106 (52/54)	-12 *vs* -14	< 0.001[a]/0.60[b]	-8.6 *vs* -8.1	< 0.001[a]/0.87[b]
Azizi *et al*[14]	2015	Stepped-care antihypertensive treatment with *vs* without RDN	106 (53/53)	-15 *vs* -9	0.15[b]	-15.8 *vs* -9.9	0.03[b]
Böhm *et al*[12]	2015	None	998	-12	< 0.00001[a]	-6.6	< 0.00001[a]

[a]*P*-value for within group change; [b]*P*-value for between group change. BP: Blood pressure; RDN: Renal sympathetic denervation; NA: Not available.

after RDN[25]. This finding might be supported by a reduced cellular matrix turnover assessed by collagen pro-peptides in patients after renal denervation in an upcoming laboratory study[28].

Atrial fibrillation: Associated with BP reduction, RDN has been shown to improve atrial conduction[26]. This might allow a look-out on renal denervation as an alternative or additional option for the treatment of symptomatic atrial fibrillation. This concept is supported by two recent animal studies in dogs, where RDN could impede the induction of atrial fibrillation[29,30]. Also, for persistent atrial fibrillation, RDN was found to reduce the heart rate in a small case-series of symptomatic patients[31]. Beyond this, several in-human trials regarding this issue are currently ongoing which will certainly help to improve our understanding of the intracardiac effects of RDN (NCT01635998, NCT01990911, NCT02064764).

Ventricular arrhythmia: As ventricular arrhythmias are more likely to occur under an elevated sympathetic activity, using RDN as a treatment for refractory ventricular arrhythmia seems a reasonable endeavor[32]. Animal studies show promising effects for RDN in ischemia-induced arrhythmias when compared to a sham procedure[33,34], while inducibility of ventricular arrhythmias cannot be prevented by RDN in healthy animals[35]. Also a first in-man cohort of 10 patients with mainly non-ischemic cardiomyopathies reveals a dramatic drop in arrhythmia burden after RDN[36]. Nonetheless, further prospective, randomized trials are needed to confirm this scope of application for RDN.

Hemodynamics and volume changes: Since the effects of RDN on renal water/sodium excretion and systemic vasculature are likely to be associated with changes in systemic volume status, it would be interesting to assess changes in intra-cardiac pressure and pressure-volume relations. Also, changes in central and peripheral hemodynamics in patients undergoing RDN are of particular interest, as they determine the incidence of heart failure and potentially the course of cardiovascular remodeling[37].

Several trials investigated central hemodynamics using non-invasive methods[15,38-40]. Herein, alterations of cardiac afterload, namely a significant reduction in central pulse pressure and aortic augmentation index after RDN could be demonstrated. Also, a reduction of non-invasively assessed pulse-wave velocity, indicating decreased arterial stiffness after RDN, was observed, even if this is conflicting with the results of a smaller cohort with unchanged invasively acquired pulse-wave-velocity 6 mo after RDN[41]. As arterial stiffness is - to some extent - a BP-dependent parameter, any changes observed after RDN have to be interpreted with caution.

An explicit effect of RDN on cardiac hemodynamics, including changes in preload, filling and contractility, has - to the present date - not been described. Assessment of hemodynamic changes can be achieved *via* echocardiography, which was part of virtually all protocols of bigger studies examining treatment effects of RDN. The paucity of published data regarding echocardiographically assessed hemodynamic changes in patients treated with RDN might imply negative findings (assuming a publication bias), might be a consequence of the limited sensitivity of echocardiography in detecting cardiac filling pressures or might just have been neglected so far. Therefore - besides invasive measurements - other non-invasive methods like MRI-based analyses (*e.g.*, the left atrial transit time) could provide additional information here[42].

Furthermore, given the described impact of RDN on the LV musculature and the arterial system, an improvement of ventricular-atrial coupling could be assumed after treatment.

However, as cardiac loading underlies marked intra-individual changes, reliable assessment of changes in central hemodynamics depend on testing of patients instantaneously under different physiologic conditions (such as rest and exercise) or under longitudinal observational trial settings.

Central and peripheral nervous changes

As illustrated above, mediated through afferent central nervous fibers RDN also affects the central nervous system. Interestingly, overall successful treatment of essential hypertension is associated with improved neuropsychological performance and to some extent with alterations in regional cerebral blood flow response to working memory tasks at short-term follow up[43]. To date, this has not been assessed for patients undergoing RDN but might be a promising task for future trials, especially since uncontrolled hypertension is a well-known risk factor for cerebrovascular diseases and might contribute to cognitive decline[44].

The link between central-nervous and peripheral sympathetic-nervous alterations in hypertensive patients could further be investigated in assessing to which extent central nervous changes are mediated indirectly by BP alterations or by increased sympathetic overdrive and afferent signaling itself.

The role of a potential sympathetic re-innervation after RDN[45,46] warrants further investigation as it might partly explain non-responsiveness and lead to negative trial results. However, BP reductions in response to effective RDN seems to be long-lasting in the data published so far[47-49].

Systemic sympathetic activity

Direct measurement of the systemic sympathetic activity is difficult to perform and is therefore underrepresented in clinical trials of RDN[50]. Indirect assessment, however, is feasible with different techniques and has been used in various trials.

Cardiac scintigraphy: Two small trials (including only 23 and 11 patients) examined alterations in the cardiac sympathetic nervous system activity after RDN using scintigraphy[51,52]. Their results were conflicting, as in one trial with only a non-significant BP drop in ambulatory BP-measurements in the RDN patients, no significant alterations in cardiac sympathetic activity were found. The other trial found a remarkable impact of RDN on ambulatory measured BP and also found a strong reduction in cardiac sympathetic activity. Since the results are inconclusive at present, further evaluation in larger, adequately powered cohorts is necessary.

Heart rate variability: Another way to measure systemic sympathetic activity is assessing heart rate variability (HRV). In a small case series, Tsioufis and coworkers were able to show RDN achieved a significant reduction in patient's HRV and arrhythmia burden, suggesting a reduced systemic sympathetic activity in the treated patients[53].

Muscle sympathetic nerve activity: Muscle sympathetic nerve activity is known to be elevated in hypertensive subjects[54], indicating a direct link to systemic sympathetic activity. Hence, direct intraneural recordings could be considered as a good marker for treatment success after RDN. So far this hypothesis has been investigated in two smaller case series which failed to show any alterations through RDN[55,56]. In contrast, a prospective controlled trial in 35 patients found significant alterations in single- and multi-unit muscle sympathetic nerve activity[57]. Despite the latter results, overall the role of muscle sympathetic activity as an outcome marker in RDN trials is not fully determined and warrants further research.

Laboratory markers: Dörr *et al*[58] investigated the role of Neuropeptide Y, a neurotransmitter that is co-released with norepinephrine and up-regulated during sympathetic activity. They were able to show a significant drop of Neuropeptide Y after RDN which can be interpreted as an expression of a reduced systemic sympathetic activity.

Successful RDN also leads to a transient downregulation of serum brain-derived neurotrophic factor immediately after denervation[59]. Since brain-derived neurotrophic factor is a neuronal growth factor, this adds further evidence for true downregulation of the sympathetic nervous system on a neuronal base through RDN.

Overall, despite the lack of data for a direct assessment of systemic sympathetic activity in RDN-trials, indirect markers strongly indicate that RDN results in significant changes of systemic sympathetic activity.

Inflammation

Arterial hypertension is associated with chronic vascular inflammation and remodeling[60-62]. In a prospective analysis of 60 patients undergoing RDN, a significant reduction of pro-inflammatory cytokine interleukine-6 and high-sensitive C-reactive protein was achieved[63]. This is in particular encouraging, as it might be related to beneficial long-term effects of RDN. It has however to be debated, if the observed changes are rather related to the BP lowering effects of RDN, which might attenuate the pathologic immune response, rather than to RDN itself.

Metabolic effects

Insulin sensitivity: An elevated sympathetic activity seems to be associated with an altered insulin sensitivity[64]. Therefore, RDN might help to improve the glucose metabolism in patients with a high sympathetic overdrive. The first trial to investigate this relation, a pilot-study in 50 patients, found a significant change in glucose metabolism and insulin sensitivity[65]. Notably, only 40% of these patients were diagnosed with diabetes mellitus and only 36% had an impaired glucose tolerance at baseline. In contrast, a smaller, uncontrolled prospective trial did not find any changes in insulin sensitivity after a follow up of 12 mo in 29 patients with metabolic syndrome[66]. Therefore, the role of RDN for improvement of insulin sensitivity remains equivocal.

However, if an effect of RDN on this very relevant end point could be proven, it could tremendously affect patients' long-term prognosis.

Exercise testing: Exercise BP, an important risk factor for future cardiovascular events[67,68], was found to be reduced after RDN in two non-randomized studies and one sham-controlled trial[69-71]. Also beneficial effects for exercise capacity and duration are described for RDN without affecting chronotropic competence in treated patients[69,71].

Orthostatic effects: Safety concerns regarding potential unfavorable orthostatic effects of RDN can largely be ruled out due to the lack of the occurrence of orthostatic side effects in the large RDN treatment trials and a smaller trial which did not find any pathologic alterations in tilt table testing for RDN-treated patients[72].

Conclusion

Beyond the still debated effects of RDN on BP in hypertensive patients, a wide range of promising effects has been shown. Most of these changes could importantly change long-term morbidity and mortality of the treated subjects, even if their BP remained unchanged. To determine the value of non-BP effects of RDN for clinical practice, further long-term data with multiple cardiovascular endpoints is needed.

Until then, it seems prudent to optimize BP outcome in RDN trials through the identification of predictors for treatment success. In the following we will give a brief overview of such predictors that have been identified so far.

PREDICTORS FOR SUCCESSFUL RDN

Baseline BP

High BP prior to renal denervation has most frequently been described as the strongest predictor of BP reduction after RDN[12,73]. However, whether this is related to a higher sympathetic activity in patients with higher baseline BP or a manifestation of the regression to mean phenomenon remains controversial and is an unresolved issue to date[74]. Thus, other predictors for treatment success in RDN are needed.

Anatomy and technological aspects

Anatomy: The anatomy of the renal arteries seems to have considerable influence on the BP response to RDN. Importantly, the anatomy of human renal vessels shows a high variability[75]. Accessory renal arteries or an early bifurcation occurs in approximately one of three patients[75]. This is important, as the presence of accessory or early bifurcated vessels seems to influence outcome negatively[76]. In principle it seems prudent to exclude these patients from renal denervation. Nevertheless, in the ongoing SPYRAL-HTN trial (NCT02439775) denervation of accessories with a diameter above or equal 3 mm is planned. This will hopefully clarify the role of accessory arteries and early bifurcations soon.

As the sympathetic nerve fibers are closer to the lumen in the distal part of the renal vessel[77], ablation of the distal main artery or even the side branches are also thought to improve outcome[78,79].

Technological aspects: One of the major shortcoming of RDN is the lack of a direct feedback mechanism during intervention[50]. Despite many promising approaches, including direct intravascular and (sub-)cutaneous measurements of renal sympathetic activity, the challenging task of a direct *in-vivo* feedback for renal denervation success is still far away from clinical practice. Nevertheless, once a direct assessment method for renal sympathetic activity is established this will be a milestone in improving renal denervation success[50].

Another technological aspect for future trial designs is that denervation success seems to be dependent of the number of ablation points as well as the experience of the interventional physician[73]. Therefore, RDN should only be performed by trained interventionalists and as many ablations as possible should be delivered to optimize BP outcome.

Most clinical trials regarding RDN were carried out using radiofrequency based catheters. The role of other devices, like ultrasound-based[80-82] or chemical approaches[83,84], remain uncertain, as head-to-head comparisons of different techniques are lacking. Nevertheless, ultrasound treatment appears to be a promising treatment option, as recent work from our group suggests: Treatment of 24 non-responders to radiofrequency based RDN with an ultrasound denervation system significantly improved BP[85].

Obesity

Obesity seems to be associated with an elevated sympathetic activity, even in normotensive subjects[86]. Therefore, it might be a good predictor for BP responsiveness to RDN. In contrast, according to one singular study[87] obesity seems to be a predictor for non-responsiveness to RDN. The results of this trial are however somewhat questionable, as this constellation was neither found in any other trial[8,73] nor in the even large multicenter Global Simplicity Registry[12]. Moreover, in two smaller trials a higher body mass index was found to be a predictor for responsiveness to RDN[47,88]. To date, obesity should not be considered to have any predictive value for RDN success until reevaluation in larger, adequately powered cohorts has been performed.

Gender

So far the effect of RDN seems to be independent of gender. Nevertheless, due to the higher incidence of hypertension and therapy resistant hypertension in men, women are strongly underrepresented in any clinical trial regarding RDN. The percentage of women included in trials of renal denervation ranges between 23 and

Table 3 Predictors for blood pressure change after renal sympathetic denervation

Ref.	Year	Patients	Predictor
Böhm *et al*[12]	2015	998	Higher baseline BP predicts better BP response to RDN
Kandzari *et al*[71]	2015	364	
Id *et al*[76]	2013	74	Less BP response to RDN if accessories are present
Ewen *et al*[89]	2015	126	Better BP response in patients with combined vs isolated systolic hypertension
Okon *et al*[41]	2016	58	Lower pulse wave velocity predicts BP response
Zuern *et al*[88]	2013	40	Better BP response in patients with impaired baroreflex sensitivity

BP: Blood pressure; RDN: Renal sympathetic denervation.

41[8,10,13,14,47]. Realizing a meta-analysis of prospective trials could clarify the role of gender for RDN success.

Age

The age of the treated patients itself was not found to have a good predictive value for the success of RDN[73]. In contrast, considerable evidence was found for vascular aging and stiffening as a predictor for renal denervation over the last years[41,89].

Vascular aging and stiffness

Arterial stiffening is associated with a high cardiovascular mortality in hypertensive patients[90,91]. It also can be regarded as a cause for essential hypertension[92,93]. Ewen *et al*[89] found, that the presence of isolated systolic hypertension - characterized by increased aortic stiffness - is associated with a diminished response to RDN. In line with these data, our group also found an increased aortic stiffness, assessed by invasive pulse wave velocity, to be an independent predictor for poor BP response to renal denervation[41]. This is a promising finding, as isolated systolic hypertension and pulse wave velocity, among other markers of vascular aging and aortic stiffness, can easily be assessed non-invasively and thereby could help improving the preselection of patients available for renal denervation. To some extent, this might also explain why a trial by Vink *et al*[94] found the presence of cardiovascular diseases (a composite of stroke, transient ischemic attack and coronary artery disease), which are associated with increased vascular stiffness, to be a predictor for BP response to RDN.

Baroreflex

An impaired cardiac baroreflex occurs frequently in hypertensive subjects[95]. This might be explained by sympathetic overactivity[88]. Therefore, the presence of an impaired cardiac baroreflex as an indicator for high sympathetic overdrive could be a good predictor for renal denervation success. This hypothesis was already confirmed by a trial in 50 patients[88], but has not been applied in other prospective trials to date.

Renal function

Patients with renal diseases have often been excluded from clinical trials for safety reasons. Despite these considerations, patients with impaired renal function show an elevated sympathetic activity[96,97], and therefore might be good candidates for RDN. Consequently, Vink *et al*[94] found an inverse relation between the estimated GFR and the change in BP after RDN in a hypertensive population off antihypertensive medication. However, when analyzing patients on antihypertensive medication, no significant predictive value for estimated GFR was observed. These interesting findings warrant further investigation, as - besides enlightening the predictive role of renal function - they might partly explain why and how antihypertensive drugs interact with the effectiveness of RDN. Several trials investigating the effect of renal denervation in chronic kidney disease are currently recruiting patients (*e.g.*, NCT02002585, NCT01442883).

Conclusion

Despite the disappointing results of the SYMPLICITY-HTN3 trial, the canon of published data identifies RDN as a promising therapeutic option for hypertensive patients. Besides direct BP-lowering effects RDN has been shown to affect a broad range of pathophysiological mechanisms and might even be a viable treatment option for patients with other conditions such as heart failure or arrhythmias.

Although various predictors for the success of RDN have been identified (Table 3), an optimization for the prediction of RDN response is highly desired and several trials are ongoing which hopefully will improve treatment success and future RDN-trial design.

Verification of specific treatment effects of RDN in carefully and well-designed trials bare the hope to secure the role for RDN in treating arterial hypertension and ideally in reducing cardiovascular morbidity and mortality in the future.

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2.3.2 Hämodynamische Effekte einer katheterbasierten Modulation des renalen Sympathikotonus

Zitierweise:

Lurz P, Kresoja KP, **Rommel KP**, von Roeder M, Besler C, Lücke C, Gutberlet M, Schmieder RE, Mahfoud F, Thiele H, Desch S, Fengler K. Changes in Stroke Volume After Renal Denervation: Insight From Cardiac Magnetic Resonance Imaging. *Hypertension. 2020 Mar;75(3):707-713.*

Changes in Stroke Volume After Renal Denervation

Insight From Cardiac Magnetic Resonance Imaging

Philip Lurz, Karl-Patrik Kresoja, Karl-Philipp Rommel, Maximilian von Roeder, Christian Besler, Christian Lücke, Matthias Gutberlet, Roland E. Schmieder, Felix Mahfoud, Holger Thiele, Steffen Desch,* Karl Fengler*

Abstract—Recent trial results support catheter-based renal denervation (RDN) for treatment of hypertension, while the exact mechanisms causing blood pressure to fall remain incompletely understood. Cardiac magnetic resonance imaging was used to assess the effects of RDN on cardiac function in patients with hypertension undergoing RDN and compared with sham treatment. Cardiac magnetic resonance imaging was used to assess stroke volume index, cardiac index, heart rate, systemic vascular resistance index, and stroke work index from aortic flow measurements. Patients with resistant hypertension from a randomized, sham-controlled RDN trial underwent cardiac magnetic resonance imaging before RDN and at follow-up (randomized cohort). Results were then validated in a cohort of patients with resistant hypertension undergoing RDN and cardiac magnetic resonance imaging (validation cohort). In total, 162 patients were included 52 patients in the randomized trial (27 shams) and 110 patients in the validation cohort. In the randomized cohort, stroke volume index was reduced by 4.7±9.8 mL/m^2 in the RDN cohort and remained unchanged in the sham cohort (P=0.008 for between-group comparison), while cardiac index and stroke work index tended to be reduced in RDN patients but not in sham patients (−0.10±5.9 versus 0.17±0.51 L/min per m^2 and −7.1±12.5 versus −1.4±10.4 g/m^2, P=0.08 for both). In contrast, systemic vascular resistance index and heart rate remained unchanged after RDN. In the validation cohort, reduction of stroke volume index was confirmed, and cardiac index and stroke work index were also reduced significantly, whereas systemic vascular resistance index and heart rate remained unchanged at follow-up. In this study of patients with resistant hypertension, RDN resulted in a reduction of stroke volume when compared with sham. (***Hypertension***. **2020;75:707-713. DOI: 10.1161/HYPERTENSIONAHA.119.14310.)**

Key Words: blood pressure ■ hemodynamics ■ magnetic resonance imaging ■ stroke volume ■ renal denervation

Renal denervation (RDN) represents a nonpharmaceutical interventional therapy for patients with uncontrolled blood pressure (BP). Recent trial results demonstrated a significant reduction in BP following RDN when compared to a sham procedure.[1–3] Importantly, these findings were consistent in both patients with and without antihypertensive medication and using 2 different technologies for RDN, that is, radiofrequency and ultrasound. With this proof of concept, the field of RDN is currently shifting more towards outcome trials, refinements in measures of procedural success, identification of responders, and exploration of indications beyond hypertension. One prerequisite, among several other, is a sound understanding of the systemic, physiological, and hemodynamic effects caused by RDN. At present, effectors causing BP to fall remain incompletely understood. Although some previous studies report a reduction in heart rate (HR) after RDN,[4–6] others describe an effect on peripheral vascular resistance without changes in HR[7,8] and other studies found a reduction in left ventricular end-systolic volume and mass, as well as an increase in ejection fraction.[9,10] To further assess the effects of RDN on cardiac function, we aimed at investigating these effects using cardiac magnetic resonance imaging (CMR) and comparing them to sham-treated patients.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure upon reasonable request to the corresponding author.

Design and Patient Cohort

The effects of RDN on cardiac function and mechanisms of BP reduction assessed by CMR imaging were analyzed in 2 cohorts (Figure 1). The prospective randomized controlled trial cohort consisted of patients with

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moderate therapy-resistant hypertension undergoing RDN or a sham procedure (prospective randomized cohort).[11] Results were validated in a validation cohort consisting of patients with resistant hypertension either undergoing RDN in the recently published Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension trial[12] or within a registry corresponding to the randomized controlled trial (validation cohort). CMR assessment was intended all patients in these trials if no contraindication existed (ie, in patients with claustrophobia, implanted pacemakers, or defibrillators). Finally, all RDN patients were pooled and compared with the sham-treated cohort (pooled study cohort). To assess the influence of different CMR parameters on BP reduction for the pooled cohort, RDN-treated patients were divided into 3 groups according to their BP change at follow-up when they underwent CMR as either nonresponders (<5 mm Hg daytime BP reduction[13]), responders (5–19 mm Hg daytime BP reduction), or profound responders (≥20 mm Hg BP reduction[14]) and compared with sham-treated patients. The studies were approved by local ethics committee and were performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The trials were registered at URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01656096 and NCT02920034. Only patients with adequate CMR imaging and data from ambulatory blood pressure measurement (ABPM) at baseline and follow-up were included (Figure 1). Follow-up assessment was performed 3 months after RDN in the RADIOSOUND-HTN trial and at 6 months post-RDN in the remaining patients.

Study Participants

The exact in and exclusion criteria for the trials have been published previously.[11,12] In brief, patients with resistant hypertension were included in both trials and the registry. Resistant hypertension was defined as an elevated systolic or diastolic BP as documented by ABPM while on ≥3 different classes of antihypertensive drugs, including a diuretic, unless intolerant to diuretics. Medication had to be at maximum tolerable dosage and under a stable drug regimen >4 weeks. Medication was intended to remain unchanged for the entire follow-up period. Patients with moderate resistant hypertension (defined as daytime systolic BP between 135 and 149 and diastolic BP between 90 and 94 mm Hg on ABPM) were included in the prospective randomized, sham-controlled trial (1:1 randomization ratio) as published previously.[11] In a registry and the RADIOSOUND-HTN trial, patients with resistant hypertension (defined as daytime systolic BP >135 mm Hg on ABPM), were included.

BP Measurement

ABPM was acquired with a cuff-based oscillometric device (Spacelabs model 90207, Spacelabs Healthcare GmbH, Feucht, Germany) at baseline and follow-up. BP recordings were taken every 15 minutes at daytime (7:00 AM–10:00 PM) and every 30 minutes during nighttime (10:00 PM–7:00 AM).

Renal Denervation

RDN was performed according to standardized protocols as described previously.[11,15,16] In brief, repeated ablation runs were delivered to each renal artery. The ablation regions were placed circumferentially to the renal artery wall from distal to proximal. All patients received intravenous remifentanil to control visceral pain. Seventy patients underwent radiofrequency ablation with a Symplicity Flex catheter and 41 with the multielectrode radiofrequency Spyral catheters (Medtronic, Minnesota, MN). Twenty-four patients underwent ablation with a balloon-based ultrasound renal denervation system (Paradise, ReCor Medical, Palo Alto, CA).[15]

Sham Procedure

For patients in the sham group, the room setup was prepared as in regular RDN procedures. Patients received saline infusion instead of

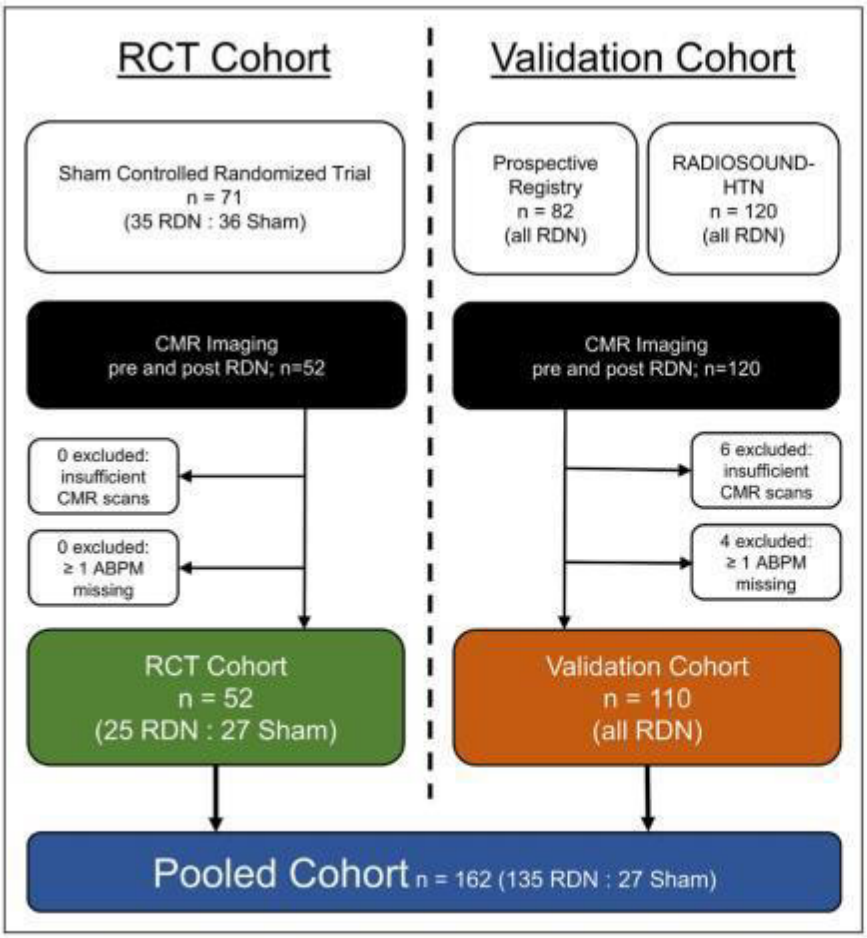

Figure 1. Study cohort. ABPM indicates ambulatory blood pressure measurement; CMR, cardiac magnetic resonance imaging; HTN, hypertension; and RDN, renal denervation.

intravenous pain medication and underwent invasive angiography of the renal arteries.

A simulated RDN procedure with 4 to 6 sham runs for each renal artery was performed, guided by 2-minute acoustic signals. Patients and study personnel (except for the interventionalists) remained blinded for 6 months.

Cardiac Magnetic Resonance Imaging

All patients underwent CMR before and at follow-up after RDN. Scans were performed on Philips (Philips Intera, Philips Healthcare, Amsterdam, the Netherlands) or Simens scanners (Verio, Siemens Healthineers, Erlangen, Germany). CMR analyses were performed by investigators blinded to patient's baseline characteristics.

Aortic flow measurements were acquired from phase-contrast imaging and left ventricular SV determined by integrating the aortic forward flow.[17] Flow measurements were indexed for body surface area and expressed in mL/m^2 (stroke volume index [SVI]). Cardiac index (CI) was calculated from SVI and HR during measurements. Images were acquired in free breathing with prospective ECG-gating. Simultaneous noninvasive BP measurements during flow measurements (conventional automated arm-cuff based measurement, average from 3 single recordings) were used to determine systemic vascular resistance index (SVRI) by dividing mean arterial pressure times 80 by cardiac output and body surface area. Stroke work index (SWI) was estimated by the formula: SVI×mean arterial pressure×0.0136.

In a subgroup of patients, short-axis stacks for right and left ventricular volumetric assessment were acquired during breath hold and indexed for body surface area.

Copeptin A, Hematocrit, and Body Weight

Copeptin A is coreleased with arginine vasopressin in humans and is a marker of body water regulation.[18] To assess its changes after RDN, copeptin A was quantified retrospectively from blood samples drawn before RDN and at the timepoint of CMR follow-up. Laboratory testing was performed by the same laboratory (University Hospital Erlangen, Friedrich-Alexander-University, Erlangen, Germany) using a dedicated, commercially available assay. Hematocrit was acquired by blood count from blood samples drawn at the time of CMR. Body weight was assessed at baseline and follow-up from self-reported weight by the patients.

Statistical Analysis

Continuous variables are presented as mean and SD, dichotomous variables as number and percentage unless indicated otherwise. Normal distribution was tested using the Kolmogorov-Smirnov test. Paired *t* tests were used for within-group comparisons. Homogeneity of variance was tested using the Levene test. ANOVA or Kruskal-Wallis test was used to compare continuous variables, Pearson χ^2 test was used to compare categorial variables. ANCOVA was used for adjusted analyses. Any *P* value <0.05 was considered significant. All statistics were calculated using SPSS 25 (IBM, NY). Any *P* value <0.05 was considered as statistically significant.

Results

The prospective randomized cohort comprised 52 patients (25 patients who had undergone RDN and 27 sham patients). The validation cohort included 110 RDN patients. The pooled cohort included 162 patients (135 RDN and 27 sham patients). BP measurements during the flow sequence were missing for one patient in the randomized cohort and for 15 patients in the validation cohort. Volumetric data were available for 26 sham-treated patients and for 25 RDN patients in the randomized cohort and for 46 patients in the validation cohort.

Prospective Randomized Cohort

Baseline Characteristics and BP Change

Clinical baseline characteristics and baseline BP were well balanced between the groups, except for younger age, and a lower frequency of dyslipidemia in the sham-treated cohort than in the RDN group (Table 1). After 6 months, systolic daytime and 24-hour mean ambulatory BP were reduced by 8.8±8.0 and 10.4±8.8 mm Hg in the RDN group and by −3.1±7.8 and −3.3±8.4 mm Hg in the sham-treated cohort (*P*=0.013 and 0.005 for between-group comparison), respectively. In contrast, corresponding diastolic ambulatory BP change did not differ between the 2 groups (−3.9±4.3 and −4.5±4.8 mm Hg in RDN patients versus −2.1±5.0 and −1.9±5.3 mm Hg in sham-treated patients, *P*=0.16 and 0.08, respectively, for between-group comparison).

Aortic Flow-Based Hemodynamic

Baseline HR during CMR, CI, SVI, SVRI, and SWI did not differ between sham-treated and RDN-treated patients. At follow-up after 6 months, SVI and SWI were reduced by 4.7±9.6 mL/m^2 and by 7.1±12.5 g/m^2 in RDN patients (*P*=0.025 and 0.010, respectively, for within-group comparison), while

Table 1. Clinical Baseline Characteristics (Randomized Cohort)

	Sham (n=27)	RDN (n=25)	*P* Value (RDN vs Sham)
Age, y	55.5±9.2	64.4±7.9	<0.001
Weight, kg	91.2±14.8	91.9±14.5	0.92
Creatinine, µmol/L	80.7±17.0	90.2±20.9	0.08
Smoker, n (%)	17 (63)	16 (64)	0.94
Diabetes mellitus, n (%)	9 (33)	14 (54)	0.10
PAD, n (%)	2 (7)	2 (8)	0.58
CAD, n (%)	11 (41)	16 (64)	0.09
Previous stroke, n (%)	3 (11)	1 (4)	0.34
Previous MI, n (%)	2 (7)	5 (20)	0.18
Atrial fibrillation, n (%)	2 (7)	1 (4)	0.60
Dyslipidemia, n (%)	15 (56)	21 (84)	0.03
No. of antihypertensive drug classes	4.3±1.2	4.1±1.2	0.50
24-h systolic blood pressure, mm Hg	140.6±5.2	141.5±4.2	0.52
24-h diastolic blood pressure, mm Hg	81.2±6.1	78.7±7.8	0.21
Daytime systolic blood pressure, mm Hg	143.1±4.4	144.8±4.8	0.17
Daytime diastolic blood pressure, mm Hg	83.3±6.3	81.0±8.4	0.27
Nighttime systolic blood pressure, mm Hg	132.9±11.1	130.4±8.0	0.35
Nighttime diastolic blood pressure, mm Hg	73.7±7.9	70.4±8.0	0.14

CAD indicates coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease; and RDN, renal denervation.

HR, CI, and SVRI did not change significantly (Table 2). In contrast, SVI and SWI remained unchanged following sham treatment. While the delta between SVI was significantly different between the groups (P=0.008), the difference in change of SVRI and SWI was not (P=0.06 and 0.08, respectively, for between-group comparison, Table 2). The difference in change of SVI between sham and RDN persisted after adjustment for baseline SVI values and age (P=0.043).

Volumetric Assessment

Patients in the sham cohort presented with higher right and left ventricular end-diastolic as well as left ventricular end-systolic volumes at baseline. Left ventricular ejection fraction was significantly lower in sham-treated patients. Left ventricular end-diastolic volume index was reduced significantly after RDN without reaching statistical significance in between-group comparison (Table 2).

Body Weight, Hematocrit, and Copeptin A

Body weight, hematocrit, and copeptin A levels were balanced between the groups at baseline and were unchanged at follow-up.

Validation Cohort

Baseline Characteristics and BP Change

Baseline characteristics of the validation cohort are shown in Table 3. At follow-up, 24-hour systolic and diastolic BP were reduced by 7.7±13.1 and 4.7±6.8 mm Hg (P<0.001).

Aortic Flow-Based Hemodynamic

Overall results for flow-based volumes in the validation cohort were comparable to the randomized RDN cohort: HR and SVRI remained unchanged, while SVI was significantly reduced at follow-up. Other than in the randomized cohort, CI and SWI were reduced significantly after RDN (Table 4).

Subgroup Volumetric Assessment

Different to the randomized cohort, left ventricular ejection fraction was reduced, and end-systolic volumes were increased numerically without reaching statistical significance. Also, right ventricular ejection fraction was reduced, and end-systolic volumes were increased significantly (Table 4).

Body Weight, Hematocrit, and Copeptin A

Similar to the prospective randomized cohort, body weight and copeptin A levels were balanced at baseline and remained unchanged at follow-up. Hematocrit was reduced from 0.42±0.04 to 0.41±0.04 after RDN (P<0.001).

Pooled Study Cohort

Similar to the prospective randomized cohort, HR, CI, SVI, SVRI, and SWI did not differ between sham-treated and RDN-treated patients at baseline. At follow-up, SVI, CI, and SWI were reduced significantly by 3.2±8.5 mL/m^2, 0.14±0.53 L/min/m^2, and −7.3±13.7 g/m^2 in RDN patients, which was found to be significant when compared to the sham group (P=0.007, <0.001, and 0.04 for between-group comparison). HR and SVRI did not change significantly after RDN (P=0.14 and 0.31, respectively). When stratified by BP response, a consistent relation between daytime systolic ambulatory BP change and change in SVI, CI, and SWI was found (Figure 2). For the pooled cohort, change in hematocrit did not reach statistical significance between RDN and sham (−0.01±0.02 versus −0.01±0.02, P=0.92). No relation was found between the extent of BP response and reduction in hematocrit, body weight, or copeptin A.

Discussion

Our study is the first to describe CMR based hemodynamic effects of RDN in direct comparison to a sham-treated cohort. Three major conclusions can be drawn: First, RDN was associated with significant changes in SVI at follow-up. Second,

Table 2. Cardiac Magnetic Resonance Imaging Results at Baseline and Change at Follow-Up (Randomized Cohort)

	Sham				RDN					
	n	Baseline	Δ Follow-Up	*P* Value (Pre vs Post)	n	Baseline	Δ Follow-Up	*P* Value (Pre vs Post)	*P* Value (RDN vs Sham Baseline)	*P* Value (Δ RDN vs Δ Sham)
HR, min^{-1}	27	62.5±11.3	1.8±11.2	0.42	25	59.1±11.1	4.7±8.3	0.01	0.28	0.29
CI, L/min per m^2	27	2.62±0.51	0.17±0.51	0.09	25	2.51±0.41	−0.10±0.59	0.42	0.37	0.08
SVI, mL/m^2	27	42.8±8.9	1.6±6.6	0.22	25	43.5±10.1	−4.7±9.6	0.025	0.81	0.008
SVRI, dynes×s×cm^{-5}×m^{-2}	27	707.6±205.0	−71.8±143.5	0.02	24	671.4±233.6	19.1±194.3	0.63	0.58	0.06
SWI, g/m^2	27	55.8±13.6	−1.4±10.4	0.49	24	51.4±12.6	−7.1±12.5	0.01	0.24	0.08
EDVI, mL/m^2	26	74.2±17.2	0.2±8.3	0.91	25	62.3±14.3	−4.7±10.8	0.035	0.009	0.10
ESVI, mL/m^2	26	30.2±14.3	−0.7±5.3	0.95	25	21.5±10.3	−1.1±6.3	0.84	0.002	0.57
EF, %	26	60.7±9.4	0.4±4.7	0.37	25	66.8±8.8	−1.9±6.3	0.16	0.02	0.15
RVEDVI, mL/m^2	26	74.8±13.0	0.5±8.7	0.76	25	65.2±10.9	−3.0±9.6	0.14	0.006	0.18
RVESVI, mL/m^2	26	30.6±7.7	0.2±5.2	0.82	25	26.8±7.7	−0.2±5.8	0.88	0.09	0.79
RVEF, %	26	59.3±5.9	0.1±5.0	0.91	25	59.3±6.9	−1.5±5.9	0.23	0.98	0.31

CI indicates cardiac index; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HR, heart rate; RDN, renal denervation; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; SVI, stroke volume index; SVRI, systemic vascular resistance index; and SWI, stroke work index.

Table 3. Clinical Baseline Characteristics (Validation Cohort)

	RDN (n=110)
Age, y	62.4±9.7
Weight, kg	91.1±14.6
Creatinine, μmol/L	85.0±23.3
Smoker, n (%)	47 (43)
Diabetes mellitus, n (%)	45 (41)
PAD, n (%)	7 (6)
CAD, n (%)	35 (32)
Previous stroke, n (%)	6 (5)
Previous MI, n (%)	15 (14)
Atrial fibrillation, n (%)	17 (15)
Dyslipidemia, n (%)	77 (70)
No of antihypertensive drug classes	5.0±1.4
24-h systolic blood pressure, mm Hg	152.6±12.4
24-h diastolic blood pressure, mm Hg	83.9±11.5
Daytime systolic blood pressure, mm Hg	155.7±13.5
Daytime diastolic blood pressure, mm Hg	86.8±12.8
Nighttime systolic blood pressure, mm Hg	143.4±16.3
Nighttime diastolic blood pressure, mm Hg	75.9±11.8

CAD indicates coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease; and RDN, renal denervation.

Table 4. Cardiac Magnetic Resonance Imaging Results at Baseline and Change at Follow-Up (Validation Cohort)

	RDN			
	n	Baseline	Δ Follow-Up	*P* Value (Pre vs Post)
HR, min^{-1}	110	63.3±10.4	0.3±8.7	0.14
CI, L/min per m^2	110	2.40±0.58	−0.15±0.52	0.002
SVI, mL/m^2	110	39.0±11.3	−2.8±8.2	<0.001
SVRI, $dynes \times s \times cm^{-5} \times m^{-2}$	95	803.0±229.5	28.7±209.3	0.31
SWI, g/m^2	95	53.7±19.4	−7.3±14.0	<0.001
EDVI, mL/m^2	46	70.9±14.9	1.1±10.4	0.47
ESVI, mL/m^2	46	25.3±10.6	1.4±5.6	0.09
EF, %	46	65.6±8.0	−1.3±4.5	0.06
RVEDVI, mL/m^2	46	71.5±13.8	2.2±9.3	0.11
RVESVI, mL/m^2	46	27.4±8.6	2.7±5.6	0.002
RVEF, %	46	62.5±6.9	−2.8±6.7	0.006

CI indicates cardiac index; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HR, heart rate; RDN, renal denervation; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; SVI, stroke volume index; SVRI, systemic vascular resistance index; and SWI, stroke work index.

previously described changes in vascular resistance may not be the only effector of RDN-induced BP reduction. Third, the reduction of SVI and BP seems to result in a reduced stroke work after RDN. These results were found in the randomized cohort and confirmed in a larger validation cohort.

RDN may affect BP by several pathways, including but not limited to reduced preload, reduced afterload, and reduced cardiac output, which all have been reported in various RDN studies previously.[4,5,7,8,19,20] Complementary to this, our results suggest that RDN affects systemic BP by altering stroke volume and, as HR remained unchanged herein, also cardiac output. In general, a reduction in stroke volume can be caused by 2 different mechanisms, preload reduction or reduced inotropy. Theoretically, RDN might affect both, as transient changes in blood volume via an increased sodium excretion or an improved splanchnic pooling by reduced systemic sympathetic activity could reduce preload, and lower cardiac systemic sympathetic activity could alter cardiac inotropy. Interestingly, volumetric data were not suggestive of blood volume or preload reduction. In addition, body weight and copeptin A levels as a surrogate for total body water content and hematocrit remained unchanged, which makes changes in plasma volume less likely. Nevertheless, an improved splanchnic pooling as described previously[20] would still be possible as an additional mechanism of BP reduction in RDN-treated patients as our analysis investigated a resting state only. Alternatively, the effect on stroke volume CI and thereby also BP could be secondary to a reduction in sympathetic-mediated cardiac inotropy. An effect on inotropy supports the concept of a reduced systemic sympathetic activity as the main effector of RDN, which has been repeatedly documented by microneurography and cardiac scintigraphy.[21,22] As we present a smaller exploratory study herein, this remains speculative unless proven in future prospective randomized controlled and mechanistic trials.

Contrary to a recently published substudy of the Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, shamcontrolled, proof-of-concept trial cohort,[4] we did not find a reduction in HR herein. This might be explained by the frequent use of β-blockers in the investigated cohort. HR reductions have also been described for patients on this medication,[5,6] but only in 2 uncontrolled trials, and other studies, including patients with β-blockers, did not report a reduced HR following RDN.[7,8] Thus, more results from future controlled trials in patients also treated with β-blockers are needed.

Changes in total peripheral resistance were not documented herein. This is surprising, as a reduced systemic as well as reduced renal sympathetic activity both are thought to affect peripheral resistance: either via a reduced renal induced activation in the medulla oblongata[23] or by reduced angiotensin activity.[24] Two previous studies described effects on peripheral resistance after RDN. The discrepancy might be explained by the methodological differences: one used a volume clamp method at a resting state to estimate peripheral resistance,[8] the other used a mathematical algorithm and a 3-element Windkessel model to calculate resistance from ambulatory BP readings.[7] Both studies used indirect measurements with its inherent limitations. Notably, systemic vascular resistance is not an exact marker of cardiac afterload and divergent results on resistance and left ventricular wall stress have been reported previously,[25] thus the clinical significance of resistance measurements is overall limited.

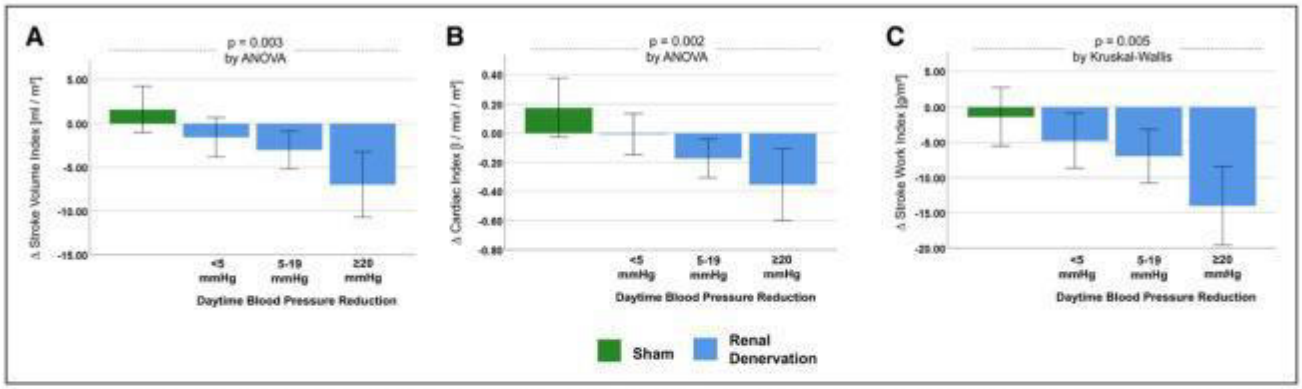

Figure 2. Change in cardiac magnetic resonance imaging (CMR) acquired hemodynamic parameters in the pooled study cohort, stratified by blood pressure response. **A**, Stroke volume index; (**B**) cardiac index; and (**C**) stroke work index. Error bars indicate 95% CI.

A reduction in SWI found after RDN has not been described previously. A reduced resting SWI in stable patients could be interpreted as a sign of beneficial remodeling, as it can also be the result of reduced wall stress, which has been reported for RDN previously.[6,9] Both, reduced wall stress and stroke work are associated with a reduced myocardial oxygen consumption.[26] Thus, RDN might have beneficial effects in patients with heart failure despite the reduction of resting stroke volume. Similar results have been found for β-blocking drugs in patients with heart failure, where this effect ultimately resulted in a reduced mortality.[27,28] Recently, the presence of a supranormal ejection fraction has been linked to increased mortality.[29] If such a hyperdynamic cardiac phenotype, eventually leading to heart failure with preserved ejection fraction, is sympathetically mediated, reduction in SV might actually represent a return to a more physiological state and could even serve as a potential therapeutic approach in this specific patient cohort.

It will be a task for future trials to assess if the hemodynamic effects of RDN observed herein have an impact on clinically meaningful end points, like heart failure hospitalization or even mortality. This would open a whole new field for RDN beyond hypertension treatment. If such a relation can be documented, CMR based hemodynamic parameters might serve as an additional measure of response to RDN beyond BP reduction in future trials.

Limitations

Several limitations have to be mentioned. First, volumetric data were available for part of the cohort only. Thus, results might be different for the entire cohort. Second, BP readings during CMR were assessed with a noninvasive measurement from brachial measurements and results might be different, when using invasive methods. Also, central venous pressure was not considered for calculation of resistance measurements. Third, as only part of this study was a randomized cohort, our sham-treated cohort is small and baseline criteria were not balanced between groups. Also, the sham-controlled trial failed its primary end point for the full cohort. However, BP changes were significantly different between sham and RDN in the CMR substudy presented here. Moreover, changes in SVI were consistent after age adjustment which strengthens our findings. Forth, our CMR protocol investigated patients in resting state only. Future trials should focus on investigating CMR acquired parameters under exercise conditions to better understand the underlying physiological mechanisms.

Conclusions

In this pooled cohort of patients undergoing RDN, our findings suggest that alterations in cardiac sympathetic activity are involved in BP reduction and affect stroke volume and cardiac output (graphical abstract). Future investigations on RDN should focus on mode of action as it might help to optimize concomitant medical treatment as well as the procedure itself.

Perspectives

Our findings suggest that alterations in cardiac sympathetic activity following RDN are involved in BP reduction and affect stroke volume and cardiac output. Lower stroke volume results in a reduced stroke work, which might be beneficial in hypertensive heart failure patients, especially in heart failure with preserved ejection fraction.

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Disclosures

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Novelty and Significance

What Is New?

- Renal denervation lowers blood pressure by stroke volume reduction.
- Other than previously described, systemic resistance is not changed in our study.

What Is Relevant?

- This might also change future indications for renal denervation, as reduced stroke volume results in reduced stroke work and wall stress.
- This could be beneficial in hypertensive heart failure patients, especially in heart failure with preserved ejection fraction.

Summary

Renal denervation lowers blood pressure by stroke volume reduction. By reduced wall stress, this might be beneficial in heart failure patients.

2.3.3 Klinische Effektivität einer katheterbasierten Modulation des renalen Sympathikotonus bei Patienten mit Herzinsuffizienz und erhaltener Pumpfunktion

Zitierweise:

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EMERGING INVESTIGATORS

Renal Sympathetic Denervation in Patients With Heart Failure With Preserved Ejection Fraction

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BACKGROUND: Arterial hypertension is the most common comorbidity in patients with heart failure with preserved ejection fraction (HFpEF) and mediates adverse hemodynamics through related aortic stiffness and increased pulsatile load. We aimed to investigate the clinical and hemodynamic implications of renal sympathetic denervation (RDN) in patients with HFpEF and uncontrolled arterial hypertension.

METHODS: Patients undergoing RDN between 2011 and 2018 in a single-center were retrospectively analyzed and classified as HFpEF (n=99) or no HF (n=65). Stroke volume index and aortic distensibility were measured through cardiac magnetic resonance imaging, and left ventricular (LV) systolic and diastolic properties were assessed echocardiographically.

RESULTS: At baseline, patients with HFpEF had higher stroke volume index (median 40 [interquartile range, 33–48] versus 33 [26–40] mL/m^2, P=0.002), pulse pressure (69 [63–77] versus 61 [55–67] mm Hg, P<0.001), but lower LV-VPES$_{100mmHg}$ (18 [10–28] versus 24 [15–40] mL, P=0.007) and aortic distensibility (1.5 [1.1–2.6] versus 2.7 [1.1–3.5] 10^{-3} mm Hg^{-1}, P=0.013) as compared to no-HF patients. Systolic blood pressure decreased comparable in patients with HFpEF and no-HF patients following RDN (−9 [−16 to −2], P<0.001). After RDN stroke volume index (−3 [−9 to +3] mL/m^2, P=0.011) decreased and aortic distensibility (0.2 [−0.1 to +1.1] 10^{-3} mm Hg^{-1}, P=0.007) and systolic stiffness (P<0.001) increased in HFpEF patients. LV diastolic stiffness and LV filling pressures as well as NT-proBNP (N-terminal pro-B-type natriuretic peptide) decreased after RDN in patients with HFpEF (P=0.032, P=0.043, and P<0.001, respectively).

CONCLUSIONS: Patients with HFpEF undergoing RDN showed increased stroke volume index, vascular, and LV stiffness as compared to no-HF patients. Following RDN those hemodynamic alterations and reduced systolic and diastolic LV stiffness were partly normalized, implying RDN might be a potential therapeutic strategy for arterial hypertension and HFpEF.

Key Words: blood pressure ■ denervation ■ heart failure ■ hemodynamics ■ hypertension

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The high prevalence and associated morbidity, as well as mortality of heart failure with preserved ejection fraction (HFpEF), remain a major clinical challenge.[1] To find a causal therapy for the heterogeneous syndrome of HFpEF, it is of importance to understand its pathophysiological pathways and to optimize individual treatment strategies. The most common characteristics of HFpEF are increased ventricular filling pressures, as well as ventricular and arterial stiffening as frequently caused by aging, diabetes, and arterial hypertension (aHT), the latter one preceding the development of overt clinical HF in 90% of cases.[2–4]

Accumulating evidence shows a strong association between aHT and vascular stiffness as well as

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WHAT IS NEW?

- Heart failure with preserved ejection fraction might be frequent among patients with uncontrolled hypertension undergoing renal sympathetic denervation.
- These patients are marked by a distinct hemodynamic profile of impaired aortic buffering capability, a higher incidence of isolated systolic hypertension, high blood pressure variability, increased end-systolic elastance, and possibly impaired ventriculo-arterial coupling.
- Those unfavorable hemodynamic alterations were partly debilitated after renal sympathetic denervation.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The diagnosis of heart failure with preserved ejection should be considered in patients with uncontrolled arterial hypertension undergoing renal sympathetic denervation as it might contribute to patients morbidity.
- Renal sympathetic denervation might pose a treatment option for patients with a specific hypertensive phenotype of heart failure with preserved ejection which warrants further investigations.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
aHT	arterial hypertension
BP	blood pressure
BPV	blood pressure variability
CMR	cardiac magnetic resonance imaging
CPOI	cardiac power output index
HFpEF	heart failure with preserved ejection fraction
IQR	interquartile range
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
LV-VPed$_{20mmHg}$	end-diastolic volume for a given end-diastolic pressure of 20 mm Hg
LV-VPes$_{100mmHg}$	end-systolic volume for a given end-systolic pressure of 100 mm Hg
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RDN	renal sympathetic denervation
SNA	sympathetic nervous activity
SVI	stroke volume index

sympathetic nervous activity (SNA) overdrive, which again might contribute to the conundrum of HFpEF.[5–7] An increased afterload, as well as a compensatory increased left ventricular (LV) contractility, to uphold a favorable ventriculo-arterial coupling, might lead to a detrimental energetic state aggravating malevolent cardiac effects in patients with HFpEF.[2,8] In fact, it has recently been shown that LV ejection fraction (LVEF) has an u-shaped relationship on mortality, where very-high states of LVEF (≥65%) are associated with impaired survival.[9]

Renal sympathetic denervation (RDN) has been shown to positively affect blood pressure (BP),[10–12] aortic stiffness,[13,14] as well as SNA.[15] Furthermore, RDN was able to improve diastolic function, as well as LV mass in patients with therapy aHT.[16]

We now aimed to investigate the clinical and hemodynamic effects of RDN in patients with therapy aHT and HFpEF as compared to patients without HF.

METHODS

This article adheres to the Transparency and Openness Promotion Guidelines. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design and Patient Cohort

For the present retrospective observational study, we pooled data from patients ≥18 years who underwent RDN at a single high-volume center between 2011 and 2018. Echocardiographic and cardiac magnetic resonance imaging (CMR) assessment was intended in all patients if no contraindication existed (ie, in patients with claustrophobia, implanted pacemakers, or defibrillators). All patients were post hoc stratified as HFpEF or no HF according to the guidelines of the European Society of Cardiology, whereas HFpEF was defined as the presence of NT-proBNP (N-terminal pro-B-type natriuretic peptide) elevation >125 pg/mL, evidence of structural heart disease (left atrial volume index >34 mL/m^2 or LV mass index ≥115 g/m^2 for males and ≥95 g/m^2) or diastolic dysfunction on echocardiography (mean E/e' ≥13 and a mean e' septal and lateral wall <9 cm/s), LVEF ≥50% and symptoms or signs of HF or loop diuretic treatment in their absence.[17] Only patients with uncontrolled aHT (as defined previously[10,12]) were considered for this analysis, no redo RDN procedures were included. Medication had to be stable for >4 weeks before and was intended to remain unchanged after RDN. Patients with a LVEF <50% and missing baseline NT-proBNP values were excluded from the current analysis. In all patients, pulse wave velocity was assessed invasively before RDN.[18] In addition, echocardiography, ambulatory BP monitoring (ABPM) readings, NT-proBNP levels and in a subgroup of patients CMR was acquired before and within 6 months post-RDN.

All study procedures were performed in accordance with the Declaration of Helsinki and were approved by a local ethics committee. All participants provided written informed consent.

BP Measurement and Variability

ABPM was acquired with a cuff-based oscillometric device (Spacelabs model 90207, Spacelabs Healthcare GmbH, Feucht, Germany) at baseline and follow-up. BP recordings were taken

every 15 minutes at daytime (7:00 AM–10:00 PM) and every 30 minutes during nighttime (10:00 PM–7:00 AM).

BP variability (BPV) was assessed by SD of systolic BP values, coefficient of variation of SBP assessed by dividing SD of systolic BP value by mean, and average real variability calculated.

Renal Denervation

RDN was performed according to standardized protocols as described previously.[10,11,19] In brief, repeated ablation runs were delivered to each renal artery. The ablation regions were placed circumferentially to the renal artery wall from distal to proximal. All patients received intravenous remifentanil to control visceral pain. Of the included patients, 115 patients underwent radiofrequency ablation (Medtronic, Minnesota, MN), and 49 patients underwent ultrasound RDN (Paradise, ReCor Medical, Palo Alto, CA). Patients with a BP reduction of ≥5 mm Hg at daytime ABPM after 3 months were defined as responders. Isolated systolic hypertension was defined as BP>135 mm Hg systolic and <85 mm Hg diastolic on daytime ABPM. Before RDN, invasive pulse wave velocity was measured as previously described.[18]

Echocardiographic Assessment and Single-Beat Estimations

Standard transthoracic echocardiographic assessment was performed before and after RDN with simultaneous noninvasive arm cuff BP measurements and central BP calculation in a subgroup (n=97) using the Complior device (Complior Analyse, 2011, ALAM Medical, Saint Quentin Fallavier, France). Pressure-volume estimations were calculated noninvasively using a single-beat estimation method, whereas the end-systolic pressure-volume relationship was calculated as proposed by Chen et al[20] and the end-diastolic pressure-volume relationship as proposed by Klotz et al[21] and outlined in the Methods in the Data Supplement in more detail. To improve comparability of systolic and diastolic estimates the volume for a given end-systolic pressure of 100 mm Hg ($LV\text{-}VPes_{100mmHg}$) and for a given end-diastolic pressure of 20 mm Hg ($LV\text{-}VPed_{20mmHg}$) was calculated.

Cardiac Magnetic Resonance Imaging

Scans were performed on Philips (Philips Intera, Philips Healthcare, Amsterdam, the Netherlands) or Siemens scanners (Verio, Siemens Healthineers, Erlangen, Germany). CMR analyses were performed by investigators blinded to patients characteristics and outcomes.[22] Aortic flow measurements were acquired from phase-contrast imaging and LV-SV determined by integrating the aortic forward flow. Flow measurements were indexed for body surface area and expressed in mL/m^2 (stroke volume index [SVI]). Cardiac index was calculated from SVI and HR during measurements. Images were acquired in free breathing with prospective ECG-gating. Simultaneous noninvasive BP measurements during flow measurements (conventional automated arm cuff-based measurement, average from 3 single recordings) were used to determine systemic vascular resistance index by dividing mean arterial pressure times 80 by SVI. Aortic distensibility (10^{-3} mm Hg^{-1}) was calculated as $(A_{max}-A_{min})/A_{min}\times$pulse pressure, where A_{max} and A_{min} represent the maximal and minimal cross-sectional area of the ascending aorta on cine CMR images measured 1 to 2 centimeters above the sinotubular junction. Cardiac power output index (CPOI) was estimated by the formula cardiac index×mean arterial pressure/451.[23]

Statistical Analysis

Paired *t* tests or Wilcoxon signed-rank test was used for within-group comparisons. Homogeneity of variance was tested using the Levene test. ANOVA, Mann-Whitney *U*, or Kruskal-Wallis test was used to compare continuous variables. In case of normal distribution (Kolmogorov-Smirnov test), data are given as the mean and corresponding SD (±), if data did not follow normal distribution they are presented as median and corresponding interquartile range (IQR). Categorical variables were compared using the Fisher exact test. Correlation of data was performed using the Spearmen ρ correlation coefficient. To account for the influence of differences in baseline characteristics ANCOVA was performed.

A 2-sided significance level of α 0.05 was defined appropriate to indicate statistical significance. Statistical analyses were performed using the SPSS software (IBM Corp, released 2017, IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp).

RESULTS

Baseline Characteristics

Two hundred eighty-seven patients underwent RDN between 2011 and 2018 at our center (Figure I in the Data Supplement). Overall, 164 patients were included, 99 patients classified as HFpEF and 65 as no HF. An overview of the criteria for classification of patients into HFpEF or no HF is given in Table I in the Data Supplement. Patients with HFpEF were older, more frequently female, had impaired exercise capacity, more comorbidities (diabetes and atrial fibrillation) and a higher pulse pressure at baseline as displayed in Table 1, baseline medication is displayed in Table II in the Data Supplement. Isolated systolic hypertension (daytime ABPM diastolic BP <85 mm Hg) was more frequent among patients with HFpEF as compared to no-HF patients (63% versus 31%, $P<0.001$). Nighttime BPV was higher in patients with HFpEF and daytime BPV also tended to be higher as compared to no-HF patients. Baseline NT-proBNP was higher in patients with HFpEF as compared to no-HF patients (301 [IQR, 214–565] versus 65 [IQR, 43–102] ng/L; $P=0.011$). At baseline, invasively assessed pulse wave velocity before RDN was higher in patients with HFpEF as compared to no-HF patients (16.2 [IQR, 13.0–19.4] versus 14.1 [IQR, 12.4–17.8] m/s, $P=0.035$). Radiofrequency ablation or ultrasound RDN technique was used in 70 (71%) and 29 (29%) of patients with HFpEF and in 45 (69%) and 20 (31%) of the no-HF patients, respectively.

Table 1. Baseline Characteristics

Variable	HFpEF (n=99)	No HF (n=65)	*P* value
Age, y	66 (61–73)	61 (54–67)	<0.001
Female sex, n (%)	34 (34)	12 (19)	0.033
BMI, kg/m^2	31 (28–35)	31 (30–35)	0.33
Symptoms			
NYHA functional class ≥II	65 (66)	31 (48)	0.035
Max Watt at exercise ECG, W	100 (100–150)	150 (100–150)	0.020
Ambulatory blood pressure			
Daytime systolic blood pressure, mm Hg	151 (144–159)	151 (142–158)	0.18
Daytime diastolic blood pressure, mm Hg	80 (76–90)	89 (83–97)	0.001
Heart rate, bpm	67 (59–74)	70 (64–82)	0.016
Past medical history			
Active smoker, n (%)	13 (13)	12 (19)	0.38
Previous smoker, n (%)	23 (23)	21 (32)	0.21
Diabetes, n (%)	58 (59)	25 (39)	0.016
IDDM, n (%)	21 (21)	12 (19)	0.70
PAD, n (%)	13 (13)	4 (6.2)	0.19
CAD, n (%)	40 (40)	26 (40)	1.00
Previous stroke, n (%)	5 (5.1)	5 (7.7)	0.52
Previous MI, n (%)	14 (14)	12 (19)	0.52
Atrial fibrillation, n (%)	18 (18)	2 (3.1)	0.003
Dyslipidemia, n (%)	78 (79)	89 (58)	0.09
No. of antihypertensive drug classes	5 (4–6)	5 (4–6)	0.94

BMI indicates body mass index; bpm, beats per minute; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; IDDM, insulin-dependent diabetes; MI, myocardial infarction; NYHA, New York Heart Association; and PAD, peripheral artery disease.

Changes in BP, NT-ProBNP, and Symptoms

At follow-up, daytime systolic and diastolic BP as well as pulse pressure decreased in both patients with HFpEF and no-HF patients to a comparable extent. There was no statistically significant difference in the number of responders between patients with HFpEF and no-HF patients (71% versus 67%, *P*=0.73). BPV at nighttime decreased to a greater extent in patients with HFpEF as compared to no-HF patients (Table 2).

NT-proBNP decreased in patients with HFpEF (Δ −24% [IQR, −42% to +12%], *P*<0.001) and slightly increased in no-HF patients (Δ +9% [IQR, −16 to +63] µg/L, *P*=0.011), with a significant between-group difference of NT-proBNP change (*P*<0.001). Likewise, patients with HFpEF showed a better improvement in New York Heart Association functional class (21% of patients improved at least one class, *P*<0.001; Figure 1A and 1B) as compared to no-HF patients (*P*=0.32, *P* value for between-group difference 0.008).

Changes in Standard Echocardiographic Parameters

At baseline, LVEF was higher in patients with HFpEF as compared to no-HF patients (64% [IQR, 59%–67%] versus 60% [IQR, 54%–66%], *P*=0.006). There was no statistically significant difference in LVEF reduction at follow-up in patients presenting with HFpEF (Δ −4 [IQR, −7 to +1]) as compared to no-HF patients (Δ −1 [IQR, −6 to +5], *P* value for between-group difference 0.10).

At baseline, patients with HFpEF had a higher ratio of early mitral inflow (Emax) to septal and lateral mitral tissue velocity (E/E′) and more severe left atrial dilation (35 [IQR, 29–41] versus 27 [IQR, 24–35] mL/m^2, *P*<0.001) as compared to no-HF patients. At follow-up, E/E′ decreased significantly in patients with HFpEF but did not show a statistically significant change in no-HF patients. Furthermore, there was no relevant between-group difference in the reduction of E/E′ (*P*=0.13; Table 3). Further echocardiographic data are shown in Table III in the Data Supplement.

Table 2. Blood Pressure Effects of Renal Sympathetic Denervation in HFpEF and No HF

	HFpEF (n=99)		*P* value (pre vs post)	No HF (n=65)		*P* value (pre vs post)	*P* value (HFpEF vs no HF baseline)	*P* value (Δ HFpEF vs Δ no HF)
	Baseline	Δ Follow-up		Baseline	Δ Follow-up			
Blood pressure								
Daytime systolic blood pressure, mm Hg	151 (144 to 159)	−9 (−17 to −2)	<0.001	151 (142 to 158)	−8 (−16 to −2)	<0.001	0.18	0.47
Daytime diastolic blood pressure, mm Hg	80 (76 to 90)	−6 (−10 to −2)	<0.001	89 (83 to 97)	−5 (−10 to −1)	<0.001	0.001	0.74
Daytime Pulse pressure, mm Hg	69 (63 to 77)	−3 (−8 to +2)	<0.001	61 (55 to 67)	−2 (−7 to +3)	0.033	<0.001	0.29
Daytime blood pressure variability	16.6 (13.6 to 20.0)	−1.5 (−4.1 to +0.9)	<0.001	15.1 (12.8 to 17.4)	−1.1 (−3.9 to +2.7)	0.10	0.06	0.35
Nighttime blood pressure variability	15.9 (12.5 to 20.0)	−1.6 (−5.0 to +1.6)	0.001	13.4 (11.3 to 16.7)	−0.6 (−3.2 to +3.7)	0.91	0.003	0.043

HFpEF indicates heart failure with preserved ejection fraction.

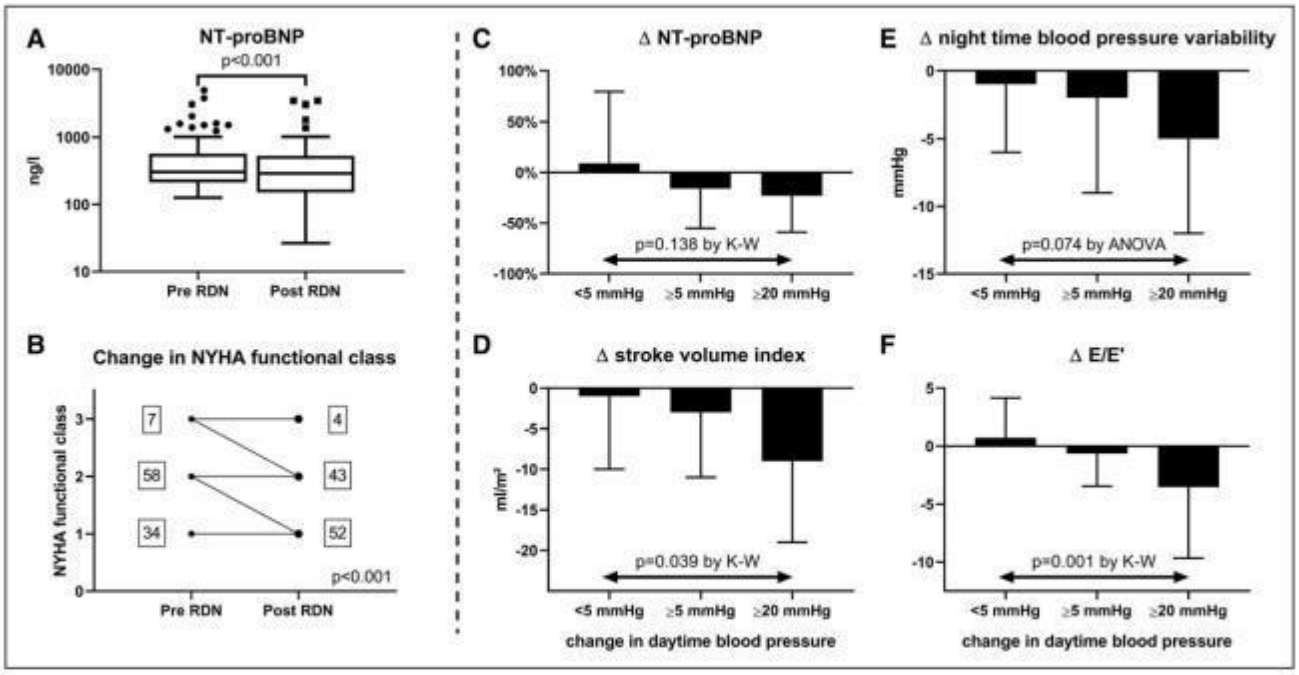

Figure 1. Changes of patients with heart failure with preserved ejection fraction (HFpEF) in (A) NT-proBNP (N-terminal pro-B-type natriuretic peptide) and (B) New York Heart Association (NYHA) functional class, as well as changes in accordance to blood pressure reduction in (C) NT-proBNP, (D) stroke volume index, (E) nighttime blood pressure variability, and (F) E/E′ in accordance to daytime blood pressure reduction after renal sympathetic denervation (RDN).
K-W indicates Kruskal-Wallis test.

Aortic Flow-Based Hemodynamics and Aortic Distensibility

CMR flow measurements were available for 55 patients with HFpEF and 35 no-HF patients. At comparable cardiac indexes, patients with HFpEF exhibited significantly lower heart rates and higher SVIs. There was no statistically significant difference in systemic vascular resistance index between patients with HFpEF and no-HF patients, but estimates of myocardial work (CPOI) were significantly higher in patients with HFpEF. After RDN, statistically significant reduction of myocardial workload was observed in patients with HFpEF, driven by a reduction of SVI, at stable systemic vascular resistance index and heart rate (Table 4). However, there was no statistically significant decrease of CPOI in the no-HF group with no statistically significant difference in the extent of CPOI reduction between patients with HFpEF and no-HF patients (P=0.14).

The HFpEF group demonstrated a lower aortic distensibility as compared to no-HF patients. After RDN, aortic distensibility improved to a greater extent in patients with HFpEF as compared to no-HF patients (P=0.035; Figure 2).

Table 3. Effects of Renal Sympathetic Denervation on Echocardiographically Assessed Diastolic and Systolic Single-Beat Estimations in HFpEF and No HF Patients

	HFpEF (n=99)		*P* value (pre vs post)	No HF (n=65)		*P* value (pre vs post)	*P* value (HFpEf vs no HF baseline)	*P* value (Δ HFpEF vs Δ no HF)
	Baseline	Δ Follow-up		Baseline	Δ Follow-up			
Diastolic properties								
Emax, m/s	0.86 (0.69 to 1.09)	−0.03 (−0.17 to +0.04)	0.015	0.68 (0.60 to 0.73)	0 (−0.01 to +0.01)	0.63	<0.001	0.24
Mean E/E′	12.8 (10.3 to 16.2)	−1.0 (−2.5 to +1.8)	0.043	9 (8.3 to 11.1)	0 (−2.2 to +2.8)	0.90	<0.001	0.13
LV-VPED$_{20mmHg}$, mL	107.6 (84.2 to 137.2)	7.7 (−12.0 to +22.1)	0.032	116.9 (101.0 to 144.8)	−0.2 (−18.7 to +19.3)	0.97	0.048	0.25
Systolic properties								
E_{es}, mm Hg/mL	2.4 (1.9 to 3.1)	−0.2 (−0.7 to +0.3)	0.014	2.1 (1.7 to 2.9)	−0.1 (−0.5 to +0.4)	0.33	0.064	0.27
V_0, mL	−22 (−34 to −11)	1 (−12 to +13)	0.54	−17 (−29 to +12)	3 (−15 to +14)	0.26	0.324	0.70
LV-VPES$_{100mmHg}$, mL	18 (10 to 28)	7 (−5 to +17)	<0.001	24 (15 to 40)	3 (−6 to +14)	0.08	0.007	0.50

HFpEF indicates heart failure with preserved ejection fraction; LV-VPED$_{20mmHg}$, estimated left ventricular end-diastolic volume at a given pressure of 20 mm Hg; LV-VPES$_{100mmHg}$, estimated left ventricular end-systolic volume at given pressure of 100 mm Hg; and V_0, volume intercept at pressure zero.

Table 4. Hemodynamic Effects of Renal Sympathetic Denervation in HFpEF and No HF as Assessed by MRI

	HFpEF (n=55)		*P* value (pre vs post)	No HF (n=35)		*P* value (pre vs post)	*P* value (HFpEF vs no HF baseline)	*P* value (Δ HFpEF vs Δ no HF)
	Baseline	Δ Follow-up		Baseline	Δ Follow-up			
Stroke volume index, mL/m²	40 (33 to 48)	−3 (−9 to +3)	0.011	33 (26 to 40)	−0 (−4 to +3)	0.36	0.002	0.28
Heart rate, bpm	59 (55 to 66)	1 (−3 to +4)	0.39	69 (61 to 72)	−1 (−7 to +4)	0.32	<0.001	0.18
Cardiac index, L/min/m²	2.4 (2.1 to 2.7)	−0.1 (−0.6 to +0.2)	0.06	2.2 (2.0 to 2.6)	−0.1 (−0.4 to +0.1)	0.05	0.144	0.94
Systemic vascular resistance index, dyne⁻⁵/m²	777 (571 to 943)	21 (−121 to +149)	0.63	732 (660 to 862)	28 (−74 to +149)	0.15	0.956	0.46
Cardiac power output index, W/m²	0.53 (0.41 to 0.64)	−0.08 (−0.18 to +0.03)	0.003	0.44 (0.40 to 0.53)	−0.02 (−0.09 to +0.04)	0.33	0.013	0.14

HFpEF indicates heart failure with preserved ejection fraction; and MRI, magnetic resonance imaging.

Echocardiographic Single-Beat Estimations

LV-VPED$_{20mmHg}$ was lower in patients with HFpEF as compared to no-HF patients. Following RDN LV-VPED$_{20mmHg}$ increased in patients with HFpEF (Table 3). Interestingly, patients with HFpEF had higher E_{es} and numerically lower V_0 resulting in a higher estimate of systolic force LV-VPES$_{100mmHg}$ as compared to controls. Furthermore, LV-VPES$_{100mmHg}$ statistically significant increased in HFpEF patients with no statistically significant change in the no-HF patients and no significant difference in the between-group change (*P*=0.50). As opposed to baseline, LV-VPES$_{100mmHg}$ was not different between patients with HFpEF and no-HF patients after RDN (*P*=0.22; Table 3).

Extent of LV Afterload Reduction and LV Function

Patients with HFpEF with the highest BP reduction had the most pronounced reduction in SVI and E/E′ and showed numerical trends for higher NT-proBNP and BPV nighttime changes as compared to patients with

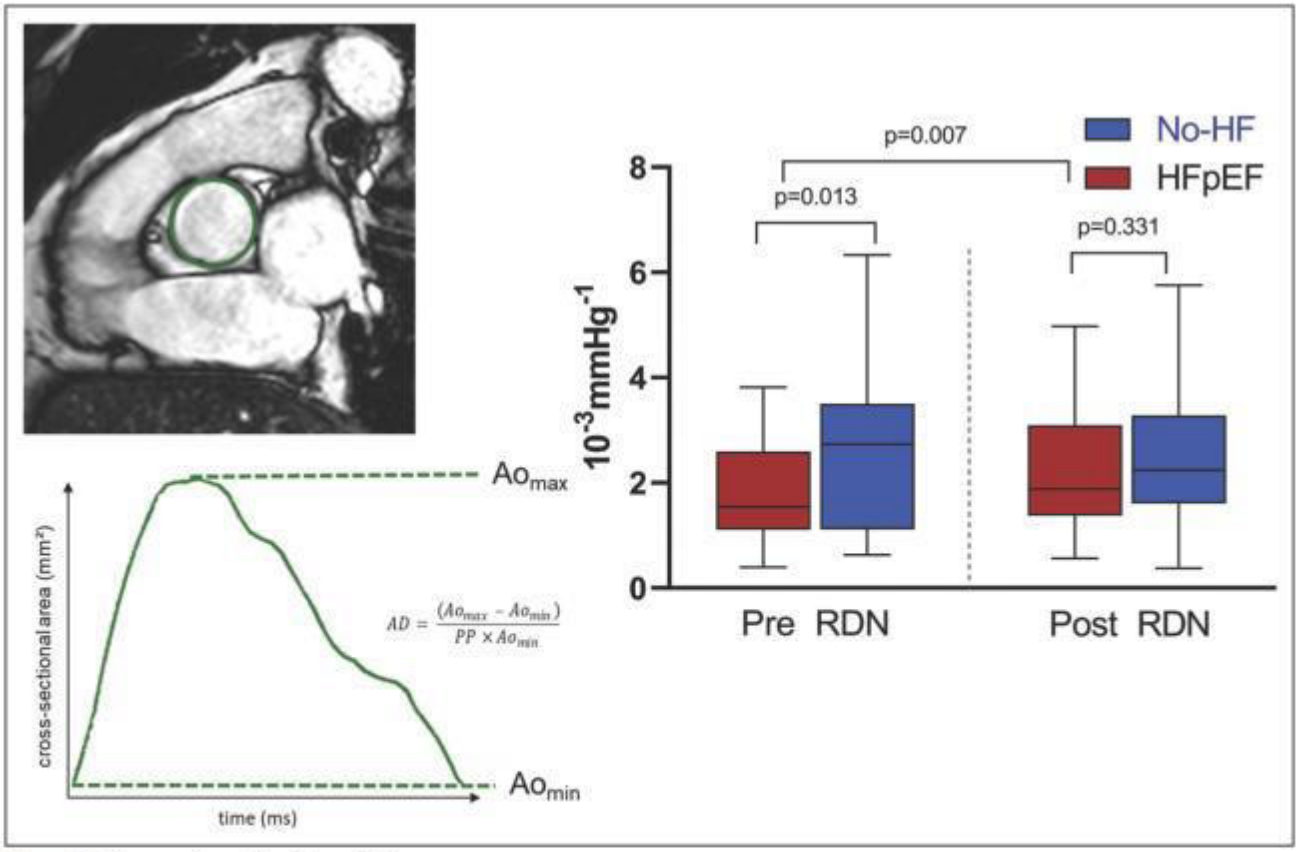

Figure 2. Changes in aortic distensibility.
Changes in aortic distensibility in patients with heart failure with preserved ejection fraction (HFpEF; red) and patients without heart failure (blue). Aomax indicates maximum aortic cross-sectional area; Aomin, minimal aortic cross-sectional area; and RDN, renal sympathetic denervation.

a lower BP reduction and no BP reduction (Figure 1C through 1F). Furthermore, the reduction in systolic stiffness was accompanied by a decrease in diastolic stiffness (Figure 3).

DISCUSSION

This is the largest study so far comparing the effects of RDN in patients with HFpEF compared with patients without HF. The main findings were that as follows:

1. the number of patients with HFpEF as defined by the European Society of Cardiology criteria[17] undergoing RDN is high,
2. patients with HFpEF undergoing RDN show an unfavorable hemodynamic phenotype with reduced aortic buffering capability, higher BPV, higher CPOI, and lower LV-$VPES_{100mmHg}$ indicating increased myocardial work at rest, and
3. that patients showed symptomatic improvement and partly reversed hemodynamic alterations to a level comparable to patients without HF following RDN.

The proposed mechanisms for these findings are summarized in Figure 4.

One of the central observations was that patients with HFpEF were marked by a stiffer vascular system as compared to controls, indicated by reduced aortic distensibility, higher pulse pressure as well as increased pulse wave velocity all possibly mediated through increased SNA or the long-term consequences thereof. This, in turn, should cause increased pulsatile afterload and consequently unfavorable ventriculo-arterial coupling.[7] It is well known that an increase in the pulsatile components of BP (systolic BP and pulse pressure) is a major risk factor for developing HF in general[24] and HFpEF in particular.[25] An impairment of arterial pulsatile function in this patient population has been described repeatedly.[2,26] Mechanistic studies have identified a relationship between diastolic dysfunction and increased arterial stiffening or increased arterial wave reflections in different populations.[27,28]

Although HF habitually has been associated with a decreased systolic stiffness (reduced E_{es} and high LV-$VPES_{100mmHg}$) and impaired SVI, we observed the opposite.[6] A possible explanation is that arterial stiffening in conjunct with compensatory ventricular hypercontractility impairs ventriculo-arterial interaction in HFpEF,[2] this exaggerates the consequences of increased aortic stiffness (more volume in a nondistensible aorta) and might cause a marked increase in LV pulsatile load resulting in both increased systolic stiffness and diastolic stiffness as proposed in the left part of Figure 4. This vicious cycle of increased afterload and stiffening causes an amplified sensitivity to afterload and volume changes leading to increased LV filling pressures and left atrial hypertension on exertion, exercise intolerance, and ultimately HF decompensation in these patients.[3,29,30] Increased SVI and stroke work have been reported to be present in patients with HFpEF[2] and patients that are at risk for the development of HFpEF (evidence of structural heart disease and elevated biomarkers but lack of symptoms) with LV hypertrophy as compared to patients without hypertrophy.[31] Our data confirm and expand these findings showing that even when compared with patients exhibiting uncontrolled aHT, SVI, and markers of cardiac work are higher in HFpEF. Recently, we proposed that normalization of high SVI is one of the driving mechanisms of BP

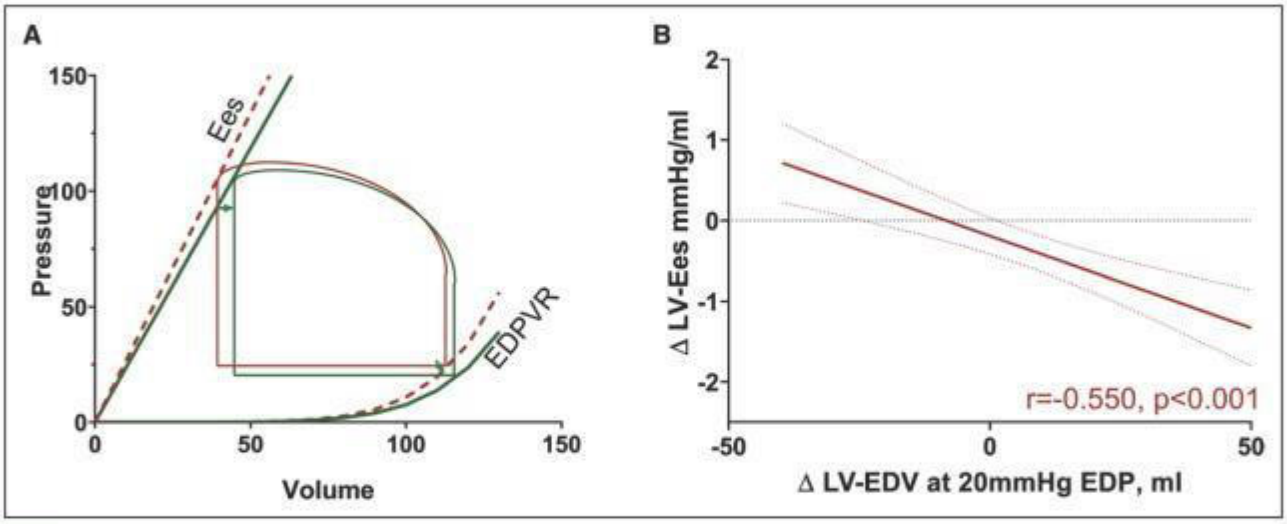

Figure 3. Changes in systolic and diastolic elastance after renal sympathetic denervation and their correlation in patients with heart failure with preserved ejection fraction (HFpEF).

A, Changes in left ventricular (LV) end-systolic elastance (E_{es}) and end-diastolic pressure-volume relationship (EDPVR) pre (red dotted line) and post (green solid line) renal sympathetic denervation. For purposes of comparability the ESPVR was calculated to V_0 =0 mL. **B**, Correlation of change in E_{es} and LV end-diastolic volume at 20 mm Hg in patients with HFpEF.

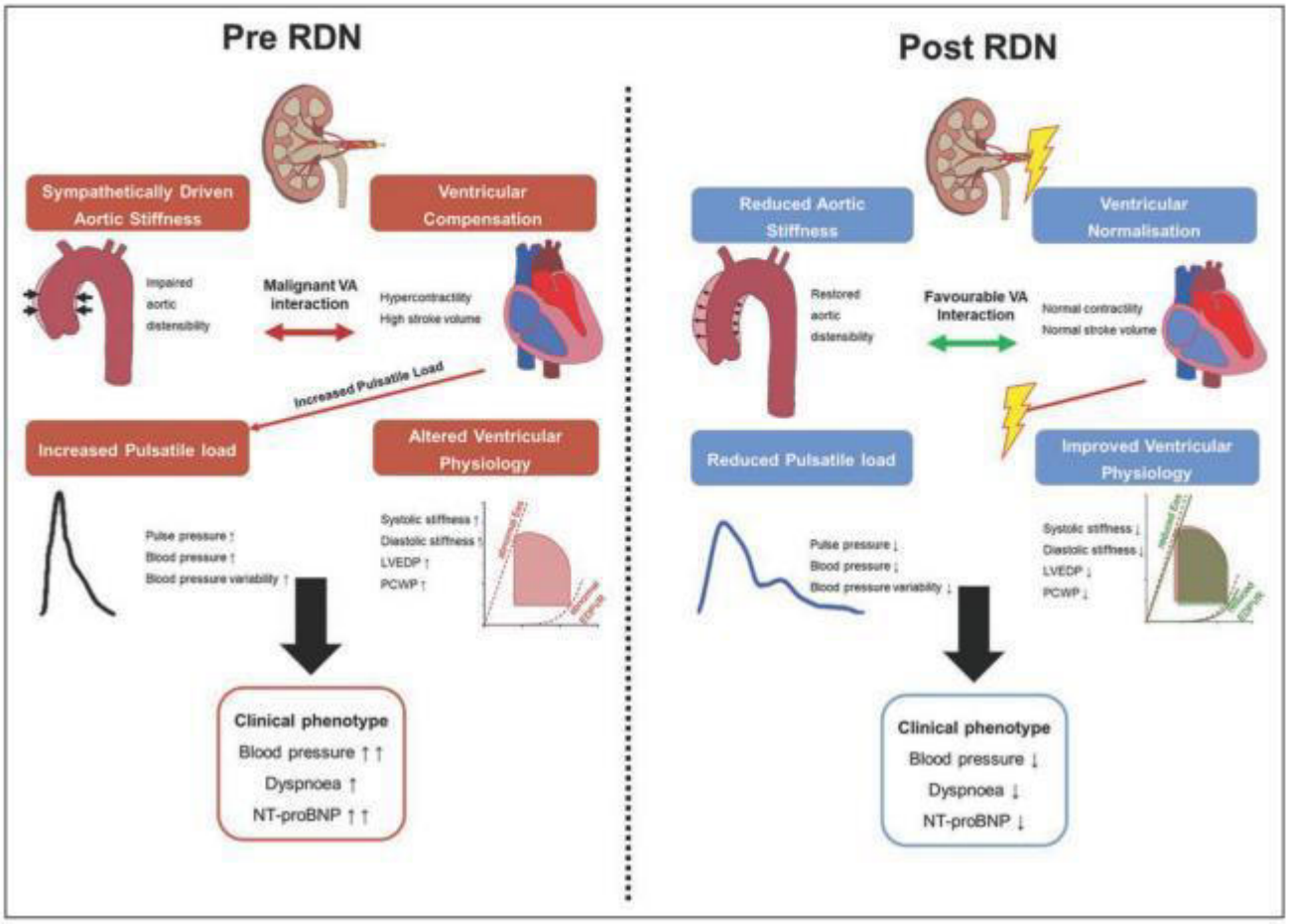

Figure 4. Proposed beneficial mechanism of renal sympathetic denervation in patients with heart failure with preserved ejection fraction (HFpEF).

Graphical abstract summarizing the interaction of increased sympathetic activity leading to increased aortic stiffness through sympathetic nervous activation and malignant ventriculo-arterial compensation leading to left ventricular hypercontractility in patients with uncontrolled hypertension. Renal sympathetic denervation alleviates these hemodynamic changes and improves symptoms and biomarkers indicative of elevated left ventricular wall stress in patients with HFpEF. ESPVR indicates end-systolic pressure-volume relationship; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; and VA, ventriculo-arterial.

reduction in the overall patient population undergoing RDN.[22] Here, we can show that this might particularly be true for patients with HFpEF where the extent of BP reduction went alongside the SVI reduction.

RDN was associated with improved aortic distensibility in a cohort of patients with uncontrolled aHT.[13] Interestingly, in our cohort, the positive effects of improving aortic distensibility were mainly confined to patients with HFpEF. While the lower aortic distensibility in patients with HFpEF might be explained by higher age as compared to the no-HF population, the favorable response following RDN contradicts the notion that age alone explains this finding as the aortic stiffness was partially reversible. As increased aortic stiffness and pulsatile load are in close causal relationship to isolated systolic hypertension,[32] which was more frequent among patients with HFpEF, our data might indicate that apart from the beneficial changes in HF patients, there might be a potential beneficial hemodynamic effect of RDN in patients with isolated systolic hypertension.

Previous studies have reported on positive effects of RDN on LV diastolic function.[16,33] Our study reinforces the finding of improved diastolic function after RDN. Of note, we observed a reduction in E/E′, as surrogate of left atrial pressures, but also a downward shift of the LV end-diastolic pressure-volume relationship. The change in diastolic stiffness correlated with the change in systolic stiffness indicating that reduced systolic force might benefit LV chamber loading conditions in patients with HFpEF undergoing RDN. Furthermore, the reduction in CPOI indicates a lower myocardial oxygen demand at rest.[23]

Therefore, RDN was associated with a reduced pulsatile load through diminishing increased vascular stiffness, leading to a more favorable ventriculo-arterial coupling and partly abolished the need for compensatory LV hypercontractility, which by itself again reduces BP and pulsatile load for the LV, ultimately leading to less systolic and diastolic stiffness (right part of Figure 4). However, the observed normalization in E_{es} might not only be

explained by improved aortic distensibility and favorable ventriculo-arterial interaction but also by more complex pathways like a direct effect of reduced SNA on the myocardium through RDN.[34]

Increased SNA has been described as one pathogenic contributor to chronic HF[35] and is associated with poor clinical prognosis.[36] It also leads to a more pulsatile BP profile which can cause a mismatch in ventriculo-arterial coupling as described above.[37] Increased SNA may be especially pronounced in hypertensive patients with concomitant patients with HFpEF compared to no-HF patients.[5] We observed a significant reduction of BPV following RDN in patients with HFpEF as a possible surrogate for normalization of SNA. Although this finding is likely the consequence of the combination of multiple pathophysiological effects, amongst them the changes in arterial and systolic LV properties discussed above, a reduction in SNA through RDN might also favorably impact on cardiac preload by enhancement of splanchnic and venous blood pooling.[38] However, BPV is only a rough estimate of SNA, and further data are needed to assess the true response of the SNA following RDN in patients with HFpEF (eg, response to Valsalva maneuver[38]).

These changes were accompanied by a reduction in NT-proBNP in patients with HFpEF, indicating some improvement in HF in this cohort. So far, only one study has prospectively assessed the role of RDN in patients with HFpEF and reported data.[39] In this well-designed study, diastolic function on echocardiography improved in patients while there was no improvement in exercise capacity or NT-proBNP. However, the study was terminated prematurely due to recruitment problems and was underpowered to identify relevant treatment effects.

Limitations

Our study comprises a pooled cohort that underwent RDN due to uncontrolled aHT, which was not primarily screened on the basis of HF symptoms. This partly explains the relatively high number of patients without specific symptoms and might represent an early stage of a hypertensive HFpEF phenotype, which might not be generalizable to the entirety of HFpEF. As such, part of our HFpEF group might be considered as pre-HFpEF stage (although all asymptomatic patients with HFpEF were on diuretic treatment). However, despite this presumably early stage, exercise capacity was limited in our patients with HFpEF and it has recently been shown that this patient group is at high risk for mortality or development of symptomatic HF and might thus be a promising cohort for therapeutic interventions.[40] Pressure-volume loop estimates of the LV were calculated using echocardiography rather than measurement through conductance catheters, although this method showed overall good correlation in its derivation cohort, it is not validated in patients with uncontrolled aHT and HFpEF, as well as in patients with atrial fibrillation with possible beat to beat variation.[20] As patients were classified as HFpEF according to the European Society of Cardiology criteria changes in variables included in the criteria might be prone to a regression to mean error. The hemodynamic estimates at baseline might in part be explained by sex and age difference at baseline. However, the observed beneficial changes after RDN still imply a possible positive effect after RDN in the subgroup of patients with HFpEF, and the observed changes following RDN were retained after adjustment for baseline differences (Table IV in the Data Supplement).

As we pooled historic data from RDN, different ablation systems were used but due to limited sample size a further analysis whether an ablation system is superior to another is precluded in the current study and needs prospective evaluation.

Finally, results of patients with HFpEF were compared to patients without HF with no sham-control cohort and adherence to medication was not monitored at baseline and throughout the duration of the study. Overall, the findings of our study should be considered hypothesis generating with the need for further validation in a dedicated randomized and shamed controlled trial.

Conclusions

Within an uncontrolled aHT cohort, patients exhibiting HFpEF are characterized by a state of hypercontractility, increased aortic stiffness as well as pathological ventriculo-arterial interaction. A similar BP reduction in patients with HFpEF and no HF and a reversal of unfavorable hemodynamic alterations in HFpEF patients with improvements in LV filling characteristics and pressures was observed after RDN. Therefore, RDN might be a potential treatment option in a hypertensive HFpEF phenotype, which warrants further investigations in prospective randomized controlled trials.

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3 SCHLUSSFOLGERUNGEN

Die HFpEF ist eine epidemiologisch bedeutsame Entität mit einer eingeschränkten Prognose und hohen Morbidität. Im Gegensatz zur Gruppe der HFrEF Patienten, für die multiple effektive Therapie in den letzten Jahren belegt werden konnten, gelang bisher nahezu keine Etablierung von effektiven Therapien für HFpEF Patienten (7). Dies wird zum großen Teil auf eine ausgeprägte Heterogenität des klinischen Syndroms zurückgeführt. Während einige Patienten auf spezifische Therapie ansprechen mögen, könnte sie in einem anderen Fall schädlich sein, sodass über die Gesamtheit der Population kein Therapieeffekt nachgewiesen werden kann. Die Heterogenität der HFpEF Population beruht historisch auf einer simplifizierten Definition auf Basis unterschiedlicher LVEF Grenzen und anamnestischen Informationen. Zur Reduktion dieser Heterogenität wurde in den letzten zwei Jahrzenten eine Definition unter Einbeziehung des Nachweises typischer Komorbiditäten, kardialer struktureller und funktioneller Veränderungen, einer Erhöhung der natriuretischen Peptide, sowie dem Nachweis erhöhter LA beziehungsweise LV Füllungsdrücke entwickelt (5). Zudem wurde die Bedeutung des Ausschlusses spezifischer alternativer Kardiomyopathien betont. Diese können als pathophysiologisch eigene Entitäten betrachtet werden, wofür zum Teil spezifische Therapieoptionen bestehen. Zum Ausschluss eines Großteils der differentialdiagnostisch in Erwägung kommenden Entitäten, wie etwa einer Myokarditis, einer Amyloidose, einer konstriktiven Perikarditis oder hypertrophen Kardiomyopathie, wird eine kardiale MRT empfohlen, was den Wert dieses Bildgebungsverfahrens in der klinischen Praxis unterstreicht (74). Doch auch mit einer strikteren Definition und dem Ausschluss differentialdiagnostischer Kardiomyopathien stellt die Gesamtheit der HFpEF Patienten ein heterogenes Kollektiv dar, weshalb die Notwendigkeit der Identifikation mechanistisch homogener Subgruppen wiederholt als Bedingung für die Etablierung effektiver Therapiekonzepte diskutiert wurde (179,211).

Es besteht aktuell Unklarheit wie diese Phänotypisierung durchgeführt werden sollte. In den letzten Jahren konnten in verschiedenen Studien eine Reihe von Ansätzen erarbeitet werden. Dazu gehört die Klassifizierung anhand zirkulierender Biomarker (212-214), anhand invasiver hämodynamischer Veränderungen unter Belastung (88,215) oder dem Vorliegen einer PHT (86), anhand des Ausmaßes einer subklinischen systolischen LV Funktionseinschränkung (72), des Vorliegens einer koronaren mikrovaskulären Dysfunktion (110,216), des Nachweises einer systemischen Inflammation (217), der spiroergometrischen Belastungsreaktion (115), des Vorliegens verschiedener Komorbiditäten wie Adipositas

(218), einer koronaren Herzerkrankung (14) oder eines Diabetes mellitus (219). Ein weiterer Ansatz ist eine computerbezogene Gruppierung von Subgruppen anhand Ähnlichkeiten in einer Vielzahl klinischer und echokardiographischer Parameter (220,221).

Die Vorstellung einer insgesamt erschöpfenden aber sich gegenseitig ausschließenden Klassifikation wird aber zum einen dadurch korrumpiert, dass sich viele dieser Phänotypen überlappen oder sogar gegenseitig direkt miteinander konkurrieren. Zum anderen ist es wahrscheinlich, dass bestimmte Phänotypen stadienspezifisch in Bezug auf den natürlichen Verlauf der Erkrankung zu beobachten sind.

Unabhängig von der Methode liegt die Qualität einer solchen Phänotypisierung in ihrer klaren Gruppentrennung, der einfachen Anwendbarkeit und der Möglichkeit verschiedene Therapieeffekte voraussagen zu können (7).

Die Phänotypisierung auf Grundlage zentraler Pathomechanismen ist in diesem Zusammenhang eine vielversprechende Lösung, da hierdurch mögliche Therapieziele direkt abgeleitet werden können.

3.1 PATHOMECHANISTISCHE PHÄNOTYPISIERUNG ANHAND DES VORLIEGENS EINER MYOKARDIALEN FIBROSE

Eine gemeinsame Endstrecke der meisten kardialen Pathologien ist die Ausbildung einer myokardialen Fibrose. Entsprechend der in Abschnitt 1.3.3.8 dargestellten zellulären pathophysiologischen Überlegungen spielt eine myokardiale Fibrose auch in HFpEF eine wichtige Rolle. Im Gegensatz zu einer fokalen Fibrosierung, die typisch ist für HFrEF Patienten, kommt es in HFpEF zu einer diffusen interstitiellen Fibrosierung (222). In symptomatischen HFpEF Patienten ist eine vergrößerte extrazelluläre Matrix, als quantitatives Maß der diffusen myokardialen Fibrose, assoziiert mit einer diastolischen Dysfunktion (54). Diese korreliert mit der Arrhythmielast, der Symptomlast und dem Outcome (223,224). Aus diesem Grund stellt die myokardiale Fibrose ein attraktives Therapieziel dar.

Der Goldstandard zur Bestimmung der myokardialen Fibrose ist die histologische Analyse, die durch ihren invasiven Charakter und die inkomplette Repräsentation des gesamten Myokards limitiert ist. Die Entwicklung neuer T1-Mapping Techniken in der kardialen MRT ermöglichen es erstmals diffuse LV Fibrose nicht-invasiv direkt zu quantifizieren. Die Bestimmung der extrazellulären Volumenfraktion (ECV) ermöglicht einen histologisch validierten Rückschluss auf eine diffuse myokardiale Fibrosierung (64).

Vor diesem Hintergrund untersuchte die in Kapitel 2.1.1 dargestellte Arbeit die Wertigkeit dieser Methode in der Abschätzung der diastolischen Funktionsstörungen und der

Identifikation pathophysiologischer Subgruppen der HFpEF. Für diese Arbeit wurden 24 Patienten mit leitlinienbasierter HFpEF Diagnose und zwölf Patienten ohne Herzinsuffizienz prospektiv mittels kardialer MRT und der invasiven Aufzeichnung von Druck-Volumen-Schleifen in Ruhe, unter Vorlastreduktion und unter körperlicher Belastung charakterisiert. Patienten mit HFpEF zeigten eine eingeschränkte Belastbarkeit mit erhöhten enddiastolischen LV Füllungsdrücken in Ruhe und einen pathologischen Anstieg des enddiastolischen Druck-Volumenverhältnis unter körperlicher Belastung. Im Vergleich zu Patienten ohne Herzinsuffizienz konnten bei HFpEF Patienten eine verlängerte aktive LV Relaxation und eine erhöhte LV Steifigkeit nachgewiesen werden. Patienten in der HFpEF Gruppe zeigten außerdem eine deutlich vermehrte ECV. Die ECV und die myokardiale Steifheitskonstante, Beta, wiesen eine direkte Korrelation auf. Während bei HFpEF Patienten mit einer ECV ≥Median die diastolische Dysfunktion hauptsächlich auf eine passive Steifigkeit des Myokards zurückzuführen war, zeigte sich in der HFpEF Gruppe mit einer ECV <Median eine pathologische vaskuläre Steifigkeit mit hypertensiver Reaktion unter Belastung und verlängerter aktiver LV Relaxation. Eine gesteigerte ECV, als Ausdruck einer vermehrten diffusen myokardialen Fibrosierung, kann als Ursache einer ausgeprägten nicht myozytären myokardialen Steifigkeit gesehen werden. Bei HFpEF Patienten mit niedrigem ECV muss vorrangig ein alternativer Mechanismus für die diastolische Dysfunktion in Betracht gezogen werden. Interessanterweise wiesen die anhand der ECV stratifizierten HFpEF Subgruppen hinsichtlich demographischer Charakteristika und echokardiographischer Befunde keine Unterscheide auf. Die Unterschiedlichkeit konnten aber eindeutig mittels kardialer MRT und erweiterter hämodynamischer Charakterisierung herausgearbeitet werden.

Die Arbeit suggeriert eine optimierte Phänotypisierung von HFpEF Patienten anhand des Ausmaßes der diffusen myokardialen Fibrose. Sie ist auch Hinweis dafür, dass es innerhalb des klinischen HFpEF Spektrums zu unterschiedlicher Ausprägung einer myokardialen Fibrosierung kommt. Dies wird bestätigt durch histologische Daten, die im Durchschnitt eine erhöhte myokardiale Fibrose im Vergleich zu gesunden Kontrollen zeigen, wobei allerdings ein signifikanter Anteil von HFpEF Patienten keine relevant erhöhte interstitielle Fibrosierung aufweist (55).

Dies hat wichtige therapeutische Implikationen. Im humanen Myokard entwickelt sich eine myokardiale Fibrose normalerweise langsam und im Verlauf über Jahre bis zur klinischen Manifestation. Dies impliziert ein Auftreten dieses Phänomens eher spät im natürlichen Verlauf der HFpEF oder als „akzelerierter fibrotischer Phänotyp“ mit der grundsätzlichen Frage einer Reversibilität. Dies wird unterstützt durch die Tatsache, dass

Patienten mit erhöhter diffuser myokardialer Fibrosierung eine eingeschränkte Prognose und höhere NT-pro-BNP Serumkonzentrationen aufweisen (225,226).

Eine Fibrose ist allerdings kein inertes, metabolisch isoliertes Gewebe, sondern unterläuft einem ständigen Remodeling, das von Fibroblasten, Immunzellen und proteolytischen Enzymen reguliert wird. Dieser Prozess ist potentiell reversibel. Die Reversibilität nimmt mit zunehmender Kollagenquervernetzung ab (222). Für Spironolacton, einen Mineralokortikoidrezeptorantagonist, wird angenommen, dass es bei früher Initiation eine Fibrosebildung reduzieren und so die Ausbildung einer Herzinsuffizienz verzögern kann (227,228). In zwei prospektiv randomisierten Therapiestudien zu Spironolacton in HFpEF konnte jedoch kein eindeutiger klinischer Nutzen der Spironolactontherapie herausgearbeitet werden (siehe Kapitel 1.3.5)(160,161). Ein Grund für diesen Befund könnte die Variabilität der untersuchten Kollektivs hinsichtlich der Ausprägung der vorbestehenden myokardialen Fibrose sein. In der Tat fand eine post-hoc Analyse der ALDO-DHF Studie, dass Spironolacton die diastolische Funktion und die subjektive Belastbarkeit nur in Patienten mit geringer Kollagenquervernetzung verbessert (229). In ähnlicher Weise wurde in der TOPCAT Studie ein positiver Behandlungseffekt von Spironolacton nur in Patienten mit niedrigeren NT-pro-BNP Serumkonzentrationen, als möglichem Hinweis auf eine weniger fortgeschrittene myokardiale Fibrosierung, beobachtet (230).

Hieraus ergibt sich ein hoher Nutzen der in Kapitel 2.1.1 vorgeschlagenen Phänotypisierung mittels ECV Bestimmung in der kardialen MRT. Anhand des quantitativen Charakters der Methode ist eine klare Gruppenzuordnung möglich, auch wenn absolute Normwerte in größeren Kohorten validiert werden müssen. Hinsichtlich der Anwendbarkeit bestehen für die kardiale MRT im Rahmen der bereits bestehenden Einbettung in die Differentialdiagnostik der HFpEF, des nicht-invasiven Charakters, der hohen Reproduzierbarkeit und der hohen Anzahl an zusätzlich zu gewinnenden Informationen große Vorteile, wobei eine universelle breite und vor allem ambulante Verfügbarkeit bis dato noch nicht gegeben ist und spezifische Kontraindikationen dem generalisierten Einsatz innerhalb der HFpEF Population entgegenstehen.

Die Prädiktion eines optimalen Therapieeffekts scheint für Patienten mit geringer ausgeprägter myokardialer Fibrosierung zu erwarten zu sein. Diese Hypothese wird unter Berücksichtigung der Ergebnisse der in Kapitel 2.1.1 genannten Arbeit aktuell in prospektiven Studien untersucht. Beispielhaft soll hier die STADIA-HFpEF Studie (Stratified Treatment to Ameliorate Diastolic left ventricular stiffness in early Heart Failure with preserved Ejection Fraction) genannt werden, die als Phase 2 Studie die Hemmung des

natriumabhängigen Glukosetransporter, SGLT-2, in Patienten mit nicht erhöhter ECV in der kardialen MRT untersucht. Rationale ist hier, dass mittels SGLT2-Hemmung positive Effekte auf die diastolische Funktion nur zu erwarten sind, wenn diese eine myozytäre und keine fibrotische Ursache hat (231).

Der gegenteilige Ansatz wird in der PIROUETTE Studie (Pirfenidone in Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction) genutzt. In dieser Phase 2 Studie wird bei Patienten mit MRT morphologisch erhöhter ECV eine Therapie mit Pirfenidon untersucht, welches in präklinischen Modellen eine Rückgang der myokardialen Fibrosierung bewirkt (232).

3.2 PATHOMECHANISTISCHE PHÄNOTYPISIERUNG ANHAND DER LINKSATRIALEN FUNKTION

Viele Studien konnten überzeugend darlegen, dass LA Dimensionen und Drücke eine diagnostische und prognostische Relevanz in HFpEF haben. Das morphologische LA Remodeling in Verbindung mit erhöhten LV Füllungsdrücken wurde daher lange vor allem als Marker der Progression der LV Dysfunktion gesehen (233).

Neben der Morphologie spielt die phasische LA Funktion eine entscheidende Rolle in der Optimierung der kardialen Funktion. Das LA moduliert die LV Füllung mit seiner Reservoirfunktion (LA Füllung während der ventrikulären Systole), Conduitfunktion (passive LA Entleerung während der frühen ventrikulären Diastole) und Boosterfunktion (aktive LA Kontraktion mit Entleerung in der späten ventrikulären Diastole), wobei im Gegenzug die LV Funktion die atriale Funktion beeinflusst. Die Reservoirfunktion wird durch die longitudinale Kontraktion des LV, den übertragenen systolischen PA Druck und intrinsische LA Eigenschaften (Relaxation und intrinsische Steifigkeit) bestimmt. Die Conduitfunktion wird durch die frühe diastolische LV Funktion (LV Relaxation und Druckniveau in der Diastase) sowie durch die intrinsischen passiven LA Rückstellkräfte beeinflusst. In der Boosterphase wird durch die aktive LA Kontraktion und Entleerung eine Zunahme der LV Füllung um etwa 20 Prozent erreicht. Diese Funktion wird moduliert durch LV Steifigkeit, LV Füllungsdrücke und die LA Kontraktilität (234).

In der in Abschnitt 2.1.2 angeführten Arbeit untersuchten wir ein HFpEF Kollektiv von 22 Patienten im Vergleich zu zwölf Patienten ohne Herzinsuffizienz mittels phasischer LA Funktionsbestimmung in der kardialen MRT, invasiver Charakterisierung der LV diastolischen Funktion mittels Druck-Volumen-Schleifen und spiroergometrischer Belastung. Alle Patienten waren zum Zeitpunkt der Untersuchung im Sinusrhythmus, hatten keine

Vorgeschichte einer Herzinsuffizienzhospitalisierung und waren nur zu etwa einem Drittel diuretisch vortherapiert, was für ein frühes Erkrankungsstadium spricht. HFpEF Patienten wiesen typische Zeichen einer LV diastolischen Dysfunktion mit erhöhter LV Steifigkeit und eingeschränkter aktiver LV Relaxation auf. Diese Gruppe war neben einem morphologischen LA Remodeling im Sinne einer LA Dilatation durch ein funktionelles LA Remodeling mit eingeschränkter LA Reservoir- und LA Conduitfunktion charakterisiert. Letztere war ein starker Prädiktor für das Ausmaß der volumetrischen frühen LV Füllung, definiert als Anteil der volumetrischen LV Füllung nach dem ersten Drittel der Diastole an der Gesamtfüllung des LV. Die LA Conduitfunktion war der stärkste Prädiktor für die spiroergometrische Belastbarkeit unabhängig von invasiv abgeleiteten Parametern der diastolischen LV Funktion. Dieser Zusammenhang kann durch die entscheidende Bedeutung der frühen diastolischen LV Füllung für die globale LV Füllung und der damit verbundenen Schlagvolumenadaptation unter körperlicher Belastung erklärt werden. Mit steigender Herzfrequenz und Verkürzung der Diastolendauer können Veränderungen der LA Conduitfunktion als Treiber einer Störung der frühen LV Füllung unabhängig zu einer Einschränkung der Herzzeitvolumenreserve und der Ausbildung einer HFpEF beitragen (235).

Der in dieser Studie gewonnene Eindruck einer unabhängigen Rolle des funktionellen LA Remodelings in der Pathophysiologie der HFpEF wurde im selben Zeitraum durch echokardiographische LA Deformationsanalysen bestätigt. In einer longitudinalen Studie die 308 HFpEF Patienten mit etwas weiter fortgeschrittenem Krankheitsstadium beobachtete, waren LA Reservoir-, Conduit- und Boosterfunktion mit dem Auftreten von Tod oder Hospitalisierung assoziiert, wobei eine eingeschränkte LA Reservoirfunktion der stärkste Prädiktor für den Endpunkt und eine eingeschränkte Belastbarkeit war (236).

Die Ergebnisse dieser beiden Arbeiten und anderer Studien gaben Anlass eine LA Myopathie als eigenständigen pathophysiologischen Faktor der HFpEF zu definieren (237). Nach dieser Vorstellung unterliegt das morphologische und funktionelle LA Remodeling einem zeitabhängigen Prozess in mehreren Stufen. Initial steigt mit Einschränkungen der LV Relaxation und Zunahme der LV Füllungsdrücke der durch die atriale Kontraktion vermittelte Anteil der LV Füllung, während die LA Conduitfunktion abnimmt (238). Eine LA Dilatation ermöglicht in diesem Zusammenhang einen gesteigerten volumetrischen LA Auswurf. Diese Anpassungen werden als protektiv für den Lungenkreislauf und das reche Herz gedeutet, da mit zunehmender diastolischer LV Dysfunktion und Steifigkeit die globale LA Funktion und insbesondere auch die Boosterfunktion abnimmt und gleichzeitig pulmonale und RV Veränderungen zunehmen (76). Der weitere Verlauf ist durch eine progrediente Abnahme der

LA Reservoirfunktion und eine gesteigerte LA Steifigkeit gekennzeichnet. Ultrastrukturell gehen diese Vorgänge mit der Entwicklung einer myokardialen LA Fibrose einher, die neben der Druckbelastung auch vom profibrotischen Milieu eines systemischen Inflammationszustands begünstigt werden könnte (237). Diese fibrotischen Veränderungen stellen das Substrat für die Entwicklung eines elektrischen Remodelings und dem Auftreten eines Vorhofflimmerns dar. Mit dem Verlust der aktiven LA Funktion im Rahmen des Auftretens eines Vorhofflimmerns geht eine weitere Einschränkung der LV Füllung und eine konsekutive LA Druckerhöhung einher. Das Auftreten eines Vorhofflimmerns ist häufig und betrifft etwa ein Drittel der HFpEF Patienten im Verlauf ihrer Herzinsuffizienz. Eine Vorhofflimmerdiagnose ist verbunden mit einem schwereren morphologischen LA Remodeling, dem häufigeren Nachweis einer PHT, ausgeprägtem RV Remodeling sowie einer eingeschränkten Belastbarkeit und Prognose (77,78). Obwohl Vorhofflimmern nicht ausschließlich als Komplikation einer Herzinsuffizienz gesehen werden kann, kann diese in mehr als 90 Prozent der Patienten mit Vorhofflimmern und Dyspnoesymptomatik invasiv diagnostiziert werden und beschriebene Risikofaktoren und Symptomatik haben signifikante Überschneidungen mit denen der HFpEF (239). Es ergibt sich das Bild einer fortschreitenden LA Myopathie im Verlauf der HFpEF mit initial subtilen Einschränkungen in der phasischen LA Funktion im Sinusrhythmus und einem im Verlauf progredienten morphologischen und funktionellem LA Remodeling, zunehmender Vorhofflimmerlast und abnehmender Prognose (240).

Ein weiterer Hinweis für die eigenständige Bedeutung der LA Funktion für die HFpEF Pathophysiologie ist die Tatsache, dass in HFpEF der PCWP, der maßgeblich durch LV und LA Eigenschaften determiniert wird, einen stärkeren Prädiktor für Mortalität und Hospitalisierung darstellt als der LVEDP, der hauptsächlich durch LV Eigenschaften bestimmt wird (241).

Klinisch kann die Ausprägung der LA Kardiomyopathie mittels Bestimmung der Vorhofflimmerlast abgeschätzt werden, wobei eine Zunahme von paroxysmalen zu persistierenden Formen des Vorhofflimmerns angenommen wird (240). Zu beachten ist, dass mit dem klinischen Auftreten eines Vorhofflimmerns die LA Myopathie bereits fortgeschritten und potentiell eingeschränkt reversibel ist. Dies kann mit einer reduzierten Effektivität spezifischer Therapieansätze oder gar mit deren schädlicher Wirkung einhergehen. Die interventionelle Pulmonalvenenisolation beispielsweise ist ein antiarrhythmischer Therapieansatz zur Erhaltung eines Sinusrhythmus, dessen Wirkprinzip auf einer Isolation von Arealen fehlgerichteter myoelektrischer Impulse mittels Schaffung

myokardialer Narbenlinien beruht. Durch die iatrogene Induktion einer atrialen Fibrose kann so eine atriale Steifigkeit verstärkt werden, wobei trotz Wiederherstellung der aktiven LA Kontraktion erhöhte LA Drücke persistieren (242).

Die Beurteilung der phasischen LA Funktion erlaubt dagegen die Identifikation von Funktionseinschränkungen in frühen Stadien der LA Myopathie. Deren enge Verbindung zu Symptomen und Funktionalität identifiziert diese als geeignetes pathomechanistisches Therapieziel zur Verbesserung der Symptomatik und Verhinderung einer Progression der HFpEF. Therapeutische Optionen sind bisher unzureichend untersucht. Eine Prävention des Neuauftretens von Vorhofflimmern durch Spironolacton wurde für Patienten mit Herzinsuffizienz suggeriert und eine frühe rhythmuserhaltende Therapie nach der Erstdiagnose eines Vorhofflimmerns reduziert kardiovaskuläre Endpunkte in Patienten mit kardiovaskulären Risikofaktoren (243,244). Interessanterweise scheint hier eine weitere Stratifizierung hinsichtlich des Therapieerfolgs der antiarrhythmischen Therapie anhand der LA Reservoir Funktion möglich (242). Ein weiterer Ansatz für diese Gruppe ist die Reduktion des LA Druckniveaus mittels Schaffung eines iatrogenen Shunts auf Vorhofebene mit Umleitung des überschüssigen Blutvolumens in das venöse System. In ersten Studien konnten die Effektivität hinsichtlich der Reduktion LA Drücke unter Belastung, eine Verbesserung der Dyspnoesymptomatik und eine Reduktion der Mortalität im Vergleich zur vorhergesagten Mortalität gezeigt werden (245).

Methodologisch ist das in Kapitel 2.1.2 beschriebene Vorgehen der LA Funktionsbestimmung mittels kardialer MRT relativ neu und mit den im Vorkapitel dargelegten Vorteilen der MRT Bildgebung verbunden. Ihre Anwendbarkeit, Reproduzierbarkeit und klinische Relevanz konnte für verschiedenen Krankheitsbilder nachgewiesen werden (246,247). In der klinischen Routine ist eine ähnliche atriale Funktionsbestimmung auch mit echokardiographischen Deformationsanalysen möglich, die den Vorteil einer besseren zeitlichen Auflösung und breiteren Verfügbarkeit bieten (248). Inwieweit diese zwei Bildgebungsmodalitäten zu gleichen Ergebnissen kommen, muss in zukünftigen Studien untersucht werden.

3.3 PATHOMECHANISTISCHE PHÄNOTYPISIERUNG ANHAND DER RECHTSVENTRIKULÄREN UND RECHTSATRIALEN FUNKTION

Während die RV Funktion in den letzten Jahren nur eine untergeordnete Rolle in der Betrachtung der Patienten mit linksseitiger Herzinsuffizienz spielte, konnte unlängst gezeigt werden, dass das Auftreten einer eingeschränkten RV Funktion häufig und mit einer

ungünstigen Prognose verbunden ist (249). Während die mechanistischen Zusammenhänge für Patienten mit HFrEF gut untersucht sind, sind diese in HFpEF unklarer.

In verschiedenen HFpEF Studien wurde eine Einschränkung der systolischen RV Funktion mit einer Prävalenz zwischen 20 und 50 Prozent beschrieben, wobei eine genaue Abschätzung durch bereits beschriebene Unterschiede in der HFpEF Definition zwischen verschiedenen Studien erschwert wird (249). Zudem scheint die Ausbildung einer systolischen RV Dysfunktion mit einer Progression des Erkrankungsstadiums verbunden zu sein. Im Verlauf von vier Jahren nach Diagnosestellung nimmt die systolische RV Funktion ab und sowohl die PA Drücke als auch die Rate an Patienten mit TI nehmen zu (250). Auch populationsbezogene Daten legen einen fortgeschrittenen HFpEF Phänotyp im Kontext einer eingeschränkten systolischen RV Funktion nahe, mit einem durchschnittlichen Alter von 80 Jahren und einer etwa 80 prozentigen Mortalität über einen Zeitraum von 8 Jahren (90). Die systolische RV Dysfunktion geht mit einer schlechteren systolischen LV Funktion, höheren PA Drücken und einer höheren Vorhofflimmerlast einher und ist ein starker Prädiktor für eine ungünstige Prognose unabhängig vom Ausmaß der PHT (80,91).

Im Gegensatz zur systolischen RV Funktion, die regelhaft echokardiographisch in der klinischen Routine abgeschätzt wird, ist die Beurteilung einer diastolischen RV Funktionsstörung nicht-invasiv schwieriger und findet in der klinischen Routine kaum Anwendung (249). Invasiv gelingt eine detaillierte Analyse ladungsabhängiger und ladungsunabhängiger systolischer und diastolischer Funktionsparameter des RV mittels Konduktanzmessungen, wie in Kapitel 1.4.1.1 beschrieben. Für die im Kapitel 2.1.3 aufgeführte Arbeit wurden 24 Patienten mit HFpEF und neun Patienten ohne Herzinsuffizienz prospektiv mittels invasiver Aufzeichnung von Druck-Volumen-Schleifen (in Ruhe, unter Vorlastreduktion und unter isometrischer körperlicher Belastung) im RV und LV untersucht. Das HFpEF Kollektiv war mit durchschnittlich 66 Jahren deutlich jünger als das in der oben genannten Kohortenstudie und wurde auf der Basis erhöhter LV Füllungsdrücke ohne Notwendigkeit des Vorliegens klinischer Rechtsherzinsuffizienzeichen eingeschlossen. Patienten mit HFpEF wiesen eine eingeschränkte Belastbarkeit auf. In den invasiven Druck-Volumenmessung zeigte sich, wie erwartet, eine erhöhte LV Steifigkeit und eine prolongierte LV Relaxation mit konsekutiv deutlich erhöhten enddiastolischen LV Druck-Volumenverhältnissen. Für den RV ergab sich in der invasiven Untersuchung keine Einschränkung der systolischen RV Funktion in der HFpEF Gruppe. Im Gegenteil, die RV Ees, als ladungsunabhängiger Kontraktionsparameter, und die RVEF, als ladungsabhängiger Kontraktionsparameter, waren erhöht. Dies kann am ehesten als Kompensation der

beobachteten, erhöhten, schlagvolumenkorrigierten RV Nachlast unter Belastung in dieser Gruppe interpretiert werden. Demgegenüber stellte sich die diastolische RV Funktion in HFpEF Patienten deutlich eingeschränkt dar, mit erhöhter intrinsischer enddiastolischer ventrikuläre Steifigkeit und pathologischer Verlängerung der aktiven Relaxationszeit sowie erhöhten RV Füllungsdrücken unter Belastung. Die diastolische RV Funktionsstörung ging dementsprechend mit einer eingeschränkten volumetrischen RV Füllung und einer daraus resultierenden reduzierten Steigerung des Herzzeitvolumens unter Belastung in der HFpEF Gruppe einher.

In einer weiterführenden Analyse dieser Kohorte, unter Zuhilfenahme der Analyse kardialer MRT Daten, konnten weitere Einblicke in die Mechanismen der gestörten RV Füllung gewonnen werden, wie in Kapitel 2.1.4 dargestellt. Hierzu wurde die RV Füllung mittels Volumen-Zeitkurven charakterisiert. Neben den klassischen volumetrischen Parametern der RVEF und RV Schlagvolumina wurde die frühe RV Füllung bestimmt, definiert als Anteil der volumetrischen RV Füllung nach dem ersten Drittel der Diastole an der Gesamtfüllung des RV. Zudem erfolgte die Charakterisierung der phasischen RA Funktion analog zu den Ausführungen zum LA in Kapitel 2.1.2. Entsprechend der invasiven Daten mit Darstellung einer gestörten diastolischen RV Funktion und Füllung, konnte so insbesondere eine Störung der frühen RV Füllung in HFpEF Patienten im Vergleich zu Kontrollen dargestellt werden. Das Ausmaß der frühen RV Füllung war der stärkste Prädiktor für die spiroergometrische Belastbarkeit der Patienten, unabhängig von invasiv bestimmten diastolischen RV Funktionsparametern. Erklärbar ist dies durch eine pathologische Interaktion des RA und RV während der frühen RV Füllung, mit deutlich eingeschränkter RA Conduitfunktion und kompensatorischer Erhöhung der aktiven RA Boosterfunktion und damit gesteigerter spätdiastolischer ventrikulärer Füllung in HFpEF Patienten.

Zusammenfassend ergeben sich in der erweiterten hämodynamischen Charakterisierung dieses frühen HFpEF Stadiums mit gering ausgeprägten morphologischen Veränderungen der rechtsseitigen Herzhöhlen und nur gering erhöhten PA Drücken Hinweise auf funktionelle pathomechanistische Alterationen bereits früh im Verlauf der HFpEF. Die Einschränkungen in der Herzzeitvolumenreserve und der Belastbarkeit sind in diesem Stadium weniger mit einer systolischen RV Dysfunktion, als mit einer eingeschränkten diastolischen RV Funktion und eingeschränkten RV Füllung zu deuten.

Mechanistische Vorstellungen zur Entwicklung einer RV Funktionsstörung basieren auf dem Effekt der periodisch erhöhten pulsatilen Nachlast und der Entwicklung einer postkapillären, durch LA Druckerhöhung bedingten, PHT (251,252). Durch den

Nachlastüberschuss und eine gesteigerte Nachlastsensitivität des RV kommt es im Verlauf zu einem maladaptiven Remodeling mit RV Hypertrophie, RV Dilatation und konsekutiver systolischer Funktionseinschränkung (249). Die Ergebnisse der Arbeiten in dieser Habilitationsschrift implizieren, dass ein funktionelles Remodelings des RV analog zu beschriebenen Störungen im LV bereits vor Manifestation einer ausgeprägten PHT auftritt und sprechen für einen gemeinsamen, systemischen, molekularen Pathomechanismus unter Beteiligung des biventrikulären und biatrialen Myokards wie in Kapitel 1.3.3.8 diskutiert.

Die spezifischen zellulären Mechanismen die dem natürlichen Verlauf einer Entwicklung der RV Dysfunktion in HFpEF unterliegen sind bisher kaum beleuchtet worden. Auf myokardialer Ebene zeigte sich in einer kürzlich veröffentlichten Studie eine erhöhte diffuse RV Fibrose in Patienten mit HFpEF und PHT, die jedoch im Gegensatz zur myokardialen Fibrose von Patienten mit primärer, durch Veränderungen der Lungenstrohmbahn bedingten, PHT nicht mit dem Ausmaß der PHT korrelierte (253). Ähnlich wie im LV können Störungen der frühen RV Füllung auch als subtile kontraktile RV Dysfunktion interpretiert werden, was auch Berichte über den Zusammenhang von Einschränkungen der atrialen Conduitfunktion mit einer systolischen ventrikulären Dysfunktion implizieren (254). Die beobachtete Erhöhung der RV Ees wäre in diesem Fall im Rahmen eines adaptiven strukturellen Remodelings und einem adaptiven Kontraktionsablauf zu erklären (249). Auf molekularer Ebene wurde kürzlich für HFpEF Patienten mit Adipositas ein reduziertes RV Sarkomeransprechen auf Calcium als Grundlage einer RV Kontraktionseinschränkung postuliert (255).

Eine detaillierte Charakterisierung von RV und RA Funktion in frühen HFpEF Stadien erlaubt zum einen die Identifikation eines frühen funktionellen RV und RA Remodelings als wichtige Mechanismen der HFpEF Pathophysiologie. Zum anderen wird eine Diskrimination der Auswirkung potentieller Therapien sowie die Etablierung dieser Störungen als potentielle Therapieziele ermöglicht. Inwieweit eine gezielte therapeutische Beeinflussung myokardialer Veränderung positive Effekte auf diese Funktionsstörungen bewirken können, muss in weiteren Studien untersucht werden. Von entscheidender Bedeutung ist die Aufklärung der individuellen Kontribution der zugrundeliegenden molekularen Mechanismen unabhängig vom Effekt der Druckbelastung auf das RV Myokard. Zu diesem Zweck wird aktuell in der, von der Deutschen Gesellschaft für Kardiologie geförderten, HFpEF-PHT Studie (Einfluss von Nachlast und myokardialer Veränderungen auf die intrinsische rechtsventrikuläre myokardiale Funktion bei Patienten mit Herzinsuffizienz und erhaltener LV Pumpfunktion)

der Zusammenhang zwischen myokardialen Veränderungen in biventrikulären Biopsien und der biventrikulären Hämodynamik untersucht.

Neben der spezifischen Adressierung der Grundlage diastolischer RV Funktionsstörungen, können aktuelle Therapieansätze im Bereich der Verbesserung der systolischen RV Funktion beziehungsweise der RV Nachlastreduktion eingeordnet werden. Kürzlich wurde für den kontraktionsmodulierenden Calciumsensitizer Levosimendan positive hämodynamische und klinische Effekte in HFpEF Patienten mit PHT demonstriert (256). Für den inhalativen ß-Agonisten Albuterol konnten positive hämodynamische Effekt mit Steigerung der RV Reserve und des Herzzeitvolumens durch eine verbesserte pulmonale Vasodilatation unter körperlicher Belastung gezeigt werden (257). Ein weiterer Ansatz, der aktuell klinisch getestet wird, ist die mechanische Reduktion der LA Drücke mittels Schaffung eines Shunts auf Vorhofebene. Dies reduziert die RV Nachlast und verbessert die pulmonalvaskuläre Dilatation, führt jedoch zu einer RA und RV Volumenbelastung, deren hämodynamische Folgen vor dem Hintergrund der Ergebnisse der Arbeiten dieser Habilitationsschrift in weiteren Studien kritisch zu beleuchten sein werden (258).

3.4 KLINISCHE PHÄNOTYPISIERUNG ANHAND DES VORLIEGENS EINER HOCHGRADIGEN TRIKUSPIDALKLAPPENINSUFFIZIENZ

Eine klinische Phänotypisierung bietet den Vorteil einer unmittelbaren Verfügbarkeit und guten klinischen Anwendbarkeit, sollte aber um therapeutische Implikationen zu ermöglichen Gruppen mit dominierenden pathomechanistischen Zusammenhängen identifizieren. Nach aktuellen Empfehlungen zur Diagnose einer HFpEF (siehe Kapitel 1.3.4) werden signifikante Klappenerkrankungen mit valvulären Kardiomyopathien den Differentialdiagnosen der HFpEF zugeordnet und spielen in der Betrachtung der HFpEF historisch eine untergeordnete Rolle. Sekundäre Insuffizienzen der Atrioventrikularklappen (Mitralklappeninsuffizienz und TI) werden aber zunehmend als Folgeerscheinung einer Herzinsuffizienz im Allgemeinen und der HFpEF im Speziellen wahrgenommen (186).

Daten des prospektiven Herzinsuffizienzregisters der Europäischen Gesellschaft für Kardiologie geben dahingehend eine ungefähre Abschätzung der epidemiologischen Situation. Während eine moderate bis schwere funktionale Mitralklappeninsuffizienz bei etwa einem Drittel der HFrEF Patienten und weniger bei HFpEF Patienten zu beobachten ist, weisen beide Entitäten eine ähnliche Rate einer moderaten bis schweren TI bei etwa einem Fünftel der Patienten auf (183). Wie in Kapitel 1.4.2.1 beschrieben ist diese ätiologisch auf eine Dilatation von RV, RA und Trikuspidalklappenanulus zurückzuführen die im Rahmen

einer Herzinsuffizienz bedingten PHT oder einer atrialen Myopathie auftreten (186). Wie in den vorangegangen Kapiteln diskutiert, ist der Nachweis dieser Faktoren typisch für den natürlichen Verlauf der HFpEF. Zur Abgrenzung des Bestehens einer TI im Zusammenhang mit einem höhergradigen Mitralvitium schlagen einige Autoren vor, dass der Nachweis einer isolierten, also ohne zusätzliches Vitium, auftretenden TI bei normaler LVEF ein hohe diagnostische Wertigkeit für das Vorliegen einer fortgeschrittenen HFpEF besitzt (81). Die Annahme, dass es sich hier um einen späten Zeitpunkt im natürlichen Verlauf der HFpEF handelt wird bestärkt durch ein höheres Alter, eine höhere Symptomlast und eine erhöhtes Risiko für Mortalität und Herzinsuffizienzhospitalisierungen dieser Patienten (184,186-188). In einem fortgeschrittenen Erkrankungsstadium mit einer Vielzahl weiterer Outcome relevanter Risikofaktoren ist es prinzipiell schwierig sich auf eine Pathologie als Therapieziel zu fokussieren. Für die TI muss daher diskutiert werden, ob sie einen tatsächlichen phänotypischen Pathomechanismus oder lediglich ein Indikator für ein fortgeschrittenes Erkrankungsstadium in HFpEF darstellt (81).

Während diese Diskussion durch Vergleiche unterschiedlicher Schweregrade der TI, unterschiedlicher Kontrollgruppen und der Debatte um die prognostische Relevanz der TI in HFrEF Patienten geprägt ist, stellt die Reduktion der negativen biventrikulären Effekte der mit der TI assoziierten RV Volumenüberladung, wie in Kapitel 1.4.2.1 dargestellt, ein attraktives hämodynamisches Therapieziel dar (81,186). Vor dem Hintergrund einer chirurgischen Unterversorgung und unklarem prognostischen Nutzen einer chirurgischen Therapie der isolierten TI, wurden in den letzten Jahren verschiedene katheterbasierte Interventionen zur Therapie dieses Vitium vorgeschlagen. Die langjährige Erfahrung zur Anwendung einer katheterbasierten „edge-to-edge“ Klappenrekonstruktion mittels Clipimplantation in Mitralposition hat dazu geführt, dass die Übertragung dieser Technik auf die Trikuspidalklappe die bis dato am häufigsten verwendete Intervention zur TTVR weltweit ist (192). Unsere und andere Arbeitsgruppen konnten in den letzten Jahren zeigen, dass diese Technik mit einer sehr hohen prozeduralen Sicherheit in Verbindung mit effektiver Reduktion der TI und einer kurz- bis mittelfristigen Symptomverbesserung verbunden ist (195,259,260). Zudem beobachteten wir und andere Gruppen einen prognostischen Nutzen dieser Therapie indirekt im Vergleich von Patienten mit und ohne prozeduralen Erfolg und direkter im Vergleich von TTVR Patienten gegen eine gematchte historische Kohorte von medikamentös behandelten Patienten mit hochgradiger TI (193,261,262).

Kapitel 2.2 umfasst Arbeiten, die grundsätzliche Fragestellungen in Bezug auf die Etablierung dieser Therapie für HFpEF Patienten adressieren und ihren potentiellen klinischen Stellenwert beleuchten.

In Kapitel 2.2.1 werden die hämodynamischen Effekte einer TTVR dargestellt. Zu diesem Zweck wurden 29 Patienten mit isolierter hochgradiger TI prospektiv mittels eines multimodalen Bildgebungsansatz vor und ein beziehungsweise sechs Monate nach erfolgreicher Prozedur untersucht. Die TTVR führte zu einer Reduktion der RV Volumenüberladung mit Rückgang des RV enddiastolischen Volumens und des volumetrischen RV Schlagvolumens. Dies war in erster Linie durch eine Reduktion des mit der TI assoziierten Pendelvolumens bedingt, denn das effektive RV Vorwärtsschlagvolumen, das mittels Flussmessung der PA in der kardialen MRT bestimmt wurde, nahm zu. Damit verbunden waren eine Verbesserung der LV Füllung und eine Steigerung des Herzzeitvolumens. Die mittels Echokardiographie abgeschätzten PA Drücke waren trotz erhöhtem PA Flüssen in den Nachuntersuchungen nicht gesteigert, was ebenfalls auf eine Verbesserung der linkseitigen Füllung und damit günstiger Beeinflussung der linksseitigen Füllungsdrücke zurückzuführen ist. Klinisch konnte nach der Intervention eine Verbesserung der Dyspnoesymptomatik, eine Reduktion des Auftretens peripherer Ödeme und eine verbesserte körperliche Belastbarkeit demonstriert werden. Das untersuchte Kollektiv bestand aus Patienten mit funktioneller isolierter hochgradiger TI, die früh nach der Etablierung des TTVR Programms am Herzzentrum Leipzig dieser Therapie unterzogen wurden. Es setzt sich zur Hälfte aus invasiv diagnostizierten HFpEF Patienten und zu je einem Viertel aus Patienten mit HFmrEF und Patienten mit zuvor korrigierten linksseitigen Herzerkrankungen (Aortenklappenstenose, Mitralklappeninsuffizienz) und normaler LVEF zusammen. Zwei Drittel der Patienten wies eine PHT auf und bei etwa 90 Prozent lag ein Vorhofflimmern vor. Diese Beobachtungen implizieren, dass HFpEF eine große Rolle in der Ätiologie der isolierten TI spielt, dass mittels TTVR vorteilhafte biventrikuläre hämodynamische und klinische Veränderungen in einem gemischten Kollektiv erzielt werden und dass diese als Ausgangspunkt für einen potentiellen Nutzen im Kontext der HFpEF Pathophysiologie bewertet werden können.

Auch die in Kapitel 2.2.2 und 2.2.3 dargestellten Arbeiten untersuchen gemischte Kollektive, hier vor allem von Patienten mit einer Kombination von hochgradiger TI und Mitralklappeninsuffizienz. Für die aktuelle Diskussion werden innerhalb der Studien jedoch nur die Gruppen mit isolierter TI als Surrogat für die Übertragung der Ergebnisse in den Kontext der HFpEF Pathophysiologie betrachtet. Die in Kapitel 2.2.2 dargestellte Arbeit

vermittelt die Bedeutung der TTVR für den klinischen Verlauf der Herzinsuffizienz. In dieser retrospektiven Studie wurde ein Kollektiv von TI Patienten aus vier führenden Zentren in Europa und Kanada zusammengetragen und hinsichtlich der Veränderung der Rate der Herzinsuffizienzhospitalisierungen, klinischer Symptome und Mortalität analysiert. In 119 Patienten mit isolierter TI, die mittels TTVR therapiert wurden, konnte ein prozeduraler Erfolg, definiert als effektive TI Reduktion in Verbindung mit einer Clipimplantation, in 82 Prozent der Patienten demonstriert werden, was in etwa der prozeduralen Erfolgsrate anderer Serien entspricht (193,263). Nach einem Jahr lag der Anteil der Patienten ohne hochgradige TI bei 72 Prozent was eine gute mittelfristige Haltbarkeit des Verfahrens belegt. Im Vergleich zum Jahr vor der Prozedur konnte eine Reduktion der Rate an Hospitalisierungen aufgrund einer Herzinsuffizienz um etwa 21 Prozent im Jahr nach der Prozedur beobachtet werden. Zudem wurden Verbesserungen der Dyspnoesymptomatik, der körperlichen Belastbarkeit und der Lebensqualität beobachtet. Ein prozeduraler Erfolg war mit einem besseren Überleben sowie der Reduktion des kombinierten Endpunkts aus Hospitalisierung und Tod (33 Prozent versus 60 Prozent) nach einem Jahr assoziiert. Interessanterweise wurden diese Effekte vor dem Hintergrund der Notwendigkeit einer Dosissteigerung der diuretischen Therapie bis zur Intervention mit Dosisstabilisierung postinterventionem beobachtet. Dies impliziert eine klinische Verbesserung der Herzinsuffizienzsymptomatik und eine positive Beeinflussung des klinischen Verlaufs in einer Patientengruppe mit hohem Risiko für das Auftreten kardiovaskulärer Ereignisse durch eine TTVR. Dieses Hochrisikoprofil spiegelt sich auch in den Patientencharakteristika wieder, wobei ein mittleres Alter von 75 Jahren, eine eingeschränkte Nierenfunktion in drei Viertel der Patienten, eine ausgeprägte Luftnotsymptomatik, reduzierte körperlicher Belastbarkeit und deutlich eingeschränkte Lebensqualität vorlagen. Obwohl eine weiterführende ätiologische Analyse der isolierten TI in der TTVR Kohorte nicht durchgeführt wurde, ist bei einer durchschnittlichen LVEF von 53 Prozent und einem Konfidenzintervall von 13% von einem relevanten Anteil von HFpEF Patienten auszugehen.

Ein wichtiger pathophysiologischer Aspekt in der Entwicklung einer signifikanten TI in HFpEF Patienten ist das Vorliegen einer PHT, wie in Kapitel 1.3.3.5 dargelegt. Daher ist eine Beurteilung der Effektivität der TTVR in Abhängigkeit des Vorliegens einer kombinierten RV Druck- und Volumenbelastung in Patienten mit hochgradiger TI von besonderer Bedeutung. Vor dem Hintergrund der starken Nachlastsensitivität der systolischen RV Funktion, wird die Aufrechterhaltung eines adäquaten RV Schlagvolumen mit RV Kontraktion gegen die geschlossene Mitralklappe vor allem von den Eigenschaften des PA

und des pulmonalvenösen Systems bestimmt (264). Die klinische Bedeutung der PHT für Patienten mit hochgradiger TI, die mittels TTVR behandelt werden, wird in Kapitel 2.2.3 beschrieben. In diesem wiederum gemischten Kollektiv aus Patienten mit kombinierter interventioneller Korrektur eines Mitral- und Trikuspidalvitiums wurde das Vorliegen einer PHT invasiv und mittels Echokardiographie untersucht. Etwa die Hälfte der Patienten mit isolierter TI wies in dieser Untersuchung eine invasiv bestätigte PHT auf. Diese Patientengruppe zeigte ein höheres prädiziertes perioperatives Risiko, schwerere Symptome, höhere NT-pro-BNP Spiegel, eine schlechtere Nierenfunktion, mehr pulmonale Vorerkrankungen und eine eingeschränktere Belastbarkeit im Vergleich zu Patienten ohne PHT. Außerdem wiesen diese Patienten eine gestörte Kopplung zwischen RV und PA auf. Während der invasive Nachweis einer PHT in Patienten mit isolierter TTVR keinen Einfluss auf den prozeduralen Erfolg hatte, war er mit dem Auftreten des kombinierten Endpunkts von Herzinsuffizienzhospitalisierung und Tod assoziiert. Interessanterweise konnte in der Hälfte der Patienten mit PHT diese nicht echokardiographisch nachgewiesen werden. Die Patientengruppe mit einer solchen diagnostischen Diskordanz (invasiver PHT Nachweis, echokardiographisch kein PHT Nachweis) wies eine Reihe ungünstiger Patienten- und Echokardiographiecharakteristika auf. Im Gesamtkollektiv waren eine eingeschränkte LV und RV Funktion, als auch Zeichen einer höchstgradigen TI unabhängig mit dem Auftreten einer diskordanten PHT Diagnose assoziiert. Somit kann diese Konstellation als Marker der ausgeprägtesten valvulären und ventrikulären Erkrankung gesehen werden. Dies hat auch klinische Implikationen, denn während TTVR Patienten mit isolierter TI und konkordanter PHT Diagnose ein ähnliches Outcome hatten wie Patienten ohne PHT, war dieses in Patienten mit einer diskordanten PHT Diagnose stark eingeschränkt und in Verbindung mit einer eingeschränkten RV-PA Kopplung unabhängig mit dem Auftreten des kombinierten Endpunkts assoziiert. Die Arbeit legt nahe, dass die interventionelle Behandlung einer isolierten TI auch in Patienten mit PHT einen klinischen Vorteil bieten kann, insbesondere wenn eine invasiv und echokardiographisch konkordante PHT Diagnose vorliegt. Die Arbeit unterstreicht zudem die prognostische Bedeutung der RV-PA Kopplung in diesem Kollektiv von Patienten mit hochgradiger TI in Analogie zur Bedeutung der RV-PA Kopplung in HFpEF Kollektiven ohne hochgradige TI (265).

Die klinische und wissenschaftliche Etablierung der interventionellen Behandlungsoption einer hochgradigen TI, die physiologischen Implikationen der Reduktion der RV Volumenüberladung, die Beobachtung der Reduktion klinischer Herzinsuffizienzendpunkte in Verbindung mit einer erfolgreichen TTVR und der Nutzten

auch in einem signifikanten Anteil von Patienten mit relevanter PHT suggerieren, dass die TTVR insbesondere für Patienten mit HFpEF und relevanter TI eine attraktive Therapieoption ist. Dies wird bestätigt durch eine Untersuchung der klinischen Implikationen der TTVR in nach leitliniengerechter Diagnose stratifizierten Kollektiven von HFpEF und HFrEF/HFmrEF Patienten mit hochgradiger TI in Kapitel 2.2.4. Während es nach TTVR mit Reduktion der TI zu einer symptomatischen und funktionellen Besserung im Gesamtkollektiv kommt, ist ein prozeduraler TTVR Erfolg nur in HFpEF Patienten mit einem besseren Outcome verbunden, sowohl im Vergleich zu Patienten mit nicht erfolgreicher Prozedur, als auch im Vergleich zu einer historischen, gematchten Kontrollgruppe, die medikamentös behandelt wurde.

Zusammenfassend ergibt sich, dass eine klinische HFpEF Phänotypisierung anhand des Vorliegens einer hochgradigen TI Patienten in fortgeschrittenen HFpEF Stadien im Sinne eines Hochrisikokollektivs identifiziert. Eine Verbesserung der biventrikulären Hämodynamik nach TTVR und die Hinweise auf symptomatische und prognostische Verbesserungen nach dieser Therapie deuten zum einen auf einen gemeinsamen dominanten Mechanismus der kardialen Pathologie in dieser Patientengruppe hin und legt zum anderen nahe, dass eine interventionelle Behandlung dieses Vitiums eine vielversprechende Behandlungsoption ist.

Weitere dahingehende Einblicke werden von spezifischen mechanistischen Beobachtungsstudien in Patienten mit HFpEF und hochgradiger TI, die mittels TTVR behandelt werden, erwartet. Die in unserem Zentrum initiierte und von der deutschen Herzstiftung geförderte HERAKLES-HFpEF Studie (Hämodynamische Charakterisierung einer interventionellen Trikuspidalklappenrekonstruktion bei Patienten mit erhaltener systolischer LV Funktion) untersucht invasiv die biventrikulären hämodynamischen Effekte der TTVR speziell in HFpEF Patienten. Die multizentrische, randomisierte TRILUMINATE-PIVOTAL Studie (Clinical Trial to Evaluate Cardiovascular Outcomes In Patients Treated With the Tricuspid Valve Repair System) untersucht in 700 Patienten mit isolierter TI prospektiv die Effektivität der Behandlung der TTVR im Vergleich zu einer optimalen medikamentösen Therapie hinsichtlich der Reduktion klinischer Endpunkte. Obwohl hier ein gemischtes Kollektiv hinsichtlich der TI Ätiologie untersucht wird, beinhaltet das Protokoll eine Rechtsherzkatheterisierung vor Einschluss, was eine detaillierte Subgruppenanalyse auch für die zu erwartend große Gruppe von HFpEF Patienten ermöglichen sollte.

3.5 KLINISCHE PHÄNOTYPISIERUNG ANHAND DES VORLIEGENS EINER RESISTENTEN ARTERIELLEN HYPERTONIE

Die arterielle Hypertonie ist ein wichtiger pathomechanistischer Faktor für die Entstehung einer HFpEF und hochprävalent im Gesamtkollektiv der HFpEF Patienten. Typische Veränderungen sind dabei eine kombinierte erhöhte arterielle und ventrikuläre Steifigkeit, welche im Sinne einer ungünstigen ventrikulo-arteriellen Kopplung zu einer erhöhten Sensitivität für Vor- und Nachlaständerungen führt. In Verbindung mit der ungünstigen Beeinflussung der diastolischen LV Funktion und der kardialen Morphologie durch pathologische Druckwellenreflexion begünstigt dies die Entwicklung einer Herzinsuffizienz mit erhöhten LV Füllungsdrücken, LA Hypertonie bei Belastung, Belastungsintoleranz bis hin zur kardiopulmonalen Dekompensation (92,102,103).

Die hohe Prävalenz der arteriellen Hypertonie im HFpEF Kollektiv suggeriert, dass diese Komorbidität unzureichend geeignet ist, um eine klinische Phänotypisierung vorzunehmen. Zudem sind mit der arteriellen Hypertonie assoziierte Veränderungen von Gefäßeigenschaften, wie in Kapitel 0 beschrieben, auch Teil des natürlichen Alterungsprozess und in ihrer dynamischen Ausprägung nicht-invasiv schwierig einzuordnen.

Einen klarer pathomechanistisch abgrenzbaren Phänotyp stellen die Patienten mit therapieresistenter arterieller Hypertonie dar. Diese Diagnose beruht auf der Persistenz arterieller Blutdruckwerte über dem Therapieziel trotz einer Dreifachkombination antihypertensiver Medikamente in maximal tolerierter Dosierung. Die Abklärung beinhaltet eine ausführliche Evaluation der Patienten zum Ausschluss sekundärer Ursachen des arteriellen Hypertonus und einer Pseudoresistenz etwa durch ungenaue Blutdruckmessungen oder unzureichende Medikamentencompliance (266). Als gemeinsamer dominierender pathomechanistischer Faktor wird hier eine gesteigerte Aktivität des sympathischen Nervensystems angenommen (267). Diese vermittelt multiple Effekte, wie eine Aggravation der arteriellen Steifigkeit, eine ventrikuläre Hyperkontraktilität und eine reduzierte Natriurese mit resultierender erhöhter pulsatiler Nachlast, die ein starker Prädiktor für die Entwicklung einer Herzinsuffizienz generell und für eine HFpEF im Speziellen ist (93,94). Darüber hinaus vermittelt ein erhöhter Sympathikotonus mannigfaltige Effekte auf andere Gefäß- und Organsysteme. Das abdominelle Gefäßbett, als größtes Reservoir des Intravasalvolumens, wird stark durch das sympathische Nervensystem moduliert. Ein erhöhter Sympathikotonus ist mit einer reduzierten Speicherkapazität verbunden und eine sympathische Aktivierung kann zu einer akuten Umverteilung vom abdominellen in das thorakale Gefäßsystem mit einer Erhöhung der kardialen Vorlast, gesteigerten LV Füllungsdrücken und resultierenden

Herzinsuffizienzsymptomen führen (268). Diese sympathische Überaktivität scheint insbesondere bei Patienten mit arterieller Hypertonie und HFpEF eine Rolle zu spielen, wobei eine gesteigerte renale Sympathikusaktivität auch prognostische Relevanz besitzt (196,197).

Therapeutische Ansätze, die auf eine Reduktion der sympathischen Überaktivierung in dieser Patientengruppe zielen, sollten zum einen die Möglichkeit bieten die Ausprägung einer Herzinsuffizienz in Risikopatienten zu verhindern und zum anderen eine hämodynamische und symptomatische Besserung einer bestehenden Herzinsuffizienz zu bewirken.

Die RDN zielt auf die Reduktion einer Sympathikusüberaktivierung mittels Reduktion der Aktivität des renalen und systemischen sympathischen Nervensystems ab. Eine partielle Ablation efferenter sympathischer Nervenfasern entlang der Nierenarterie führt zur Normalisierung der renalen tubulären Wasser und Natriumausscheidung, renaler vaskulärer Wiederstände und Reninausschüttung. Die Reduktion der efferenten sympathischen Signale zu den Nieren, die experimentell mit einer verminderten renalen Noradrenalinausschüttung einhergeht, stellt eine wesentliche Rationale für eine sympathikusmodulierende Therapie der arteriellen Hypertonie dar. Ein weiterer Aspekt betrifft die Reduktion der afferenten (sensorischen) Signale von den Nieren zum zentralen sympathischen Nervensystem, die über eine generelle Reduktion des Sympathikotonus positive Effekte auf multiple Organsysteme vermittelt (269-272). Dementsprechend bietet die RDN theoretisch die Möglichkeit komplexe physiologische Therapieeffekte zu erzeugen, mit positiver Beeinflussung unter anderem der Nierenfunktion, der Insulinsensitivität, der Arrhythmielast sowie der systolischen und diastolischen kardialen Funktion. Eine Übersicht potentieller Effekte und Prädiktoren eines Prozedurerfolgs ist in Kapitel 2.3.1 beschrieben. Aufgrund initial vielversprechender Ergebnisse unkontrollierter klinischer Studien zur Reduktion der arteriellen Hypertonie durch die RDN und dem in der Folge fehlenden Nachweis der Überlegenheit der Intervention im Vergleich zu einer medikamentösen Therapie unter kontrollierten Studienbedingungen wurde die generelle Effektivität dieser Therapie in den letzten Jahren kontrovers diskutiert (273). Kürzlich konnte jedoch in vier streng kontrollierten randomisierten Studien mit Scheinprozedur die Wirksamkeit dieser Therapie in Bezug auf die Reduktion der arteriellen Hypertonie nachgewiesen werden (207-210). RDN senkt hierbei sowohl den Ruhe- als auch den Belastungsblutdruck über den gesamten Tagesverlauf unabhängig von potentiellen pharmakodynamischen Effekten einer antihypertensiven Medikation („always-on Effekt“) und weist ein günstiges Sicherheitsprofil auf (274-276). Der Erfolg dieser Studien geht neben Verbesserungen im Studiendesign auch auf technische und methodologische Entwicklungen zurück, wobei hier hauptsächlich ein ausführliches Training des Interventionalisten und die

Weiterentwicklungen des Radiofrequenzverfahrens mit Erweiterung der Intervention auf distale Abschnitte der Nierenarterien und die Entwicklung ultraschallbasierter Verfahren zu erwähnen sind. In einer prospektiven randomisierten Studie konnte unsere Arbeitsgruppe die Wirksamkeit der verschiedenen RDN Methoden hinsichtlich der Blutdruckreduktion demonstrieren, wobei sich geringe Vorteile im Ausmaß der Reduktion für das Ultraschallverfahren zeigten (277). Während der Effekt der RDN auf die Sympathikusaktivität klinisch schwierig direkt zu messen ist, wurde eine Reihe von Surrogatparametern zur Beurteilung der Reduktion des Sympathikotonus postinterventionem vorgeschlagen, darunter etwa die Reduktion der Blutdruckvariabilität, eine reduzierte Blutdrucküberkompensation unter Valsalva Manöver oder eine Herzfrequenzreduktion (198,271,278). Insgesamt kann davon ausgegangen werden, dass die RDN ein gutes Modell bietet um die Effekte einer Reduktion der Sympathikusaktivität auf die globale Hämodynamik im Allgemeinen und bei Herzinsuffizienzpatienten im Speziellen zu beleuchten.

In Kapitel 2.3.2 werden hämodynamische Änderungen nach RDN in Patienten mit resistenter Hypertonie beschrieben. Hierbei wurden mittels kardialer MRT determinierte Schlag- und Herzzeitvolumina, die Herzfrequenz, der systemische vaskuläre Widerstand und die Herzarbeit in insgesamt 135 Patienten vor und nach RDN und in 27 Patienten vor und nach Scheinprozedur analysiert. Eine Blutdruckreduktion nach RDN wurde in diesem Kollektiv durch einer Reduktion des LV Schlagvolumens vermittelt, wobei die peripheren Widerständen unbeeinflusst blieben und die Herzarbeit reduziert war. Bei unveränderter Herzfrequenz war dies auch mit einer Reduktion des Herzzeitvolumens in Ruhe nach RDN verbunden. Theoretisch ist eine Schlagvolumenreduktion im Zusammenhang mit der RDN durch zwei Mechanismen erklärbar. Zum einen ist eine Reduktion der Vorlast durch eine erhöhte Natriurese und ein gesteigertes abdominelles Pooling des Blutvolumens mit konsekutiv reduzierter kardialer Vorlast als Effekt der Reduktion des systemischen Sympathikotonus vorstellbar. Zum anderen kann eine Reduktion der kardialen sympathischen Aktivierung zu einer Reduktion der Inotropie führen. Volumetrische und serologische Daten dieser Patienten sprachen nicht für eine ausgeprägte Reduktion des zirkulierenden Blutvolumens, wobei transiente Effekte in Zusammenhang mit Pooling aus dem abdominellen Kompartment trotzdem möglich scheinen. Eine Reduktion der LV Inotropie wird unterstützt durch szintigraphische Daten, die eine reduzierte kardialen Sympathikusaktivität nach RDN nahelegen (272). Im Gegenteil zu anderen Arbeiten konnte in dieser Arbeit keine Reduktion der Herzfrequenz dokumentiert werden, was durch einen hohen Anteil von Patienten mit Betablockertherapie und einer weniger systematischen Beurteilung der Herzfrequenz mittels

Langzeitmessung erklärt werden kann (198,271,278). Die insgesamt reduzierte Herzarbeit nach RDN kann in dieser Kohorte von Patienten mit normaler LV Funktion als Faktor für ein positives Remodeling mit gleichzeitiger Reduktion der LV Wandspannung interpretiert werden. Sowohl eine reduzierte Herzarbeit als auch eine reduzierte Wandspannung sind mit einer Verringerung des myokardialen Sauerstoffverbrauchs verbunden, was einen positiven Effekt auch in Herzinsuffizienzpatienten trotz der Reduktion des LV Schlagvolumens nahelegt (279). Ähnliche hämodynamische Effekte sind auch für eine medikamentöse Betablockertherapie beschrieben und in HFrEF mit einer günstigen Prognose assoziiert (280). Auch für Patienten mit HFpEF könnte dieser Effekt vorteilhaft sein. Kürzlich konnte gezeigt werden, dass eine supranormale LVEF (>65 Prozent) mit einer erhöhten Mortalität verbunden ist (202). Die Patienten in der aktuellen Studie wiesen im Mittel eine LVEF von 66 Prozent auf, was für einen Zusammenhang eines hyperdynamen kardialen Phänotyps mit einer erhöhten Sympathikusaktivität spricht. Eine damit verbundene unvorteilhafte ventrikulo-arterielle Kopplung, wie sie typische für HFpEF Patienten ist, könnte somit durch die RDN günstig beeinflusst werden.

Die Übertragung dieser Beobachtungen auf ein spezifischeres HFpEF Kollektiv ist in Kapitel 2.3.3 dargestellt. Hierfür wurden Patienten, die eine RDN in unserem Zentrum erhielten, verfügbare NT-pro-BNP Werte und eine LVEF ≥ 50 Prozent hatten hinsichtlich des Vorliegens einer HFpEF stratifiziert und die hämodynamischen und klinischen Effekt der RDN mittels serieller MRT, Echokardiographie und Serumanalysen untersucht. Der Anteil der leitliniengerecht diagnostizierten HFpEF Patienten im Gesamtkollektiv von 164 Patienten lag bei 60 Prozent, was die hohe Prädisposition von Patienten mit resistenter Hypertonie zur Entwicklung einer HFpEF unterstreicht. In Analogie zu den vorherigen Ausführungen wiesen HFpEF Patienten ein höheres Schlagvolumen und eine gesteigerte Herzarbeit auf. Zusätzlich konnte mittels MRT eine erhöhte aortale und echokardiographisch eine gesteigerte LV Steifigkeit beobachtet werden. Die Blutdruckvariabilität als Surrogat für den systemischen Sympathikotonus war in HFpEF Patienten erhöht. Während eine Reduktion des systolischen Blutdrucks für beide Gruppen beobachtet wurde, zeigte sich für die HFpEF Gruppe eine Reduktion sowohl des Schlagvolumens, der Herzarbeit als auch der aortalen und ventrikulären Steifigkeit. Dies ging mit einer Verbesserung der diastolischen LV Funktion, der LV Füllungsdrücke, der NT-pro-BNP Werte und der Dyspnoesymptomatik sowie einer Normalisierung der Blutdruckvariabilität in HFpEF Patienten einher. Diese Beobachtungen erhärten den Eindruck eines spezifischen HFpEF Phänotyps mit resistenter arterieller Hypertonie, der

pathomechanistisch durch einen gesteigerten Sympathikotonus, LV Hyperkontraktilität und arterielle Steifigkeit mit ungünstiger ventrikulo-arterieller Kopplung charakterisiert ist. Gleichzeitig dient diese Arbeit als Hinweis für einen klinischen Nutzen der Modulation des Sympathikotonus in HFpEF Patienten. Diese wird unterstützt durch kürzlich erschienene Berichte über positive klinische und hämodynamische Effekte einer interventionellen Reduktion der Signalübertragung in einem proximaleren Bereich des sympathischen Nervensystems, der Nervi splanchnici, in Patienten mit HFrEF und HFpEF (281-283). Diese Beobachtungen werden aktuell in prospektiven klinischen Studien zur chirurgischen und endovaskulären Ablation der Nervi splanchnici in HFpEF Patienten untersucht (clinicaltrials.gov: NCT03715543 und NCT04592445).

Prospektive Daten zur Rolle der RDN in Patienten mit HFpEF stammen aus einer einzigen randomisierten englischen Arbeit (284). In dieser gut designten Studie verbesserte sich die diastolische LV Funktion und die Belastbarkeit häufiger in Patienten in der RDN Gruppe. Infolge des im Rekrutierungszeitraum aufkommenden Diskurses um die allgemeine Effektivität einer RDN verlief der Patienteneinschluss verzögert, sodass eine vorzeitige Terminierung nach 25 eingeschlossenen Patienten erfolgte und keine eindeutige Aussage zur klinischen Effektivität der Intervention abgeleitet werden kann. In der selbstinitiierten randomisierten und scheinkontrollierten Pilotstudie UNLOAD-HFpEF (Renal Denervation to Treat Heart Failure with Preserved Ejection Fraction) wird aktuell die Effektivität einer RDN in 64 HFpEF Patienten mit resistenter arterieller Hypertonie in Bezug auf die Reduktion LV Füllungsdrücke unter Belastung, der ventrikulo-arteriellen Kopplung sowie auf eine Reihe klinischer Endpunkte geprüft.

Zusammenfassend erlaubt die klinische Stratifizierung anhand des Vorliegens einer resistenten arteriellen Hypertonie eine HFpEF Phänotypisierung mit breiter klinischer Anwendbarkeit, die ein pathomechanistisch homogenes Kollektiv identifiziert, für das darüber hinaus positive Therapieeffekte durch eine RDN erwartet werden können.

3.6 LIMITATIONEN DIESER ARBEIT UND AUSBLICK

Die Ergebnisse dieser Habilitationsschrift zeigen, dass mittels unterschiedlicher Methoden eine Phänotypisierung des Gesamtkollektivs von HFpEF Patienten möglich ist. Hierbei konnte demonstriert werden, dass durch eine detaillierte pathomechanistische Charakterisierung mittels Kombination invasiver und erweiterter nicht-invasiver Untersuchungen phänotypspezifische Pathologien aufzuzeigen sind. Diese können im besten Fall, wie in Kapitel 3.1 und 3.2 dargestellt, Implikationen für künftige Therapiestudien liefern

oder Ausgangspunkt für weitere Untersuchungen bilden, wie in Kapitel 3.3 ausgeführt. Ob so gewonnene Erkenntnisse sich auch in einen therapeutischen Vorteil umsetzten lassen, wurde aktuell nicht untersucht und muss in weiteren Arbeiten geklärt werden.

Auch eine klinische Phänotypisierung ermöglicht die Identifikation homogenerer Subgruppen, wobei die Aufarbeitung pathomechanistischer Zusammenhänge und deren Reversibilität eine direkte Implikation für das Therapieziel bieten und bereits bestehende therapeutische Ansätze unmittelbar geprüft werden können. In der Habilitationsschrift konnte am Beispiel der TTVR und RDN gezeigt werden, wie es möglich ist, bestehende Therapiekonzepte auf die HFpEF Pathophysiologie anzuwenden und klinisch zu evaluieren. Auffällig im Vergleich der klinischen HFpEF Kollektive aus Kapitel 2.2.4 und 2.3.3 ist, dass sich trotz ähnlicher HFpEF Diagnosekriterien zwei Phänotypen unterschiedlichen Alters und kardiovaskulären Risikos darstellen, wobei die TI Gruppe ein deutlich ungünstigeres Profil und eine eingeschränkte Prognose aufwies. Dies ist ein indirekter Beleg für die bestehende Heterogenität der HFpEF und zeigt, dass bereits eine klinische Phänotypisierung in der Homogenisierung behilflich sein kann. Der Unterschied der klinisch identifizierten Kollektive impliziert aber auch pathomechanistische Unterschiede verschiedener Stadien des natürlichen Verlauf der HFpEF mit im Verlauf progredient eingeschränkter Prognose (149). Daraus ergibt sich die Notwendigkeit Patienten früh in der Entwicklung der Herzinsuffizienz zu identifizieren um ein Fortschreiten zu verhindern.

Durch das Fehlen von Arbeiten zu dezidiert pathomechanistisch begründeten Therapiestudien und longitudinalen Beobachtungen des natürlichen Verlaufs der HFpEF in dieser Habilitationsschrift bleibt das Potential der positiven Beeinflussung der Erkrankungsprogression durch eine Phänotypisierung oder pathomechanistische Charakterisierung spekulativ. Aus diesem Grund sollten die Identifikation und Charakterisierung sehr früher Erkrankungsstadien und der mit der Progression assoziierten Mechanismen in zukünftigen Studien weiter untersucht werden, da sie das größte Potential für die Entwicklung spezifischer Interventionen zur Verhinderung später Erkrankungsstadien mit eingeschränkter Prognose bieten. Hierbei ist zu bemerken, dass gerade asymptomatische Patienten mit struktureller Herzerkrankung und kardiovaskulären Risikofaktoren ein hohes Risiko für die Entwicklung einer Herzinsuffizienz und bereits erhöhte kardiovaskuläre Ereignisraten im Vergleich zu gesunden Kontrollpatienten aufweisen (40). Die Identifikation von progressionstreibenden Mechanismen in dieser Gruppe bietet die Chance therapeutische Ziele für Interventionen im Sinne einer Prävention ermöglichen zu können. Gerade vor dem Hintergrund der steigenden HFpEF Prävalenz scheint dieser Ansatz vielversprechend. Die

selbstinitiierte und von der Roland Ernst Stiftung geförderte PREDICT-HFpEF Studie (Prädiktoren der Entwicklung einer Herzinsuffizienz mit erhaltener Pumpfunktion) ist eine longitudinale Beobachtungsstudie von etwa 1000 kardiovaskulären Risikopatienten ohne Herzinsuffizienz, die aktuell die Entwicklung einer HFpEF in Abhängigkeit verschiedener laborchemischer, metabolischer und molekulargenetischer Faktoren über einen Zeitraum von acht Jahren prüft. Mittels Identifikation von Prädiktoren einer HFpEF Entstehung sollen so die Voraussetzungen für optimierte, präventive Therapieansätze geschaffen werden.

In der bestehenden Literatur wurden zusätzlich zu den hier ausgeführten Phänotypen klinische und pathomechanistische Faktoren zur Stratifizierung der HFpEF vorgeschlagen. Zu erwähnen sei hier beispielsweise ein mit Adipositas assoziierter HFpEF Phänotyp, der aufgrund ausgeprägter hämodynamischer und klinischer Veränderungen und der steigenden Adipositasprävalenz in der westlichen Gesellschaft von besonderer Bedeutung ist (218). Inwieweit eine Interaktion dieses Phänotyps mit den hier präsentierten Phänotypen besteht, bleibt aktuell unklar und muss durch zukünftige Studien geklärt werden. Weltweit bestehen hierzu große Forschungsaktivitäten (285), wobei unsere Arbeitsgruppe aktuell molekulare Pathomechanismen diese Phänotyps im Rahmen der SLIM-HFpEF Studie (Adipose Tissue Inflammation in the Development, Maintenance and Functional Impairments in Heart Failure with preserved Ejection Fraction) aufarbeitet.

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5 ERKLÄRUNGEN

Hiermit erkläre ich an Eides statt,

1. dass die vorliegende Habilitationsordnung der Medizinischen Fakultät der Universität Leipzig anerkannt wird;

2. dass die Habilitationsschrift in dieser oder ähnlicher Form an keiner anderen Stelle zum Zweck eines Graduierungsverfahrens vorgelegt wurde;

3. dass die Habilitationsschrift selbstständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden;

4. dass die Einhaltung der „Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis“ in der Erstfassung vom 17. April 2015 Grundlage der Forschungstätigkeit war.

Leipzig, den 08.03.2021 Dr. med. Karl-Philipp Rommel

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Veröffentlichungen: 66 Publikationen, davon 16 als Hauptautor, kumulative Impact Faktoren > 700, h-index 24

Preise und Stipendien u.a.:

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Stipendiat Clinician Scientist Programm Medizinische Fakultät Universität Leipzig 07/2017-07/2020

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Forschungsstipendium DGK ab 11/2018 („Funktionelle und strukturelle biventrikuläre Myokardveränderungen und deren Abhängigkeit von chronisch erhöhter Nachlast bei Patienten mit HFpEF")

DGK Young Investigators Award 2019 ("Genome-Wide Gene Expression Analysis to Unpuzzle the Pathomechanistic Traits of Heart Failure with Preserved Ejection Fraction", 1.Platz)

Publikationspreis der AG Chronische Herzinsuffizienz 2019 ("Load-Independent Systolic and Diastolic Right Ventricular Function in Heart Failure With Preserved Ejection Fraction", 2.Platz)

Leipzig, den 08.03.2021

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