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Neue Aspekte der pulmonalen Hämodynamik zur Klassifikation, Prognoseabschätzung und Therapieevaluierung von Patienten mit Herzinsuffizienz

Habilitationsschrift
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INHALTSVERZEICHNIS

1. Der Arbeit zugrundeliegende Publikationen

Diese kumulative Habilitationsschrift beruht auf den folgenden Publikationen:

1) **Rieth A**, Richter MJ, Gall H, Seeger W, Ghofrani HA, Mitrovic V, Hamm CW.
Hemodynamic phenotyping based on exercise catheterization predicts outcome in patients with heart failure and reduced ejection fraction.
J Heart Lung Transplant. 2017 Aug;36(8):880-889.
doi: 10.1016/j.healun.2017.02.022.

2) **Rieth AJ**, Richter MJ, Tello K, Gall H, Ghofrani HA, Guth S, Wiedenroth CB, Seeger W, Kriechbaum SD, Mitrovic V, Schulze PC, Hamm CW.
Exercise hemodynamics in heart failure patients with preserved and mid-range ejection fraction: key role of the right heart.
Clin Res Cardiol. 2022 Apr;111(4):393-405.
doi: 10.1007/s00392-021-01884-1.

3) Kriechbaum SD, Birmes J, Wiedenroth CB, Adameit MSD, Grün D, Vietheer J, Richter MJ, Guth S, Roller FC, Rademann M, Fischer-Rasokat U, Rolf A, Liebetrau C, Hamm CW, Keller T, **Rieth AJ**.
Exercise MR-proANP unmasks latent right heart failure in CTEPH.
J Heart Lung Transplant. 2022 Aug 27;S1053-2498(22)02084-8
doi: 10.1016/j.healun.2022.08.017.

4) **Rieth AJ**, Grün D, Zarogiannis G, Kriechbaum SD, Wolter S, Richter MJ, Tello K, Kruger U, Mitrovic V, Rosenkranz S, Hamm CW, Keller T.
Prognostic Power of Pulmonary Arterial Compliance Is Boosted by a Hemodynamic Unloading Test With Glyceryl Trinitrate in Heart Failure Patients With Post-capillary Pulmonary Hypertension.
Front Cardiovasc Med. 2022;9:838898.
doi: 10.3389/fcvm.2022.838898.

5) **Rieth AJ**, Kriechbaum SD, Richter MJ, Wenninger E, Fischer-Rasokat U, Tello K, Gall H, Ghofrani HA, Guth S, Wiedenroth CB, Mitrovic V, Hamm CW, Liebetrau C, Walther C.
Exercise Hemodynamic Profiling Is Associated With Outcome in Patients Undergoing Percutaneous Mitral Valve Repair.
Circ Cardiovasc Interv. 2021 Sep;14(9):e010453.
doi: 10.1161/CIRCINTERVENTIONS.120.010453.

6) **Rieth AJ**, Rivinius R, Lühring T, Grün D, Keller T, Grinninger C, Schüttler D, Bara CL, Helmschrott M, Frey N, Sandhaus T, Schulze C, Kriechbaum S, Vietheer J, Sindermann J, Welp H, Lichtenberg A, Choi Y-H, Richter M, Tello K, Richter M, Hamm CW, Boeken U.
Hemodynamic markers of pulmonary vasculopathy for prediction of early right heart failure and mortality after heart transplantation.
J Heart Lung Transplant. 2022 Oct 9;S1053-2498(22)02168-4.
doi: 10.1016/j.healun.2022.10.002.

2. Einleitung

Die Erstbeschreibung des menschlichen Blutkreislaufs durch William Harvey 1628 („Exercitatio anatomica de motu cordis et sanguinis in animalibus“, „Über die Bewegung des Herzens und des Blutes“) führte zu einer Abkehr von der antiken Humorallehre.[1] Stephen Hales (1677 – 1761) betrieb experimentelle Forschungen zum Blutkreislauf und war einer der Ersten, der den Blutdruck bei verschiedenen Tieren direkt und akkurat maß.[2] Mit zunehmendem Wissen um die Zusammenhänge zwischen Herzaktion und Blutkreislauf entstand der Begriff der „Herzkatheterisierung“ um das Jahr 1840. Erst im Jahr 1929 führte Werner Forßmann die erste dokumentierte Sondierung des Herzens beim Menschen durch, indem er sich selbst einen Ureterkatheter bis in den rechten Vorhof vorschob.[3]

Die Erkenntnisse über die Physiologie des Lungenkreislaufs wuchsen langsam in den folgenden Jahrzehnten; die entscheidende Weiterentwicklung technischer Art folgte erst 1970 mit dem so genannten „Einschwemmkatheter“ mit einem Ballon an der Spitze, entwickelt von Jeremy Swan und William Ganz.[4] Der entscheidende Vorteil der neuen Technik war ein atraumatischer Kathetervorschub und der mögliche Verzicht auf Röntgendurchleuchtung. Weiterhin war es durch die so genannte Ballonokklusionstechnik erstmals möglich, über eine Sondierung der rechtsseitigen Herzhöhlen und der Lungenarterien indirekt Informationen über die Druckverhältnisse im linken Herzen zu gewinnen, ohne dieses mit erhöhtem Risiko direkt sondieren zu müssen. Bald darauf (1971) folgte die Vorstellung einer neuen Methode zur Messung des Herzzeitvolumens durch dieselbe Arbeitsgruppe, der so genannten Thermodilutionstechnik, die genauere Messungen des bewegten Volumens pro Zeiteinheit ermöglichte.[5] Bis heute hat sich an diesen Grundprinzipien der Rechtsherzkatheter-untersuchung nichts geändert, aus der primär Daten über Druckwerte und Blutfluss gewonnen werden.

Bereits in den Jahren ab 1960 gab es ein lebhaftes Interesse an den hämodynamischen Veränderungen im menschlichen Kreislauf während Belastung, welches sich in entsprechenden Publikationen zu kardialen Kathetermessungen in Ruhe und unter Belastung widerspiegelte.[6, 7] Parallel dazu erschienen diverse Publikationen zu den hämodynamischen Veränderungen, die bei Herzinsuffizienz beobachtet werden können, ebenfalls in Ruhe und unter Belastung.[8-10]

In späteren Jahrzehnten gerieten die Erkenntnisse, die aus derartigen Untersuchungstechniken für die Patientenversorgung gewonnen werden können, vor allem im Zuge der breiten Einführung der nichtinvasiven Echokardiographie in Vergessenheit. Weiterhin verlor der Rechtsherzkatheter (RHK) nach der Publikation der ESCAPE-Studie im Jahr 2005 an Verbreitung, in der sich bei dessen Einsatz zum hämodynamischen Monitoring bei

herzinsuffizienten Patienten eine erhöhte Komplikationsrate gezeigt hatte.[11] Erst etwa in den letzten 10 Jahren ist das Bewusstsein für das Potenzial invasiver Hämodynamik für die Behandlung herzinsuffizienter Patienten wieder deutlich gestiegen.[12]
In der Abteilung Kardiologie der Kerckhoff-Klinik in Bad Nauheim ist der RHK entgegen des allgemeinen Trends in der Medizin über Jahrzehnte bei ausgewählten Patienten kontinuierlich durchgeführt worden. Dadurch blieben entsprechende Kenntnisse zur Durchführung und vor allem Interpretation der Messwerte erhalten, so dass kontinuierlich Rückschlüsse für die Versorgung von Patienten mit Herzinsuffizienz, Herzklappenvitien, weiteren Herzkrankheiten und pulmonaler Hypertonie gezogen werden konnten. Insbesondere spielte die Interpretation der Hämodynamik unter körperlicher Belastung und nach pharmakologischer Testung (vorzugsweise mit sublingual appliziertem Glyceroltrinitrat) eine wichtige Rolle, was nur an relativ wenigen anderen Herzzentren weltweit der Fall war.
Als Problem stellte sich im Laufe der jüngeren Zeit jedoch eine mangelnde evidenzbasierte Standardisierung der Interpretation von hämodynamischen Messergebnissen insbesondere nach Provokation mit Belastung oder mit Pharmaka dar. Mit stetig wachsendem Anspruch an belastbare Belege für medizinische Interpretationen und das abgeleitete ärztliche Handeln schien es daher sinnvoll und nützlich, die an einigen Zentren regelmäßig geübte Praxis hämodynamischer Messungen nach Provokation systematisch zu untersuchen.

Der Inhalt dieser Habilitationsschrift umfasst entsprechend im Wesentlichen Arbeiten, die sich mit der systematischen Evaluierung von RHK-Messungen nach Provokation mittels Ergometerbelastung oder Glyceroltrinitrat bei Patienten mit Herzinsuffizienz unterschiedlicher Genese beziehungsweise mit Mitralinsuffizienz befassen. Eine weitere Arbeit hatte ursprünglich die multizentrische Erfassung von geübter Praxis und Konsequenzen einer pharmakologischen Testung im Rahmen des RHK bei Patienten vor einer Herztransplantation zum Ziel. Letztendlich war die Testung nur bei sehr wenigen Patienten zum Einsatz gekommen; umfassende Analysen der „nativen“ Hämodynamik ließen aber grundlegende Erkenntnisse in diesem Kollektiv zu.

3. Pulmonale Hämodynamik und Herzinsuffizienz

3.1. Standardverfahren zur Messung der pulmonalen Hämodynamik

Die Rechtsherzkatheteruntersuchung wird heutzutage weitgehend standardisiert durchgeführt. Ein Standard-Swan-Ganz-Katheter verfügt über 3 getrennte Lumina: eines für die Druckmessung via Flüssigkeitssäule an der Katheterspitze; eines zur Injektion gekühlter Flüssigkeit für die Herzzeitvolumenmessung mittels Thermodilution, welches 30 cm vor der Katheterspitze endet; und ein Lumen zur Luftinflation eines auf der Katheterspitze montierten Latexballons. Nach Punktion einer geeigneten Vene (V. femoralis, V. cephalica oder V. jugularis interna) erfolgt die Einlage eines Einführungsbestecks (Schleuse), über die der Katheter über die untere oder obere Hohlvene ins rechte Atrium, den rechten Ventrikel und dann in die Pulmonalarterie vorgeschoben wird. Dieser Vorgang erfolgt unter Inflation von Luft in den Ballon ab Erreichen der Hohlvene, so dass der Katheter atraumatisch entlang des Blutstroms vorwärts gelangt („Einschwemmen“).[13] Alternativ kann bei entsprechend geeigneten Kathetern ein durch ein Hauptlumen geschobener Draht für die Platzierung zu Hilfe genommen werden, was aber die Verwendung von Röntgendurchleuchtung zur Lagekontrolle erfordert. Im RHK-Labor der Kerckhoff-Klinik erfolgt die Katheterplatzierung zu über 95% ohne Draht und Röntgen, die Lagekontrolle der Katheterspitze erfolgt hierbei alleine durch die charakteristischen Druckkurven in den rechtsseitigen Herzhöhlen bzw. der Pulmonalarterie. Ein wichtiger Vorteil dieses Vorgehens ist es, dass eine Röntgenanlage und alle damit verbundenen Strahlenschutzmaßnahmen nicht notwendig sind. Weiterhin ist hierbei der Zugangsweg über Hals- oder Armvenen Standard, wohingegen unter Röntgendurchleuchtung aus Strahlenschutzgründen regelhaft der Zugang über die V. femoralis gewählt wird. Letzteres macht einen suffizienten fahrradergometrischen Belastungstest während der Untersuchung praktisch unmöglich, während dieses beim druckkontrollierten Vorgehen über die im Bereich der oberen Körperhälfte gelegenen Venen problemlos möglich ist.

Vor Beginn der eigentlichen Messungen müssen geeignete Voraussetzungen geschaffen werden, die die Korrektheit der Messwerte sicherstellen: Einstellen der Druckmesseinheit („levelling“) auf den korrekten Nullpunkt in der Mitte des Thoraxdurchmessers, die meist der Lage des linken Vorhofs entspricht[14] (**Abbildung 1**). Weiterhin ist ein Nullabgleich der Messeinheit auf den Atmosphärendruck notwendig („zeroing“).[15]

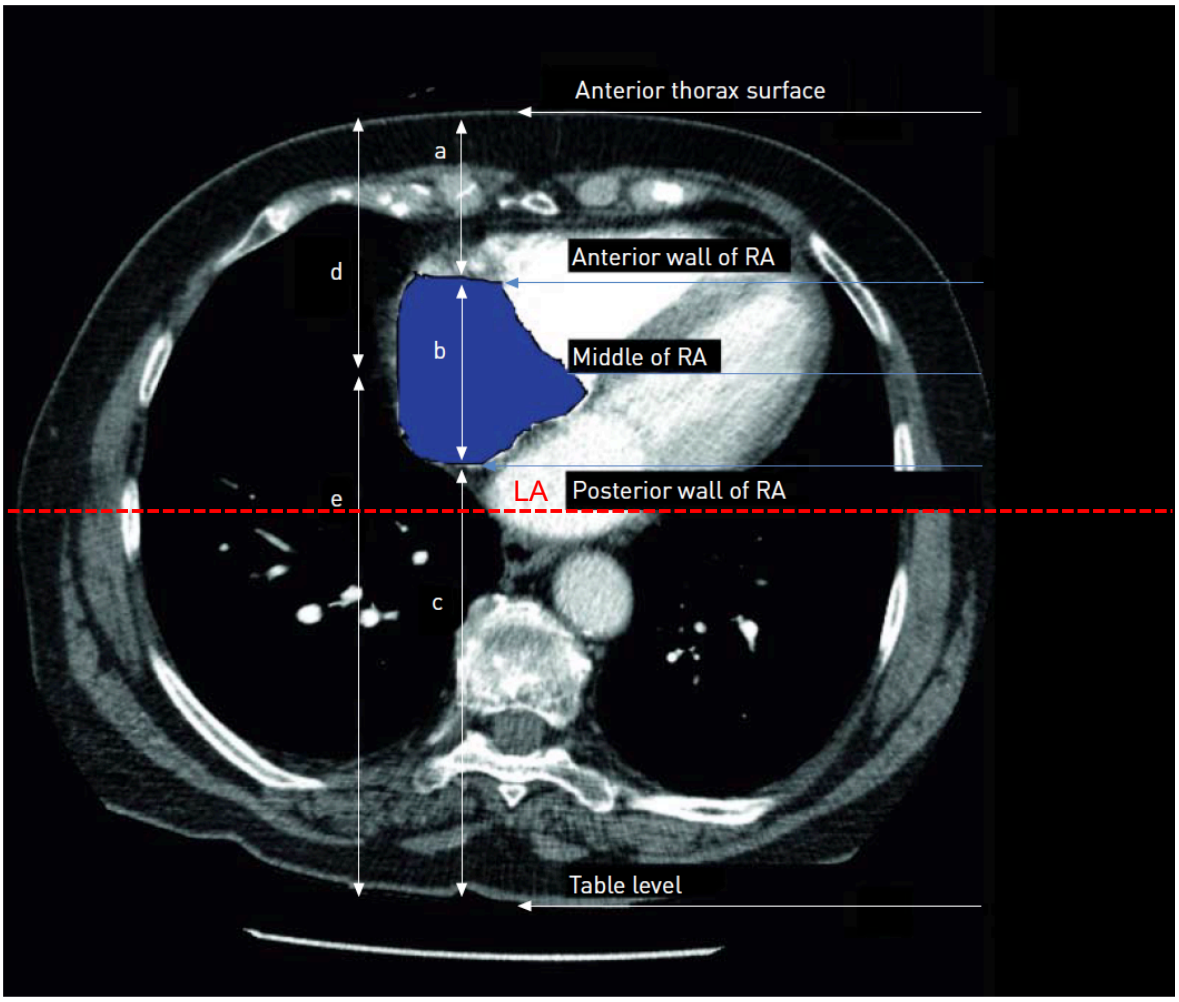


Abbildung 1: Lage des rechten Vorhofs (RA) und seine Beziehung zu benachbarten Strukturen *(Reproduced with permission of the © ERS 2023: European Respiratory Journal 42 (6) 1586-1594;* ***DOI:*** *10.1183/09031936.00050713 Published 30 November 2013)*
Modifiziert aus Referenz 14; die hinzugefügte rote Linie verläuft durch die Thoraxmitte und den linken Vorhof (LA).

Anterior thorax surface, ventrale Thoraxbegrenzung; anterior wall of RA, ventrale RA-Wand; middle of RA, Mitte des RA; posterior wall of RA, dorsale Wand des RA; table level, Ebene der Unterlage = dorsale Thoraxbegrenzung.

Entsprechend der aktuellen Leitlinie[15] (2022 ESC (European Society of Cardiology)/ERS (European Respiratory Society) Guidelines for the diagnosis and treatment of pulmonary hypertension) sind obligatorisch zu erhebende Messwerte (gebräuchliche Abkürzungen in Klammer):

- rechtsatrialer Mitteldruck (RAP)
- Systolischer, diastolischer und mittlerer pulmonalarterieller Druck (sPAP, dPAP, mPAP)
- pulmonalarterieller Verschlussdruck (PAWP)
- Herzzeitvolumen (CO)
- Gemischt venöse Sauerstoffsättigung (SvO_2)
- Arterielle Sauerstoffsättigung (SaO_2)
- Systemischer Blutdruck (RR)

Dabei stellt die Messung des PAWP eine Besonderheit dar, die sowohl technisch herausfordernd sein kann also auch entscheidende Bedeutung für die Interpretation der gesamten hämodynamischen Untersuchung hat. Mittels Balloninflation in einem mittelgroßen Ast der Pulmonalarterie (PA) wird der orthograde Blutfluss blockiert, so dass an der Katheterspitze nur noch der nach rückwärts übertragene Füllungsdruck des linken Vorhofs gemessen wird. Aus der Höhe dieses Druckwerts wird im Wesentlichen die Information abgeleitet, ob eine linkskardiale Pathologie vorliegt (PAWP > 15 mmHg) oder nicht vorliegt (PAWP ≤ 15 mmHg). Bei Vorliegen einer pulmonalen Hypertonie (PH, aktuelle Definition: mPAP > 20 mmHg) entscheidet die Höhe des PAWP wesentlich über das weitere diagnostische und therapeutische Procedere. Mögliche Fehlerquellen der PAWP-Messung sind inkomplette Blockade des aus der PA orthograd fortgeleiteten Drucks und Atemartefakte, aber auch inadäquate klinische Voraussetzungen wie Volumenüberschuss oder -mangel und andere mehr.[16] Gleichzeitig ist bei Balloninflation in distaler Katheterlage das – insgesamt sehr geringe – Komplikationsrisiko in Form einer PA-Verletzung mit konsekutiver pulmonaler Hämorrhagie am größten.

Die folgenden berechneten Parameter sollen laut der genannten Leitlinie obligatorisch erhoben werden:

- Pulmonalvaskulärer Widerstand und Widerstandsindex (PVR, PVRI)
- Totaler pulmonaler Widerstand (TPR)
- Herzindex (CI)
- Schlagvolumen und Schlagvolumenindex (SV, SVI)
- Pulmonalarterielle Compliance (PAC)

3.2. Stellenwert von Provokationstests

In der Wissenschaftlichen Diskussion zum Stellenwert hämodynamischer Messungen setzt sich zunehmend die Erkenntnis durch, dass einzelne Ruhemessungen infolge großer intraindividueller Schwankungen beispielsweise durch starke Änderungen des Volumenstatus von beschränkter Aussagekraft sind.[17] Hier werden in erster Linie Belastungstests als Erweiterung des Ruhe-RHK als geeignet angesehen, um die Aussagekraft der Untersuchung zu steigern - „You have to stress a system in order to assess its capabilities“[18] – wenn man die Kapazität eines Systems untersuchen will, dann muss man es belasten (**Abbildung 2**).

Abbildung 2: Rechtsherzkatheteruntersuchung via Armvene rechts mit Ergometerbelastung im Liegen im Rechtsherzkatheterlabor der Kerckhoff-Klinik.

Nachdem es hierzu seit den einleitend erwähnten “Pionierarbeiten” der 1960 und 70er Jahre kaum Forschungsaktivitäten gab, erschienen beispielsweise 2013 mehrere wesentliche experimentelle und grundlagentheoretische Arbeiten.[19, 20] Den damaligen Stand des Wissens fasste 2017 ein vielbeachtetes Positionspapier der European Respiratory Society zusammen.[21] Einer der wesentlichen Punkte war ein Vorschlag zur Definition eines pathologischen mPAP-Anstiegs im Verhältnis zum Herzzeitvolumen, also einer „pulmonalen Hypertonie unter Belastung“. Als pathologisch wurde dabei ein mPAP > 30 mmHg in Verbindung mit einem TPR > 3 Wood Einheiten (WU) unter maximaler Belastung definiert, abgeleitet aus einer einzelnen Publikation.[22] Ansonsten finden sich in dem genannten Positionspapier überwiegend offene Fragen mit Empfehlung zur weiteren empirischen Abklärung.

Die oben genannte PH-Leitlinie von 2022[15] widmet dem Belastungs-RHK einen kurzen Abschnitt, in dem dieser zur Abklärung einer Belastungsdyspnoe unbekannter Ursache zur Diagnostik von Frühstadien einer pulmonalvaskulären Erkrankung oder einer Linksherzdysfunktion genannt wird. Die wenigen benannten Grenzwerte einer pathologischen Belastungsreaktion betreffen die Anstiegssteilheit des mPAP im Verhältnis zu CO (mPAP/CO slope > 3 mmHg/L/min), des PAWP im Verhältnis zum CO (PAWP/CO slope > 2

mmHg/L/min) und einen absoluten PAWP-Anstieg > 25 mmHg. Allerdings wird deren Aussagekraft mangels Datenbasis relativiert, und es fehlen beispielsweise Vorschläge zu pathologischen Werten der CO-Steigerung oder des RAP-Anstiegs unter Belastung.

Eine andere Form des Provokationstests stellt die Vasoreaktivitätstestung (VRT) dar. Diese ist etabliert bei der Primärdiagnostik von bestimmten Unterformen der so genannten pulmonal arteriellen Hypertonie (PAH), die grundlegend durch die Abwesenheit einer linkskardialen Pathologie sowie die Abwesenheit einer hypoxischen und einer thromboembolischen Lungenerkrankung definiert ist. Besteht eine Linksherzinsuffizienz, so besitzt die VRT bisher alleine im Vorfeld einer Herztransplantation einen Stellenwert. Sie soll dabei Auskunft darüber geben, ob möglicherweise eine irreversible pulmonale Vaskulopathie vorliegt, die nach erfolgter Herztransplantation zu einer kritischen Nachlasterhöhung des transplantierten rechten Herzens und damit zum potenziell letalen Rechtsherzversagen führen könnte. Die Datenbasis hierzu ist relativ spärlich, so dass sich die Leitlinienempfehlungen über die Jahre nicht verändert haben.[23, 24] Insgesamt kann die VRT im Rahmen eines RHK als wenig verstanden gelten.[25]

Bei beiden dargestellten Formen eines hämodynamischen Provokationstests fehlen Daten mit signifikanter prognostischer Aussagekraft bei Patienten mit Herzinsuffizienz.

3.3. Hämodynamik zur Definition einer Herzinsuffizienz

Nach aktuellen Empfehlungen wird eine Herzinsuffizienz wie folgt definiert: es handelt sich um ein klinisches Syndrom mit Kardinalsymptomen wie Belastungsluftnot, Flüssigkeitsretention und abnormaler Abgeschlagenheit (fatigue), begleitet von objektiven Zeichen wie Jugularvenenstauung oder peripheren Ödemen. Weitere Bestandteile der Definition sind strukturelle und / oder funktionelle Abnormalitäten des Herzens, die in erhöhten kardialen Füllungsdrücken und / oder einem inadäquaten Herzzeitvolumen in Ruhe und / oder unter Belastung resultieren. Die Dokumentation einer systemischen Kongestion soll bildgebend oder mittels Messung erhöhter natriuretischer Peptide zur Unterstützung der Diagnose dienen.[26, 27] Im klinischen Alltag, vor allem aber als zentrales Einschlusskriterium für klinische Studien, ist hingegen die linksventrikuläre Ejektionsfraktion (LVEF) als der Haupteinteilungsparameter für Patienten mit Herzinsuffizienz fest etabliert. Andere Komponenten der Definition wie beispielsweise inadäquates Herzzeitvolumen unter Belastung oder auch die Rechtsherzfunktion werden dagegen häufig vernachlässigt. Auch wenn die LVEF als Voraussetzung für die therapeutische Wirksamkeit verschiedener Pharmaka und anderer Interventionen als unverzichtbar gilt, gibt es doch anhaltende substanzielle Kritik an dem

dominierenden „LVEF-zentristischen“ Paradigma in der Kardiologie.[28-30] Vorgeschlagen wird beispielsweise eine viel stärkere Gewichtung der Kongestion in Form von Biomarkern (natriuretischen Peptiden) oder der Rechtsherzfunktion und erweiterten echokardiographischen Parametern.[31, 32] Andere sehen hämodynamische Parameter unter Belastung als geeignet, um elementare Bestandteile einer Herzinsuffizienz wie ventrikuläres Vor- und Rückwärtsversagen, pulmonalvaskuläre Reserve und andere zu erfassen. Neben einer profunderen Charakterisierung der individuellen Konstellation werden hämodynamische Parameter auch als potenzielle therapeutische Ziele diskutiert.[12]

3.4. Funktionelle Auswirkungen unterschiedlicher kardialer Pathologien

Ein komplexes Thema ist die Differenzierung zwischen Links- und Rechtsherzinsuffizienz mittels Messungen, die beim RHK nur im rechten Herzen und im Lungenkreislauf lokalisiert sind. Der schon beschriebene PAWP stellt den einzigen Messwert mit Aussagekraft über Pathologien dar, die relativ eindeutig dem linken Herzen zugeordnet werden können. Zwischen linkem Vorhof und Ventrikel kann allerdings durch den PAWP-Mitteldruck alleine nicht differenziert werden. In erster Linie problematisch ist die Zuordnung des Herzzeitvolumens, welches ja letztendlich durch die beiden in Serie geschalteten Ventrikel generiert wird. Entsprechend ist eine Verminderung des CO zunächst nicht eindeutig kausal einer Seite des Herzens zuzuordnen. Erst die Zuhilfenahme der Echokardiographie und weiterer hämodynamischer Parameter macht hier eine vertiefende Interpretation möglich. Insbesondere die Abkehr vom Paradigma des Druckanstiegs in der Pulmonalarterie unter Belastung als per se "unerwünscht" ist hierfür eine wichtige Voraussetzung. Die Generierung von Druck in der Pulmonalarterie als Zeichen einer zumindest „erhaltenen“ Rechtsherzfunktion und damit einer besseren Prognose wurde erstmals 2013 bei Patienten mit PAH gezeigt, allerdings mittels doppler-echokardiographischer Abschätzung des PA-Drucks.[33] Weiterhin lässt sich mit Hilfe differenzierter hämodynamischer Indices zwischen Pathologien der rechtsventrikulären (RV) Nachlast (meist als Folge einer pulmonalen Vaskulopathie) und der RV-Kontraktilität unterscheiden.[34-42] Ein Druckanstieg im rechten Vorhof unter Belastung lässt auf ein RV-Rückwärtsversagen schließen, auch wenn hierzu insbesondere zu Normwerten wenig Literatur vorhanden ist.[43, 44] Den Goldstandard zur hämodynamischen Bestimmung der RV-Funktion stellt die Messung von Druck-Volumenkurven im RV mittels Konduktanzkatheter dar.[45] Dieses ist jedoch aufwändig und wird nur an wenigen Zentren, teilweise allerdings auch unter Belastung praktiziert.[46] Konduktanzmessungen sind nicht Gegenstand der vorliegenden Arbeit.

Ein in der Kardiologie traditionell auch mittels Hämodynamik beurteiltes Herzklappenvitium ist die Mitralklappeninsuffizienz (MI) – zumindest bedarfsweise in unklaren Fällen, wenn echokardiographisch nicht zwischen mittel- und hochgradig unterschieden werden kann, also bei „unklarer funktioneller Signifikanz“. Aktuelle Bedeutung hat dieses Thema im Zusammenhang mit dem mittlerweile weitverbreiteten Verfahren der interventionellen Mitralklappenreparatur (aktuelle Bezeichnung: transcatheter edge-to-edge repair, TEER) mittels Kathetertechnik gefunden. Vor allem bezüglich der Indikationsstellung und damit Kandidatenselektion bei Patienten mit Herzinsuffizienz (HI) und sekundärer, funktioneller MI gibt es größere Unsicherheiten. Zwei große multizentrische Studien zum TEER bei MI kamen zu gegensätzlichen Ergebnissen, und bis zu 50% der interventionell behandelten Patienten in beiden Studien hatten wenig bis gar nicht von der Behandlung profitiert.[47] Letztlich stehen zwei Aspekte zur Diskussion: die Schwere der MI im Verhältnis zur Schwere der HI, wobei die Konstellation schwerere MI - leichtere HI gute Voraussetzungen für TEER zu bieten scheint und umgekehrt. Diese beiden Faktoren werden überwiegend anhand echokardiographischer Parameter bestimmt, allenfalls noch zusätzlich mittels Biomarkern und / oder klinischer Faktoren. Die Schwere von HI und MI mittels Belastungshämodynamik zu evaluieren, war bisher in der Literatur nicht beschrieben, stellt aber vom Prinzip her einen vielversprechenden Ansatz dar.

3.5. Prognosemarker bei Herzinsuffizienz

Die Prognose von Patienten mit Herzinsuffizienz hängt von einer Vielzahl von Faktoren ab, sie ist mit bis zu 67 % Mortalität fünf Jahre nach der Diagnosestellung im Allgemeinen relativ ungünstig. Obgleich die LVEF für sich genommen einen starken prognoserelevanten Faktor darstellt, existieren zu den Mortalitätsrisiken von Patienten mit Herzinsuffizienz und reduzierter versus leicht reduzierter oder erhaltener LVEF unterschiedliche Studienergebnisse.[26, 32] Weitere starke prognostische Faktoren sind die Funktionsklasse (NYHA (New York Heart Association)-Stadien), die Zahl der Krankenhausbehandlungen wegen kardialer Dekompensation und der Plasmaspiegel des natriuretischen Peptids NT-proBNP (N-terminales pro brain natriuretic peptide).[48-50] Weiterhin werden diverse Scores (MAGGIC, Seattle Heart Failure Model und andere) unter Einbeziehung verschiedener Variablen für prognostische Modelle verwendet.[51, 52] Vor allem für die Indikationsstellung zur Herztransplantation hat sich die Spiroergometrie durchgesetzt, deren prognostische Aussagekraft als unabhängig von anderen Parametern gilt.[23, 53] Invasiv-hämodynamische Variablen sind für prognostische Aussagen im Bereich der Herzinsuffizienz wenig verbreitet

und kommen in der aktuellen ESC-Herzinsuffizienzleitlinie nicht vor, während zumindest einige wenige hämodynamische Parameter (RAP, CI, SVI, SvO_2; jeweils in Ruhe gemessen) für Patienten mit PAH als elementare Risikomarker gelten.[15]

4. Darstellung der eigenen Arbeit

4.1. Hämodynamische Provokationstests zur Charakterisierung und prognostischen Evaluierung von Patienten mit Herzinsuffizienz

4.1.1. Hämodynamische Charakterisierung von Patienten mit Herzinsuffizienz und reduzierter Ejektionsfraktion auf der Basis von Belastungsmessungen ermöglicht Aussagen über deren Prognose (Publikation 1: Hemodynamic phenotyping based on exercise catheterization predicts outcome in patients with heart failure and reduced ejection fraction. J Heart Lung Transplant. 2017)

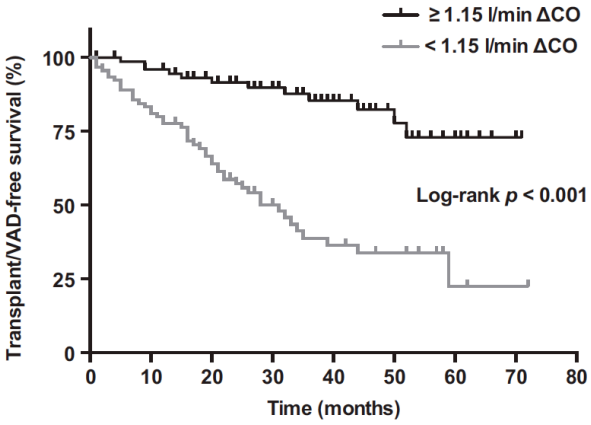
Bei Patienten mit Herzinsuffizienz und reduzierter LVEF, genannt „heart failure with reduced ejection fraction“ (HFrEF) beruhen prognostische Aussagen überwiegend auf nichtinvasiv erhobenen Daten wie Echokardiographie und Spiroergometrie.[54-58] Trotz deren unbestrittenem Wert sind Limitationen vorhanden, so dass invasiv-hämodynamische Messungen zusätzliche Informationen erbringen könnten.[59] Auch der prognostische Stellenwert von hämodynamischen Ruhemessungen ist wiederholt gezeigt worden, insbesondere bei kombiniert prä- und postkapillärer pulmonaler Hypertonie und bei Vorhandensein einer Rechtsherzdysfunktion.[60-70] Dennoch spielen derartige Messungen keine Rolle für die Risikostratifizierung von Patienten mit stabiler HFrEF.[71]

In dieser Studie haben wir versucht, die Vorteile von Provokationstests mittels Belastung während eines RHK zu zeigen, indem wir die Daten im Hinblick auf die Rechtsherzfunktion und auf die Identifikation bestimmter hämodynamischer Muster während der Belastung sowie deren prognostische Aussagekraft untersuchten.[72-76]

Es wurden Daten konsekutiver Patienten mit HFrEF (abweichend von der aktuellen Leitliniendefinition hier als Patienten mit LVEF ≤ 45% definiert) aus dem Kerckhoff-Klinik Herzinsuffizienz-Register untersucht, die zwischen 2009 und 2014 einen RHK mit Belastung erhalten hatten. Die Untersuchungen wurden nach üblichen Standards[77-79] mittels Fahrradergometer in liegender Position mit Laststufen von 5 – 75 Watt durchgeführt.[77, 79-86] Die Belastungen wurden jeweils auf individueller Basis bei subjektiver Ausbelastung der Patienten beendet. Diverse hämodynamische Indices wurden mit zuvor veröffentlichen Formeln berechnet.[20, 87-89]

Der primäre Endpunkt war das Gesamtüberleben ohne Herztransplantation (HTX) oder Implantation eines ventrikulären Unterstützungssystems (VAD).

Insgesamt wurden 167 Patienten eingeschlossen, die unter anderem folgende Charakteristika aufwiesen: LVEF im Mittel 25%, 72% in NYHA-Klasse III, medianes NT-proBNP 2000 pg/ml. Die mittlere Nachbeobachtungszeit betrug 29 Monate, und das HTX-/VAD-freie Überleben 48% nach 5 Jahren. In der univariaten Analyse zeigten sich viele der erhobenen Parameter mit dem HTX-/VAD-freien Überleben assoziiert; in einem multivariaten Modell blieben als unabhängige Risikofaktoren die NYHA-Klasse, die LVEF, der systolische Blutdruck in Ruhe und der Anstieg des Herzzeitvolumens unter Belastung (ΔCO) übrig. Der mittels ROC-Analyse (Grenzwertoptimierungskurve) ermittelte ΔCO-Grenzwert von ≥ 1,15 Liter/Minute zeigte sich auch in der Kaplan-Meier-Analyse als aussagekräftig (**Abbildung 3**).



Number at risk	Time (years)				
	1	2	3	4	5
ΔCO ≥ 1.15 l/min	68	53	36	19	8
ΔCO < 1.15 l/min	67	38	16	7	2

Abbildung 3: Kaplan-Meier-Kurven für HTX-/VAD-freies Überleben aufgeteilt nach ΔCO-Grenzwert bei HFrEF-Patienten.

(n = 167; 5-Jahresüberleben frei von HTX/VAD = 22,5% bei ΔCO < 1,15 l/min vs 72,9% bei ΔCO ≥ 1,15 l/min; log-rank p < 0,001)

	Transplant/VAD-free survival	
Variables	HR (95% CI)	*p*-value
WHO functional class		
II	Reference	
III vs II	12.47 (1.58–98.25)	0.017
IV vs II	9.66 (0.97–95.73)	0.05
Systolic BP at rest, mm Hg	0.96 (0.93–0.99)	0.004
LVEF, %	0.90 (0.82–0.97)	0.006
ΔCO/ΔsPAP phenotype		
ΔCO ≥1.15 liter/min/ΔsPAP ≥ 17.5 mm Hg (I)	Reference	
ΔCO ≥1.15 liter/min/ΔsPAP <17.5 mm Hg vs (I)	0.46 (0.05–3.99)	0.48
ΔCO <1.15 liter/min/ΔsPAP ≥17.5 mm Hg vs (I)	2.28 (0.71–7.35)	0.17
ΔCO <1.15 liter/min/ΔsPAP <17.5 mm Hg vs (I)	7.39 (2.27–24.05)	0.001

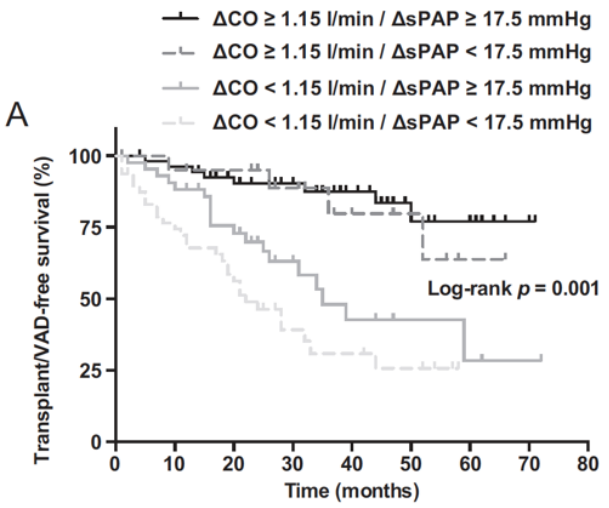
Tabelle 1: Hazard Ratios und 95% Konfidenzintervalle für das HTX-/VAD-freie Überleben, stratifiziert nach hämodynamischem Phänotyp in schrittweiser multivariater Cox Regressionsanalyse[a] in der Gesamtgruppe der Patienten mit HFrEF.

Δ, Anstieg unter Belastung; BP, Blutdruck; CI, Konfidenzintervall; CO, Herzzeitvolumen; HFrEF, Herzinsuffizienz mit reduzierter Ejektionsfraktion; HR, hazard ratio; LVEF, linksventrikuläre Ejektionsfraktion; sPAP, systolischer Pulmonalarteriendruck; VAD, ventrikuläres Unterstützungssystem; WHO, Weltgesundheitsorganisation.

[a]Die schrittweise Analyse wurde auf alle Variablen der multivariablen Analyse und die hämodynamischen Phänotypen basiert auf ΔCO/ΔsPAP angewendet.

Zusätzlich wurde mittels ROC-Analyse ein prognostisch relevanter Grenzwert für den Anstieg des systolischen Pulmonalarteriendrucks (ΔsPAP) berechnet, der bei 17,5 mmHg lag. Ein hämodynamischer Phänotyp definiert durch ΔCO < 1,15 l/min und ΔsPAP < 17,5 mmHg war in einem multivariablen Modell signifikant mit reduziertem HTX-/VAD-freiem Überleben assoziiert (**Tabelle 1**). Dagegen hatten Patienten mit ΔCO ≥ 1,15 l/min und ΔsPAP ≥ 17,5 mmHg ein signifikant besseres 5-Jahresüberleben. Die Überlebenskurven dieser beiden sowie weiterer hämodynamischer Phänotypen sind in **Abbildung 4** dargestellt. Die genannten

Ergebnisse waren in verschiedenen Subgruppen konsistent, und sie korrelierten mit den Ergebnissen der Spiroergometrie. Dabei konnte aber gezeigt werden, dass die hämodynamischen Parameter ΔCO und ΔsPAP bei Patienten mit deutlich pathologischer Einschränkung der Belastungskapazität unter Verwendung der genannten Grenzwerte die Risikostratifizierung weiter differenzieren können (**Abbildung 5**).



Number at risk	Time (years)				
	1	2	3	4	5
ΔCO ≥ 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	52	38	28	15	12
ΔCO ≥ 1.15 l/min / ΔsPAP < 17.5 mmHg	19	15	9	6	4
ΔCO < 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	37	24	9	8	2
ΔCO < 1.15 l/min / ΔsPAP < 17.5 mmHg	33	18	7	5	5

Abbildung 4: Kaplan-Meier-Kurven für HTX-/VAD-freies Überleben aufgeteilt nach hämodynamischem Phänotyp definiert durch ΔCO / ΔsPAP bei allen 167 Patienten.

ΔCO und ΔsPAP wurden den Ergebnissen von ROC-Analysen entsprechend dichotomisiert. Das HTX-/VAD-freie Überleben war 25,7%, wenn ΔCO < 1,15 l/min und ΔsPAP < 17,5 mmHg lag; 28,5% bei ΔCO < 1,15 l/min und ΔsPAP ≥ 17,5 mmHg; 63,8% bei ΔCO ≥ 1,15 l/min und ΔsPAP < 17,5 mmHg; 77,2% bei ΔCO ≥ 1,15 l/min und ΔsPAP ≥ 17,5 mmHg (log-rank p = 0.001).

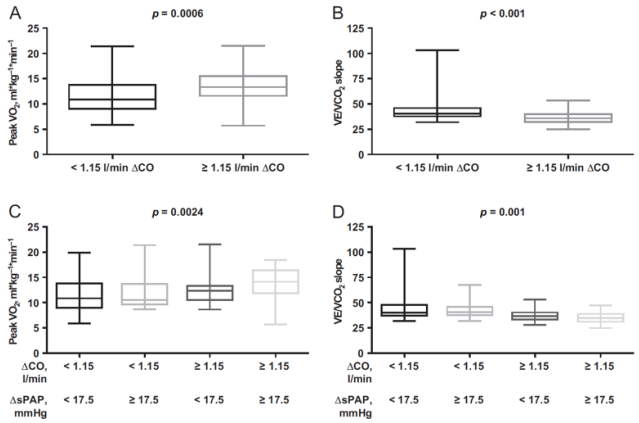


Abbildung 5: maximal erreichte Sauerstoffaufnahme (peak V´O2) und Anstiegssteilheit der Ateminеffizienz (V´E/V´CO2 slope) aufgeteilt nach ΔCO und nach hämodynamischem Phänotyp (ΔCO / ΔsPAP).

ΔCO und ΔsPAP wurden den Ergebnissen von ROC-Analysen entsprechend dichotomisiert.
(A) signifikanter Unterschied von peak $V\dot{O}_2$ zwischen den Gruppen mit ΔCO < / ≥ 1,15 l/min (t-test).
(B) ebenso bezüglich VÉ/V`CO_2 slope (t-test).
(C) signifikante Unterschiede von peak $V\dot{O}_2$ zwischen den hämodynamischen Phänotypen (einseitige Varianzanalyse).
(D) ebenso bezüglich VÉ/V`CO_2 slope (einseitige Varianzanalyse).

Schlussfolgerung

In dieser Studie konnte gezeigt werden, dass ΔCO in unserer HFrEF-Kohorte ein von anderen Standardparametern unabhängiger prognostischer Faktor war. Eine weitere Subdifferenzierung der Patienten mit mehr oder weniger stark ausgeprägtem Anstieg des Pulmonalisdrucks führte zur Entwicklung von vier unterschiedlichen hämodynamischen Phänotypen mit mehr oder weniger stark differierender Prognose. Wir interpretierten dabei den höheren Druckanstieg in der Pulmonalarterie als Ausdruck einer besseren Rechtsherzfunktion mit entsprechend besserer Prognose als bei geringerem Anstieg. Auf diese Weise könnte der rechtsventrikulären Komponente am gesamten Herzzeitvolumen Rechnung getragen werden, im Sinne einer hämodynamischen Differenzierung durch Kombination verschiedener Parameter.
Insgesamt könnte die hämodynamische Phänotypisierung von Patienten mit HFrEF zur Erweiterung der prognostischen Einschätzung dienen, beispielsweise zur individualisierten Risikoabschätzung im Rahmen einer Evaluierung zur Herztransplantation.

4.1.2. Belastungshämodynamik von Patienten mit Herzinsuffizienz und erhaltener und mäßig reduzierter Ejektionsfraktion: Schlüsselrolle des rechten Herzens (Publikation 2: Exercise hemodynamics in heart failure patients with preserved and mid-range ejection fraction: key role of the right heart. Clin Res Cardiol. 2022)

Im Jahr 2016 wurde mit Erscheinen der aktualisierten Herzinsuffizienzleitlinie „2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" der neue Terminus "Herzinsuffizienz mit mäßig reduzierter linksventrikulärer Ejektionsfraktion" (HFmrEF, linksventrikuläre Ejektionsfraktion (LVEF) 40-49%) eingeführt.[90] Damit wurde eine neue Entität zwischen „Herzinsuffizienz mit erhaltener Ejektionsfraktion" (HFpEF, LVEF ≥ 50%) und „Herzinsuffizienz mit reduzierter Ejektionsfraktion" (HFrEF, LVEF < 40%) vorgeschlagen. Es entstand eine breite Diskussion darüber, ob dieser neue Terminus zielführend sei – Patienten mit HFmrEF teilen einige Gemeinsamkeiten mit HFpEF und HFrEF, profitieren aber mehr von HFrEF-Medikation als HFpEF-Patienten.[91, 92] Nicht zuletzt aufgrund dieser Inkonsistenzen wird das Konzept der rein LVEF-basierten Herzinsuffizienzklassifikation immer wieder in Frage gestellt, und es wurde ein mehr pathophysiologisch orientierter Ansatz (beispielsweise an hämodynamischen Charakteristika orientiert) vorgeschlagen.[93-96]

Eine Gemeinsamkeit von HFpEF- und HFmrEF-Patienten ist die rechtsventrikuläre (RV) Dysfunktion, die unter anderem mittels Echokardiographie dargestellt werden kann.[97] Hierzu hat sich der relativ neue Parameter „TAPSE/PASP“ (Ratio aus „tricuspid annular plane systolic excursion“ als Maß der RV-Kontraktilität und „pulmonary arterial systolic pressure“, also der echokardiographisch abgeschätzte Druck in der Pulmonalarterie, als Maß der RV-Nachlast) bei Patienten mit HFpEF und pulmonaler Hypertonie als symptomatisch und prognostisch bedeutsam bewährt.[55, 98, 99] Er gilt als Surrogatparameter des so genannten „couplings“, also der Koppelung zwischen dem RV und seiner Nachlast in der Pulmonalarterie.[100, 101]

Unsere Hypothese war, dass die Einteilung in HFpEF und HFmrEF zur Vorhersage relevanter Unterschiede der Belastungshämodynamik ungeeignet sein könnte, dass aber eine Einteilung nach der Rechtsherzfunktion mittels TAPSE/PASP-Terzilen vorteilhaft sein könnte.

Wir analysierten retrospektiv Daten aus dem Kerckhoff-Klinik Herzinsuffizienz-Register und dem Gießener Pulmonale Hypertonie-Register.[102] Nach Identifikation von Patienten, die zwischen 2009 und 2017 einen RHK mit Belastung erhalten hatten, wurden diejenigen Patienten ausgeschlossen, die letztlich nicht die Diagnose einer HFpEF oder HFmrEF[90] erhalten hatten und Patienten, bei denen die TAPSE/PASP-Ratio nicht zur Verfügung stand. Im zweiten Schritt erfolgte der Vergleich mit einem Teil einer zuvor publizierten Kohorte von HFrEF-Patienten.[96]

Die Belastungsprovokation wurde in der Kerckhoff-Klinik nach dem bereits zuvor publizierten Standard[96] mittels Fahrradergometrie in Liegendposition durchgeführt, und die Belastungsintensität wurde schrittweise bis zur Erschöpfung des Patienten erhöht. In Gießen sah das Standard-Belastungsprotokoll eine halbliegende Position mit schrittweiser Erhöhung der Belastungsstufen vor. In beiden Zentren wurde der Druckwandler entsprechend der Empfehlungen positioniert, und alle Druckmessungen wurden über mehrere Atemzyklen gemittelt.[21] Die Berechnung abgeleiteter hämodynamischer Variablen erfolgte gemäß publizierten Formeln.[39, 45, 83, 103-106]

Insgesamt wurden 125 Patienten mit HFpEF und 41 mit HFmrEF analysiert. In beiden Gruppen befanden sich die meisten Patienten im NYHA-Stadium III, und es gab keinen signifikanten Unterschied der NT-proBNP-Spiegel und der Spiroergometrie-Parameter „maximal erreichte Sauerstoffaufnahme“ (peak $V'O_2$) als Maß der globalen Belastungskapazität und „Anstiegssteilheit des Ventilations / CO_2-Verhältnisses“ ($V'E/V'CO_2$ slope) als Maß der Atemeffizienz. Echokardiographisch zeigte sich in beiden Gruppen eine diastolische LV-Dysfunktion, die Patienten mit HFpEF hatten aber eine signifikant höhere TAPSE/PASP-Ratio bei ähnlichem PASP. Der umfangreiche Vergleich der hämodynamischen Ruhe- und

Belastungsparameter ergab keinerlei signifikante Unterschiede zwischen HFpEF- und HFmrEF-Patienten (**Tabelle 2**).

Parameters	At rest				During exercise			
	n	HFpEF	HFmrEF	*P* value*	*n*	HFpEF	HFmrEF	*P* value*
mPAP, (mmHg)	166	24 [20–30]	23 [20–36]	0.680[a]	166	41 [35–50]	44 [36–53]	0.341[a]
PAWP, (mmHg)	166	15 [12–20]	16 [12–22]	0.503[a]	166	28 ± 6	27 ± 7	0.901[b]
TPG, (mmHg)	166	9 [7–12]	10 [7–14]	0.312[a]	166	15 [10–20]	16 [12–24]	0.208[a]
RAP, (mmHg)	165	7 [4–10]	7 [4–11]	0.794[a]	114	15 ± 7	17 ± 7	0.352[b]
CO, (L/min)	166	4.2 [3.5–4.8]	4.4 [3.4–5.3]	0.351[a]	166	6.1 [4.7–7.7]	6.1 [4.7–7.2]	0.535 [a]
PAC, (mL/mmHg)	165	2.4 [1.9–3.4]	2.4 [1.7–3.1]	0.862[a]	165	1.6 [1.3–2.1]	1.5 [1.2–2.0]	0.521 [a]
PAPi, (mmHg)	165	3.5 [2.7–6.9]	3.7 [2.8–6.1]	0.824[a]	114	2.8 [2.0–4.1]	2.5 [2.1–3.3]	0.381 [a]
RVSWI, (g/m^2/beat)	165	8.0 [6.3–9.9]	7.9 [5.7–11.0]	0.814[a]	116	13 ± 6	13 ± 6	0.932[b]
PVR, (WU)	166	2.0 [1.2–2.9]	2.1 [1.2–3.2]	0.644[a]	165	2.6 [1.8–3.9]	2.8 [1.8–4.4]	0.536 [a]
TPR, (WU)	166	6.0 [4.7–7.5]	5.6 [4.5–8.3]	0.983[a]	166	6.9 [5.5–9.3]	7.8 [6.1–10.1]	0.137 [a]
Heart rate, (beats/min)	165	65 [59–75]	66 [62–72]	0.673[a]	165	90 [76–105]	86 [75–96]	0.324 [a]
Systolic blood pressure, (mmHg)	165	129 ± 20	127 ± 19	0.483[b]	164	151 ± 26	145 ± 24	0.224[b]
Ea, (mmHg/mL)	165	0.50 [0.38–0.70]	0.52 [0.33–0.86]	0.836[a]	165	0.92 [0.68–1.3]	0.97 [0.72–1.3]	0.616 [a]
Total RV power, (watts)	166	0.29 [0.23–0.39]	0.31 [0.23–0.46]	0.301[a]	166	0.74 [0.56–0.95]	0.78 [0.59–0.91]	0.785[a]
mPAP/CO slope, (mmHg/L/min)	–	–	–	–	160	9.4 [5.9–16.5]	11.8 [7.2–21.7]	0.119[a]
PAWP/CO slope, (mmHg/L/min)	–	–	–	–	159	6.1 [3.5–12.1]	6.8 [3.9–11.6]	0.583[a]
ΔCO, (L/min)	–	–	–	–	166	1.7 [1.0–2.8]	1.1 [0.6–2.4]	0.074[a]
Workload, (W)	–	–	–	–	145	30 [25–50]	25 [25–50]	0.431[a]
Atrial fibrillation/flutter during RHC, *n* (%)	–	–	–	–	165	72 (57.6)	26 (63.4)	0.545[c]

Tabelle 2: Ruhe- und Belastungshämodynamik bei Patienten mit HFpEF im Vergleich mit Patienten mit HFmrEF.
Die Werte sind als Mittelwerte mit (±) Standardabweichung oder Mediane mit [Interquartilsabstand] dargestellt, wenn nicht anders bezeichnet.

CO, Herzzeitvolumen; Δ, Anstieg unter Belastung; Ea, pulmonal-arterielle Elastanz; HFmrEF, Herzinsuffizienz mit mäßig reduzierter Ejektionsfraktion; HFpEF, Herzinsuffizienz mit erhaltener Ejektionsfraktion; mPAP, mittlerer pulmonalarterieller (PA) Druck; PAC, PA-Compliance; PAPi, PA-Pulsatilitätsindex; PAWP, PA-Okklusionsdruck; PVR, pulmonalvaskulärer Widerstand; RAP, rechtsatrialer Druck; RC time, Konstante des Lungenkreislaufs; RV, rechtsventrikulär; RVSWI, RV-Schlagarbeitsindex; TPG, transpulmonaler Gradient; WU, Wood-Einheiten.

*Kruskal-Wallis-Test für unabhängige Proben zum Vergleich aller 3 TAPSE/PASP-Terzile, sofern nicht anders bezeichnet
[a]Pearson Chi-Quadrat-Test
[b]Varianzanalyse

Eine Stratifizierung nach TAPSE/PASP-Terzilen[98, 99] (Terzil I: < 0.35 mm/mmHg; Terzil II: 0.35–0.51 mm/mmHg; Terzil III: > 0.51 mm/mmHg) hingegen führte zu signifikanten Unterschieden nicht-hämodynamischer Parameter wie NT-proBNP-Spiegel und V´E/V´CO_2 slope und auch relevanter hämodynamischer Belastungsparameter zwischen den Gruppen. Die Patienten in TAPSE/PASP-Terzile I - mit dem ungünstigsten Verhältnis von RV-Kontraktilität zu Nachlast - zeigten ein höheres Ausmaß an LV-Rückwärtsversagen, krankhaftere Parameter der pulmonalvaskulären Pathologie und damit der RV-Nachlast und eine schwächere Herzzeitvolumen-Reserve (**Tabelle 3**). Einige der genannten Parameter wiederum waren signifikant mit etablierten Spiroergometrie-Parametern assoziiert (**Abbildung 6**).

Der Vergleich von HFmrEF- und HFrEF-Patienten (aus unserer historischen HFrEF-Kohorte) ergab deutlich höhere NT-proBNP-Spiegel bei HFrEF als Zeichen der

Krankheitsschwere, jedoch keine signifikant unterschiedlichen Werte der TAPSE/PASP-Ratio. Die Belastungshämodynamik zeigte wesentliche Unterschiede (schwächere Herzzeitvolumen-Reserve, krankhaftere Parameter der pulmonalvaskulären Pathologie/ RV-Nachlast bei HFrEF).

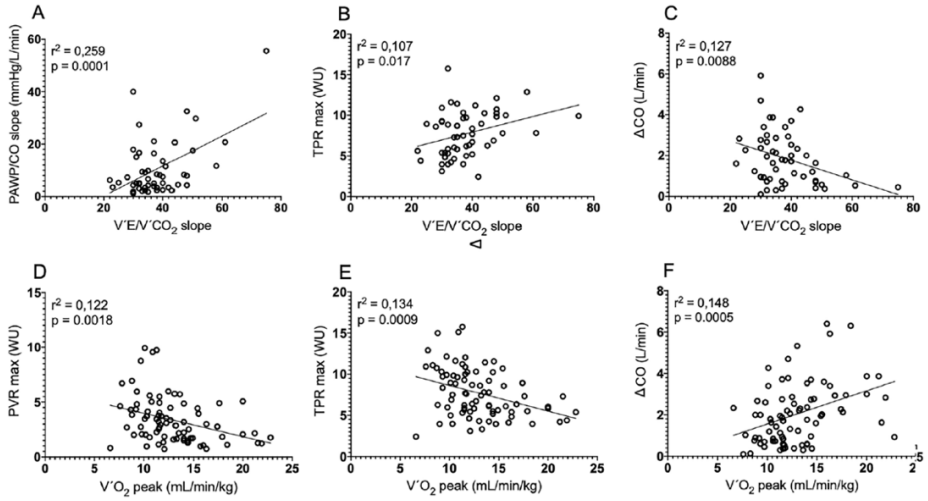


Abbildung 6: Assoziationen zwischen belastungshämodynamischen und spiroergometrischen Parametern.

Obere Reihe: Atemeffizienz (V´E/V´CO_2 slope) mit **A** PAWP/CO slope, **B** maximaler TPR unter Belastung, **C** ΔCO
Untere Reihe: Belastungskapazität (V´O_2 peak) mit **D** maximaler PVR **E** maximaler TPR **F** ΔCO
Berechnung mittels einfacher linearer Regression.

CO, Herzzeitvolumen; Δ, Anstieg unter Belastung; max, maximaler Wert unter Belastung; PAWP, PA-Okklusionsdruck; PVR, pulmonalvaskulärer Widerstand; TPR, totaler pulmonaler Widerstand; V´E/V´CO_2, Ventilation/Kohlendioxidproduktion pro Minute; V´O_2 peak, maximal erreichte Sauerstoffaufnahme; WU, Wood-Einheiten.

Parameters	At rest				During exercise			
	I	II	III	*P* value*	I	II	III	*P* value*
mPAP, (mmHg)	30 [22–37]	24 [20–30]	22 [19–24]	< 0.001	47 [39–55]	42 [35–48]	39 [34–47]	< 0.001
PAWP, (mmHg)	18 [15–22]	15 [12–22]	13 [11–17]	0.001	29 [25–33]	28 [24–32]	25 [22–30]	0.036
RAP, (mmHg)	8 [6–10]	6 [3–10]	6 [4–9]	0.128	17 [12–22]	15 [10–20]	15 [10–19]	0.328
CO, (L/min)	4.3 [3.4–5.0]	4.2 [3.5–5.0]	4.1 [3.4–5.0]	0.905	5.5 [4.3–6.9]	6.3 [4.8–7.6]	6.3 [4.8–8.3]	0.041
PAC, (mL/ mmHg)	2.0 [1.5–2.7]	2.4 [2.0–3.5]	2.7 [2.0–3.5]	< 0.001	1.4 [1.1–1.7]	1.7 [1.4–3.5]	1.8 [1.4–2.8]	< 0.001
PAPi, (mmHg)	3.5 [2.9–6.0]	3.7 [2.2–8.0]	3.8 [2.8–5.3]	0.866	2.8 [2.2–3.6]	2.8 [1.9–4.5]	2.8 [2.0–3.6]	0.820
RVSWI (g/m^2/beat)	9.5[6.8-12.0]	10.0 ± 4.1	8.0 ± 3.1	0.012	13.0 ± 6.1	15.0 ± 6.6	13.0 ± 6.0	0.392[b]
PVR, (WU)	2.9 [2.0–3.7]	1.7 [1.2–2.4]	1.7 [1.1–2.5]	< 0.001	3.7 [2.4–5.0]	2.3 [1.6–3.2]	2.2 [1.6–3.4]	< 0.001
TPR, (WU)	6.7 [5.2–9.3]	5.8 [4.3–7.3]	5.2 [4.2–7.2]	0.002	8.6 [6.7–10.7]	6.7 [5.4–8.8]	6.2 [4.9–8.4]	< 0.001
Ea, (mmHg/mL)	0.65 [0.45–0.96]	0.49 [0.34–0.70]	0.47 [0.33–0.61]	< 0.001	1.1 [0.85–1.5]	0.90 [0.63–1.3]	0.85 [0.59–1.0]	< 0.001
Total RV power, (watts)	0.35 [0.25–0.53]	0.28 [0.20–0.40]	0.27 [0.22–0.34]	0.007	0.79[0.59–0.94]	0.75 [0.57–0.98]	0.71 [0.53–0.85]	0.711
Heart rate (beats/min)	66 [60–75]	65 [59–75]	65 [57–71]	0.292	89 [75–102]	89 [78–101]	90 [71–102]	0.901
mPAP/CO slope, (mmHg/L/min)	–	–	–	–	14.1 [8.9–26.9]	8.7 [5.7–13.6]	7.5 [4.9–13.8]	< 0.001
PAWP/CO slope, (mmHg/L/min)	–	–	–	–	7.6 [4.5–16.2]	6.1 [3.6–10.4]	5.1 [2.8–8.9]	0.009
ΔCO, (L/min)	–	–	–	–	1.0 [0.5–2.0]	1.6 [1.0–2.7]	2.1 [1.1–3.4]	< 0.001
Workload, (W)	–	–	–	–	25 [25–40]	35 [25–50]	43 [25–50]	0.086
Atrial fibrillation/flutter during exercise RHC, *n* (%)	–	–	–	–	42 (76.4)	34 (60.7)	22 (40.0)	< 0.001[a]

Tabelle 3: Ruhe- und Belastungshämodynamik bei Patienten mit HFpEF und HFmrEF, eingeteilt nach TAPSE/PASP-Terzilen (I-III).
Die Werte sind als Mittelwerte mit (±) Standardabweichung oder Mediane mit [Interquartilsabstand] dargestellt.
CO, Herzzeitvolumen; Δ, Anstieg unter Belastung; Ea, pulmonalarterielle Elastanz; HFmrEF, Herzinsuffizienz mit mäßig reduzierter Ejektionsfraktion; HFpEF, Herzinsuffizienz mit erhaltener Ejektionsfraktion; mPAP, mittlerer pulmonalarterieller (PA) Druck; PAC, PA-Compliance; PAPi, PA-Pulsatilitätsindex; PAWP, PA-Okklusionsdruck; PVR, pulmonalvaskulärer Widerstand; RAP, rechtsatrialer Druck; RHC, Rechtsherzkatheter; RV, rechtsventrikulär; RVSWI, RV-Schlagarbeitsindex; TPR, totaler pulmonaler Widerstand; WU, Wood-Einheiten.

[*]HFpEF vs HFmrEF
[a]Mann-Whitney U-Test
[b]Unabhängiger "Student´s t test"
[c]Pearson Chi-Quadrat-Test

Schlussfolgerung

Die Einteilung unserer Studienkohorte in HFpEF und HFmrEF korrespondierte ebenso wenig mit dem belastungshämodynamischen Profil wie mit der generellen Belastungslimitierung. Wurden die Patienten hingegen nach einem echokardiographischen Surrogatparameter der Kopplung zwischen dem rechten Herzen und der nachgeschalteten Pulmonalarterie stratifiziert, so zeigten sich relevante Unterschiede in der Belastungshämodynamik, den Ergebnissen der Spiroergometrie und im klinischen Profil (**Abbildung 7**). Aus der Belastungshämodynamik abgeleitete Charakteristika könnten die Echokardiographie ergänzen und beispielsweise als Basis für klinische Entscheidungen und Studieneinschlusskriterien erprobt werden.
Unsere Studie unterstreicht das rechte Herz als Schlüsseldeterminante des Syndroms Herzinsuffizienz bei HFpEF und HFrEF und stellt die aktuelle Herzinsuffizienzklassifikation auf alleiniger Basis der LVEF aus hämodynamischer Sicht in Frage.

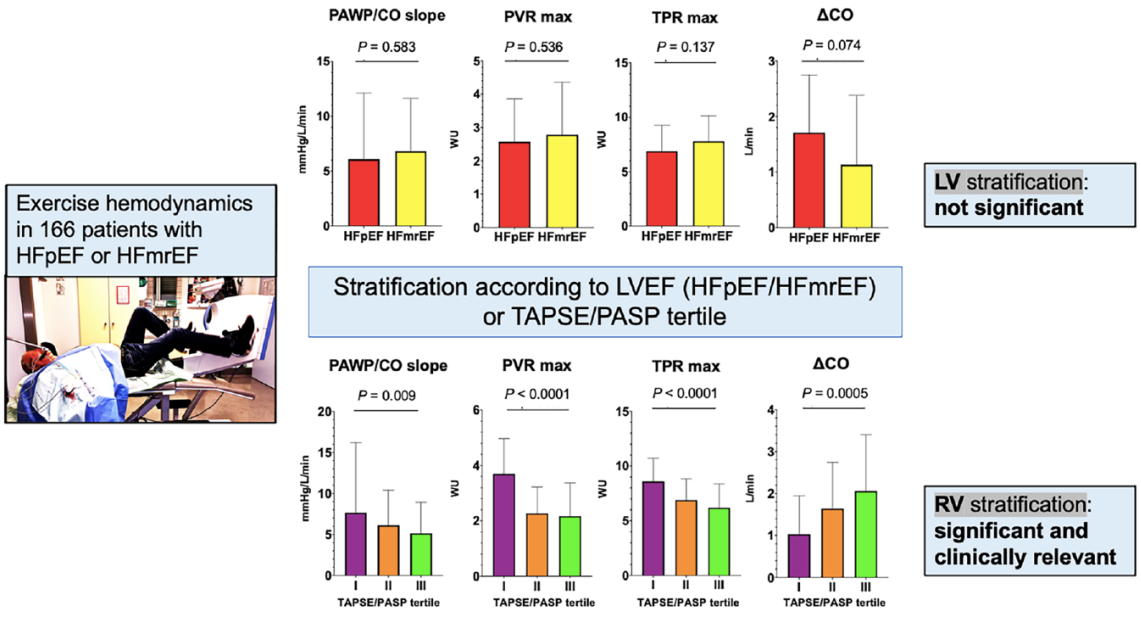


Abbildung 7: graphisches Abstract.

4.1.3. Demaskierung einer latenten Rechtsherzinsuffizienz durch Bestimmung von MR-proANP unter Belastung bei Patienten mit chronisch thromboembolischer pulmonaler Hypertonie (Publikation 3: Exercise MR-proANP unmasks latent right heart failure in CTEPH. J Heart Lung Transplant. 2022)

Bei Patienten mit chronisch thromboembolischer pulmonaler Hypertonie (CTEPH) führt die erhöhte RV-Nachlast zur Rechtsherzinsuffizienz (RHI).[107-109] Eine Folge davon ist die eingeschränkte RV-Füllungskapazität mit Volumen- und Drucküberlastung[107] des rechten Vorhofs (RA), der hierdurch eine gesteigerte Wandspannung erfährt. Ein erhöhter RA-Druck in Ruhe (RAP) ist bei Patienten mit PH und kardialen Erkrankungen als Zeichen eines erhöhten Mortalitätsrisikos etabliert;[110-115] bei PH wird der RAP für die individuelle Risikostratifizierung und als Therapieziel verwendet.[75] Der RHK unter Ruhebedingungen stellt als invasive Prozedur den Goldstandard für hämodynamische Messungen dar,[75] kann jedoch naturgemäß dynamische Prozesse unter Belastung nicht erfassen. Der RHK unter Belastung (B-RHK) hat sich zu einer sinnvollen Ergänzung der Ruheuntersuchung entwickelt, um eine isolierte Belastungs-PH und belastungsprovozierte hämodynamische Pathologien zu erkennen.[21, 107] Trotz eines zunehmenden Interesses an der Belastungshämodynamik bei PH-Patienten ist über die RA-Hämodynamik unter Belastung und deren Bedeutung für das Ausmaß einer RHI relativ wenig bekannt. Der RA-Druck unter Belastung (B-RAP) steigt bei Gesunden nur gering oder gar nicht an;[43, 116-119] einige Autoren nutzen einen erhöhten RAP – in Ruhe oder unter Belastung – zur Definition der RHI.[120] Weiterhin werden hämodynamische Indices unter Verwendung des RAP für die Berechnung - wie beispielsweise der PA-Pulsatilitätsindex (PAPi) – zur Beschreibung der Rechtsherzfunktion verwendet.[121] Bei Patienten mit Linksherzinsuffizienz zeigte sich ein größerer Anstieg des B-RAP assoziiert mit pulmonaler Vaskulopathie und RHI.[44]

Das „atriale natriuretische Peptid“ (ANP) und sein Vorläufer, das „midregionale proatriale natriuretische Peptid“ (MR-proANP), reflektieren das Ausmaß atrialer Wandspannung[122, 123] und korrelieren mit dem RAP bei Patienten mit Linksherzinsuffizienz und mit einer isolierten RHI.[123-125] Unbekannt ist, ob die genannten Biomarker auch kurzzeitige Änderungen des RAP unter Belastung widerspiegeln – es gibt spärliche Daten hierzu bei Patienten mit CTEPH und allgemein PH, jedoch ohne Bezug zu invasiver Hämodynamik.[126-128] In der vorliegenden Studie wollten wir die Dynamik von RAP und MR-proANP unter Ergometerbelastung bei CTEPH-Patienten untersuchen, um herauszufinden, ob diese Parameter als Maß für die belastungsabhängige RA-Wandspannung als Ausdruck einer RHI dienen könnten.

In diese Studie wurden Patienten mit CTEPH oder chronisch-thromboembolischer Lungenerkrankung (CTEPD, CTEPH-Kriterien ohne manifeste PH in Ruhe)[75] eingeschlossen, die einen B-RHK im Rahmen der standardmäßigen diagnostischen Evaluierung in der Kerckhoff-Klinik erhalten hatten.[129, 130] Vor und nach dem B-RHK sollten die Patienten komplette Ruhe für 2 Stunden einhalten. Blutproben für die Biomarkermessungen wurden in Ruhe vor dem RHK, sofort nach Erreichen des Belastungsmaximums und nach einer Erholungszeit von 2 Stunden entnommen. Der B-RHK wurde nach zentrumsinternem Standard durchgeführt,[96, 131] bei dem alle gemessenen Druckwerte über mehre Atemzyklen gemittelt werden, um respiratorische Schwankungen auszugleichen.[132]

Die Biomarkermessungen erfolgten wie folgt: die ersten drei Proben während des RHK wurden direkt aus der Pulmonalarterie entnommen, die 2-Stunden-Probe in Erholung jedoch aus einer peripheren Vene.

Bei der Datenanalyse wurde ein RAP ≤ 7 mmHg als normal definiert,[21, 75, 118] und die Patienten entsprechend des Risikomodells der Europäischen PH-Leitlinie[75] in 3 Subgruppen eingeteilt: Gruppe 1 mit normalem RAP, Gruppe 2 mit moderat erhöhtem RAP (8-14 mmHg) und Gruppe 3 mit stark erhöhtem RAP (> 14 mmHg). Für den B-RAP existiert kein etablierter Normalwert; unter Berücksichtigung der vorhandenen Daten wurde für die vorliegende Studie ein B-RAP von 15 mmHg als obere Normgrenze definiert.[43, 116-119, 133] Es erfolgten Berechnungen zur Untersuchung der Beziehung zwischen nichtinvasiven Parametern und der Zielvariable B-RAP. Weiterhin erfolgten Analysen zur Erfassung des Biomarkerspiegels, der mit dem als pathologisch definierten B-RAP > 15 mmHg am besten korrelierte.

Untersucht wurden insgesamt 100 Patienten (88 CTEPH, 12 CTEPD), davon 53 Frauen, mittleres Alter 61,7 Jahre. Bei 60 Patienten war der RHK Teil der Basisevaluierung, und bei 40 Patienten Teil der Nachuntersuchungen nach pulmonaler Ballonangioplastie (n = 31) oder chirurgischer pulmonaler Endarteriektomie (n = 9). Die mediane Belastungsdauer des B-RHK betrug 8 (Interquartilsabstand [7-11]) Minuten und die mediane Belastungsstufe 50 [25-75] Watt. Die RHK-Messwerte wurden für die Gesamtgruppe sowie separat für die Subgruppen mit B-RAP ≤ oder > 15 mmHg dargestellt (**Tabelle 4**).

Unter Belastung stieg der RAP bei allen Patienten außer einem an, von im Mittel 6 auf 16 mmHg (prozentualer Anstieg 160%). Parallel fiel der mediane PAPi von 6,4 auf 4,2, und der RV-Schlagarbeitsindex (RVSWI) stieg von 11,9 auf 24,6 g x m/m^2. Die mediane Ratio aus RAP und PA-Verschlussdruck (RAP/PAWP) stieg von 0,6 auf 0,9 unter Belastung. Der RAP zeigte eine moderate Korrelation mit der RAP/PAWP-Ratio (r_s = 0,61) und dem PAPi (r_s = – 0,50) in Ruhe, und der B-RAP eine starke Korrelation mit RAP/PAWP (r_s = 0,69) und dem

PAPi (r_s = –0,67) unter Maximalbelastung. Die Korrelationen des mittleren PA-Drucks (mPAP) mit RAP (r_s = 0,47) und B-RAP (r_s = 0,44) waren moderat. Alle genannten Veränderungen und Korrelationen waren auf derselben Stufe signifikant (p < 0,001).

Parameter		Rest	Peak exercise	*p*-value*
HR, beats/min;	All	74 ± 12	119 ± 20	<0.001
	eRAP ≤ 15mmHg	72 ± 12	121 ± 19	<0.001
	eRAP > 15mmHg	76 ± 11	117 ± 21	<0.001
	#	*p* = 0.16	*p* = 0.35	
MAP, mmHg	All	96 ± 13	122 ± 19	<0.001
	eRAP ≤ 15mmHg	97 ± 12	122 ± 18	<0.001
	eRAP > 15mmHg	96 ±14	121 ± 20	<0.001
	#	*p* = 0.65	*p* = 0.72	
mPAP, mmHg	All	33 ± 12	59 ± 14	<0.001
	eRAP ≤ 15mmHg	26 ± 9	52 ± 13	<0.001
	eRAP > 15mmHg	40 ± 12	65 ± 12	<0.001
	#	*p* < 0.001	*p* < 0.001	
mPAP increase, %	All	84 (54-130)		
	eRAP ≤ 15mmHg	100 (76-137)		
	eRAP > 15mmHg	69 (40-89)		
	#	p<0.001		
PVR, WU	All	5.3 ± 3.5	5.9 ± 3.9	<0.001
	eRAP ≤ 15mmHg	3.7 ± 2.6	4.1 ± 2.6	<0.001
	eRAP > 15mmHg	6.8 ± 3.5	7.6 ± 4.1	0.002
	#	*p* < 0.001	*p* < 0.001	
PVR increase, %	All	11 (0-25)		
	eRAP ≤ 15mmHg	11 (-1-26)		
	eRAP > 15mmHg	12 (-2-25)		
	#	*p* = 1.0		
RAP, mmHg	All	6 ± 4	16 ± 7	<0.001
	eRAP ≤ 15mmHg	4 ± 2	10 ± 3	<0.001
	eRAP > 15mmHg	7 ± 4	21 ± 5	<0.001
	#	*p* < 0.001	*p* < 0.001	
RAP increase, %	All	160 (100-260)		
	eRAP ≤ 15mmHg	150 (71-212)		
	eRAP > 15mmHg	200 (133-300)		
	#	*p* = 0.007		
PAPi	All	6.4 (4.6-9.4)	4.2 (3.1-5.4)	<0.001
	eRAP ≤ 15mmHg	6.5 (4.5-9.5)	5.2 (3.9-6.5)	0.001
	eRAP > 15mmHg	6.4 (4.6-9.4)	3.4 (2.7-4.5)	<0.001
	#	*p* = 0.94	*p* < 0.001	
CI, L/min/m²	All	2.6 ± 0.6	4.6 ± 1.5	<0.001
	eRAP ≤ 15mmHg	2.7 ± 0.5	5.3 ± 1.2	< 0.001
	eRAP > 15mmHg	2.5 ± 0.6	3.9 ± 1.5	<0.001
	#	*p* = 0.06	*p* < 0.001	
CI increase, %	All	69 (38-112)		
	eRAP ≤ 15mmHg	88 (61-140)		
	eRAP > 15mmHg	50 (27-77)		
	#	*p* < 0.001		
RVSWI, g x m/m²/beat	All	11.9 (8.4-16.7)	24.6 (17.6-29.6)	<0.001
	eRAP ≤ 15mmHg	10.8 (7.3-14.1)	26.4 (19.8-31.2)	<0.001
	eRAP > 15mmHg	12.7 (9.9 – 19.5)	20.6 (15.1 – 28.8)	<0.001
	#	p=0.01	p=0.007	
TPR, WU	All	7.2 ± 3.7	7.9 ± 4.3	<0.001
	eRAP ≤ 15mmHg	5.4 ± 2.8	5.7 ± 3.0	0.024
	eRAP > 15mmHg	8.9 ± 3.7	10.0 ± 4.3	<0.001
	#	p<0.001	p<0.001	
TPR increase, %	All	7 (-2-18)		
	eRAP ≤ 15mmHg	2 (-4-14)		
	eRAP > 15mmHg	14 (1-23)		
	#	*p* = 0.008		
RAP / PCWP	All	0.6 (0.4 – 0.8)	0.9 (0.7 – 1.2)	<0.001
	eRAP ≤ 15mmHg	0.6 (0.4 – 0.7)	0.7 (0.5 – 0.8)	0.001
	eRAP > 15mmHg	0.7 (0.5 – 1.0)	1.2 (1.0 – 1.7)	<0.001
	#	p=0.002	p<0.001	
SvO2 saturation, %	All	71 ± 6	36 ± 11	<0.001
	eRAP ≤ 15mmHg	72 ± 5	42 ± 10	<0.001
	eRAP > 15mmHg	69 ± 6	30 ± 9	<0.001
	#	*p* = 0.002	*p* < 0.001	

Tabelle 4: Hämodynamik in Ruhe (Rest) und unter maximaler Belastung (Peak exercise).
HR, Herzfrequenz; MAP, arterieller Mitteldruck; mPAP, mittlerer pulmonalarterieller (PA) Druck; PVR, pulmonalvaskulärer Widerstand; RAP, rechtsatrialer Druck; PAPi, PA-Pulsatilitätsindex; PCWP, PA-Okklusionsdruck; CI, Herzindex; RVSWI, rechtsventrikulärer Schlagarbeitsindex; TPR, totaler pulmonaler Widerstand; SvO_2 saturation, gemischtvenöse Sauerstoffsättigung.

*p-Werte sind für den Vergleich zwischen Ruhe- und Belastungswerten (*) und für den Vergleich der beiden Subgruppen mit Belastungs-RAP (eRAP) ≤ oder > 15 mmHg (#) wiedergegeben.

Wie **Abbildung 8** zeigt, stiegen bei der Mehrheit der Patienten die medianen MR-proANP-Spiegel unter Belastung an und gingen nach 2 Stunden Erholung auf Ausgangsniveau zurück.

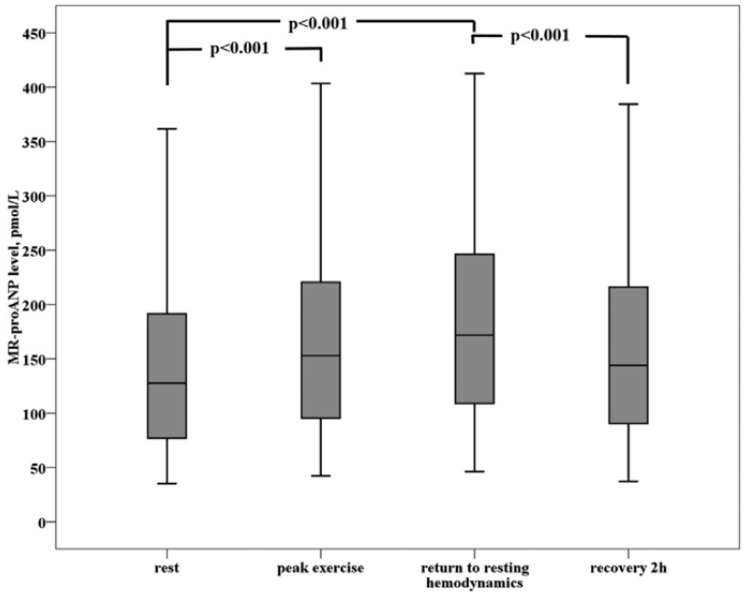


Abbildung 8: Verlauf der MR-proANP-Spiegel vor (rest), während (peak exercise) und direkt nach (return to resting hemodynamics) sowie 2 Stunden nach (recovery 2h) Belastungs-Rechtsherzkatheter.

Das „Box-und Whisker"-Diagramm zeigt signifikante Änderungen der Biomarkerspiegel.
MR-proANP, midregionales proatriales natriuretisches Peptid.

In **Abbildung 9** sind die Korrelationen von MR-proANP mit RAP und B-RAP zu sehen. Patienten mit B-RAP > 15 mmHg hatten höhere MR-proANP-Maximalspiegel (226 [163–347] vs 123 [77–196] pmol/l; p < 0,001) und höhere 2-Stunden-Erholungswerte (204 [141–290] vs 94 [65–150] pmol/l; p < 0,001) als diejenigen mit B-RAP ≤ 15 mmHg.

Die univariate Regressionsanalyse umfasste diagnostische Parameter, die sich zwischen Patienten mit B-RAP ≤ und > 15 mmHg unterschieden sowie weitere Faktoren mit möglichem Einfluss auf die Biomarkerspiegel, wie Alter, Bluthochdruck und andere. Im abschließenden multivariaten Modell blieben nach Adjustierung folgende Faktoren signifikant mit einem B-RAP > 15 mmHg assoziiert: maximaler MR-proANP-Spiegel (p = 0,004), RA-Fläche im Echokardiogramm (p < 0,001), der MR-proANP-Spiegel in Ruhe war knapp nicht signifikant (p = 0,05). Ein mittels Grenzwertoptimierungsanalyse ermittelter Grenzwert für maximales MR-proANP von ≥ 139 pmol/l (Fläche unter der Kurve, AUC = 0,81; 95% Konfidenzintervall [0,73–0,89]; Wahrscheinlichkeitsverhältnis, OR = 14,5 [4,9–43,1]; p < 0,001) und für MR-proANP nach 2 Stunden Erholung von ≥ 159 pmol/l (AUC = 0,82 [0,73–0,89]; OR 9,1 [3,6–22,9]; p < 0,001) erwiesen sich als starke Prädiktoren eines B-RAP > 15 mmHg und waren den MR-proANP-Spiegeln in Ruhe (AUC = 0,78 [0,69–0,87]) überlegen.

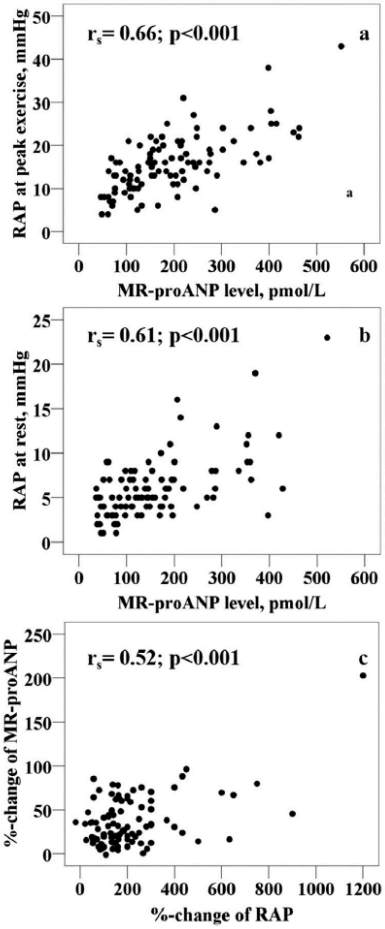


Abbildung 9 a-c: Korrelation von MR-proANP-Spiegeln und rechtsatrialem Druck.

In Ruhe (a) und unter maximaler Belastung (b), bivariate Pearson-Korrelation der relativen Änderungen unter Belastung (c).
RAP, rechtsatrialer Druck; MR-proANP, midregionales proatriales natriuretisches Peptid.

Ein normaler RAP war bei 77 Patienten vorhanden (Gruppe 1), ein moderat erhöhter bei 20 Patienten (Gruppe 2), und ein stark erhöhter bei 3 Patienten (Gruppe 3). Die Dynamik des B-RAP in diesen Gruppen ist in **Abbildung 10** dargestellt.

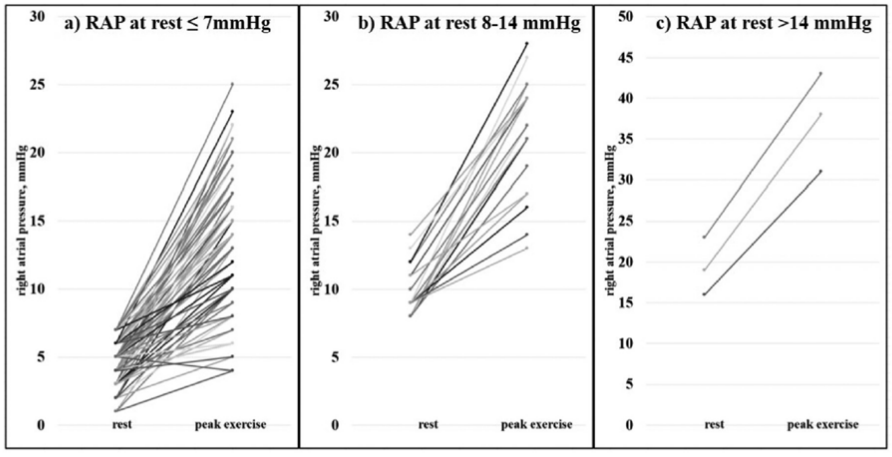


Abbildung 10: a-c: Dynamik des rechtsatrialen Drucks während des Belastungs-Rechtsherzkatheters.

Daten der einzelnen Patienten sind nach normalem (a), moderat (b) und stark erhöhtem (c) rechtsatrialem Druck aufgeteilt.
RAP, rechtsatrialer Druck; rest, Ruhe; peak exercise, maximale Belastung.

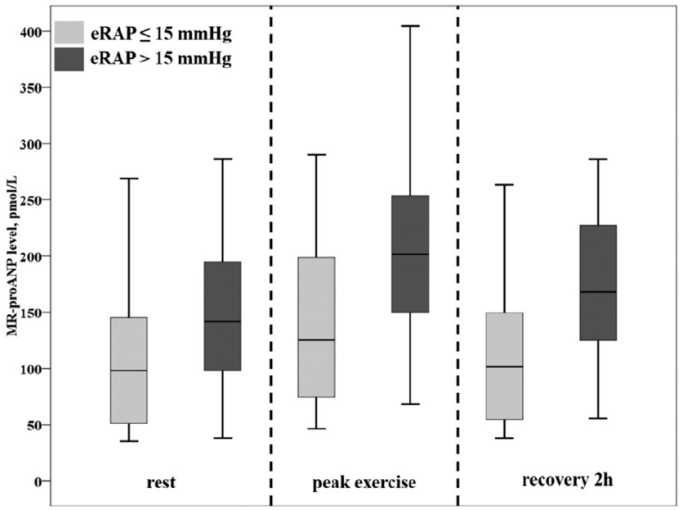


Abbildung 11: Vergleich der MR-proANP-Dynamik bei Patienten der Gruppe 1 (normaler RAP in Ruhe) mit normalem und pathologischem RAP-Anstieg unter Belastung.

Das „Box-und Whisker"-Diagramm zeigt die medianen Biomarkerspiegel zu verschiedenen Zeitpunkten, aufgeteilt nach rechtsatrialem Druck unter Belastung.

MR-proANP, midregionales proatriales natriuretisches Peptid; eRAP, rechtsatrialer Druck unter Belastung; rest, Ruhe; peak exercise, maximale Belastung; recovery 2h, 2 Stunden nach Belastung.

Die folgenden Analysen beziehen sich exklusiv auf die Patienten in Gruppe 1 mit normalem Ruhe-RAP. Hier zeigten die Patienten mit B-RAP > 15 mmHg und diejenigen mit B-RAP ≤ 15 mmHg vergleichbare Ruhe-RAP-Werte (p = 0,11). Jedoch war bei denen mit B-RAP > 15 mmHg der prozentuale Anstieg des MR-proANP deutlicher (p = 0,005), und die Spitzenwerte (p < 0,001) waren ebenso wie die 2-Stundenwerte (p < 0,001) höher (**Abbildung 11**).

Die für MR-proANP identifizierten Grenzwerte unter Belastung (> 139 pmol/l; OR 10,5 95% CI [3,1–35,0]; p < 0,001) und nach 2 Stunden Erholung (> 159 pmol/l; OR 4,8 95% CI [1,8–13,2]; p = 0,003) waren prädiktiv für einen B-RAP > 15 mmHg.

Die Patienten in Gruppe 1 mit pathologischem B-RAP hatten im Vergleich zu denen mit B-RAP ≤ 15 mmHg eine niedrigere GFR (p = 0,04), eine größere RA-Fläche (p = 0,007), einen größeren RV-Durchmesser (p = 0,04) und schlechtere Werte für mPAP, PVR und TPR in Ruhe. Diese prognostisch relevanten Unterschiede zwischen diesen beiden Subgruppen der Gruppe 1 waren anhand von etablierten hämodynamischen Risikoparametern in Ruhe (Herzindex CI, RAP gemischtvenöse Sauerstoffsättigung SvO_2) und nicht-hämodynamischen Risikoparametern (6-Minuten Gehtest, maximal erreichte Sauerstoffaufnahme in der Spiroergometrie) nicht zu identifizieren (**Tabelle 5**).

Parameter	Subgroup 1 (N = 77)		eRAP ≤ 15 mmHg (N = 47)		eRAP > 15 mmHg (N = 30)		P-Value (eRAP groups)	
Age, years	61.7 ± 13.6		59.3 ± 14.6		65.5 ± 10.9		0.05	
BMI, kg/m²	26.8 ± 5.3		26.2 ± 4.8		27.9 ± 5.8		0.16	
Biomarkers								
eGFR, mL/min	92.0 ± 27.4		97.2 ± 27.6		83.8 ± 25.6		0.04	
NT-proBNP, ng/L	157 (62-406)		114 (55-241)		338 (115-896)		0.001	
WHO -FC I	8		4 (9)		4 (13)		0.10	
II	33		25 (53)		8 (27)			
III	35		17 (36)		18 (60)			
IV	1		1 (2)		0 (0)			
Echocardiography								
RV diameter, mm	37 ± 7		36 ± 7		39 ± 7		0.04	
TAPSE, mm	19 ± 5		19 ± 5		18 ± 5		0.30	
RA area, cm²	18 ± 5		17 ± 4		20 ± 4		0.007	
6-MWD, m	413 ± 81		427 ± 98		390 ± 42		0.45	
CPET								
Peak VO_2, ml/kg/min	16.1 ± 5.3		16.6 ± 5.2		15.3 ± 5.6		0.41	
Right heart catheter	rest	exercise	rest	exercise	rest	exercise	rest	exercise
mPAP, mmHg	30 ± 11	58 ± 14	26 ± 9	53 ± 13	36 ± 12	65 ± 12	<0.001	<0.001
PVR, WU	4.5 ± 3	5.0 ± 3.1	3.7 ± 2.6	4.1 ± 2.7	5.7 ± 3.2	6.3 ± 3.3	0.003	0.002
CI, L/min/m²	2.7 ± 0.6	5.0 ± 1.3	2.7 ± 0.5	5.3 ± 1.2	2.6 ± 0.6	4.5 ± 1.4	0.07	0.004
RAP, mmHg	5 ± 2	14 ± 5	4 ± 2	11 ± 3	5 ± 1	18 ± 3	0.11	<0.001
TPR, WU	6.2 ± 3.2	6.8 ± 3.5	5.4 ± 2.8	5.7 ± 3.0	7.6 ± 3.4	8.6 ± 3.6	0.002	0.001
SvO2 saturation, %	71 ± 5	38 ± 10	72 ± 5	41 ± 10	70 ± 4	32 ± 9	0.05	<0.001
RAP/PCWP	0.7 (0.4-0.7)	0.8 (0.6-1.0)	0.6 (0.4-0.7)	0.7 (0.5-0.8)	0.5 (0.4-0.6)	1.0 (0.9-1.3)	0.91	<0.001
PAPi	7.5 (4.8-11.0)	4.6 (3.4-5.9)	6.8 (4.7-9.5)	5.2 (4.0-6.5)	8.3 (5.1-12.4)	4.0 (2.8-4.7)	0.01	<0.001
RVSWI, g x m²/beat	11.9 (8.0-16.6)	26.3 (19.2-31.3)	11.0 (7.2-14.3)	26.5 (20.0-31.2)	12.4 (10.3-20.5)	24.7 (18.0-31.6)	0.02	0.44

Tabelle 5: Vergleich klinischer Eigenschaften Patienten der Gruppe 1 (normaler rechtsatrialer Druck (RAP) in Ruhe) mit normalem (Belastungs-RAP ≤ 15 mmHg) und pathologischem (Belastungs-RAP > 15 mmHg) Anstieg unter Belastung.
Die angegebenen Werte zeigen die Anzahl N (%), die Mittelwerte ± Standardabweichung oder Mediane [Interquartilsabstand].
(e)RAP, (Belastungs-) rechtsatrialer Druck; BMI, Körpermassenindex; eGFR, geschätzte glomeruläre Filtrationsrate; NT-proBNP, N-terminales pro brain natriuretic peptide; WHO-FC, Weltgesundheitsorganisations-Funktionsklasse; RV diameter, rechtsventrikulärer Diameter; TAPSE, systolische Exkursion des lateralen Trikuspidalklappenrings; RA area, rechtsatriale endsystolische Fläche; 6-MWD, 6 Minuten Gehstrecke; CPET, Spiroergometrie; peak VO_2, maximale Sauerstoffaufnahme; mPAP, mittlerer pulmonalarterieller (PA) Druck; PVR, pulmonalvaskulärer Widerstand; WU, Wood-Einheiten; CI, Herzindex; TPR, totaler pulmonaler Widerstand; SvO_2 saturation, gemischtvenöse Sauerstoffsättigung; PCWP, PA-Okklusionsdruck; PAPi, PA-Pulsatilitätsindex; RVSWI, RV-Schlagarbeitsindex.

Schlussfolgerung

Der besondere Nutzen unserer Ergebnisse könnte darin liegen, die Risikostratifizierung von Patienten mit PH zu verfeinern. Ein normaler RAP spricht nämlich – für sich genommen - für ein niedriges Risiko. Durch Unterteilung der Patienten mit normalem RAP in solche mit nicht-pathologischem und pathologischem B-RAP konnten wir aber zeigen, dass letztere eher einer intermediären als niedrigen Risikoklasse zuzuordnen sind (definiert durch RA-Fläche, Spiegel des „N-terminalen pro brain natriuretic peptide“, NT-proBNP und 6-Minuten-Gehstrecke). Diese Demaskierung einer in Ruhe nicht erkennbaren RHI durch die Belastungshämodynamik spiegelt sich in der MR-proANP-Dynamik wider. In zukünftigen Studien mit standardisierten Belastungsprotokollen wären validierte Grenzwerte für RA-Hämodynamik und Biomarker zu definieren, mit dem Ziel, durch eine Belastungs-Biomarkermessung die invasive Hämodynamik verzichtbar zu machen.

4.1.4. Prognostische Aussagekraft einer Veränderung der pulmonal-arteriellen Compliance unter Einfluss von Glyceroltrinitrat bei Patienten mit postkapillärer pulmonaler Hypertonie

(Publikation 4: Prognostic Power of Pulmonary Arterial Compliance Is Boosted by a Hemodynamic Unloading Test With Glyceryl Trinitrate in Heart Failure Patients With Post-capillary Pulmonary Hypertension. Front Cardiovasc Med. 2022)

Das Vorhandensein einer PH gilt als etablierter Risikofaktor bei Patienten mit Linksherzinsuffizienz (LHI), insbesondere wenn die PH zu einem fortgeschrittenen Umbauprozess des pulmonalen Gefäßbetts geführt hat. Dieser wiederum führt zu einer Erhöhung der rechtsventrikulären Nachlast und letztlich zur RHI mit der Folge einer erhöhten Mortalität.[41] Es gibt jedoch eine anhaltende Debatte darüber, welche hämodynamischen Parameter das Ausmaß der pulmonalen Gefäßschädigung am besten widerspiegeln und damit die beste Vorhersage einer schlechten Prognose ermöglichen. Der pulmonale Gefäßwiderstand (PVR) und die pulmonalarterielle Compliance (PAC) scheinen die stärkste prognostische Aussage bei Patienten mit PH bei LHI zu ermöglichen.[134-137] In einer Modifikation der PH-Leitlinien von 2016 wurde ein PVR-Wert ≥ 3 WU vorgeschlagen, um eine so genannte „kombinierte postkapilläre PH“ (Cpc-PH) und damit ein erhöhtes Mortalitätsrisiko anzuzeigen.[75, 138]

Die Aussagekraft einzelner hämodynamischer Messungen wird dadurch eingeschränkt, dass häufig spontane Veränderungen zu beobachten sind. Serielle Messungen hingegen, beispielsweise nach einer VRT scheinen die prognostische Vorhersagekraft zu verbessern.[17, 73] Eine VRT spielt aber bei Patienten mit PH bei LHI bisher lediglich bei einem kleinen Teil der Patienten eine Rolle, nämlich im Vorfeld einer Herztransplantation zur Diagnostik einer so genannten „fixierten“ PH.[23, 75] Darüber hinaus ist die Aussagekraft einer VRT bei LHI-Patienten unklar, möglicherweise aufgrund der Heterogenität der verwendeten Vasodilatatoren, fehlender Standardprotokolle und des Fehlens von Studien mit prognoserelevantem Endpunkt.[139] Trotz weithin fehlender Daten wird eine VRT mittels Glyceroltrinitrat (GTN) in manchen Herzzentren regelmäßig durchgeführt. GTN besitzt bei LHI prinzipielle Vorteile gegenüber pulmonalvaskulär-selektiven Vasodilatatoren, wie sie bei anderen PH-Formen für eine VRT eingesetzt werden.[139, 140]

Ziel dieser Studie war es nun, den Stellenwert einer solchen Testung mit GTN für prognostische Aussagen bei Patienten mit PH bei LHI zu untersuchen. Unsere Hypothese lautete, dass eine VRT mit GTN die prognostische Aussage hämodynamischer Messungen bei

diesen Patienten verbessern könnte, indem „fixierte“ pulmonale Gefäßschäden demaskiert werden.

Untersucht wurden 154 Patienten der Kerckhoff-Klinik, die wegen einer Herzinsuffizienz (HI) zwischen 2009 und 2016 einen RHK mit VRT unter Verwendung von GTN durchlaufen hatten. Der mPAP musste mit > 20 mmHg erhöht sein, und der PAWP > 15 mmHg; bei 12 Patienten war der PAWP zwischen 10 und 15 mmHg in Ruhe, diese hatten aber einen PAWP-Anstieg > 25 mmHg unter Belastung oder eindeutige echokardiographische Zeichen einer LHI wie Hypertrophie, reduzierte LVF und / oder Vergrößerung des linken Vorhofs. Ausschlusskriterien waren fehlende Nachverfolgungsdaten (mindestens eine Folgevisite nach dem initialen RHK war erforderlich).

Der primäre Endpunkt wurde als Überleben frei von Herztransplantation (HTX) und Implantation eines Linksherzunterstützungssystems (LVAD) definiert.

Im Rahmen eines Standard-RHK[96] erhielten geeignete Patienten, die zum Zeitpunkt der Untersuchung stabil, rekompensiert sowie adäquat mittels HI-Medikation therapiert sein mussten, GTN sublingual in der initialen Standarddosis von 1,2 mg, wenn der systolische Blutdruck > 100 mmHg lag. Die GTN-Gabe wurde bis zum Erreichen eines deutlichen Effekts wiederholt, ohne dass im Vorhinein definiert war, wann eine VRT als „positiv“ zu werten sei.

Die Patienten waren median 71 Jahre alt, 39% waren Frauen, und 75% waren im NYHA-Stadium III. Die NT-proBNP-Spiegel zeigten sich deutlich erhöht mit median 1890 [973–4182] pg/ml. Gemäß Einteilung nach der LVF ergab sich folgende Aufteilung in der untersuchten Kohorte: 48% HFpEF, 8% HFmrEF und 44% HFrEF.

Die mittlere im Rahmen der VRT verabreichte GTN-Dosis betrug 2,4 [1,6–3,2] mg. Hierunter zeigten sich signifikante Veränderungen der meisten gemessenen hämodynamischen Parameter (außer Herzfrequenz und ratio aus dem pulmonalvaskulären / systemischen Widerstand). Die Ergebnisse mit zusätzlicher Stratifizierung nach unserem (weiter unten näher beschriebenen) PAC-GTN-Grenzwert finden sich in **Tabelle 6**.

Diejenigen Patienten, die den primären Endpunkt erreichten, zeigten zwar einen stärkeren Anstieg des Schlagvolumens (SV), aber einen deutlich geringeren Abfall des Pulsdrucks (PP = Differenz zwischen systolischem und diastolischem PA-Druck) und infolgedessen eine geringere Verbesserung der PA-Compliance (PAC = SV/PP; höhere Werte bedeuten eine geringere PA-Steifigkeit) als die ohne HTX / LVAD Überlebenden.

Die mediane Nachverfolgungszeit betrug 30 [8-57] Monate, innerhalb derer 40,3 % der Patienten verstarben, 1,9% HTX und 0,6% ein LVAD erhielten. Das Gesamtüberleben frei von HTX und LVAD betrug 57,2%. In der univariaten Regressionsanalyse fanden sich multiple

Assoziationen zwischen hämodynamischen Parametern und dem Endpunkt sowohl vor als auch nach VRT. Es wurden nun Berechnungen durchgeführt, die das Potenzial der einzelnen Variablen zur Verbesserung der Vorhersagekraft des etablierten „MAGGIC"-Scores (eines HI-Risikoscores, der 13 klinische Variablen umfasst) zeigen sollten.

	BASELINE					GTN				
Data availability (D.a.)	D.a.	PAC-GTN > 2.55 $n = 66^{\S}$	D.a.	PAC-GTN ≤ 2.55 $n = 82^{\S}$	*p*-Value*	D.a.	PAC-GTN > 2.55 $n = 66^{\S}$	D.a.	PAC-GTN ≤ 2.55 $n = 82^{\S}$	*p*-Value*
Systolic BP, mmHg	66	134.0 (±25.0)	82	119 [106-136]	0.006[a]	66	124.0 (±22.0)	82	112 [101-128]	0.003[a]
Mean BP, mmHg	66	93 [84–106]	81	88 [80–97]	0.016[a]	65	88.0 (±14.0)	81	82.0 (±12.0)	0.003[b]
Heart rate, beats/min	66	67.0 (±10.0)	82	70.0 (±9.5)	0.098[b]	66	67 [61–73]	82	69 [62–75]	*0.286*[a]
PAWP, mmHg	66	21.0 [18–24]	82	26.0 (±5.0)	<0.0001[a]	66	13.0 [9.0–18.0]	82	20.0 [16.0–24.0]	<0.0001[a]
sPAP, mmHg	66	51.0 (±11.0)	82	68.0 [56–73]	<0.0001[a]	66	35.0 [29–45]	82	55.0 (±13.0)	<0.0001[a]
mPAP, mmHg	66	33.0 (±6.3)	82	41.0 (±6.7)	<0.0001[b]	66	23.0 (±6.0)	82	32.0 (±7.3)	<0.0001[b]
dPAP, mmHg	66	20.0 (±4.8)	82	25.0 (±5.6)	<0.0001[b]	66	*15.0 (±4.7)*	82	19.0 (±5.8)	<0.0001[b]
PP, mmHg	66	30.0 [25.0–37.0]	82	40.0 [32.0–47.0]	<0.0001[a]	66	20.0 [17.0–25.0]	82	36.0 [29.0–42.0]	<0.0001[a]
RAP, mmHg	66	11.0 [7.0–13.0]	82	12.0 [9.0–17.0]	0.009[a]	63	7.0 [5.0–10.0]	71	9.0 (±4.9)	0.056[a]
TPG, mmHg	66	11.0 [8.0–14.0]	81	15.0 [11.0–19.0]	<0.0001[a]	66	9.6 (±3.7)	81	14.0 (±5.3)	<0.0001[b]
DPG, mmHg	66	−0.92 (±4.1)	81	−1.0 [−4.0-3.0]	0.572[a]	66	1.4 (±3.9)	81	0.28 (±5.3)	0.169[b]
CO-TD, l/min	66	5.0 [4.1–5.9]	82	3.7 [3.1–4.5]	<0.0001[a]	66	5.4 (±1.3)	82	4.2 [3.5–5.1]	<0.0001[a]
CI-TD, l/min/m^2	66	2.5 [2.2–2.8]	82	2.0 [1.7–2.3]	<0.0001[a]	66	2.7 (±0.63)	82	2.2 [2.0–2.6]	<0.0001[a]
SV-TD, mL	66	72.0 [62.0–92.0]	82	54.0 [45.0–69.0]	<0.0001[a]	66	77.0 [64.0–91.0]	82	61.0 [49.0–77.0]	<0.0001[a]
PVR, WU	66	2.3 (±0.9)	81	3.6 [2.9–5.4]	<0.0001[a]	66	1.9 (±0.74)	81	3.0 [2.2–4.2]	<0.0001[a]
SVR, WU	66	19.0 [16.0–22.0]	82	24 (±6.5)	<0.0001[a]	66	17.0 [13.0–20.0]	81	20 (±5.3)	0.002[a]
PVR/SVR	66	0.12 [0.08–0.16]	80	0.16 [0.13–0.22]	<0.0001[a]	65	0.11 (±0.05)	80	0.17 (±0.07)	<0.0001[b]
TPR, WU	66	6.6 (±1.5)	82	11.0 [8.8–13.0]	<0.0001[a]	66	4.5 (±1.2)	82	7.6 [6.0–8.9]	<0.0001[a]
PAC, mL/mmHg	66	2.4 [2.1–3.0]	82	1.4 [1.1–1.7]	<0.0001[a]	66	3.5 [3.0–4.5]	82	1.9 [1.4–2.2]	<0.0001[a]
Ea, mmHg/mL	66	0.63 (±0.18)	82	1.0 [0.89–1.4]	<0.0001[a]	66	0.40 (±0.14)	82	0.73 [0.57–0.87]	<0.0001[a]
PAPi	66	3.0 [2.2–4.0]	82	3.3 [2.2–4.8]	0.263[a]	63	3.0 [2.3-4.2]	71	4.3 [3.2–6.3]	<0.0001[a]
RAP/PAWP	66	0.53 [0.40–0.64]	80	0.53 [0.36–0.62]	0.906[a]	63	0.56 [0.42–0.65]	74	0.43 (±0.21)	0.006[a]
RV power$_{oscill}$, W	66	0.11 [0.08–0.13]	82	0.10 [0.08–0.13]	0.524[a]	66	0.08 [0.06–0.11]	82	0.09 [0.07–0.12]	0.093[a]

Tabelle 6: Hämodynamik vor (BASELINE) und nach (GTN)Verabreichung von Glyceroltrinitrat.
Die Werte sind als Mittelwerte mit (±) Standardabweichung oder Mediane mit [Interquartilsabstand] dargestellt, wenn nicht anders bezeichnet. GTN, Glyceroltrinitrat; BP, Blutdruck; PAWP, pulmonalarterieller (PA) Okklusionsdruck; sPAP, systolischer PA-Druck; mPAP, mittlerer PAP; dPAP, diastolischer PAP; PP, PA-Pulsdruck; RAP, rechtsatrialer Druck; TPG, transpulmonaler Gradient; DPG, diastolischer pulmonaler Druckgradient; CO, Herzzeitvolumen; TD, Thermodilutionsmethode zur CO-Bestimmung; CI, Herzindex; SV, Schlagvolumen; PVR, pulmonalvaskulärer Widerstand; WU, Wood-Einheiten; SVR, systemvaskulärer Widerstand; TPR, totaler pulmonaler Widerstand; PAC, PA-Compliance; Ea, berechnete pulmonal-arterielle Elastanz; PAPi, PA-Pulsatilitätsindex; RV, rechter Ventrikel; oscill, oszillatorisch; W, Watt.
*PAC-GTN > 2,55 vs PAC-GTN ≤ 2,55 ml/mmHg. §Schlagvolumen nach GTN-Gabe und damit PAC-GTN war bei 6 Patienten nicht verfügbar. [a]Mann-Whitney U-Test. [b]"Student´s" t-Test. D.a. = data availability, Zahl der Patienten mit verfügbaren Daten des jeweiligen Parameters.

Diejenigen Variablen mit den niedrigsten adjustierten p-Werten und gleichzeitig höchsten AUC-Werten in der ROC-Analyse waren alle nach VRT erhoben worden, nämlich Ea (berechnete PA-Elastanz)-GTN, TPR-GTN und PAC-GTN. Das Wahrscheinlichkeitsverhältnis (Odds Ratio) war – adjustiert für die Variablen des etablierten MAGGIC-Scores[26, 27, 141] – je Anstieg um eine Standardabweichung für Ea-GTN 2,26 (Konfidenzintervall 1,30–3,92, p=0,004), für TPR-GTN 2,29 (1,34–3,93, p = 0,003) und für PAC-GTN 0,45 (0,25–0,80, p = 0,006). Es wurden Grenzwerte berechnet und deren prädiktiver Wert für den primären Endpunkt mit dem prädiktiven Wert anderer etablierter Parameter (PAC, Vorhandensein einer Cpc-PH – hier nach geltender PH-Leitlinie definiert als PVR > 3 WU und / oder diastolischer Druckgradient ≥ 7 mmHg) und dem eines weiteren, nicht etablierten Parameters (Unterschied zwischen PAC vor / nach VRT, delta PAC) in einer multivariablen Analyse verglichen. Hier

zeigte sich PAC-GTN als einziger Parameter mit signifikant unabhängiger Assoziation zum HTX- / LVAD-freien Überleben (**Abbildung 12**).

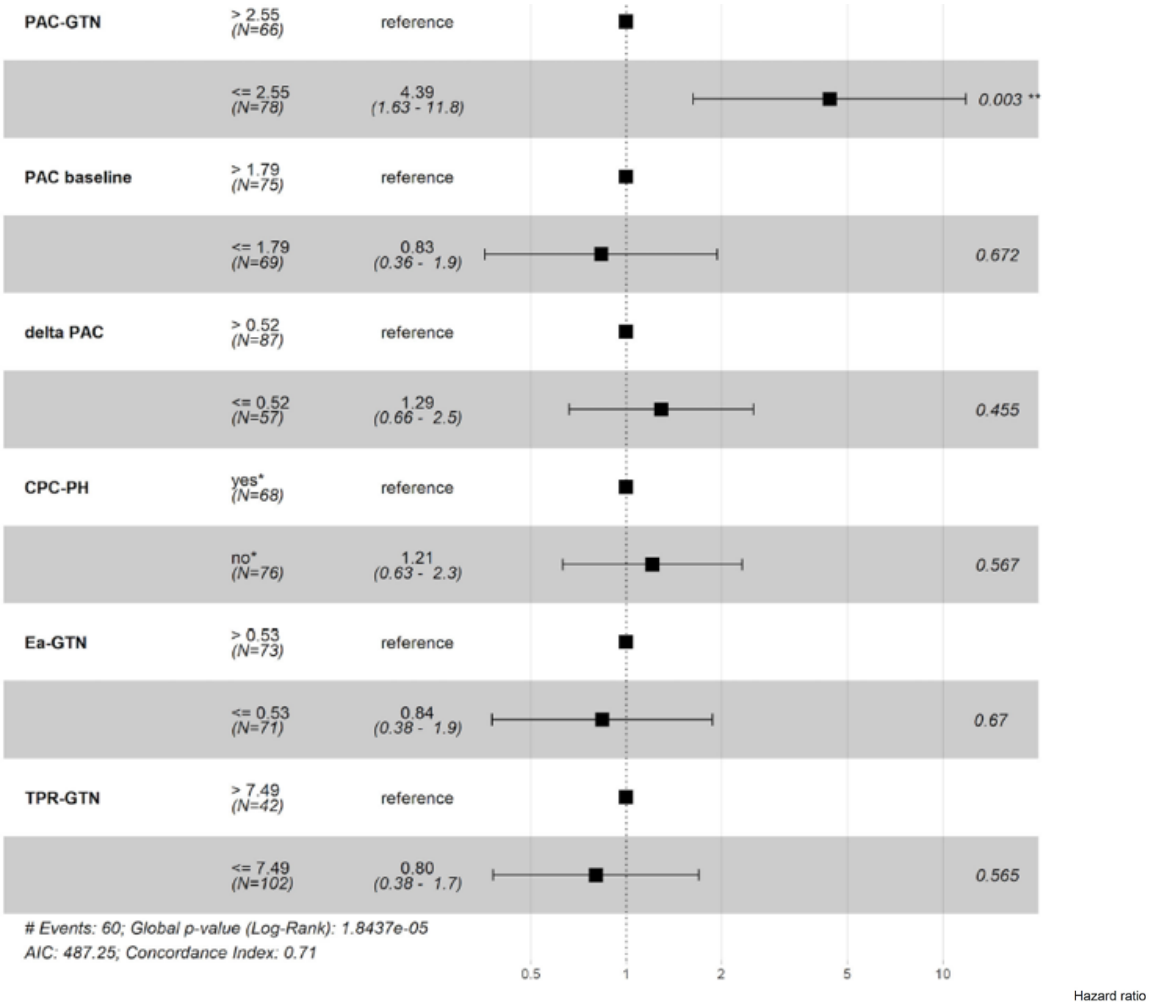


Abbildung 12: Forest Plot-Darstellung des Einflusses verschiedener hämodynamischer Parameter auf das Risiko, den Endpunkt Tod oder Herztransplantation oder Implantation eines Linksherzunterstützungssystems zu erreichen (multivariable Analyse).

PAC, pulmonalarterielle Compliance; Cpc-PH, kombiniert post- und präkapilläre pulmonale Hypertonie („yes“, wenn pulmonalvaskulärer Widerstand > 3 Wood-Einheiten und / oder diastolischer Druckgradient ≥ 7 mmHg); GTN, Glyceroltrinitrat; Ea, berechnete pulmonalarterielle Elastanz; TPR, totaler pulmonaler Widerstand.

Basierend auf diesen Ergebnissen wurden weitere Berechnungen durchgeführt. PAC-GTN war in der Lage, die AUC der ROC-Analyse der MAGGIC-Score-Variablen zur Vorhersage einer ungünstigen Prognose zu verbessern (**Abbildung 13**). Es bestand kein signifikanter Zusammenhang zwischen PAC-GTN / Δ PAC und der verabreichten GTN-Dosis.

Eine Kaplan-Meier-Überlebensanalyse bestätigte den Vorhersagewert von PAC-GTN; zwar zeigten sich das Vorhandensein einer Cpc-PH und die PAC vor VRT ebenfalls mit dem Überleben assoziiert, PAC-GTN war aber von überlegenem Vorhersagewert (**Abbildung 14**).

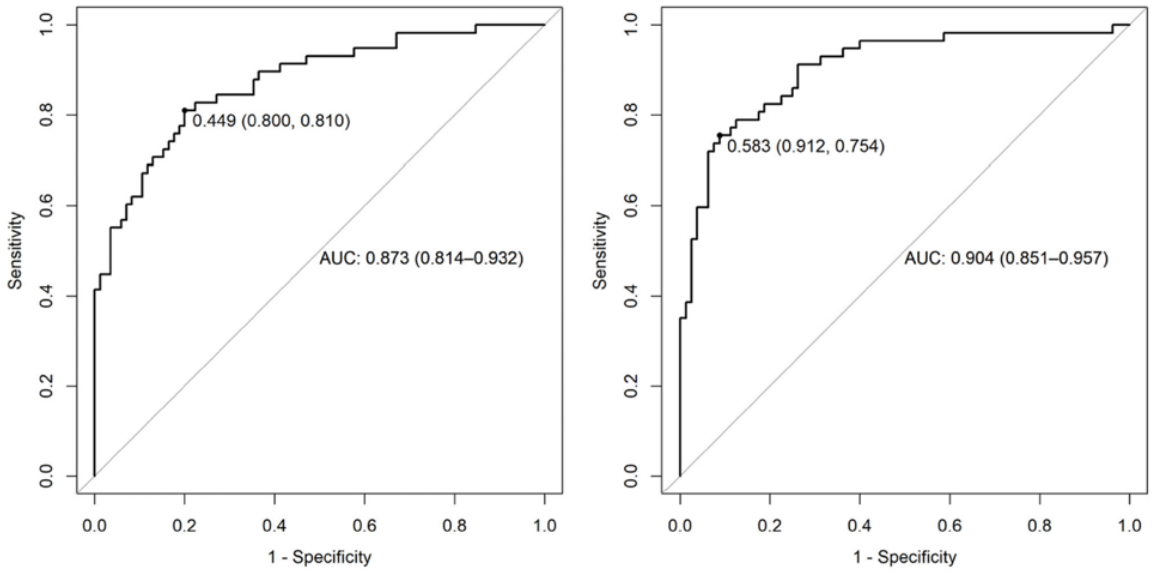


Abbildung 13: AUC (Fläche unter der Kurve) der ROC-Analyse (Flächenoptimierungskurve) für die Vorhersage des Herztransplantations- und Linksherzunterstützungssystem-freien Überlebens.

Links:Variablen des MAGGIC-Scores; rechts: Variablen des MAGGIC-Scores + PAC-GTN

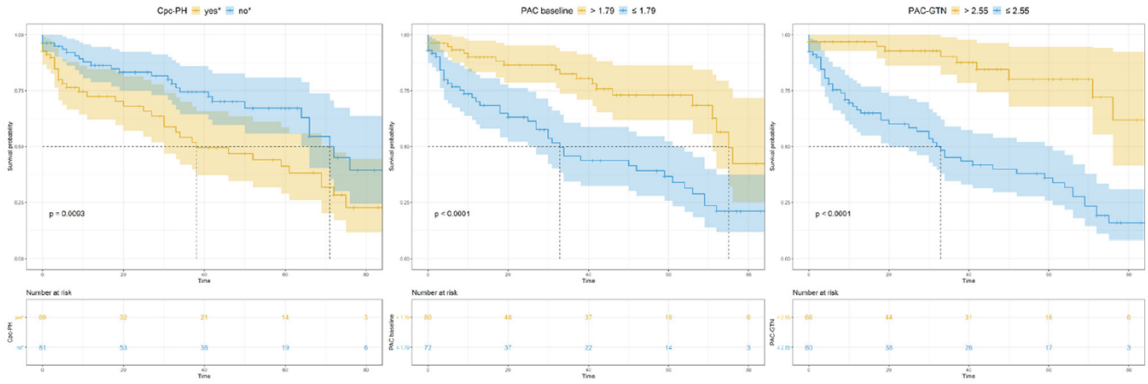


Abbildung 14: Kaplan-Meier Analyse der Schlüsselvariablen Cpc-PH, PAC vor (baseline) und nach (PAC-GTN) Verabreichung von GTN.

Cpc-Cpc-PH, kombiniert post- und präkapilläre pulmonale Hypertonie („yes“, wenn pulmonalvaskulärer Widerstand > 3 Wood-Einheiten und / oder diastolischer Druckgradient ≥ 7 mmHg); PAC, pulmonalarterielle Compliance; GTN, Glyceroltrinitrat.

Interessanterweise wirkte sich die GTN-Gabe stärker auf die so genannte oszillatorische Nachlast des RV als auf den PVR (entsprechend der stetigen RV-Nachlast) aus. Um ein Bild davon zu gewinnen, ob eine Klassifizierung entsprechend unseres PAC-GTN-Grenzwerts anstelle des Vorhandenseins einer Cpc-PH zu einer praxisrelevanten Änderung in der prognostischen Einschätzung führen würde, führten wir eine Reklassifikationsanalyse durch. Letztendlich würde sich hierdurch für 25 % der untersuchten Patienten die prognostische Aussage ändern (9% von Hoch- zu Niedrigrisiko, 16% umgekehrt).

Schlussfolgerung

Hämodynamische Messungen nach Durchführung eines „Entlastungstests“ unter Nutzung von GTN könnte das Ausmaß einer strukturellen pulmonalen Gefäßerkrankung besser als „native“ Messungen zur Darstellung bringen. Bei Patienten mit postkapillärer PH bei LHI könnte ein GTN-Test den prognostischen Wert des Parameters PAC verbessern (**Abbildung 15**), was in prospektiven Studien weiter untersucht werden sollte. Unklar ist derzeit, welche therapeutischen Maßnahmen bei den derart identifizierten Hochrisikopatienten eingesetzt werden könnten, um ihre Prognose zu verbessern.

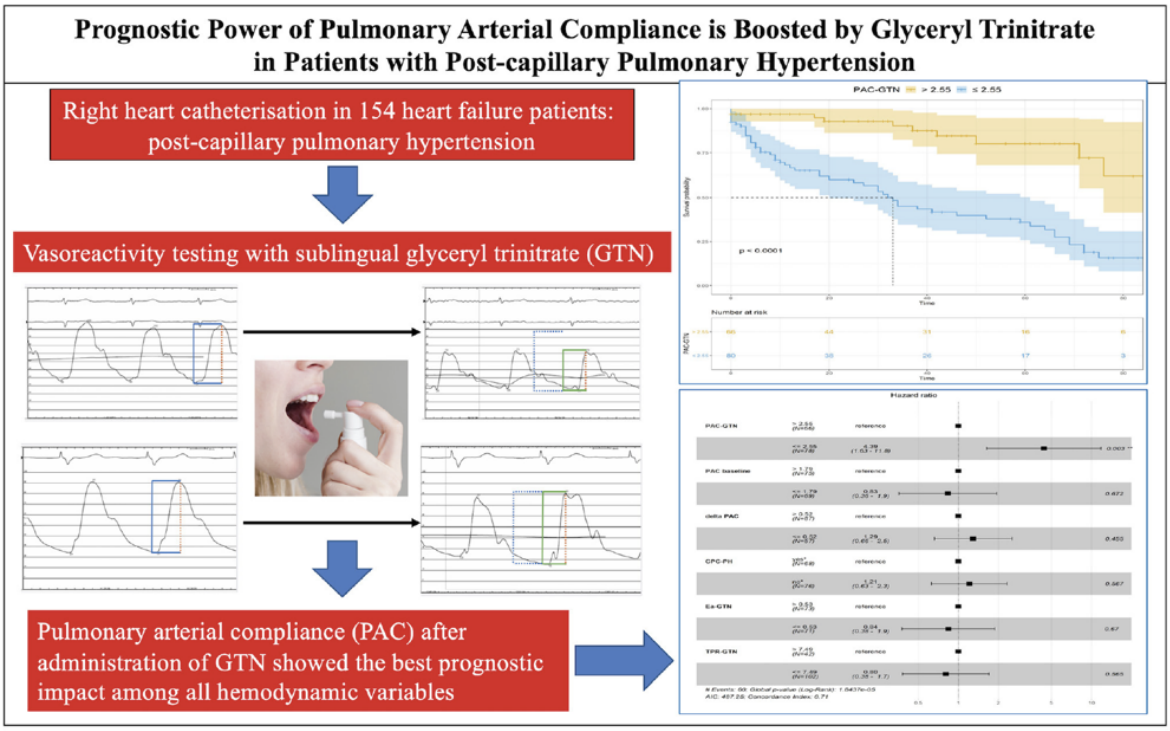


Abbildung 15: graphisches Abstract.

4.2. Hämodynamische Provokationstests zur Evaluierung einer interventionellen Therapie von Patienten mit Herz- und Mitralinsuffizienz

4.2.1. Das hämodynamische Profil unter Belastung erlaubt prognostische Aussagen bei Patienten, die mittels perkutaner Mitralklappenintervention behandelt werden

(Publikation 5: Exercise Hemodynamic Profiling Is Associated With Outcome in Patients Undergoing Percutaneous Mitral Valve Repair. Circ Cardiovasc Interv. 2021)

Die Identifikation von Patienten mit schwerer sekundärer Mitralinsuffizienz (MI), die längerfristig von einer perkutanen Klappenreparatur (percutaneous mitral valve repair, PMVR) profitieren werden, ist komplex. Zwei aktuelle Studien (MITRA-FR[142] und COAPT[143]) haben gezeigt, dass der Kandidatenselektion eine entscheidende Rolle zukommt: Tod und fortgesetzte Symptome der Herzinsuffizienz betrafen etwa ein Drittel bis die Hälfte der mittels PMVR behandelten Patienten in der Einjahresnachverfolgung.[47] Registerdaten bezüglich Patienten mit primärer MI zeigen ein ähnliches Bild.[144, 145] Die postinterventionellen Ergebnisse nach PMVR zeigen insgesamt eine so große Heterogenität, dass Optimierungsbedarf bezüglich der Auswahlkriterien besteht.[146, 147]

Bislang beruht die Indikation zum PMVR hauptsächlich auf echokardiographischen Kriterien in Kombination mit klinischen Befunden.[148] Die zusätzliche Berücksichtigung hämodynamischer Daten aus einem Rechtsherzkatheter mit Belastung (B-RHK) erscheint vielversprechend, da der PAWP durch retrograde Transmission Rückschlüsse auf die Druckverhältnisse im linken Vorhof zulässt.[149, 150] Durch einen B-RHK können nicht nur Informationen zu den hämodynamischen Auswirkungen einer MI gewonnen werden, sondern auch zum Schweregrad einer Herzinsuffizienz.[21, 96] Dies könnte von besonderer Bedeutung für die Identifikation von Patienten mit optimaler Nutzen-Risiko-Konstellation sein, was ein wesentlicher Faktor für die Vermeidung nutzloser PMVR-Interventionen bei Hochrisikopatienten ist.

Ziel dieser Studie war es daher, einerseits neue Parameter zur Diagnose einer hämodynamisch schweren MI mit fundierter Indikation zum PMVR aus dem B-RHK abzuleiten, und andererseits Hochrisikopatienten zu identifizieren, die aufgrund ihrer schweren HI nicht von dem Eingriff profitieren würden.

Wir führten ein Screening bei Patienten des Kerckhoff-Klinik Herzinsuffizienzregisters retrospektiv durch, die zur Evaluierung einer MI mittels B-RHK präinterventionell untersucht

worden waren. Diejenigen, die danach aufgrund einer Herzteam-Entscheidung mittels PMVR behandelt wurden, wurden in die Studie eingeschlossen, wenn der RHK mit kompletten Daten innerhalb von 6 Monaten vor dem Eingriff durchgeführt worden war und Nachverfolgungsdaten einschließlich Vitalstatus vorlagen. Zudem musste der PMVR erfolgreich durchgeführt worden sein (Reduktion des MI-Schweregrades um ≥ 1 Grad), da ein erfolgreicher Eingriff für die Beurteilung einer adäquaten Indikationsstellung Voraussetzung ist.

Die echokardiographische Einteilung des MI-Schweregrades erfolgte primär nach den geltenden Leitlinien in leicht-, mittel- und schwergradig;[148, 151] allerdings ist eine Einteilung in 4 Schweregrade (zusätzlich mittel-bis-schwergradig, III) im Kontext eines PMVR üblich,[143] so dass im Wesentlichen diese Graduierung (in römischen Ziffern angegeben) verwendet wurde. Die MI wurde bei normaler LVEF als primär klassifiziert, und bei < 55% reduzierter LVEF als sekundär oder gemischt.

Der B-RHK wurde nach Standard[96, 152] durchgeführt, wobei die Druckregistrierung über 3-5 Zyklen gemittelt und vor Verwendung auf Plausibilität überprüft wurde. Um den Faktor Gebrechlichkeit abzubilden, wurde ein modifizierter Gebrechlichkeitsindex[153] berechnet. Hierzu waren von ursprünglich 40 genannten Defiziten 16 aus den Krankenakten unserer Patienten verfügbar (beziehungsweise 15, wenn eine aktuelle Lungenfunktionsprüfung nicht vorhanden war). Der Gebrechlichkeitsindex (frailty index, FI) besteht aus dem Verhältnis der vorhandenen Defizite zu den abgefragten; die Gebrechlichkeit steigt also, je mehr sich der Index dem Wert 1,0 nähert.

Der primäre Endpunkt wurde gemäß Empfehlung des Mitralklappen-Forschungskonsortiums als Gesamtsterblichkeit jeder Ursache nach PMVR festgelegt.[154] Sekundärer Endpunkt war der klinische Erfolg der Intervention, definiert als Verbesserung des NYHA-Stadiums um mindestens eine Stufe innerhalb von 12 Monaten nach PMVR (wobei Tod innerhalb dieses Zeitraums als ausbleibende Besserung gewertet wurde).

Die Analyse beinhaltete 68 Patienten mit MI Grad III und IV, davon 65% mit sekundärer Genese. Die Patienten der letztgenannten Gruppe hatten deutlich erhöhte NT-proBNP-Werte, waren zu einem hohen Prozentsatz im NYHA-Stadium III und zeigten eine eingeschränkte LVEF, erhöhte PAWP-Werte und ein reduziertes Herzzeitvolumen sowie mehrere Komorbiditäten. Diese Subgruppe entsprach damit von den echokardiographischen und klinischen Merkmalen her weitgehend den Patienten, die in die COAPT-Studie eingeschlossen wurden.[143] Einen mPAP > 24 mmHg hatten 74% der Patienten, und 47% einen PVR > 3 WU

als Ausdruck einer fortgeschrittenen pulmonalvaskulären Schädigung. Alle Patienten erhielten eine leitliniengerechte Medikation.

Innerhalb der medianen Nachverfolgungszeit von 19 [9-32] Monaten, verstarben 32% der Patienten. Mehrere hämodynamische Parameter unter Belastung zeigten sich in der Cox-Regressionsanalyse mit der Gesamtsterblichkeit assoziiert (**Abbildung 16**).

Derjenige Einzelparameter mit der größten AUC in der ROC-Analyse war der Anstieg der V-Welle der PAWP-Druckkurve unter Belastung (ΔV-Welle) mit einem Risikoquotienten (Hazard Ratio, HR), von 0,91 [0,87–0,96], p<0,001; AUC 0,79 [0,67–0,92]. Für den mittels Youden-Index kalkulierten ΔV-Welle-Grenzwert von ≥ 17 mmHg zeigte sich ein signifikant reduziertes Sterberisiko (HR 0,11 [0,04–0,33], p<0,001), was durch eine Kaplan-Meier-Analyse bestätigt wurde (**Abbildung 17 A**).

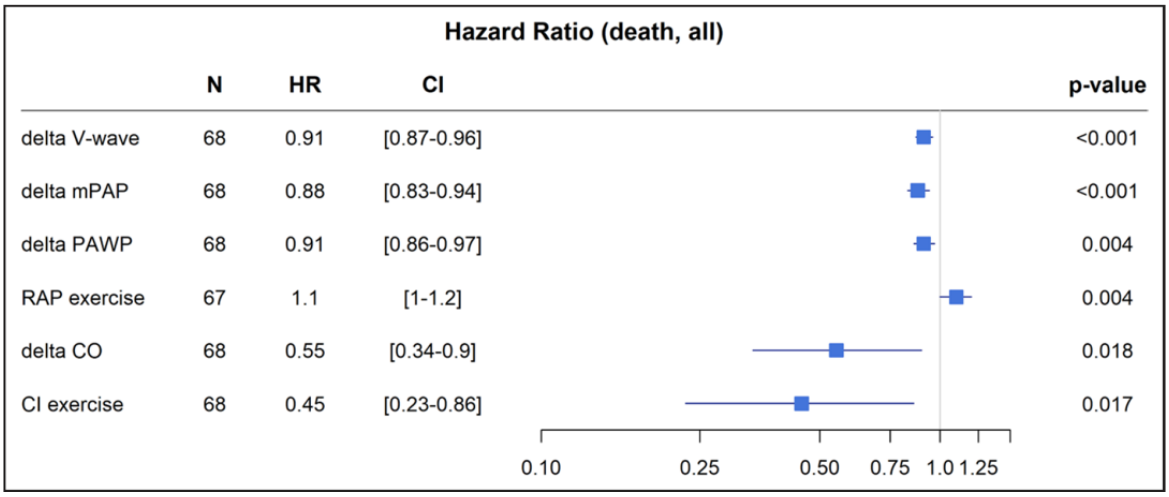


Abbildung 16: Vergleich der univariaten Risikoquotienten (Hazard Ratio) für Gesamtsterblichkeit der signifikanten belastungshämodynamischen Parameter in der Gesamtgruppe (Cox Regression).

CI, Herzindex (l/min/m^2); CO, Herzzeitvolumen (l/min); delta, Anstieg unter Belastung; mPAP, mittlerer Pulmonalarteriendruck; PAWP, pulmonalarterieller Okklusionsdruck; RAP, rechtsatrialer Druck.

In einer multivariaten Analyse zeigte ΔV-Welle eine von Alter, Gebrechlichkeitsindex und Belastungsstufe des B-RHK unabhängige Signifikanz. Weiterhin zeigte sich eine Unabhängigkeit vom MI-Schweregrad (III oder IV) vor PMVR und vom Druckgradienten sowie vom Ausmaß einer residualen MI bei der echokardiographischen Nachkontrolle. Eine Untersuchung in der Subgruppe mit sekundärer MI zeigte vergleichbare Ergebnisse (**Abbildung 17 B**).

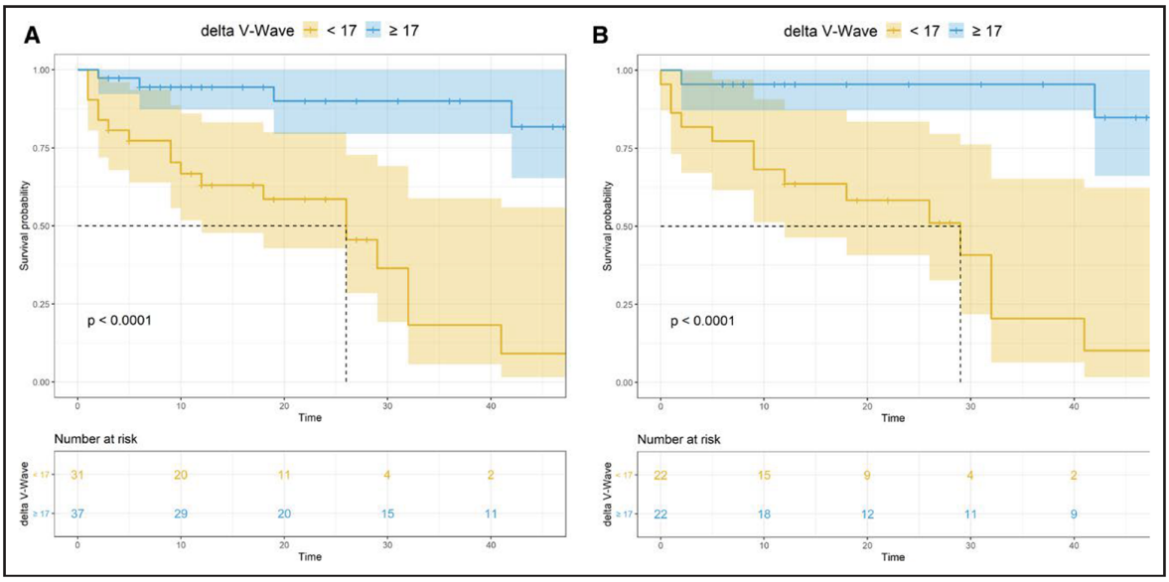


Abbildung 17: Kaplan-Meier Überlebenskurven als Funktion des hämodynamischen Profils basierend auf ΔV-Welle, dichotomisiert nach einem Grenzwert, der aus einer ROC-Analyse abgeleitet wurde (Zeitachse bei 48 Monaten gekürzt).

A, alle Patienten; **B**, nur Patienten mit sekundärer Mitralinsuffizienz.

Bezüglich der NYHA- Klasse nach PMVR fand sich eine Besserung bei 54%, und auch hier war ΔV-Welle – bei primärer und sekundärer MI gleichermaßen - mit dem Endpunkt assoziiert (OR 1,14 [1,07–1,24], p<0,001; AUC 0,84 [0,74–0,95]). Die Patienten wurden nach einem errechneten Grenzwert von ≥ 15 mmHg für ΔV-Welle aufgeteilt und der Anteil derer mit oder ohne Verbesserung der NYHA-Klasse nach PMVR dargestellt (**Abbildung 18**). Die Verteilung der NYHA-Klassen vor und nach PMVR zeigte Folgendes: 79% der Patienten mit ΔV-Welle ≥ 15 mmHg waren danach gebessert in NYHA-Klasse I und II, bei < 15 mmHg waren es nur 28% (**Abbildung 19**).

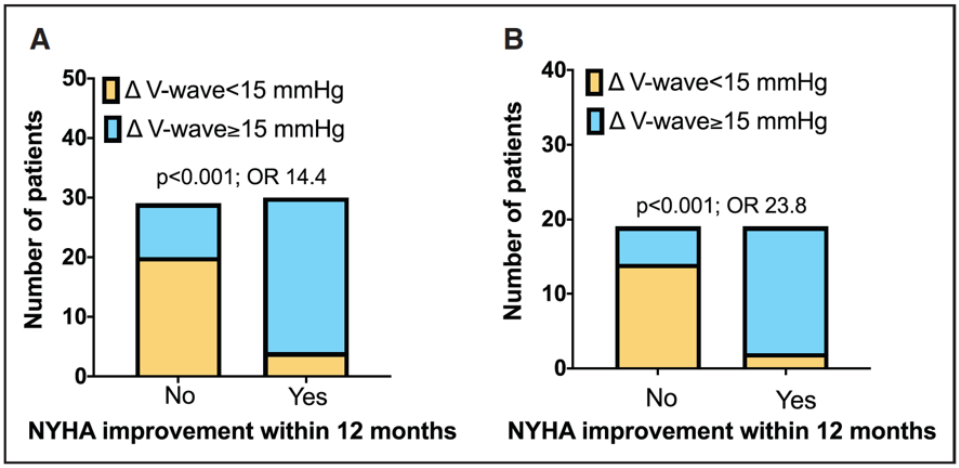


Abbildung 18: Patienten mit (Yes) oder ohne (No) Verbesserung der NYHA-Klasse innerhalb von 12 Monaten (Tod in diesem Zeitraum = No), aufgeteilt nach ΔV-Welle-Grenzwert aus einer ROC-Analyse.

A, alle Patienten; **B**, nur Patienten mit sekundärer Mitralinsuffizienz.

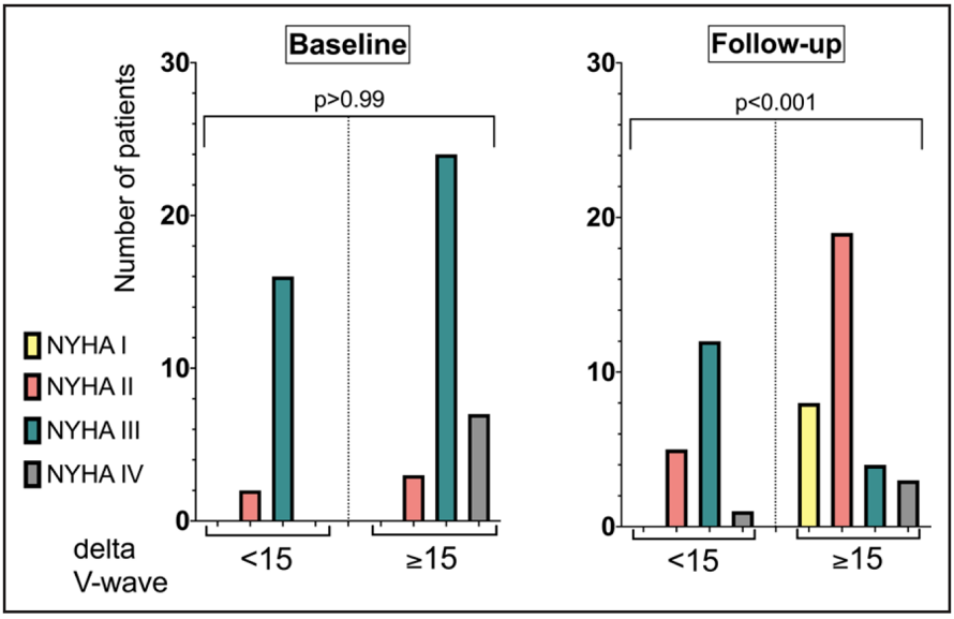


Abbildung 19: Verteilung der NYHA-Klassen (n=52) vor und nach Mitralklappenintervention, aufgeteilt nach ΔV-Welle-Grenzwert aus einer ROC-Analyse.

Außer den Druckparametern war auch der Anstieg des Herzzeitvolumens (ΔCO) mit einer NYHA-Verbesserung assoziiert (**Abbildung 20**).

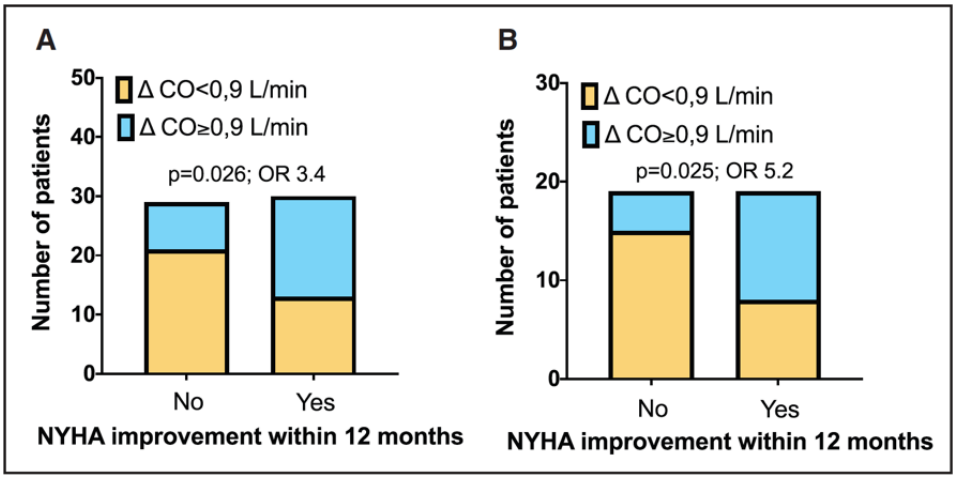


Abbildung 20: Patienten mit (Yes) oder ohne (No) Verbesserung der NYHA-Klasse innerhalb von 12 Monaten (Tod in diesem Zeitraum = No), aufgeteilt nach ΔCO (Herzzeitvolumen)-Grenzwert aus einer ROC-Analyse.

A, alle Patienten; **B**, nur Patienten mit sekundärer Mitralinsuffizienz.

Schlussfolgerung

Unser belastungshämodynamischer Ansatz könnte als Hilfe zur Entscheidungsfindung für oder gegen eine Intervention in unklaren Fällen bei Patienten mit mittelschwerer bis schwerer MI dienen. Wir schlagen ein Konzept vor, das ausgewählte Parameter der Belastungshämodynamik mitberücksichtigt (**Abbildung 21**). Vor einer systematischen Aufnahme in den

Evaluierungsprozess sind aber weitere, prospektive Untersuchungen mit größeren Patientenzahlen notwendig.

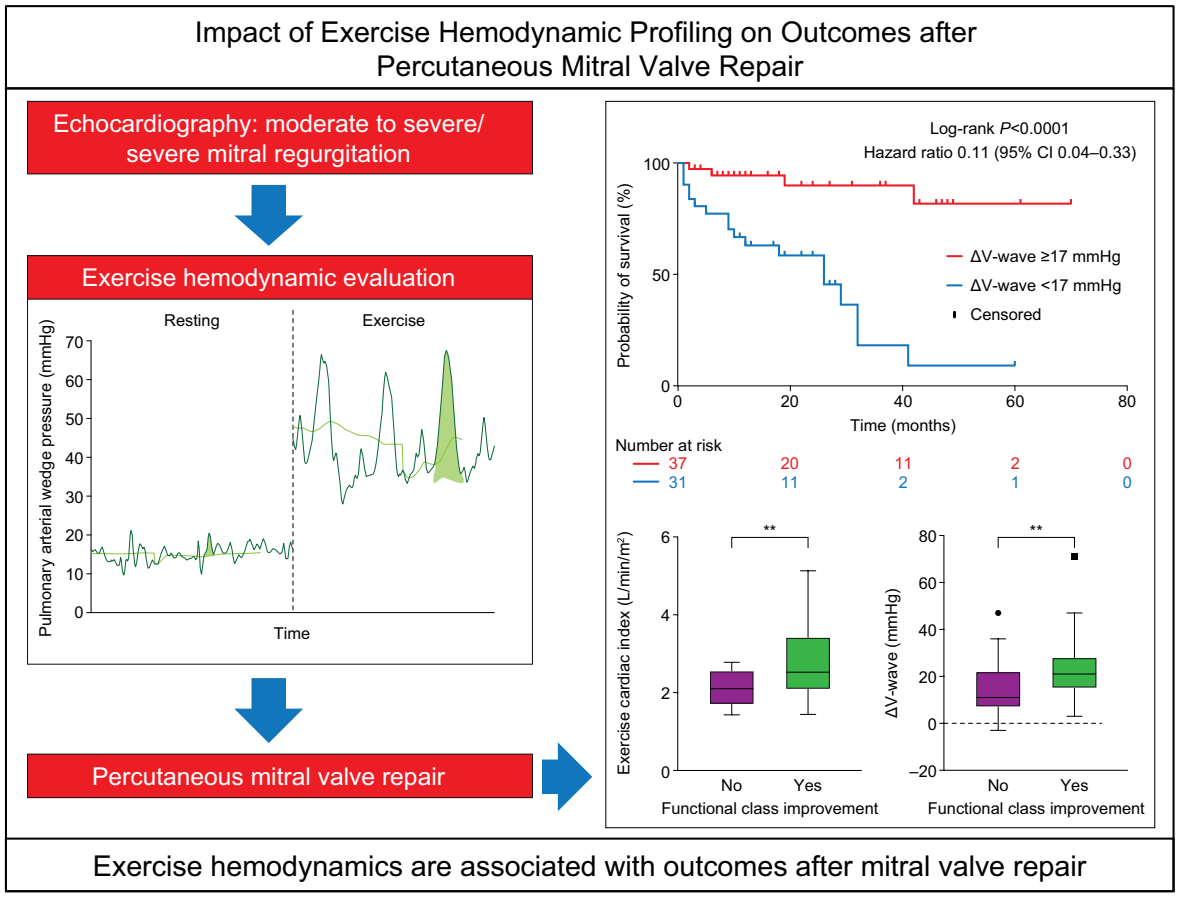


Abbildung 21: graphisches Abstract.

4.3. Hämodynamische Risikostratifizierung von Patienten mit Herzinsuffizienz und geplanter Herztransplantation

4.3.1. Hämodynamische Indizes einer pulmonalen Vaskulopathie zur Vorhersage eines frühen Rechtsherzversagens und der Sterblichkeit nach Herztransplantation

(Publikation 6: Hemodynamic markers of pulmonary vasculopathy for prediction of early right heart failure and mortality after heart transplantation. J Heart Lung Transplant. 2022)

Die Einjahres-Sterblichkeit nach einer HTX ist mit vielen Einflussfaktoren auf der Empfängerseite vergesellschaftet, einschließlich einer PH, definiert über den mPAP und den

PVR.[155] Aus diesem Grund soll gemäß den Empfehlungen der „International Society for Heart and Lung Transplantation“ (ISHLT) von 2016 bei allen Kandidaten in Vorbereitung einer HTX ein RHK initial durchgeführt und danach jährlich wiederholt werden. Liegen bestimmte Kriterien vor (systolischer PAP ≥ 50 mmHg und entweder transpulmonaler Gradient (TPG) ≥ 15 mmHg oder PVR ≥ 3 WU), dann wird die Durchführung einer VRT empfohlen; werden hierbei die genannten Grenzwerte nicht unterschritten, dann soll eine intensivierte medikamentöse Therapie erfolgen und bei deren Misserfolg die Behandlung mit einem Linksherzunterstützungssystem erwogen werden. Als Ziel wird in den Empfehlungen eine „akzeptable Hämodynamik“ genannt, ohne dass diese näher definiert wird.[23]

Dies könnte daran liegen, dass die Datenlage zur Bedeutung des PVR und seines Grenzwerts von 3 WU für die Sterblichkeit nach HTX uneinheitlich ist.[156-163] Weiterhin ist unklar, welche Bedeutung ein Rechtsherzversagen nach HTX als Folge einer „kritischen“ PH des Empfängers in der heutigen Zeit der strengen Empfängerselektion aufgrund des Organmangels noch hat.[155]

In dieser Studie wollten wir herausfinden, wie häufig es in einer zeitgemäßen Kohorte von Patienten nach HTX zu einem Rechtsherzversagen kommt und wie dieses sich auf die Mortalität auswirkt. Weiterhin sollte der übliche PVR-Grenzwert von 3 WU auf seine Relevanz für das Überleben nach HTX hin überprüft und mit einem niedrigeren Grenzwert[164, 165] sowie komplexeren hämodynamischen Parametern[42] verglichen werden.

Wir führten eine retrospektive, multizentrische Analyse von HTX-Patienten aus sieben deutschen Zentren durch, die zwischen 2011 und 2015 transplantiert worden waren, mit einem RHK innerhalb von 365 Tagen vor HTX und mit einer Nachverfolgungszeit von mindestens 12 Monaten. Neben den hämodynamischen Daten (**Tabelle 7**) und nach publizierten Formeln errechneten Indices[12, 39, 45, 103, 104, 106, 166, 167] sowie deren Werte nach einem VRT (sofern durchgeführt) wurden auch viele weitere relevante Empfängervariablen erhoben.[163, 168]

Weiterhin wurden Spenderdaten von der Eurotransplant-Datenbank angefordert, um die errechnete rechtsseitige Herzmasse von Spender und Empfänger vergleichen und ein signifikantes Größenmissverhältnis (≥ 30% Differenz) erfassen zu können.[169, 170]

Der primäre Endpunkt wurde als Gesamtsterblichkeit jeder Ursache nach der HTX festgelegt. Sekundäre Endpunkte waren die 12-Monatssterblichkeit und ein postoperatives Rechtsherz-versagen nach INTERMACS-Definition.[171]

In die Analyse flossen letztlich Daten von 333 Patienten ein, von denen 28% Frauen waren und deren medianes Alter 54 Jahre betrug. Der RHK wurde im Median 52 [Interquartilsabstand 26–129] Tage vor der HTX durchgeführt; zum Zeitpunkt des RHK waren 13,5% mit einem LVAD behandelt, und 44,7% standen unter Katecholamintherapie oder Levosimendan.

Parameter	all (n=333)	Ea missing value (n=81)	Ea ≤1.45 mmHg/mL (n=218)	Ea >1.45 mmHg/mL (n=34)	P value*
Ea (mmHg/mL), median [IQR]	0.87 [0.55–1.23]	n. a.	0.79 [0.49–1.06]	1.68 [1.57–1.96]	< 0.0001 [a]
SAP (mmHg), median [IQR]	100.00 [90.00–110.00]	106.00 [93.50–113.00]	100.00 [90.00–110.00]	100.00 [90.00–106.00]	0.5 [a]
MAP (mmHg), median [IQR]	77.00 [70.00–85.00]	80.00 [73.00–85.75]	75.50 [70.00–85.00]	75.00 [68.50–81.00]	0.6 [a]
HR (beats per minute), median [IQR]	73.00 [67.00–84.00]	62.00 [52.00–85.00]	72.00 [66.00–80.00]	90.00 [73.25–98.75]	< 0.0001 [a]
sPAP (mmHg), median [IQR]	45.00 [34.00–55.00]	45.00 [34.50–56.00]	41.00 [32.00–52.00]	58.00 [50.00–60.00]	< 0.0001 [a]
dPAP (mmHg), median [IQR]	22.00 [16.00–28.00]	21.00 [16.00–28.00]	20.00 [15.00–26.00]	30.00 [29.00–34.00]	< 0.0001 [a]
PP (mmHg), median [IQR]	22.00 [17.00–29.00]	24.00 [16.00–29.00]	21.00 [16.00–28.00]	26.00 [20.00–30.00]	0.02 [a]
mPAP (mmHg), median [IQR]	30.00 [23.00–38.00]	31.00 [24.00–38.00]	28.50 [22.00–35.00]	41.00 [36.25–43.50]	< 0.0001 [a]
TPG (mmHg), median [IQR]	8.00 [5.00–10.50]	9.00 [5.75–12.25]	7.00 [5.00–10.00]	9.00 [6.00–12.00]	0.1 [a]
DPG (mmHg), median [IQR]	0.00 [-3.00–2.00]	-1.00 [-3.75–3.00]	0.00 [-3.00–2.00]	0.00 [-3.00–2.50]	0.9 [a]
PVR (WU), median [IQR]	2.11 [1.47–2.89]	2.48 [1.51–3.18]	2.00 [1.41–2.68]	2.83 [2.14–4.46]	< 0.0001 [a]
PVRI (WU*m^2), median [IQR]	3.95 [2.92–5.63]	4.14 [2.86–6.08]	3.75 [2.82–5.12]	5.33 [3.91–8.17]	0.0002 [a]
TPR (WU), median [IQR]	8.60 [5.86–11.14]	8.87 [6.17–11.41]	7.80 [5.24–10.03]	13.86 [12.44–16.05]	< 0.0001 [a]
RAP (mmHg), median [IQR]	12.00 [7.00–15.00]	12.00 [8.00–17.75]	10.00 [7.00–15.00]	15.00 [11.00–15.00]	0.007 [a]
PAWP (mmHg), median [IQR]	23.50 [16.00–28.00]	23.50 [15.00–28.00]	22.00 [15.00–27.00]	30.00 [28.00–33.00]	< 0.0001 [a]
RAP/PAWP (no unit), median [IQR]	0.50 [0.36–0.67]	0.60 [0.37–0.74]	0.50 [0.38–0.65]	0.44 [0.34–0.50]	0.02 [a]
CO (l/min), median [IQR]	3.60 [3.12–4.22]	3.65 [3.00–4.44]	3.77 [3.30–4.34]	2.80 [2.43–3.10]	< 0.0001 [a]
SV (ml), median [IQR]	50.03 [40.19–59.88]	n. a.	52.52 [43.32–61.47]	33.60 [24.91–38.16]	< 0.0001 [a]
SVI (g*m/m^2), median [IQR]	25.78 [21.84–30.63]	n. a.	26.82 [23.61–32.30]	19.02 [13.85–22.20]	< 0.0001 [a]
RVSWI (g*m/m^2), median [IQR]	7.43 [4.87–9.31]	n. a.	7.50 [4.87–9.31]	6.79 [4.82–8.97]	0.8 [a]
CI (l/min/m^2), median [IQR]	1.91 [1.70–2.18]	1.90 [1.65–2.17]	2.00 [1.74–2.20]	1.50 [1.33–1.88]	< 0.0001 [a]
CPO (W), median [IQR]	0.62 [0.50–0.76]	0.64 [0.50–0.80]	0.64 [0.52–0.76]	0.43 [0.40–0.53]	< 0.0001 [a]
CPI (W/m^2), median [IQR]	0.32 [0.27–0.39]	0.35 [0.28–0.41]	0.33 [0.28–0.39]	0.25 [0.19–0.35]	0.0002 [a]
PAPI (mmHg), median [IQR]	2.00 [1.39–3.14]	1.96 [1.32–3.38]	2.14 [1.47–3.06]	1.91 [1.40–2.25]	0.2 [a]
PAC (mL/mmHg), median [IQR]	2.13 [1.68–3.14]	n. a.	2.43 [1.79–3.44]	1.28 [1.08–1.64]	< 0.0001 [a]
Total RV power (W), median [IQR]	0.31 [0.25–0.39]	0.32 [0.27–0.43]	0.31 [0.24–0.39]	0.32 [0.27–0.37]	0.7 [a]
Oscillatory RV load (W), median [IQR]	0.07 [0.06–0.09]	0.07 [0.06–0.10]	0.07 [0.05–0.09]	0.07 [0.06–0.09]	0.7 [a]
RC-time (s), median [IQR]	0.29 [0.22–0.37]	n. a.	0.30 [0.22–0.37]	0.24 [0.19–0.31]	0.03 [a]

Tabelle 7: Hämodynamische Parameter aller Patienten (all) und aufgeteilt nach Ea-Werten (missing value = fehlender Wert).
Die Werte sind als Mediane mit [Interquartilsabstand] dargestellt. n.a., nicht verfügbar; Ea, berechnete pulmonal-arterielle Elastanz; SAP, systemischer arterieller Druck; MAP, mittlerer SAP; HR, Herzfrequenz; sPAP, systolischer pulmonalarterieller (PA)-Druck; dPAP, diastolischer PAP; PP, PA-Pulsdruck; mPAP, mittlerer PAP; TPG, transpulmonaler Gradient; DPG, diastolischer pulmonaler Druckgradient; PVR, pulmonalvaskulärer Widerstand; WU, Wood-Einheiten; TPR, totaler pulmonaler Widerstand; PAWP, PA Okklusionsdruck; RAP, rechtsatrialer Druck; CO, Herzzeitvolumen; CI, Herzindex; CPO, cardiac power output; CPI, CP-Index; SV, Schlagvolumen; SVI, SV-Index; RVSWI, rechtsventrikulärer Schlagarbeitsindex; PAPi, PA-Pulsatilitätsindex; PAC, PA Compliance; RV, rechter Ventrikel; RC, Widerstand und Compliance.

*Ea≤1.45 vs. Ea >1.45 mmHg/mL; [a]Mann-Whitney-U test

Bei 16,5% der Patienten lag nach aktueller Definition (mPAP < 21 mmHg) keine PH vor, und insgesamt zeigte sich der mPAP mit im Median 30 [23–38] mmHg nur moderat erhöht. Ebenso war der PVR mit 2,1 [1,5–2,9] WU bei den meisten Patienten unter dem Grenzwert von 3 WU. Ein signifikantes Größenmissverhältnis in Form eines zu kleinen Spenderherzens nach obiger Definition lag bei nur 5 Patienten vor. Die mediane Ischämiezeit betrug 240 [206–274] Minuten. Innerhalb der medianen Nachverfolgungszeit von 52 [16–74] Monaten verstarben 119 von 333 Patienten, und innerhalb von 12 Monaten 79. Ein postoperatives Rechtsherzversagen trat bei 76 Patienten (22,8%) auf, und dieses war signifikant mit der 12-Monats- und der Gesamtsterblichkeit assoziiert (**Abbildung 22**).

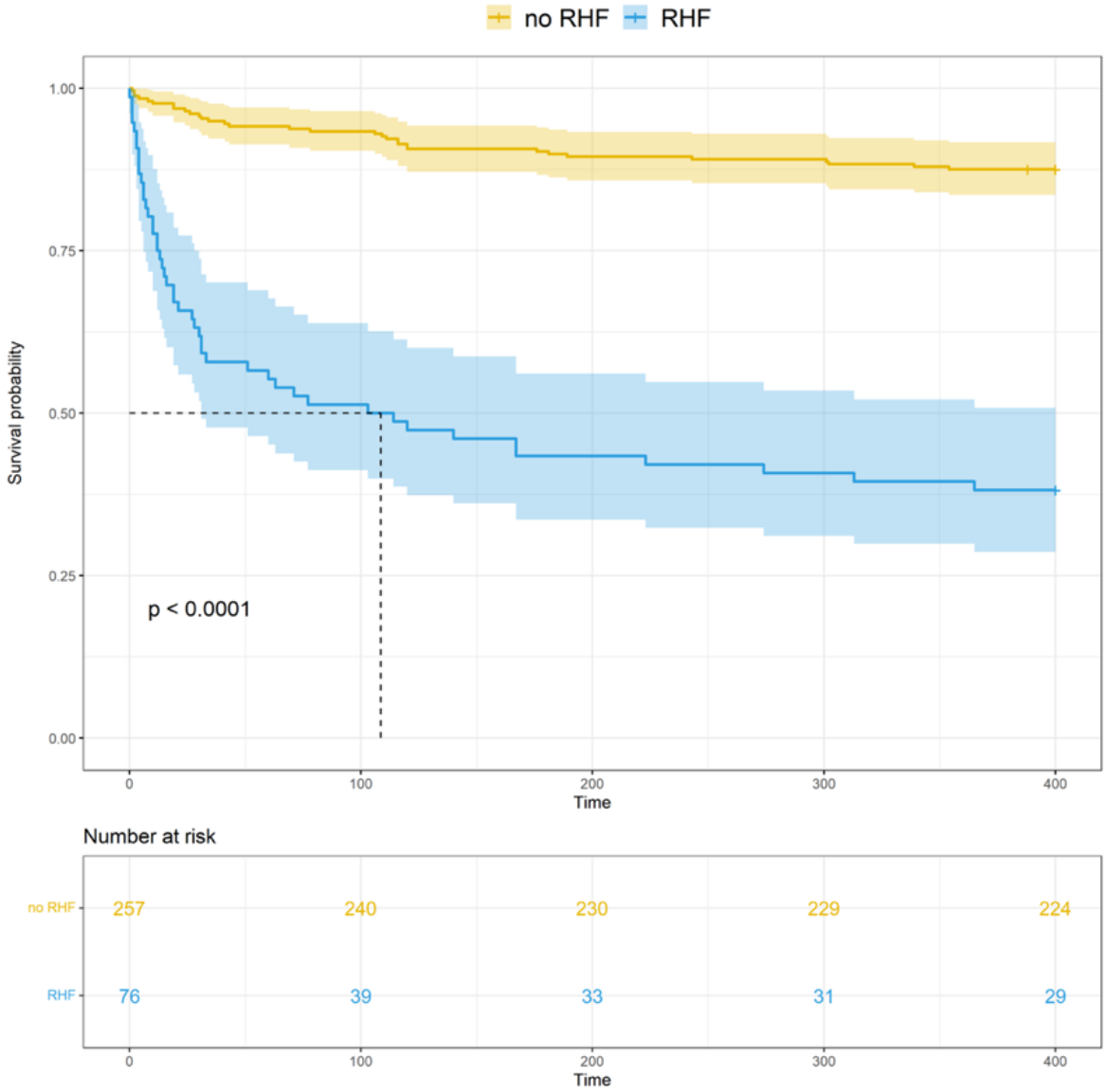


Abbildung 22: Kaplan-Meier-Analyse zum Einfluss eines Rechtsherzversagens (RHF) auf das Gesamtüberleben nach Herztransplantation.

Der primäre Endpunkt zeigte sich signifikant assoziiert mit folgenden nicht-hämodynamischen Faktoren: mechanische Kreislaufunterstützung zum Zeitpunkt der HTX, Infektionen mit intravenöser Therapie, Körperoberfläche, maschinelle Beatmung und Körpergröße. Nur die beiden letztgenannten waren in der multivariaten Analyse unabhängig mit der Gesamtsterblichkeit assoziiert. Die Einnahme einer gezielten Medikation zur Behandlung einer PH sowie das Ausmaß des Größenmissverhältnisses zwischen Spender- und Empfängerorgan waren nicht signifikant assoziiert.

Unter den hämodynamischen Variablen fanden sich die folgenden signifikant mit dem primären Endpunkt assoziiert: TPG, PVR, TPR und Ea, wobei letzteres den stärksten Risikofaktor darstellte (**Abbildung 23**). In der multivariaten Analyse von je einem der genannten hämodynamischen Faktoren mit allen univariat signifikanten nicht-hämodynamischen Faktoren waren nur TPR und Ea unabhängig mit der Gesamtsterblichkeit assoziiert. Ea wurde in weiteren multivariablen Modellen unter anderem mit Alter, Geschlecht, Nierenfunktion etc. sowie dem Vorhandensein einer mechanischen Kreislaufunterstützung und einer Katecholamintherapie getestet und zeigte sich jeweils als unabhängiger Risikofaktor.

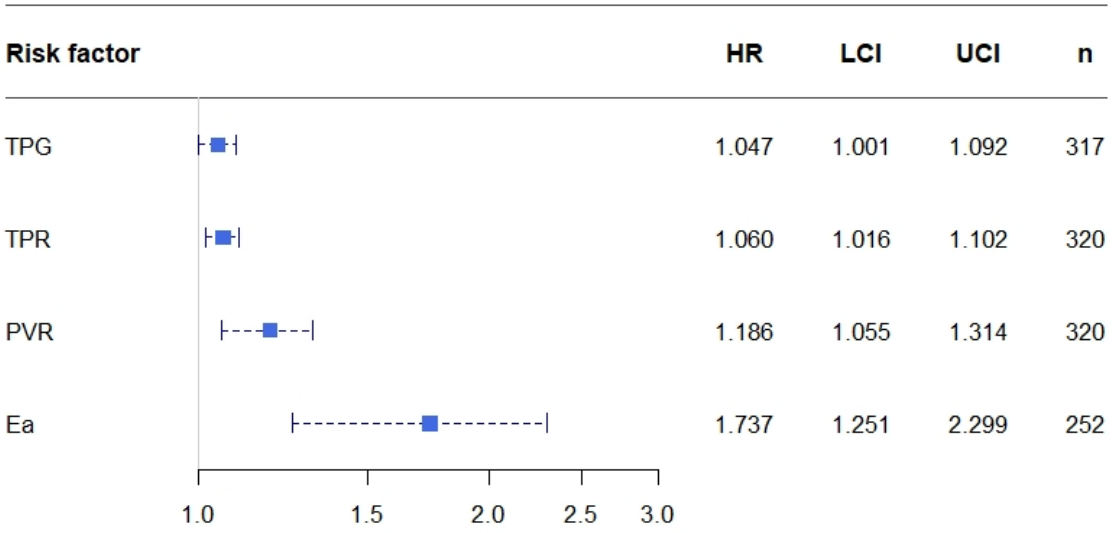


Abbildung 23: Forest Plot-Darstellung der univariaten Cox Regressionsanalyse von hämodynamischen Parametern und Gesamtsterblichkeit jeder Ursache nach Herztransplantation.

TPG, transpulmonaler Gradient; TPR, totaler pulmonaler Widerstand; PVR, pulmonalvaskulärer Widerstand; Ea, berechnete pulmonal-arterielle Elastanz; LCI / UCI, unteres / oberes Konfidenzintervall.

Schließlich wurde für Ea mittels ROC-Analyse ein Grenzwert berechnet und mittels Kaplan-Meier-Analyse auf unsere Kohorte angewendet (**Abbildung 24**). Ea-Werte unter dem Grenzwert von 1,45 mmHg/ml führten zu einem signifikant um 62% reduzierten Mortalitätsrisiko (log-rank HR 0,38, $p < 0{,}0001$). Wurde die Überlebensanalyse mit dem üblichen PVR-Grenzwert von ≤ 3 WU durchgeführt, dann ergab sich kein signifikantes

Ergebnis. Wenn hingegen ein kürzlich als relevant für Patienten mit PH diskutierter PVR-Grenzwert von < 2,2 WU[164] verwendet wurde, dann ergab sich ein knapp signifikantes Ergebnis (p = 0,04).

Eine VRT erhielten nur 21 Patienten, was angesichts der relativ niedrigen PA-Druck- und PVR-Werte nicht verwundert.

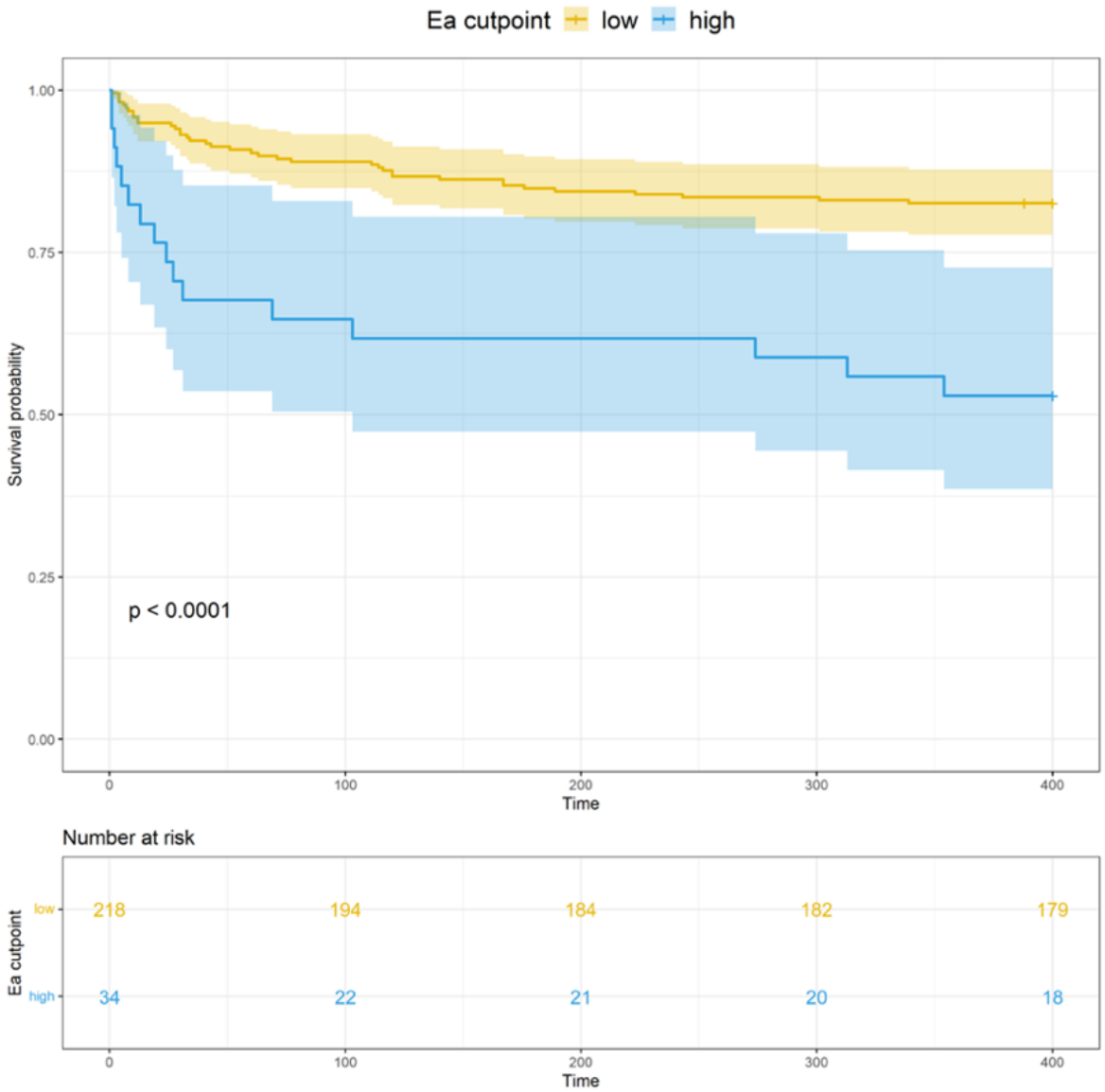


Abbildung 24: Kaplan-Meier-Analyse zum Einfluss der berechneten pulmonalarteriellen Elastanz (Ea) auf das Gesamtüberleben nach Herztransplantation.

Ea cutpoint low = Ea ≤ 1,45 mmHg/ml; Ea cutpoint high = Ea > 1,45 mmHg/ml.

Die Ergebnisse bezüglich der sekundären Endpunkte finden sich in den **Abbildungen 25** und **26**.

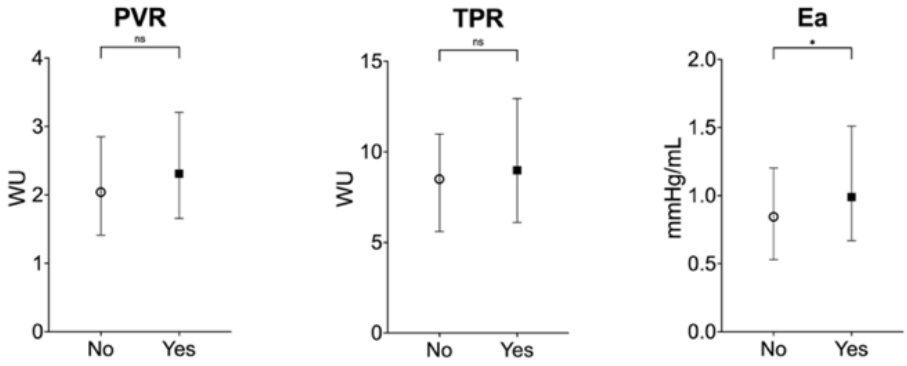


Abbildung 25: Hämodynamische Parameter aufgeteilt nach Vitalstatus 12 Monate nach Herztransplantation.

No = lebend nach 12 Monaten; Yes = verstorben nach 12 Monaten.
PVR, pulmonalvaskulärer Widerstand; TPR, totaler pulmonaler Widerstand; Ea, berechnete pulmonalarterielle Elastanz; ns, nicht signifikant; $^{*}p < 0.05$.

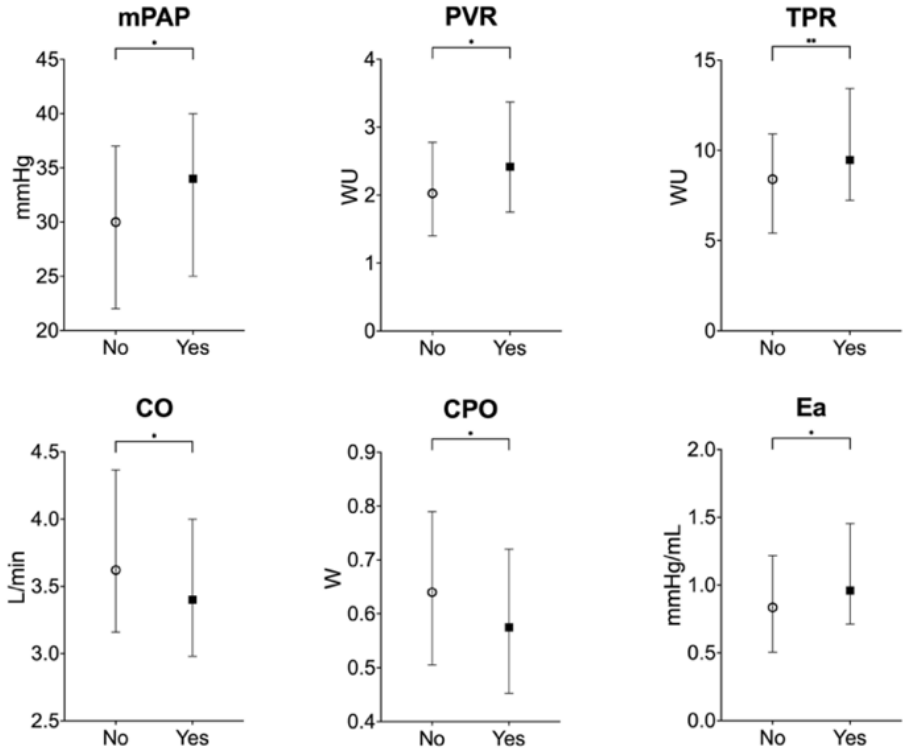


Abbildung 26: Hämodynamische Parameter aufgeteilt nach Vorhandensein eines Rechtsherzversagens nach Herztransplantation.

No = kein Rechtsherzversagen; Yes = Rechtsherzversagen.
mPAP, mittlerer pulmonalarterieller Druck; PVR, pulmonalvaskulärer Widerstand; TPR, totaler pulmonaler Widerstand; CO, Herzzeitvolumen; CPO, „cardiac power output" = (Herzzeitvolumen x arterieller Mitteldruck) / 451; Ea, berechnete pulmonalarterielle Elastanz; $^{*}p < 0,05$; $^{**}p<0,01$.

Die Kombination aus Rechtsherzversagen und Tod innerhalb von 12 Monaten nach HTX in verschiedenen hämodynamischen Subgruppen ist in **Abbildung 27** dargestellt; der höchste Anteil der Patienten, die diesen kombinierten Endpunkt erreichten, war in der Gruppe mit Ea > 1,45 mmHg/ml.

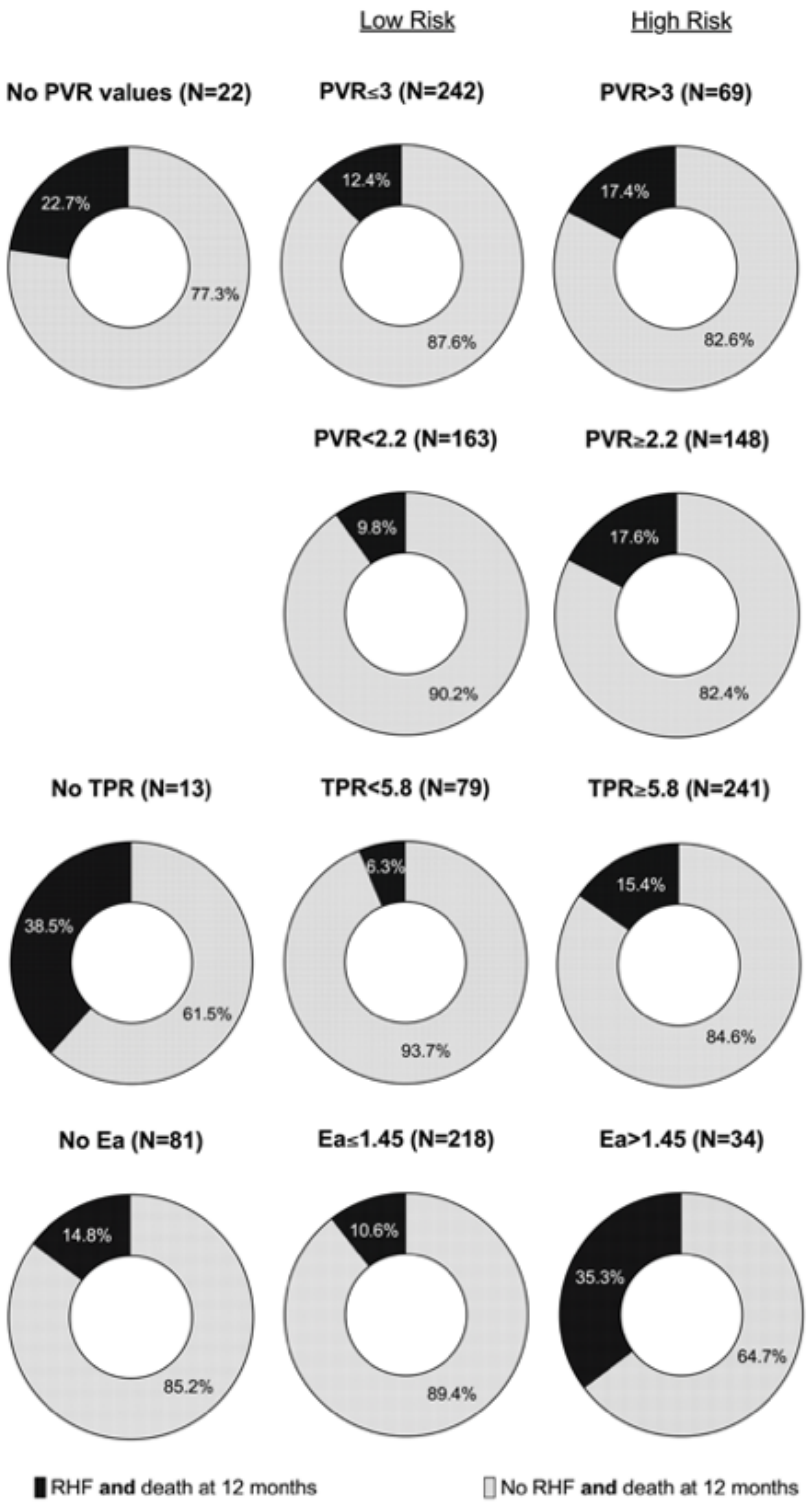


Abbildung 27: Einfluss verschiedener Grenzwerte auf Rechtsherzversagen und 12-Monats-überleben nach Herztransplantation in hämodynamischen Risikogruppen.

Low Risk = Niedrigrisikogruppe entsprechend der jeweiligen Einteilung; High Risk = hohes Risiko.
PVR, pulmonalvaskulärer Widerstand mit unterschiedlichen Grenzwerten; TPR, totaler pulmonaler Widerstand mit Grenzwert 5,8 Wood-Einheiten (1. Terzil); Ea, berechnete pulmonalarterielle Elastanz; Endpunkt: kombiniertes Ereignis Rechtsherzversagen *und* Tod innerhalb von 12 Monaten.

Schlussfolgerung

In unserer Studie konnte gezeigt werden, dass trotz weitgehender Einhaltung der Leitlinien zu hämodynamischen Grenzwerten das Rechtsherzversagen nach Herztransplantation als wesentliche Todesursache unterschätzt sein könnte. In der untersuchten Kohorte mit überwiegend leicht ausgeprägter pulmonaler Hypertonie war unter allen hämodynamischen Parametern Ea als Maß der pulmonalen Vaskulopathie am stärksten mit der Sterblichkeit nach Herztransplantation verbunden, was unabhängig von anderen nicht hämodynamischen Risikofaktoren war. Eine Absenkung der PVR-Grenze und die Berücksichtigung von hämodynamischen Parametern, die möglicherweise aussagekräftiger das Ausmaß der pulmonalen Gefäßschädigung widerspiegeln, könnte die Risikostratifizierung verbessern und individualisierte Therapieansätze zur Verbesserung der HTX-Ergebnisse ermöglichen. Eine derartige Strategie sollte daher in die ohnehin ausgeübte Praxis des RHK bei Herztransplantationskandidaten integriert werden, um dessen Potenzial besser auszuschöpfen.

5. Diskussion und Einordnung der Studienergebnisse

Hämodynamische Messungen im Lungenkreislauf sind von begrenztem Aussagewert, wenn sie nur als Momentaufnahme durchgeführt und interpretiert werden. Die diagnostische Wertigkeit wird durch die Nutzung nur weniger Standardparameter weiter eingeschränkt. Die Durchführung von Provokationstests und die Nutzung komplexerer Parameter könnte die Evaluierung von Patienten mit Herzinsuffizienz wesentlich bereichern, jedoch fehlen hierfür weithin ausreichende Belege. An dieser Stelle ein Stück der erforderlichen Datenbasis zu liefern ist Inhalt dieser Habilitationsschrift. Die Publikationen 1 bis 4 beschäftigen sich mit der prognostischen Aussagekraft und pathophysiologischen Differenzierung von Patienten mit Herzinsuffizienz unterschiedlicher Art durch Provokationstests. Hintergrund ist, dass die Erhebung von Messungen nur zu einem Zeitpunkt und in Ruhe wesentliche Faktoren gar nicht erfassen kann, weil diese beispielsweise nur unter Belastung oder nach einer pharmakologischen Intervention zutage treten.

Ein Kernelement der Herzinsuffizienzdefinition ist das Unvermögen zur adäquaten Adaptation an die Erfordernisse unter Belastungsbedingungen. Dieses Unvermögen für eine aussagekräftige hämodynamische Charakterisierung zu nutzen kann entsprechend nur gelingen, wenn eine Untersuchung auch unter Belastung durchgeführt wird. In Publikation 1 konnte bei Patienten mit Herzinsuffizienz und reduzierter LVEF gezeigt werden, dass eine in diesem Sinne vorgenommene hämodynamische Charakterisierung einen hohen prognostischen Vorhersagewert hat, der herkömmliche Prognoseparameter ergänzen kann. Die neuartigen Befunde dieser Studie waren wie folgt: (1) der Parameter ΔCO als Ausdruck der Herzzeitvolumenreserve unter Belastung war mit dem Überleben frei von HTX und LVAD assoziiert (2) die Kombination aus ΔCO unter dem errechneten Grenzwert von 1,15 Liter/Minute und ΔsPAP < 17,5 mmHg war mit einer besonders ungünstigen Prognose vergesellschaftet (3) die hämodynamische Charakterisierung auf der Basis von ΔCO und ΔsPAP war unabhängig von zahlreichen Basischarakteristika einschließlich Vorhandensein einer PH unter Ruhebedingungen mit der Prognose assoziiert (4) die beschriebenen hämodynamischen Phänotypen waren mit den prognoserelevanten Parametern der Spiroergometrie peak $V'O_2$ und $V'E/V'CO_2$ assoziiert.

Das Unvermögen zur adäquaten Steigerung des CO entsprechend des erhöhten Sauerstoffbedarfs des Organismus unter Belastung kann durch verschiedene Komponenten erklärt werden. Von Seiten des rechten Herzens und des Lungenkreislaufs kommen unter anderem die folgenden Faktoren dafür infrage: eine reduzierte kontraktile Reserve des RV,[20]

eine inadäquate Schlagvolumenreserve[172] in Verbindung mit einer chronotropen Inkompetenz,[72] erhöhter RV-Nachlast und RV-Rückwärtsversagen,[173] sowie dynamische RV-Dysfunktion.[76] Das Ausmaß des Druckanstiegs in der Pulmonalarterie unter Belastung kann nicht nur als Ausdruck einer pulmonalvaskulären Schädigung, sondern auch als Ausdruck der Fähigkeit des RV gesehen werden, Druck zu generieren.[76] In unserem Modell führte die Kombination aus dem Ausmaß des ΔCO mit dem Anstieg des sPAP zu einer Subdifferenzierung der Risikostratifizierung, worin wir die rechtsventrikuläre Komponente der CO-Generierung dargestellt sehen.

Eine wesentliche Rolle für die Standardisierung hämodynamischer Messungen unter Belastung kommt dem verwendeten Belastungsprotokoll zu. Zunächst sollten die Messungen unter konstanten, so genannten „steady state"-Bedingungen durchgeführt werden, die bezüglich des CO nach ca. 2 -3 Minuten Belastung auf einer Laststufe erreicht sind.[174, 175] In aktuellen Studien wurde Belastung im Liegen mit Belastung über 3 – 5 Minuten auf einer Stufe und Messungen während der letzten 1 – 2 Minuten der jeweiligen Stufe verwendet.[22, 77, 176] Bezüglich der Detektion einer submaximalen Belastung hat sich ein Wert der gemischtvenösen Sauerstoffsättigung (SvO_2) von etwa 30% bewährt, zumindest was die CO-Messung zur Detektion einer kardialen Dysfunktion angeht.[175] In unserer Kohorte war die durchschnittliche SvO_2 unter Belastung um 30%, so dass wir von einem ausreichenden Ausbelastungslevel ausgehen. Insgesamt sehen wir das verwendete Belastungsprotokoll als durch die Literatur gut begründet an. Zu den Limitationen dieser Studie zählen die Durchführung in einem einzelnen Zentrum, eine fehlende Validierungskohorte und eine fehlende internationale Standardisierung des Belastungsprotokolls.

Die weit verbreitete HI-Klassifikation entsprechend der LVEF hat sich in vielen Studien bewährt und hat erhebliche Auswirkungen auf die Therapie. Allerdings lässt sie viele andere Aspekte außer Acht, und Patienten mit ähnlicher LVEF können in ganz unterschiedlichem Ausmaß Symptome und Zeichen einer Herzinsuffizienz aufweisen. In Publikation 2 konnten wir darstellen, dass sich Patienten mit einer LVEF ≥ 50% in ihrem belastungshämodynamischen Profil von Patienten mit LVEF 41-49% kaum unterschieden. Schließlich zeigte der Vergleich dieser beiden Entitäten mit einer HFrEF-Kohorte, dass letztere sich in Bezug auf die Belastungshämodynamik deutlich unterschied, so dass letztlich HFmrEF (belastungs-) hämodynamisch eher der HFpEF ähnlich war.

Die LVEF ist allgemein als Kontraktilitätsindex akzeptiert, hat aber eine niedrige Spezifität, so dass eine detailliertere Charakterisierung von Patienten mit Herzinsuffizienz wünschenswert ist.[32, 66, 177] Unsere Ergebnisse stehen mit dieser Einschätzung insofern im Einklang, als es nur

wenige Assoziationen zwischen den LVEF-Klassen HFpEF / HFmrEF und den hämodynamischen Profilen in Ruhe und unter Belastung gab.

Eine Vorab-Stratifizierung nach dem Echokardiographie-Parameter TAPSE/PASP, der die RV-Kontraktilität im Verhältnis zu dessen Nachlast als Surrogat für das so genannte „coupling" reflektiert, führte hingegen zur Identifikation mehrerer relevanter Unterschiede im hämodynamischen, spiroergometrischen und klinischen Profil unabhängig von der LVEF-Einteilung als HFpEF / HFmrEF. Insbesondere die Unterschiede der nach TAPSE/PASP eingeteilten hämodynamischen Subgruppen in prognostisch relevanten Parametern der Spiroergometrie[94] sehen wir als Beleg für die zentrale Rolle des rechten Herzens für den Schweregrad der Herzinsuffizienz bei Patienten mit HFpEF und HFmrEF. Diejenigen Patienten mit stärker beeinträchtigtem coupling-Surrogat zeigten eine stärkere Reduktion der Fähigkeit, das Herzzeitvolumen unter Belastung zu steigern und höhere Indices der RV-Nachlast unter Belastung. Die Indices der RV-Kontraktilität zeigten sich allerdings nicht unterschiedlich, was für eine dominierende Rolle der RV-Nachlast sprechen könnte. In Analogie ist der Echoparameter der longitudinalen RV-Kontraktilität „TAPSE“ zwar von gewissem prognostischem Wert, in Bezug auf eine umfassendere Abbildung der RV-Funktion jedoch begrenzt.[178-181]

Nur auf den ersten Blick verwunderlich, konnten mittels eines eingeschränkten TAPSE/PASP-Verhältnisses auch diejenigen Patienten mit der schwereren Linksherzdysfunktion vorab identifiziert werden – denn letztlich ist das linke Herz bei diesen Patienten Ursprung und Motor der dysfunktionalen Einheit aus rechtem Herzen und pulmonaler Vaskulatur.[17, 182] Zahlreiche Publikationen haben die Bedeutung des rechten Herzens zur Einordnung von Symptomatik und Risiko bei Patienten mit HFpEF und HFrEF gezeigt.[183-185] Aufgrund einer relativ breiten Streuung echokardiographischer Parameter wurde Bedenken geäußert, diese systematisch zur Risikostratifizierung einzusetzen.[186] Invasiv-hämodynamische Parameter könnten die Echokardiographie ergänzen und somit zu einer solideren Basis für klinische Entscheidungen und vielleicht sogar für die Definition von Einschlusskriterien in klinische Studien beitragen.[44]

Zu den Limitationen der vorliegenden Studie gehört, dass erweiterte Echoparameter der RV-Funktion wie Deformationsbildgebung (strain) und „fractional area change“ (FAC) nicht verfügbar waren, ebenso wenig wie Echokardiographie unter Belastung. Weiterhin standen uns keine systematisch erhobenen Verlaufsdaten der Patienten zur Verfügung, so dass die Anzahl der erfassten Ereignisse für eine aussagekräftige Analyse von prognostischer Relevanz nicht ausreichte.

Die Manifestation einer Rechtsherzinsuffizienz in Form einer RA-Druckerhöhung in Ruhe ist gut bekannt, in Form eines pathologischen RA-Druckanstiegs unter Belastung bei normalem Ruhe-RAP aber wenig beschrieben. In Publikation 3 konnten wir zeigen, dass der Belastungs-RAP mit prognostisch bedeutsamen Variablen und zudem mit einem Marker der RA-Wandspannung - MR-proANP - assoziiert ist. Die wesentlichen Resultate dieser Studie über die Dynamik von RAP und MR-proANP-Spiegeln unter physischer Belastung bei CTEPH-Patienten lassen sich wie folgt zusammenfassen: (1) körperliche Belastung führt auch bei normalem Ruhe-RAP bei einem Teil der Patienten zu einem RAP-Anstieg, der eine RHI nahelegt (2) in diesem Zusammenhang korrelieren die MR-proANP-Spiegel mit dem RAP (3) MR-proANP-Spiegel unter und nach Belastung können als Surrogatparameter für eine pathologische RA-Hämodynamik angesehen werden. Nach unserer Einschätzung sind diese Befunde nicht spezifisch für CTEPH-Patienten, sondern sie lassen sich wahrscheinlich auch auf andere Formen der Rechtsherzinsuffizienz übertragen; das Grundprinzip kann jedoch modellhaft bei der gewählten CTEPH-Kohorte dargestellt werden, da deren Pathophysiologie einer isolierten RHI entspricht.

Die Entwicklung einer RHI markiert in besonderer Weise die Progression der Grunderkrankung bei CTEPH und anderen PH-Formen und sollte frühestmöglich detektiert werden.[111, 112, 115, 187-190] Besonders bei Patienten mit normalen oder grenzwertigen Befunden in Ruhe ist ein B-RHK in der Lage, eine latente hämodynamische Beschränkung zu demaskieren.[21, 107] Hierbei könnte ein invasiv gemessener pathologischer RAP-Anstieg als besonders sensitiver Parameter zur Beschreibung einer RV-Dysfunktion genutzt werden.[44, 120] Während der RAP bei Gesunden bis maximal 15 mmHg ansteigt,[43, 116-119, 191] reichen die medianen B-RAP-Werte bei Patienten mit PH und unterschiedlichen Formen der Herzinsuffizienz in einen Bereich zwischen 13 und 17 mmHg,[43, 192, 193] und in einer Studie wurde jeglicher RAP-Anstieg unter Belastung als Indikator einer ungünstigen Prognose gezeigt.[43] In unserer Kohorte zeigte sich ein signifikanter Anstieg des RAP auf im Mittel 16 mmHg unter Belastung, vergleichbar mit den Ergebnissen in einer gemischten PH-Kohorte.[43] Unter Verwendung des Grenzwerts von 15 mmHg hatten 51% unserer Patienten einen pathologischen B-RAP als Hinweis auf eine RHI unter Belastung. Nach unserer Bewertung geht ein pathologischer B-RAP auf eine unzureichende Kapazität des RV zurück, den RA adäquat zu entleeren. Diese Komponente der RV-Dysfunktion geht sicherlich teilweise auf einen belastungsabhängigen Anstieg der RV-Nachlast zurück, aber auch beispielsweise auf eine reduzierte Kontraktilitätsreserve des RV. Diejenigen Patienten unserer Untersuchung mit einem B-RAP > 15 mmHg zeigten offenbar eine maladaptive Belastungsreaktion trotz eines vergleichbaren oder sogar niedrigeren Anstiegs der RV-

Nachlast, gemessen als Anstieg des mPAP. Zwar könnte die Definition einer RHI unter Belastung durch den B-RAP eine zu starke Vereinfachung des komplexen RV-Belastungsverhaltens darstellen, jedoch korrelierte der B-RAP in unserer Untersuchung gut mit dem etablierteren Parameter PAPi. Allerdings existieren keine Daten zum PAPi unter Belastung in der Literatur.

Natriuretische Peptide (NP) werden vom Myokard als Reaktion auf Volumen- oder Drucküberlastung sezerniert,[122] und der Ursprung atrialer NP aus den Vorhöfen sowie deren Korrelation mit atrialen Ruhedrücken ist präzise beschrieben.[123] Bei Patienten mit Linksherzinsuffizienz beschrieben Kato et al. einen Belastungsanstieg der ANP-Spiegel, der ausgeprägter war als derjenige von gesunden Kontrollpersonen.[194, 195] Bei PH-Patienten gibt es zur Dynamik von natriuretischen Peptiden unter Belastung nur wenige Berichte,[126-128] und gar keine im Zusammenhang mit invasiver Hämodynamik. Dieser Zusammenhang ist jedoch entscheidend für den Nachweis von hämodynamischer Stressbelastung als Hauptverursacher der NP-Freisetzung.[122] In unserer Studie beobachteten wir eine starke Korrelation zwischen MR-proANP-Spiegeln und dem RAP an allen gemessen Zeitpunkten; eine Regressionsanalyse zeigte darüber hinaus einen Anstieg des B-RAP von 0,6 mmHg je 10 pmol/l MR-proANP Höchstwert. Unsere Daten legen nahe, dass auch die MR-proANP 2-Stunden-Erholungswerte dafür genutzt werden können, um Patienten mit pathologischem B-RAP zu identifizieren. Der arterielle Blutdruck und der PAWP hatte keinen relevanten Einfluss auf die B-RAP- und MR-proANP-Werte. In unserer multivariaten Analyse wurden verschiedene weitere Einflussfaktoren untersucht, jedoch verblieben nur die RA-Fläche und der MR-proANP-Höchstwert als signifikant unabhängig mit dem B-RAP assoziiert.

An Limitationen der vorliegenden Studie ist die relativ kleine Gruppengröße zu nennen, was die statistische Aussagekraft schmälert. Allerdings ging es uns darum, prinzipielle Mechanismen darzustellen, wofür die Homogenität der untersuchten Kohorte eine Grundbedingung darstellt. Die generierten Hypothesen müssen vor einer möglichen Ausdehnung auf andere Patientengruppen an weiteren Kohorten untersucht werden.

Verschiedene hämodynamische Parameter (allen voran der PVR), die das Ausmaß einer pulmonalvaskulären Schädigung in Folge einer HI reflektieren, sind als prognostische Marker allgemein akzeptiert. Deren Aussagekraft scheint jedoch nicht so überzeugend zu sein, dass sich die invasive Bestimmung dieser Parameter bei HI-Patienten zur Risikoklassifizierung im klinischen Alltag und in Leitlinienempfehlungen durchgesetzt hätte. Insbesondere auch die Durchführung einer VRT, wie sie beispielsweise vor HTX üblich ist, besitzt gegenwärtig bei LHI ohne HTX-Kontext keinen Stellwert. In Publikation 4 konnten wir zeigen, dass drei nach

Verabreichung von GTN erhobene Parameter des Verhältnisses zwischen Druck und Fluss in der PA (PAC, Ea und TPR) einen signifikanten prognostischen Wert hatten. Der beste prognostische Marker war dabei PAC-GTN, der sich etablierten Markern wie PAC[173] und der Gegenwart von Cpc-PH überlegen zeigte. Eine signifikante Besserung von PAC nach GTN schien auf eine erfolgreiche Reduktion der oszillatorischen RV-Nachlast zurückzugehen. Es gibt einige Berichte über prognostische Implikationen einer VRT bei präkapillärer PH, also per Definition in Abwesenheit einer LHI.[25, 196] Wie bereits ausgeführt, wird bei LHI-Patienten außerhalb der Evaluierung für eine HTX eine VRT derzeit nicht empfohlen, und schlüssige Protokolle fehlen ebenso wie die fundierte Definition eines „positiven" Testresultats.[197, 198] Ghio und andere fanden bei der Untersuchung einer VRT mit intravenös verabreichten Nitraten bei 156 LHI-Patienten ein signifikant reduziertes Überleben, wenn der Test „negativ" ausfiel.[199] Lim und andere beschrieben eine Assoziation zwischen PAC vor Testung sowie einem nach der Testung um mindesten 20% reduzierten PVR und dem Überleben.[200] In einer anderen Studie hingegen konnten Al-Naamani und andere keine prognostische Relevanz eines VRT bei Patienten mit PH und LHI zeigen.[87]

Unsere Ergebnisse sind insofern neuartig, als eine prognostische Relevanz unabhängig von einer Einteilung in „Cpc-PH" und „Ipc-PH" und vor allem von einer prädefinierten, jedoch willkürlichen Festlegung einer „positiven" VRT gezeigt werden konnte. Ein Faktor könnte hierzu entscheidend beigetragen haben: der von uns untersuchte Vasodilatator und seine Dosierung zur Durchführung eines „Entlastungstests" des Lungenkreislaufs. Die meisten für eine VRT eingesetzten Substanzen sind mehr oder weniger selektive pulmonale Vasodilatatoren, die den linksventrikulären Füllungsdruck (PAWP) nur wenig senken oder ihn gar in unerwünschter Weise erhöhen. Aufgrund der Formel für die PVR-Berechnung (mPAP – PAWP / Herzzeitvolumen) resultiert durch einen höheren PAWP nach VRT ein niedrigerer PVR im Sinne eines „positiven" Testresultats. Die Reduktion von PAP, PAWP und RAP durch GTN, also Vor- und Nachlast des linken und rechten Herzens durch venöse und arterielle Gefäßerweiterung führt indirekt zu vermehrtem subendokardialen Blutfluss.[139, 201] GTN bewirkt also viel mehr als eine pulmonale Vasodilatation: die gesamte Sequenz aus rechtem Herzen, PA und linkem Herzen wird entlastet, so dass die Bezeichnung „Entlastungstest" besser geeignet scheint als „Vasoreaktivitätstest". Entsprechend zeigte sich als entscheidende Komponente für die Verbesserung von PAC nach GTN-Gabe in unserer Kohorte eine Reduktion des PA-Pulsdrucks (PP), wohingegen die Steigerung des Schlagvolumens (SV) relativ gering ausfiel. Dazu passend zeigte der PA-Pulsatilitätsindex als Index der RV-Kontraktilität[40] keine prognostische Relevanz. In unserer Kohorte zeigten Patienten mit

erhaltener LVEF eine stärkere Reduktion des PP als diejenigen mit reduzierter LVEF, während die Steigerung des SV schwächer ausfiel.

Die Nachteile hämodynamischer Einzelmessungen, die durch situative Einflüsse wie beispielsweise Vasokonstriktion oder Erhöhung des systemischen Blutdrucks verzerrt werden können, könnten durch wiederholte Messungen nach Applikation eines Vasodilatators mit kardialer Entlastung ausgeglichen werden. Wenn die Entlastung nicht zu einer signifikanten Verbesserung der Druck-/Flussverhältnisse (welche die Basis für die gefundenen drei Schlüsselvariablen darstellen) führt, könnte dies als Zeichen einer strukturellen pulmonalen Vaskulopathie gewertet werden.

In unserer Analyse wurden zahlreiche prognostisch etablierte hämodynamische Parameter ausgewertet, und Ea, TPR und PAC als Maß der RV-Nachlast[42] - gemessen nach GTN-Gabe - zeigten die beste Assoziation mit der Prognose der Patienten. PAC könnte dem PVR überlegen sein, weil dieser Parameter die Folgen eines erhöhten PVR und erhöhter linksventrikulärer Füllungsdrücke für die RV-Nachlast subsummiert.[173] Weiterhin integriert PAC resistive, pulsatile und passive Komponenten der RV-Nachlast und könnte daher am besten einen PA-Gefäßumbau darstellen.[39] Allerdings gibt es eine große Schwankungsbreite der Grenzwerte, die für PAC als Risikomarker publiziert sind;[166, 173, 202] wiederholte Messungen nach VRT könnten ein Weg sein, konsistentere Grenzwerte zu erhalten.

Eine Reduktion der oszillativen RV-Nachlast ist wahrscheinlich der dominierende Effekt des PAC-Anstiegs nach VRT in unserer Kohorte, denn der Rückgang der oszillativen RV-Nachlast war deutlicher in der Gruppe mit Verbesserung des PAC-GTN über den Grenzwert, und der Rückgang der stetigen Komponente der RV-Nachlast (PVR) war relativ gering ausgeprägt.

Als Limitation ist zum einen zu nennen, dass wir Patienten mit unterschiedlichen Formen der Herzinsuffizienz (HFpEF, HFmrEF und HFrEF) gemeinsam untersucht haben, was eine Fehlerquelle darstellen könnte. Jedoch resultiert die Linksherzerkrankung bei allen Formen in einer vergleichbaren Pathophysiologie, indem erhöhte LV-Füllungsdrücke zu einer Druckerhöhung im Lungenkreislauf führen. Die getrennte Untersuchung von HFpEF-Patienten und HFmrEF/HFrEF-Patienten bestätigte unsere Hauptergebnisse in beiden Subgruppen. Weiterhin waren bei 23 Patienten (12,5% der Ausgangskohorte, die auf Eignung für unsere Analyse hin untersucht wurde) keine Verlaufsdaten verfügbar, weshalb sie nicht in die finale Analyse einbezogen wurden. Diese Rate befindet sich jedoch in einem akzeptablen Bereich.[203]

Die traditionell ausgeübte hämodynamische Evaluierung von Herzklappenvitien wie der MI besitzt aktuell keinen wesentlichen Stellenwert für therapeutische Entscheidungen. In Publikation 5 stellen wir dar, dass eine differenzierte hämodynamische Evaluierung unter

Belastungsbedingungen für die Entscheidungsfindung zur interventionellen Versorgung (PMVR) einer mittel- bis hochgradigen und hochgradigen MI wichtige Zusatzinformationen für die Herzteam-Entscheidung für oder gegen eine interventionelle Klappenreparatur erbringen kann. Der Parameter ΔV-Welle war in unserer Studie mit dem Überleben nach PMVR assoziiert, unabhängig vom Alter, der Gebrechlichkeit und der Belastungsstufe. Weiterhin zeigten ΔV-Welle und ΔCO eine Assoziation zur Verbesserung der NYHA-Klasse innerhalb von 12 Monaten nach dem Eingriff. Diese Resultate waren in der Gesamtgruppe und der Subgruppe mit sekundärer MI signifikant.

Das Konzept einer dynamischen MI, also einer Zunahme des hämodynamischen Schweregrades unter Belastungsbedingungen wurde bereits vor Jahrzehnten entwickelt.[204] Der ausgeprägtere Anstieg der V-Wellen (ΔV-Welle) unter Belastung bei einem Teil unserer Patienten deutet auf eine ausgeprägtere hämodynamische Auswirkung der MI, also eine schwerere dynamische MI hin. Je bedeutsamer die MI für die individuelle hämodynamische Pathophysiologie ist, desto besser scheinen die Voraussetzungen dafür zu sein, dass der PMVR offenbar am pathophysiologisch entscheidenden Punkt ansetzt und damit die Prognose und Symptomatik verbessern kann. Prominente V-Wellen in der PAWP-Druckkurve unter Ruhebedingungen wurden schon vor Jahrzehnten als Hinweis auf eine schwergradige MI beschrieben,[205] sie können aber auch beim so genannten Syndrom des steifen linken Vorhofs („stiff LA syndrome“) und anderen Zuständen mit Volumenüberladung des LA beobachtet werden. Auch schließt die Abwesenheit signifikanter V-Wellen in Ruhe eine relevante MI nicht aus.[150] Bei unseren Patienten war kein signifikanter Volumenüberschuss vorhanden (mittlerer RA-Druck 9 ± 4 mmHg), und es bestanden keine Hinweise auf ein stiff LA-Syndrom.

Auf der anderen Seite scheint eine wichtige Ursache für einen klinisch nicht erfolgreichen PMVR eine zu stark ausgeprägte Herzinsuffizienz zu sein.[206-209] Geeignete hämodynamische Voraussetzungen für einen erfolgreichen PMVR sind bei gleichzeitig vorliegender Herzinsuffizienz schwierig zu definieren.[210] In unserer Untersuchung zeigte sich, dass eine unzureichende Steigerung des Herzzeitvolumens unter Belastung eine zu geringe kardiale Reserve für eine erfolgreiche Mitralklappenreparatur anzeigen könnte. Hieraus ergibt sich eine hämodynamische Analogie zu dem kürzlich vorgestellten Konzept der disproportionalen MI, das eine im Verhältnis zur linksventrikulären Erweiterung überproportional ausgeprägte MI beinhaltet.[211] Entsprechend stellt eine relativ stark ausgeprägte MI bei relativ gering ausgeprägter Herzinsuffizienz eine gute Voraussetzung für den PMVR dar und umgekehrt. Dieses Konzept sehen wir in der Belastungshämodynamik bestätigt, indem Patienten mit der Kombination aus höherem ΔV-Welle (also schwererer dynamischer MI) und höherem Δ CO

(also geringerer LV-Dysfunktion) am meisten profitierten. Die Limitationen dieser Studie umfassen die Durchführung in einem Einzelzentrum und das Fehlen einer Validierungskohorte, so dass die Ergebnisse als hypothesengenerierend anzusehen sind. Die gemeinsame Analyse von Patienten mit primärer und sekundärer MI könnte prinzipiell eine Fehlerquelle darstellen, jedoch zeigten sich die Ergebnisse in der Gesamtgruppe und der Subgruppe mit sekundärer MI weithin kongruent.

Im Vorfeld einer HTX werden regelmäßige RHK empfohlen, der Stellenwert der dabei erhobenen Parameter ist jedoch unklar, so dass an jedem HTX-Zentrum unterschiedlich damit umgegangen wird. Zudem sind in keinem gängigen Score zur Abbildung des Empfängerrisikos Hämodynamik-Parameter enthalten. In Publikation 6 berichten wir über unsere umfassende Analyse hämodynamischer und allgemeiner Parameter vor HTX mit folgenden Hauptergebnissen: obwohl die hämodynamischen Grenzwerte leitliniengemäß überwiegend eingehalten wurden, zeigte sich eine hohe Inzidenz von Rechtsherzversagen nach HTX und eine damit verbundene erhebliche Sterblichkeit. Unter Verwendung der leitliniengemäßen Grenzwerte der etablierten Parameter PVR und TPG ergaben sich keine signifikanten Assoziationen bezüglich der Gesamtsterblichkeit in der untersuchten Kohorte mit weitgehend gering ausgeprägter PH, wohl aber unter Verwendung eines niedrigeren PVR-Grenzwerts. Unabhängig von anderen allgemeinen Risikofaktoren zeigte der Parameter Ea als Maß für die pulmonale Vaskulopathie und rechtsventrikuläre Nachlast unter allen hämodynamischen Variablen den stärksten Einfluss auf das Überleben nach HTX. Ea und auch TPR waren signifikant mit dem Rechtsherzversagen nach Transplantation assoziiert.

Ea lässt sich leicht aus PA-Druck und Schlagvolumen errechnen und könnte die Nachlast, der das transplantierte rechte Herz nach HTX ausgesetzt ist, durch Integration von resistiver und pulsatiler RV-Nachlast umfassender widerspiegeln als der PVR.[39] Eine prognostische Überlegenheit von Ea gegenüber PVR und TPG wurde bei Patienten mit PH und Linksherzinsuffizienz schon früher gezeigt.[42, 212] In zwei Studien erwies sich Ea zudem als hilfreich zur Prädiktion eines Rechtsherzversagens nach LVAD-Implantation.[213, 214]

Die Ergebnisse einer HTX hängen entscheidend von einer optimierten Kandidatenselektion ab. In einer aktuellen Metaanalyse wurden diverse Scores zur Erfassung des Sterblichkeitsrisikos nach HTX untersucht, von denen die meisten keine sehr gute Vorhersagekraft besaßen; als fundiertester erwies sich der so genannte IMPACT-Score.[215] Hämodynamische Risikofaktoren einschließlich PVR spielen in fast keinem der untersuchten Scores eine Rolle und könnten als hilfreicher Faktor zur individualisierten Risikostratifizierung unterschätzt sein,[159, 215, 216] zumal ein regelmäßig wiederholter RHK routinemäßig empfohlen wird.[217] Bezüglich des PVR könnte

ein niedrigerer als der traditionelle Grenzwert von 3 WU eine größere Aussagekraft besitzen.[164] Eine Subgruppenanalyse unserer Kohorte zeigte, dass die Aussagekraft der hämodynamischen Variablen umso stärker war, je geringer der zeitliche Abstand zwischen RHK und HTX war, so dass die Untersuchungsintervalle bei Hochrisikopatienten relativ eng, beispielsweise alle 2-3 Monate, gewählt werden sollten. Um die Risikoprädiktion in Bezug auf das Ausmaß der pulmonalen Gefäßschädigung weiter zu verbessern, könnten hämodynamische Belastungstests oder andere Provokationstest nützlich sein.[12, 41, 165, 218] Konsequenz aus einer hämodynamischen Hochrisikokonstellation könnte eine Intensivierung der Therapie[219] bis hin zu einer LVAD-Implantation[220] sein, wie sie als frühzeitige Maßnahme in einer aktuellen Studie untersucht wird (VAD-DZHK3).

Unter den Studienlimitationen ist unter anderem das Fehlen der Herzfrequenz zur Berechnung des Schlagvolumens und damit von Ea bei 24 % der Patienten zu nennen, was eine Fehlerquelle darstellen könnte. Weiterhin zeigte sich ein relativ breites Konfidenzintervall für Ea, was auf unterschiedliche Methoden der Herzzeitvolumenmessung (Fick´sche Methode oder Thermodilution) zurückgehen könnte. Trotz aller Limitationen stammen unsere Ergebnisse aus einem großen multizentrischen Register mit hoch signifikanten Ergebnissen, die als hypothesengenerierend anzusehen sind, solange keine prospektiven Daten vorliegen.

6. Zusammenfassung

Hämodynamische Diagnostik gewinnt an Aussagekraft, wenn sie unter Belastung, nach pharmakologischer Veränderung der Lastverhältnisse und / oder unter Nutzung komplexerer Parameter und modifizierter Grenzwerte durchgeführt wird. Hierfür möchte die vorliegende Arbeit Belege aus der klinischen Forschung liefern.

Die Pathophysiologie der Herzinsuffizienz besteht neben der Tendenz zur Flüssigkeitsretention hauptsächlich in einem Unvermögen zur adäquaten Anpassung des Herzzeitvolumens an die Erfordernisse des Belastungsmetabolismus. Dieses Unvermögen im Rahmen eines hämodynamischen Belastungstests darzustellen und zu quantifizieren, könnte eine fundamentale Verbesserung in der HI-Diagnostik darstellen, beispielsweise für die Kandidatenselektion für Ausnahmetherapien wie HTX und LVAD. Als Ergänzung zu etablierten Risikoparametern wie Biomarkern oder der maximal erreichten Sauerstoffaufnahme in der Spiroergometrie konnte gezeigt werden, dass die Steigerung des CO (ΔCO) im Rahmen eines submaximalen hämodynamischen Belastungstests bei Patienten mit HFrEF aussagekräftige Informationen zur Schwere ihrer HI liefert. In Kombination mit der Steigerung des sPAP ergaben sich unterschiedliche hämodynamische Profile, bei denen ein Δ sPAP in Kombination mit ΔCO unter den definierten Schwellenwerten die schlechteste Prognose bedeutete und vice versa. Mit der Nutzung von Δ sPAP scheint es möglich, die RV-Komponente des Gesamt-CO gesondert zu betrachten und die herausragende Bedeutung der RHI für den Schweregrad der LHI deutlich zu machen.

Die Klassifizierung von Patienten mit HI alleine anhand ihrer LVEF lässt wichtige Komponenten außer Acht, was am Beispiel von Patienten mit HFpEF und HFrEF untersucht wurde. Hierbei stellte sich heraus, dass die Schwere der HI - definiert durch Δ CO und andere Parameter der Belastungshämodynamik - sich nicht wesentlich zwischen diesen beiden LVEF-Klassen unterschied. Andere Faktoren schienen für die Erkrankungsschwere ausschlaggebend zu sein, und die Forschungshypothese war, dass die Rechtsherzfunktion hier eine entscheidende Rolle spielt. Diese Hypothese wurde durch die Ergebnisse einer Sekundäranalyse gestützt, in der zunächst eine Einteilung des gesamten Kollektivs unabhängig von der LVEF nach der Rechtsherzfunktion (unter Nutzung des Parameters TAPSE/PASP) erfolgte. Diese Stratifizierung führte zu signifikanten Unterschieden der Belastungshämodynamik mit klinischer Relevanz. Auch an diesem Patientenkollektiv ließ sich mit der Kombination aus Rechtsherzechokardiographie und Belastungs-RHK eine Schlüsselrolle des rechten Herzens bei Patienten mit LHI demonstrieren.

Die Kombination aus Belastungs-RHK und Biomarkermessungen unter Belastung wurde an einem Kollektiv von Patienten mit CTEPH / CTEPD untersucht, die keine Anhaltspunkte für eine LHI aufwiesen. Ein übermäßiger Anstieg des RAP unter Belastung als Ausdruck der RV-Insuffizienz ermöglichte unabhängig vom Ruhe-RAP signifikante Aussagen über die Risikoklassifizierung und damit die Schwere der RHI. Die parallel durchgeführten Biomarkermessungen zeigten einen engen Zusammenhang mit der rechtsatrialen Hämodynamik, so dass die Biomarkerfreisetzung aufgrund von RA-Wandspannung damit belegt werden konnte. Auch hier stellte sich die Belastungshämodynamik als hilfreiches Mittel dar, die Pathophysiologie der RHI besser zu verstehen und herkömmliche Risikostrategien - wie in diesem Fall das ESC-PH-Risikomodell - differenziert zu ergänzen.

Nicht nur eine Belastungsprovokation ist in der Lage, Mechanismen der HI aufzudecken, sondern auch die Gabe von Pharmaka. Traditionell als so genannte "Vasoreagibilitätstestung" mit ungewisser Aussagekraft durchgeführt, kam in unserer Untersuchung von Patienten mit postkapillärer PH und LHI (mit unterschiedlicher LVEF) eine eher als "Entlastungstest" anzusehende Intervention zum Einsatz. In einer umfassenden Analyse zahlreicher Parameter des Ruhe-RHK vor und nach Gabe von GTN waren drei davon von herausragender Aussagekraft für die Prognose der Patienten. Es handelte sich um komplexere Parameter der Beziehung von Druck zu Fluss im Lungenkreislauf - und alle drei waren nach GTN-Gabe gemessen. Insgesamt ragte der Parameter PAC heraus, der durch die GTN-Gabe wesentlich an Aussagekraft hinzugewann. Nach unserer Interpretation wurden diejenigen Patienten durch die Intervention charakterisiert, die trotz der pharmakologischen Entlastung des Lungenkreislaufs noch ein hohes Maß an oszillatorischer RV-Nachlast aufwiesen und von einer reduzierten Lebenserwartung letztlich durch RHI betroffen waren.

Bei der interventionellen Klappenreparatur einer MI spielt die Kandidatenauswahl für den Erfolg eine wesentliche Rolle. Wir untersuchten an Patienten mit primärer und sekundärer MI, inwieweit belastungshämodynamische Parameter einen Erfolg der nachfolgend durchgeführten Klappenreparatur vorhersehbar machen. Es zeigte sich, dass vor allem ein Parameter signifikant mit dem Überleben und der klinischen Verbesserung nach dem Eingriff verbunden war: der Anstieg der Höhe der V-Welle in der PAWP-Druckkurve. Je höher der Anstieg, desto eher wurden Überleben und Symptomatik verbessert, was wir dahingehend interpretieren, dass der Eingriff bei den Patienten mit hohem Anstieg den entscheidenden Punkt in der Pathophysiologie bei hämodynamisch schwergradigem Vitium positiv beeinflusste. Der CO-Anstieg unter Belastung spielte für den Interventionserfolg ebenfalls eine Rolle, so dass die

präinterventionelle Belastungshämodynamik relevante Informationen sowohl zur hämodynamischen Signifikanz der MI als auch zur Schwere der HI liefern konnte.

Die Kandidatenauswahl spielt ebenfalls eine herausragende Rolle für die erfolgreiche Durchführung einer HTX. Hier gibt es eine Fülle bekannter Risikofaktoren für einen ungünstigen Verlauf, von denen allerdings nur ein Teil beeinflusst werden kann. Wir untersuchten den Stellenwert standardmäßiger und komplexerer hämodynamischer Parameter für die Überlebenswahrscheinlichkeit und RHI nach HTX. Ein bisher in der Routine nicht benutzter Index des Verhältnisses zwischen Druck und Fluss in der Pulmonalarterie (Ea) zeigte die stärkste Assoziation mit Sterblichkeit und RHI nach HTX in unserer Kohorte. Der etablierte Parameter PVR zeigte eine untergeordnete Relevanz, die jedoch verbessert wurde, wenn für die Kategorisierung ein niedrigerer als der leitliniengemäß etablierte PVR-Grenzwert verwendet wurde. Eine Übertragung dieser Ergebnisse in die klinische Praxis würde bedeuten, dass mittels entsprechend erhöhter Werte für Ea oder PVR (mit reduziertem Grenzwert) mehr Risikopatienten für einen ungünstigen Verlauf nach HTX identifiziert werden würden. Diese könnten dann vor der HTX bis hin zur frühzeitigen LVAD-Implantation intensiviert behandelt werden, um ihren Verlauf nach HTX zu verbessern.

Zusammenfassend konnte in dieser Habilitationsschrift beschrieben werden, wie die Aussagekraft hämodynamischer Messungen durch Belastungstests, pharmakologische Provokation und Nutzung komplexerer Parameter an Aussagekraft gewinnen kann. Hierdurch wird eine Nutzung der Hämodynamik für konkrete klinische Entscheidungen in besonderen Situationen ermöglicht, wie sie bisher im klinischen Alltag wenig stattfindet.

7. English Summary

Haemodynamic diagnostics gain significance when obtained during exercise, after pharmacological modification of the load conditions and / or when using more complex parameters and modified threshold values. The aim of this cumulative *Habilitation* thesis is to provide more evidence of this from clinical research.

The pathophysiology of heart failure (HF) consists mainly of an inability to adequately adapt cardiac output to the demands of exercise metabolism, except for the tendency for fluid retention. To be able to visualize and quantify this inability in the context of a haemodynamic exercise test could represent a fundamental improvement in HF diagnostics, for example for the selection of candidates for exceptional therapies such as HTX and LVAD. As a complement to established risk parameters such as biomarkers or maximal oxygen uptake achieved in cardiopulmonary exercise testing, we showed that increasing CO (ΔCO) in the context of a submaximal haemodynamic exercise test in patients with HFrEF provides meaningful information on the severity of their HF. In combination with the increase in sPAP, different haemodynamic profiles emerged in which sPAP combined with ΔCO below the defined thresholds signified the worst prognosis and vice versa. With the use of sPAP, it is possible to consider the RV component of total CO separately and to highlight the prominent role of right heart failure (RHF) and the severity of left heart failure (LHF).

Classifying patients with HF based on their LVEF alone ignores important components, which was investigated using the example of patients with HFpEF and HFrEF. It was found that the severity of HF – defined by ΔCO and other parameters of exercise haemodynamic parameters – did not differ significantly between the two LVEF classes. Disease severity was apparently determined by other factors, and the research hypothesis was that RV function plays a crucial role here. This hypothesis was supported by the results of a secondary analysis in which the entire collective was first stratified according to right heart function independently of LVEF using the parameter TAPSE/PASP. This stratification led to significant differences in exercise haemodynamics with clinical relevance. A key role of the right heart in patients with LHF was demonstrated also in this patient collective, using the combination of right heart echocardiography and exercise RHC.

The combination of exercise RAP and biomarker measurements under stress was investigated in a collective of patients with CTEPH / CTEPD who had no evidence of LHF. An excessive increase in RAP under stress as an expression of RV failure allowed significant conclusions to be drawn about the risk classification and thus the severity of HF, independent of the resting

RAP. The biomarker measurements performed in parallel showed a close correlation with RA haemodynamics, so that the biomarker release due to RA wall tension was able to be demonstrated. Again, exercise haemodynamics were shown to be a helpful tool to better understand the pathophysiology of RHF and to complement conventional risk strategies - such as the ESC PH risk model in this case - in a differentiated way.

In addition to exercise provocation, the administration of drugs is also able to reveal mechanisms of HF. Traditionally performed as a so-called "vasoreactivity test" with uncertain significance, our study of patients with postcapillary PH and LHF (without taking LVEF into account) used an intervention that can rather be regarded as an "unloading test". In a comprehensive analysis of numerous parameters of resting RHC before and after administration of GTN, three of them were of outstanding significance for the prognosis of the patients. These were relatively complex parameters of the relationship of pressure to flow in the pulmonary circulation - and all three were measured after GTN administration. Overall, the parameter PAC stood out, which gained significantly in significance through GTN administration. According to our interpretation, those patients were characterized by the intervention who, despite pharmacological relief of the pulmonary circulation, still had a high level of oscillatory RV afterload and were affected by a reduced life expectancy ultimately due to RHF.

Candidate selection plays an important role for the success of interventional valve repair of mitral insufficiency (MI). We investigated in patients with primary and secondary MI to what extent haemodynamic parameters during exercise predict the success of the subsequently performed valve repair. One parameter in particular was found to be significantly associated with survival and clinical improvement after surgery: the increase in the height of the V-wave in the PAWP pressure curve. The higher the rise, the more likely survival and symptoms were improved, which we interpret as a positive influence of the intervention on the crucial point in the pathophysiology of a haemodynamically severe defect in those patients with high rise in V-wave. The CO increase during exercise also played a role in the intervention success, so that pre-interventional exercise haemodynamics could provide relevant information on both the haemodynamic significance of MI and the severity of HF.

Candidate selection also plays a prominent role in the successful implementation of HTX. There is a plethora of known risk factors for an unfavourable outcome, only some of which can be influenced. We investigated the significance of standard and more complex haemodynamic parameters for the probability of survival and RHF after HTX. A previously unused index of pulmonary artery pressure/flow ratio (Ea) showed the strongest association with mortality and RHF after HTX in our cohort. The established parameter PVR showed a subordinate relevance,

but this was improved when a lower than guideline-established PVR threshold was used for categorization. The translation of these results into clinical practice would mean that, by using correspondingly increased values for Ea or PVR (with reduced threshold value), more high risk patients expected to have an unfavourable course after HTX would be identified. These patients could then be treated intensively before HTX up to early LVAD implantation in order to improve their clinical course after HTX.

In summary, this *Habilitation* thesis describes how the significance of haemodynamic measurements can be increased by exercise tests, pharmacological provocation and the use of more complex parameters. This enables the use haemodynamics for making concrete clinical decisions in special situations, which has thus far been rarely possible.

8. Abkürzungsverzeichnis

ANP	Atriales Natriuretische Peptid
AUC	Area Under the Curve
B-RAP	Right Atrial Pressure unter Belastung
B-RHK	Rechtsherzkatheter unter Belastung
BMI	Body Mass Index
BP	Blood Pressure
CI	Cardiac Index
CI	Confidence Interval
CO	Cardiac Output
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
Cpc-PH	Combined post-capillary PH
CPET	Cardiopulmonary Exercise Testing
CPI	Cardiac Power Index
CPO	Cardiac Power Output
CTEPD	Chronic Thromboembolic Pulmonary Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
Δ	Anstieg unter Belastung
dPAP	diastolic Pulmonary Arterial Pressure
DPG	Diastolic Pressure Gradient
Ea	Pulmonary arterial Elastance
eGFR	estimated Glomerular Filtration Rate
ERS	European Respiratory Society
ESC	European Society of Cardiology
FI	Frailty Index
GTN	Glycerol Trinitrate
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HI	Herzinsuffizienz
HR	Hazard Ratio, Heart Rate
HTX	Herztransplantation

INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IQR	Interquartile Range
ISHLT	International Society for Heart and Lung Transplantation
LHI	Linksherzinsuffizienz
LVAD	Left Ventricular Assist Device
LVEF	Linksventrikuläre Ejektionsfraktion
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MAP	Mean Arterial Pressure
MI	Mitralklappeninsuffizienz
MITRA-FR	Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation
mPAP	mean Pulmonary Arterial Pressure
MR-proANP	Midregionales proatriales Natriuretisches Peptid
NT-proBNP	N-Terminal pro Brain Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonalarterie
PAC	Pulmonalarterielle Compliance
PAH	Pulmonalarterielle Hypertonie
PAPi	PA-Pulsatilitätsindex
PASP	Pulmonary Arterial Systolic Pressure
PAWP	Pulmonary Arterial Wedge Pressure
PH	Pulmonale Hypertonie
PMVR	Percutaneous Mitral Valve Repair
PP	Pulse Pressure
PVR	Pulmonary Vascular Resistance
PVRI	Pulmonary Vascular Resistance Index
RA	Right Atrium
RAP	Right Atrial Pressure
RC	Resistance Compliance
RHI	Rechtsherzinsuffizienz
RHK	Rechtsherzkatheter
ROC	Receiver Operating Characteristic
RR	Systemischer Blutdruck (nach Riva-Rocci)
RV	Rechter Ventrikel, rechtsventrikulär

RVSWI	Right Ventricular Stroke Work Index
SaO_2	Arterielle Sauerstoffsättigung
SAP	Systemic Arterial Pressure
6-MWD	6 Minutes Walk Distance
sPAP	Systolic Pulmonary Arterial Pressure
SV	Stroke Volume
SVI	Stroke Volume Index
SvO_2	Gemischt venöse Sauerstoffsättigung
TAPSE	Tricuspid Annular Plane Systolic Excursion
TD	Thermodilution
TEER	Transcatheter Edge-to-Edge Repair
TPG	Transpulmonaler Gradient
TPR	Total Pulmonary Resistance
VAD	Ventricular Assist Device
$V'E/V'CO_2$ slope	Anstiegssteilheit der Atemeffizienzkurve
$V'O_2$	Sauerstoffaufnahme
VRT	Vasoreaktivitätstestung
WHO	World Health Organization
WHO-FC	World Health Organization Functional Class
WU	Wood Units

9. Abbildungs- und Tabellenverzeichnis

9.1. Abbildungsverzeichnis

9.2. Tabellenverzeichnis

10. Literaturverzeichnis

10.1. Zitierte Literatur

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10.2. Publikationen des Verfassers

10.2.1. Erstautorenschaften / Seniorautorenschaften

1. **Rieth A**, Richter MJ, Gall H, Seeger W, Ghofrani HA, Mitrovic V, Hamm CW. Hemodynamic phenotyping based on exercise catheterization predicts outcome in patients with heart failure and reduced ejection fraction.
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12. Zugrundeliegende Publikationen

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Hemodynamic phenotyping based on exercise catheterization predicts outcome in patients with heart failure and reduced ejection fraction

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KEYWORDS:
exercise right heart catheterization;
survival;
prognostic factor;
heart failure with reduced ejection fraction;
hemodynamic phenotype

BACKGROUND: Exercise right heart catheterization (RHC) unmasks different phenotypes based on hemodynamic response to exertion in patients with heart failure. The prognostic relevance of this approach in patients with heart failure and reduced ejection fraction (HFrEF) is uncertain.
METHODS: We analyzed 167 patients with HFrEF from the Kerckhoff-Klinik Heart Failure Registry who underwent supine exercise RHC with constant external workload between September 2009 and August 2014. The primary outcome was heart transplant/assist device–free survival. Hemodynamic parameters that significantly predicted outcome were identified by multivariate Cox regression analysis and assessed further by Kaplan-Meier analysis after dichotomization using cutoffs derived from receiver operating characteristic analysis. Hemodynamic phenotypes were defined based on a dichotomized flow response (exercise-induced change in cardiac output [ΔCO]) combined with a dichotomized pressure response (exercise-induced change in systolic [ΔsPAP] or mean pulmonary arterial pressures).
RESULTS: ΔCO independently predicted transplant/assist device–free survival (multivariate hazard ratio [HR] 1.67; 95% confidence interval [CI], 1.09–2.58; $p = 0.02$). Patients with ΔCO $\geq$1.15 liter/min had significantly better 5-year transplant/assist device–free survival than patients with lower ΔCO (72.9% vs 22.5%; log-rank $p < 0.001$ [Kaplan-Meier analysis]). The hemodynamic phenotype of ΔCO $<$1.15 liter/min combined with ΔsPAP $<$17.5 mm Hg was associated with worse transplant/assist device–free survival than ΔCO $\geq$1.15 liter/min combined with ΔsPAP $\geq$17.5 mm Hg (multivariate HR 7.39; 95% CI, 2.27–24.05; $p = 0.001$).
CONCLUSIONS: Exercise RHC parameters are important prognostic indices in HFrEF. Hemodynamic phenotyping using ΔCO and ΔsPAP allows enhanced risk stratification.
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Much of the available data on prognostication in heart failure (HF) has been obtained using non-invasive methods. For example, alterations of the pulmonary circulation during exercise were associated with pathophysiologic phenotypes in echocardiographic analyses of patients with HF with reduced ejection fraction (HFrEF).[1,2] Moreover, parameters

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derived from cardiopulmonary exercise testing (CPET) are of major clinical and prognostic relevance in HF, having been shown to reflect the cardiac output (CO) response to exercise in patients with various cardiac diseases[3] as well as significantly predicting outcome in patients with HF[4] and being significantly associated with overall mortality in patients with HFrEF.[5] However, these non-invasive parameters (although well studied and relatively straightforward to measure) have certain limitations,[6] and invasive hemodynamic measurements could add valuable information.

The prognostic relevance of resting pulmonary hemodynamic parameters in patients with HF due to left heart disease (HF-LHD) has been repeatedly demonstrated, and the value of these parameters as markers of increased mortality is independent of the left ventricular ejection fraction.[7,8] In addition, the presence of combined post-capillary and pre-capillary pulmonary hypertension (PH) is useful in discriminating patients with HF-LHD with the highest mortality risk.[9–13] The strongest predictor of mortality is the combination of PH and right ventricular (RV) dysfunction in patients with HF-LHD.[14–18] Nevertheless, hemodynamic measurements do not yet play a role in routine risk stratification of patients with stable HFrEF.[19]

To overcome the limitations of single resting hemodynamic measurements, provocation tests that employ exercise, saline loading, vasoreactivity testing, or continuous hemodynamic monitoring have been suggested.[20,21] Exercise hemodynamic measurements were found to be more sensitive than saline loading for detecting early signs of HF with preserved ejection fraction,[21] but only a few publications have addressed their prognostic significance in LHD.[22,23] Moreover, current guidelines have not set recommendations for the performance and interpretation of hemodynamic measurements during exercise because of a lack of sufficient data and standardization of exercise protocols.[24] Therefore, the aims of the present study were to collect invasive pulmonary hemodynamic data reflecting RV function during exercise in patients with HFrEF, to assess the association of exercise hemodynamic parameters with outcome, and to define hemodynamic phenotypes with prognostic relevance based on pressure/flow responses to exercise.

Methods

Patients

Data collection and analyses were approved and the need to obtain written informed consent from each patient was waived by the ethics committee of the Faculty of Medicine at the University of Giessen (Approval No. 116/15). We analyzed data from the prospectively recruiting, single-center Kerckhoff-Klinik Heart Failure Registry. The analysis included consecutive patients registered from September 2009 to August 2014 with available exercise right heart catheterization (RHC) data and a diagnosis of HFrEF according to current guidelines,[19] with left ventricular ejection fraction $\leq$45%. Patients without adequate medical treatment or with severe valve defects (left-sided stenosis and regurgitation more than moderate),[25] ventricular assist devices (VADs), or acute untreated HF were excluded (Figure 1). Baseline

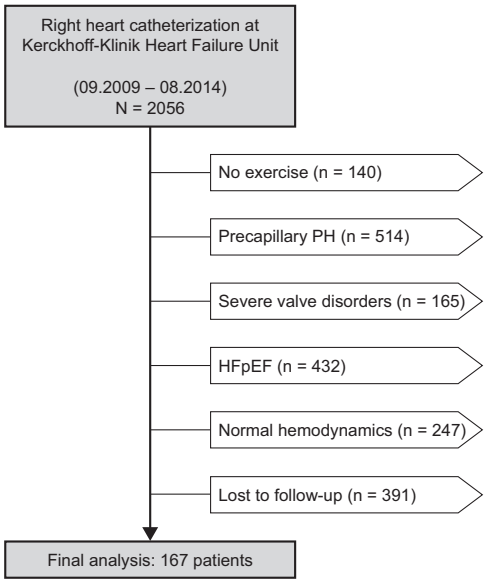


Figure 1 Patient flowchart. HFpEF, heart failure with preserved ejection fraction.

parameters derived from laboratory measurements, echocardiography (including systolic pulmonary arterial pressure and tricuspid annular plane systolic excursion assessed by transthoracic echocardiography),[26] CPET, and World Health Organization functional class were included in the analysis as available. Current diagnostic criteria from the European PH guidelines were applied to identify patients with isolated post-capillary PH (Ipc-PH) and combined pre-capillary and post-capillary PH.[24]

Exercise RHC

Patients underwent RHC by insertion of a Swan-Ganz catheter (7F thermodilution catheter; Biosensors International, Singapore) via the internal jugular vein or a cubital vein under local anesthesia, mainly by the same investigator (A.R.) not blinded to the clinical records. The zero reference level for the pressure transducer was placed at midthoracic level in the supine position.[27,28] Approximately 30 minutes after catheter insertion, resting measurements were performed during end-expiratory breath hold with the system averaging a minimum of 3 heart cycles, whereas during exercise all pulmonary pressures were averaged over several respiratory cycles (Figure S1, available in the online version of this article at www.jhltonline.org).[24,29] The following parameters were measured: systolic, diastolic, and mean pulmonary arterial pressure (sPAP, dPAP, and mPAP, respectively); right atrial pressure (RAP); pulmonary arterial wedge pressure (PAWP); mixed venous oxygen saturation (Svo_2); and CO by the thermodilution technique, averaging 3 (with deviation of $<10\%$) of 5 output determinations. The following parameters were calculated: cardiac index = CO/body surface area; transpulmonary gradient = mPAP − PAWP; pulmonary vascular resistance = mPAP − PAWP/CO; pulmonary arterial capacitance = stroke volume/pulse pressure = (CO/heart rate)/(sPAP − dPAP)[30]; and slopes of hemodynamic parameters/CO and Svo_2/CO as described previously.[31,32] Based on published data from healthy volunteers, an mPAP/CO slope of 0.5 to 3.0 mm Hg/liter/min was considered to represent an adequate increase in pulmonary arterial pressure (PAP) and CO, respectively.[31,33]

Exercise was performed on a standard cycle ergometer in the supine position according to previously published protocols of exercise RHC in patients with PH[27,28,34,35] or HF,[21,36] with an

adjusted constant external workload of 5, 10, 15, 25, 50, or 75 W. The workload was determined based on the workload achieved during CPET[27] (aiming for approximately 40%–60% of the CPET workload) with adjustment on an individual, clinical basis (Figure S2, available in the online version of this article at www.jhltonline.org)[37] to allow measurement of hemodynamic parameters at steady-state conditions after 3 minutes of exercise, with a total duration of 5 to 7 minutes.[28,38–40]

Outcome measure

The primary outcome was survival without a heart transplant or implantation of a VAD (left ventricular or biventricular).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY). Data are expressed as mean ± SD or median (interquartile range) for normally or non-normally distributed parameters, respectively. Between-group differences were analyzed with 2-tailed *t*-test or paired *t*-test for normally distributed parameters, Mann-Whitney test for non-normally distributed parameters, and Pearson chi-square test for categorical parameters as appropriate, with $p < 0.05$ considered statistically significant.

Independent predictors of transplant/VAD-free survival were identified using Cox proportional hazards regression models in univariate analyses followed by backward stepwise multivariate analyses based on likelihood ratio (multivariate Model 1). A strict univariate *p*-value criterion ($p < 0.001$) was used to select the variables entered into the multivariate model. Colinearity was assessed using bivariate linear regression between continuous variables or Wilcoxon tests across categorical variables. When ≥2 selected variables were intimately associated (correlation coefficient >0.45), the variable with the highest Wald statistic was chosen for the multivariate model. In all multivariate analyses, $p < 0.05$ was considered statistically significant.

The exercise response parameter that remained a significant predictor of outcome in multivariate Model 1 (exercise-induced change in CO [ΔCO]) was further assessed using Kaplan-Meier analyses with log-rank tests. Cutoffs for dichotomization were determined using receiver operating characteristic (ROC) analysis and the Youden Index. In addition, cutoffs for ΔsPAP and ΔmPAP[41] were determined using ROC analysis, and dichotomized ΔsPAP and ΔmPAP were then combined with dichotomized ΔCO to define hemodynamic phenotypes (ΔCO/ΔsPAP and ΔCO/ΔmPAP). To determine further the prognostic impact of dichotomized ΔCO and the hemodynamic phenotypes, we developed separate stepwise multivariate Cox regression models that included significant variables of Model 1 with the following modifications: replacement of continuous ΔCO with dichotomized ΔCO (Model 2a); addition of ΔCO/ΔsPAP phenotype (Model 2b); and addition of ΔCO/ΔmPAP phenotype (Model 2c).

Results

Baseline characteristics

The analysis included 167 patients with HFrEF. Left ventricular ejection fraction was markedly reduced, and most patients were in World Health Organization functional class III (Table 1). Many of the patients had a pacemaker or

Table 1 Baseline Characteristics in All Patients With HFrEF

	HFrEF
Patients, *n*	167
Male/female, *n/n*	125/42
Age, years	65.2 ± 12.2
BMI, kg/m^2	27.3 ± 4.7
WHO functional class, *n* (%)	
I	0
II	40 (24)
III	120 (71.9)
IV	7 (4.2)
Etiology, *n* (%)	
Ischemic heart disease	67 (40.1)
Dilated cardiomyopathy	80 (47.9)
Hypertensive heart disease	5 (3)
Other/unknown	15 (9)
Clinical characteristics, %	
Hypertension	73.1
Diabetes mellitus	31.7
Coronary artery disease	46.1
Atrial fibrillation/flutter	46.7
Chronic renal failure	37.7
Pacemaker/ICD	66.5
Mitral regurgitation grade, %	
None	34.7
Mild	41.3
Moderate	24.0
Tricuspid regurgitation grade, %	
0	30.3
1	47.7
2	20.0
3	1.9
Medications, %	
ACEI/ARB	86.6
Beta blocker	97.0
Diuretic	94.0
MRAs	82.0
Amiodarone	17.4
Digoxin	28.1
Laboratory	
NT-proBNP, pg/ml	2,020.5 (3,513.8)
Creatinine, mg/dl	1.3 ± 0.6
GFR, liter/min/m^2	68.6 ± 32.6
Echocardiography	
LVEF, %	24.7 ± 8.7
LA dilatation, %	84.9
LV dilatation, %	76.3
RA dilatation, %	48.4
RV dilatation, %	22.9
TAPSE, mm	15.8 ± 5.5
sPAP, mm Hg	50.0 ± 14.2
CPET	
Workload, W	57.5 ± 24.4
Peak V_{O_2}, ml • kg^{-1} • min^{-1}	12.4 ± 3.1
V_E/V_{CO_2} slope	40.5 ± 11.2

Values represent mean ± SD or median (interquartile range).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CPET, cardiopulmonary exercise testing; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal prohormone brain natriuretic peptide; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; V_E/V_{CO_2} slope, rate of increase in ventilation per unit increase in carbon dioxide production; V_{O_2}, oxygen uptake; WHO, World Health Organization.

implantable cardioverter-defibrillator, and 78 (46.7%) had atrial fibrillation/flutter (Tables S1 and S2, available in the online version of this article at www.jhltonline.org). PH was present at rest in 89 (53.3%) patients, 55 (61.8%) of whom had Ipc-PH (Tables S3 and S4, available in the online version of this article at www.jhltonline.org).

Exercise RHC

During exercise, patients with HFrEF had steep pressure-flow slopes compared with published data in healthy individuals,[31,33] resulting from substantial increases in pulmonary pressures accompanied by inadequate increases in CO. Heart rate and systemic blood pressure increased significantly during exercise (Table 2). Patients with resting mPAP $\geq$25 mm Hg, RAP $\geq$10 mm Hg, or PAWP $\geq$15 mm Hg showed a significant inability to increase CO and substantially steeper pressure-flow slopes (but no difference in heart rate) compared with patients who had lower resting pressures (Table S5, available in the online version of this article at www.jhltonline.org). Patients with atrial fibrillation/flutter during RHC had a lower maximum ΔCO and a higher RAP than patients without atrial fibrillation/flutter (Table S6, available in the online version of this article at www.jhltonline.org). Compared with patients with Ipc-PH, patients with combined pre-capillary and post-capillary PH showed a lower maximum cardiac index/CO, maximum PAWP, ΔPAWP, and maximum workload and a higher maximum sPAP, maximum mPAP, and exercise-induced change in pulmonary vascular resistance during exercise (Table S7, available in the online version of this article at www.jhltonline.org).

Outcome analysis

The mean follow-up period was 29.2 months $\pm$ 17.7 (median [interquartile range]: 26 [28] months), during which 60 (35.9%) patients died, 8 (4.8%) underwent heart transplantation, and 5 (3.0%) underwent VAD implantation. The overall 1-, 3-, and 5-year transplant/VAD-free survival

Table 2 Resting and Exercise Pulmonary Hemodynamics in All Patients With HFrEF

	HFrEF		
	Rest	Maximum	*p*-value[a]
Parameters			
sPAP, mm Hg	43.3 $\pm$ 15.1	64.2 $\pm$ 15.0	<0.001
mPAP, mm Hg	27.3 $\pm$ 9.4	43.1 $\pm$ 9.9	<0.001
dPAP, mm Hg	17.3 $\pm$ 7.5	27.9 $\pm$ 8.1	<0.001
PAWP, mm Hg	18.0 $\pm$ 8.0	29.0 $\pm$ 8.7	<0.001
RAP, mm Hg	7.6 $\pm$ 5.1	—	<0.001
TPG, mm Hg	9.3	14.3	<0.001
PVR, dyne • sec • cm^{-5}	192.0 $\pm$ 107.6	292.1 $\pm$ 185.3	<0.001
CO, liter/min	4.3 $\pm$ 1.1	5.7 $\pm$ 2.1	<0.001
Cardiac index, liter/min/m^2	2.2 $\pm$ 0.5	2.8 $\pm$ 1.0	<0.001
PAC, ml/mm Hg	2.9 $\pm$ 1.7	2.3 $\pm$ 3.2	0.008
Svo_2, %	65.6 $\pm$ 6.0	35.4 $\pm$ 11.8	<0.001
Heart rate, beats/min	69.5 $\pm$ 11.7	91.4 $\pm$ 24.0	<0.001
Systolic BP, mm Hg	111.6 $\pm$ 19.8	128.7 $\pm$ 29.4	<0.001
Diastolic BP, mm Hg	68.4 $\pm$ 10.5	74.4 $\pm$ 13.3	<0.001
Workload, W		35.3 $\pm$ 19.0	
Changes during exercise			
sPAP/CO slope, mmHg/liter/min	18.4 $\pm$ 13.4		
dPAP/CO slope, mmHg/liter/min	9.1 $\pm$ 8.6		
mPAP/CO slope, mmHg/liter/min	13.8 $\pm$ 9.6		
PAWP/CO slope, mmHg/liter/min	9.3 $\pm$ 8.6		
Svo_2/CO slope, %/liter/min	−30.1 $\pm$ 26.5		
ΔsPAP, mm Hg	20.9 $\pm$ 11.7		
ΔmPAP, mm Hg	15.8 $\pm$ 8.5		
ΔdPAP, mm Hg	10.6 $\pm$ 7.5		
ΔPAWP, mm Hg	11.0 $\pm$ 8.0		
ΔTPG, mm Hg	4.9 $\pm$ 6.5		
ΔPVR, dyne • sec • cm^{-5}	95.9 $\pm$ 134.3		
ΔPAC, ml/mm Hg	−0.68 $\pm$ 3.2		
ΔCO, liter/min	1.4 $\pm$ 1.4		
ΔHeart rate, beats/min	21.9 $\pm$ 22.3		

Values represent mean $\pm$ SD.

Δ, exercise-induced change; BP, blood pressure; CO, cardiac output; dPAP, diastolic pulmonary arterial pressure; HFrEF, heart failure with reduced ejection fraction; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; Svo_2, mixed venous oxygen saturation; TPG, transpulmonary gradient.

[a]*p*-Values are given for comparisons between groups using paired *t*-test.

was 85.9%, 61.1%, and 48.3%. In patients who survived (regardless of transplant/VAD status), the proportion in World Health Organization functional class II was significantly higher, N-terminal prohormone brain natriuretic peptide levels were significantly lower, and the prevalence of chronic renal failure, pacemakers/implantable cardioverter-defibrillators, use of digoxin, and RV dilatation was significantly lower than in non-survivors (Table S8, available in the online version of this article at www.jhltonline.org). Non-survivors had higher resting mPAP, dPAP, and PAWP than survivors, but resting CO was not significantly different between the 2 groups (Table S9, available in the online version of this article at www.jhltonline.org). During exercise, non-survivors had signifi cantly lower ΔCO than survivors as well as steeper pressure-flow slopes, lower pulmonary arterial capacitance, and lower ΔsPAP and ΔmPAP, whereas the change in heart rate was not different between the 2 groups.

Impact of exercise RHC parameters on outcome

Multiple parameters were significantly associated with transplant/VAD-free survival in the univariate analysis, and several parameters showed an independent relationship with outcome in multivariate Model 1, including ΔCO (hazard ratio [HR] 1.67; 95% confidence interval [CI], 1.09–2.58; $p = 0.02$) (Table 3 and Table S10, available in the online version of this article at www.jhltonline.org). According to ROC analysis, ΔCO of 1.15 liter/min showed the best prognostic cutoff with a sensitivity of 69.8% and a specificity of 83.3% (Figure S3, available in the online version of this article at www.jhltonline.org).

Table 3 Hazard Ratios and 95% Confidence Intervals for Independent Predictors of Transplant/VAD-Free Survival Identified by Stepwise Multivariate Cox Regression Analysis[a] in All Patients With HFrEF

	Transplant/VAD-free survival	
Variables	HR (95% CI)	*p*-value
WHO functional class		
II	Reference	
III vs II	8.70 (1.15–65.74)	0.04
IV vs II	12.21 (1.22–122.33)	0.03
LVEF, %	1.13 (1.05–1.23)	0.001
Systolic BP at rest, mm Hg	0.97 (0.94–1.00)	0.03
ΔCO, liter/min	1.67 (1.09–2.58)	0.02

Δ, exercise-induced change; BP, blood pressure; CI, confidence interval; CO, cardiac output; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; V_E/V_{CO_2} slope, rate of increase in ventilation per unit increase in carbon dioxide production; VAD, ventricular assist device; WHO, World Health Organization.

[a]Stepwise multivariate analysis was applied to all variables that were significant ($p \leq 0.001$) in the univariate analysis and after assessment of colinearity (Table S10, available in the online version of this article at www.jhltonline.org). Variables included in the multivariate analysis were PAWP/CO, ΔCO, systolic BP at rest, WHO functional class, RAP at rest, maximum cardiac index, V_E/V_{CO_2} slope, and LVEF.

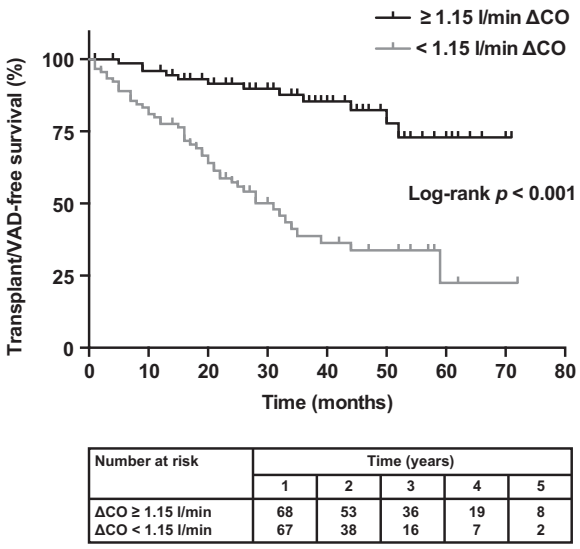


Figure 2 Kaplan-Meier transplant/VAD-free survival curves as a function of ΔCO in patients with HFrEF ($n = 167$; 5-year transplant/VAD-free survival, 22.5% [ΔCO <1.15 liter/min] vs 72.9% [ΔCO ≥1.15 liter/min]; log-rank $p < 0.001$).

This was confirmed by Kaplan-Meier analysis, which showed that patients with ΔCO ≥1.15 liter/min had significantly better 5-year transplant/VAD-free survival than patients with ΔCO <1.15 liter/min (72.9% vs 22.5%, respectively; log-rank $p < 0.001$) (Figure 2). A similar pattern was observed in the subgroups with Ipc-PH (log-rank $p = 0.01$) and mild to moderate mitral regurgitation (MR) (log-rank $p < 0.001$) (Figures S4 and S5, available in the online version of this article at www.jhltonline.org). In addition, patients with atrial fibrillation/flutter and CO ≥1. 15 liter/min had significantly better 3-year transplant/VAD-free survival than patients with ΔCO <1.15 liter/min (log-rank $p < 0.001$) (Figure S6, available in the online version of this article at www.jhltonline.org). In the full study population, dichotomized ΔCO remained an inde pendent predictor of outcome in multivariate Model 2a (HR 4.27; 95% CI, 1.58–11.49; $p = 0.004$) (Table S11, available in the online version of this article at www.jhltonline.org).

Impact of exercise hemodynamic phenotypes on outcome

ROC analysis–defined cutoffs for ΔsPAP and ΔmPAP were 17.5 mm Hg and 12.5 mm Hg, respectively (Figures S7 and S8, available in the online version of this article at www.jhltonline.org). The hemodynamic phenotype of ΔCO <1.15 liter/min and ΔsPAP <17.5 mm Hg was significantly associated with decreased transplant/VAD-free survival in multivariate Model 2b (HR 7.39; 95% CI, 2.27–24.05; $p = 0.001$) (Table 4). The hemodynamic phenotype based on ΔCO and ΔmPAP was not independently associated with outcome in multivariate Model 2c (data not shown).

Further Kaplan-Meier analysis revealed that patients with ΔCO ≥1.15 liter/min and ΔsPAP ≥17.5 mm Hg had greater 5-year transplant/VAD-free survival than patients with ΔCO <1.15 liter/min and ΔsPAP <17.5 mm Hg

(log-rank $p = 0.001$) (Figure 3A). The hemodynamic phenotype based on ΔCO/ΔsPAP also significantly discriminated 5-year transplant/VAD-free survival in the subgroup with Ipc-PH (log-rank $p = 0.026$) (Figure 3B) as well as 3-year transplant/VAD-free survival in the subset of patients with mild to moderate MR (log-rank $p < 0.001$) (Figure 3C). Although the PAWP/CO slope was not independently associated with outcome (Table 3), it differed significantly between the hemodynamic phenotypes, being steeper in the groups with more compromised CO (analysis of variance $p < 0.001$) (Figure S9, available in the online version of this article at www.jhltonline.org). The groups with more compromised hemodynamic parameters also had significantly lower peak oxygen uptake (V_{O_2}) and a higher rate of increase in ventilation per unit increase in carbon dioxide production (V_E/V_{CO_2} slope) (Figure 4).

Discussion

We have presented a comprehensive analysis of invasive hemodynamic parameters during exercise in patients with HFrEF. Novel findings of our study include the following: (1) ΔCO was associated with outcome; (2) the hemodynamic phenotype characterized by ΔCO <1.15 liter/min combined with ΔsPAP <17.5 mm Hg was associated with a poor prognosis; (3) both ΔCO and the hemodynamic phenotype based on ΔCO/ΔsPAP remained independently associated with outcome after adjustment for numerous baseline characteristics including characteristics reflecting resting PH; and (4) the hemodynamic phenotype based on ΔCO/ΔsPAP was associated with important CPET parameters (peak V_{O_2} and V_E/V_{CO_2}).

Despite 100% of our study population being treated with diuretics, 41 patients presented with RAP ≥10 mm Hg and 101 presented with PAWP ≥15 mm Hg. Pressure measurements are known to be highly dependent on volume load[42]; our data indicate that this limitation can be overcome by measuring ΔCO, which is an important independent prognostic parameter even when adjusted for multiple baseline characteristics. The inability to increase CO adequately might be caused by impaired ventricular contractile reserve,[31] an inadequate stroke volume reserve[43] coupled to chronotropic incompetence,[21] increased afterload,[44] backward failure,[44] dynamic RV dysfunction,[22] dynamic MR,[45] and intraventricular dyssynchrony. Accordingly, ΔCO was lower in patients with vs without atrial fibrillation/flutter detected during RHC; intermittent ineffective systolic actions known as pulse deficit caused by atrial arrhythmia could explain this. Moreover, RAP at rest was significantly elevated (indicating a tendency toward volume overload) in the group with atrial fibrillation/flutter. Atrial fibrillation may contribute to RV dysfunction via an increase in left-sided filling pressures leading to post-capillary PH.[46] However, the ability of ΔCO to discriminate transplant/VAD-free survival remained significant in the atrial fibrillation/flutter subgroup.

In daily clinical practice, certain hemodynamic phenotypes can be observed among patients with HFrEF, characterized by various combinations of left ventricular forward failure (reduced CO but no PH) and left ventricular backward failure (PH but preserved CO). We aimed to identify equivalents of these hemodynamic phenotypes during exercise and demonstrated for the first time that patients with the forward failure phenotype (i.e., low ΔCO and low ΔsPAP) have the worst outcome. Moreover, an increase in PAP alone was not adequate to predict outcome in our cohort. In pre-capillary PH, the elevated PAP is mainly caused by remodeling and vasoconstriction, so a pronounced increase in PAP during exercise is dependent only on the ability of the right ventricle to generate pressure.[41] In left-sided HF, the increase in sPAP during exercise is also influenced to a significant extent by backward transmission from the left ventricle, but RV contractility may still be of major relevance. In our model, the better outcome of patients with higher ΔsPAP and higher ΔCO may be explained by better preserved RV function. A previous study in patients with HFrEF identified a "plateau pattern" with stagnation of PAP after a steep initial increment, which was associated with increased mortality[22] and could indicate RV failure. Non-invasively assessed load-independent contractility during exercise was found to be preserved in HFrEF compared with HF with preserved ejection fraction,[36] which could mirror our high-flow/high-pressure hemodynamic phenotype. Moreover, a low tricuspid annular plane systolic excursion/sPAP ratio (reflecting RV contractility/afterload) in combination with

Table 4 Hazard Ratios and 95% Confidence Intervals for Transplant/VAD-Free Survival Stratified by Hemodynamic Phenotypes in Stepwise Multivariate Cox Regression Analysis[a] in All Patients With HFrEF

	Transplant/VAD-free survival	
Variables	HR (95% CI)	*p*-value
WHO functional class		
II	Reference	
III vs II	12.47 (1.58–98.25)	0.017
IV vs II	9.66 (0.97–95.73)	0.05
Systolic BP at rest, mm Hg	0.96 (0.93–0.99)	0.004
LVEF, %	0.90 (0.82–0.97)	0.006
ΔCO/ΔsPAP phenotype		
ΔCO ≥1.15 liter/min/ΔsPAP ≥ 17.5 mm Hg (I)	Reference	
ΔCO ≥1.15 liter/min/ΔsPAP <17.5 mm Hg vs (I)	0.46 (0.05–3.99)	0.48
ΔCO <1.15 liter/min/ΔsPAP ≥17.5 mm Hg vs (I)	2.28 (0.71–7.35)	0.17
ΔCO <1.15 liter/min/ΔsPAP <17.5 mm Hg vs (I)	7.39 (2.27–24.05)	0.001

Δ, exercise-induced change; BP, blood pressure; CI, confidence interval; CO, cardiac output; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary arterial pressure; VAD, ventricular assist device; WHO, World Health Organization.

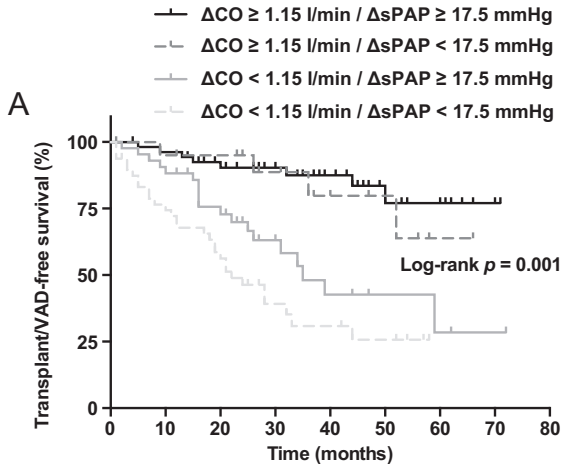
[a]Stepwise analysis was applied to all variables of the multivariate analysis (Table 3) and hemodynamic HFrEF phenotype based on ΔCO/ΔsPAP (Figure 3).

CPET parameters predicted survival in HF.[2] The exercise-induced increase of sPAP on echocardiography has been described as a marker of RV contractile reserve with prognostic relevance in pulmonary arterial hypertension[41]; our data suggest that ΔCO/ΔsPAP may be an additional prognostic surrogate for ventricular contractile reserve in HFrEF. The low-flow/high-pressure exercise response in our cohort was associated with a worse outcome than the high-flow/low-pressure pattern. This finding highlights the importance of CO, suggesting that this invasive measure might identify at-risk patients who would be missed by non-invasive sPAP measurement.

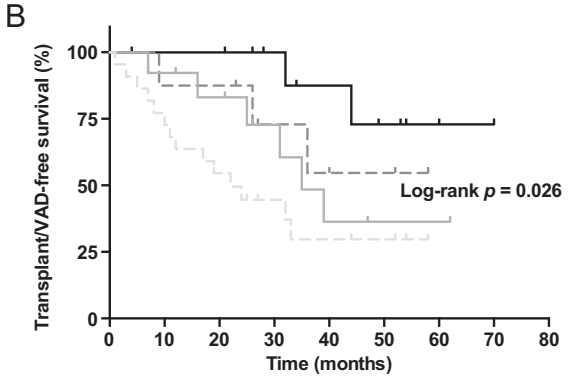
Recently, Guazzi et al[1] defined HFrEF subgroups based on the pattern of tricuspid annular plane systolic excursion at rest and during exercise (reflecting RV contractile reserve). In analogy to our invasive data, they observed different RV adaptive patterns with steeper pressure/flow curves (mPAP/CO), lower peak V_{O_2}, and a tendency toward a higher cardiac event rate in the more advanced phenotypes.[1] Therefore, our invasive data complement the described non-invasively measured RV adaptive patterns. Our data (Figure 4) also suggest that hemodynamic phenotyping may identify at-risk patients who would be missed by peak V_{O_2} assessment and vice versa; hemodynamic phenotyping might therefore add to established and standard prognostic CPET markers, such as peak V_{O_2}[5] and V_E/V_{CO_2},[47] for risk stratification of patients with HFrEF.

MR was significantly associated with survival in HF in previous studies.[48,49] We observed robust and significant associations of ΔCO and hemodynamic phenotypes based on ΔCO/ΔsPAP with transplant/VAD-free survival in patients with mild to moderate MR. Although our univariate model showed no significant association of mild to moderate MR with outcome, our data indicate that MR might make a relevant contribution to the hemodynamic phenotype and the primary outcome of our study. The hemodynamic phenotype based on ΔCO/ΔsPAP also discriminated transplant/VAD-free survival in patients with Ipc-PH in our study, highlighting the importance of RV function in these patients.

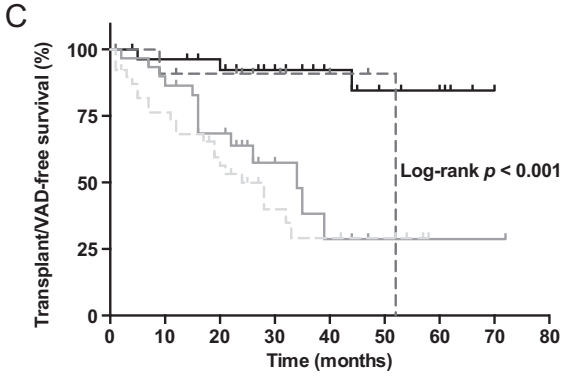
Limitations of this study include its single-center design, lack of validation in a control group, and the fact that exercise hemodynamic measurements were not repeated in individual patients to assess reproducibility. Furthermore, the exercise protocol has not yet been internationally standardized.[37] Measurement in the supine position allows the inclusion of patients with severe disease who might not tolerate a seated or semi-supine position. However, the



Number at risk	Time (years)				
	1	2	3	4	5
ΔCO ≥ 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	52	38	28	15	12
ΔCO ≥ 1.15 l/min / ΔsPAP < 17.5 mmHg	19	15	9	6	4
ΔCO < 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	37	24	9	8	2
ΔCO < 1.15 l/min / ΔsPAP < 17.5 mmHg	33	18	7	5	5



Number at risk	Time (years)				
	1	2	3	4	5
ΔCO ≥ 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	11	10	6	5	1
ΔCO ≥ 1.15 l/min / ΔsPAP < 17.5 mmHg	7	6	3	2	1
ΔCO < 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	10	8	4	2	1
ΔCO < 1.15 l/min / ΔsPAP < 17.5 mmHg	14	9	4	3	1



Number at risk	Time (years)		
	1	2	3
ΔCO ≥ 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	26	20	14
ΔCO ≥ 1.15 l/min / ΔsPAP < 17.5 mmHg	10	6	3
ΔCO < 1.15 l/min / ΔsPAP ≥ 17.5 mmHg	25	14	4
ΔCO < 1.15 l/min / ΔsPAP < 17.5 mmHg	27	15	5

Figure 3 Kaplan-Meier transplant/VAD-free survival curves as a function of hemodynamic phenotype based on ΔCO/ΔsPAP in (A) all patients with HFrEF ($n = 167$), (B) the subset with Ipc-PH ($n = 55$), and (C) the subset with mild/moderate MR ($n = 109$). ΔCO and ΔsPAP were dichotomized at cutoffs derived from receiver operating characteristic analyses (Figures S3 and S7, available in the online version of this article at www.jhltonline.org). The 5-year transplant/VAD-free survival in all patients with HFrEF was 25.7% (ΔCO <1.15 liter/min/ΔsPAP <17.5 mm Hg) vs 28.5% (ΔCO <1.15 liter/min/ΔsPAP ≥ 17.5 mm Hg) vs 63.8% (ΔCO ≥ 1.15 liter/min/ΔsPAP <17.5 mm Hg) vs 77.2% (ΔCO ≥ 1.15 liter/min/ΔsPAP ≥ 17.5 mm Hg) (log-rank $p = 0.001$). The corresponding percentages in the subset with Ipc-PH were 29.8% vs 36.3% vs 54.7% vs 72.9% (log-rank $p = 0.026$). The corresponding percentages for 3-year transplant/VAD-free survival in the subset with mild to moderate MR were 29.1% vs 38.3% vs 90.9% vs 92.3% (log-rank $p < 0.001$).

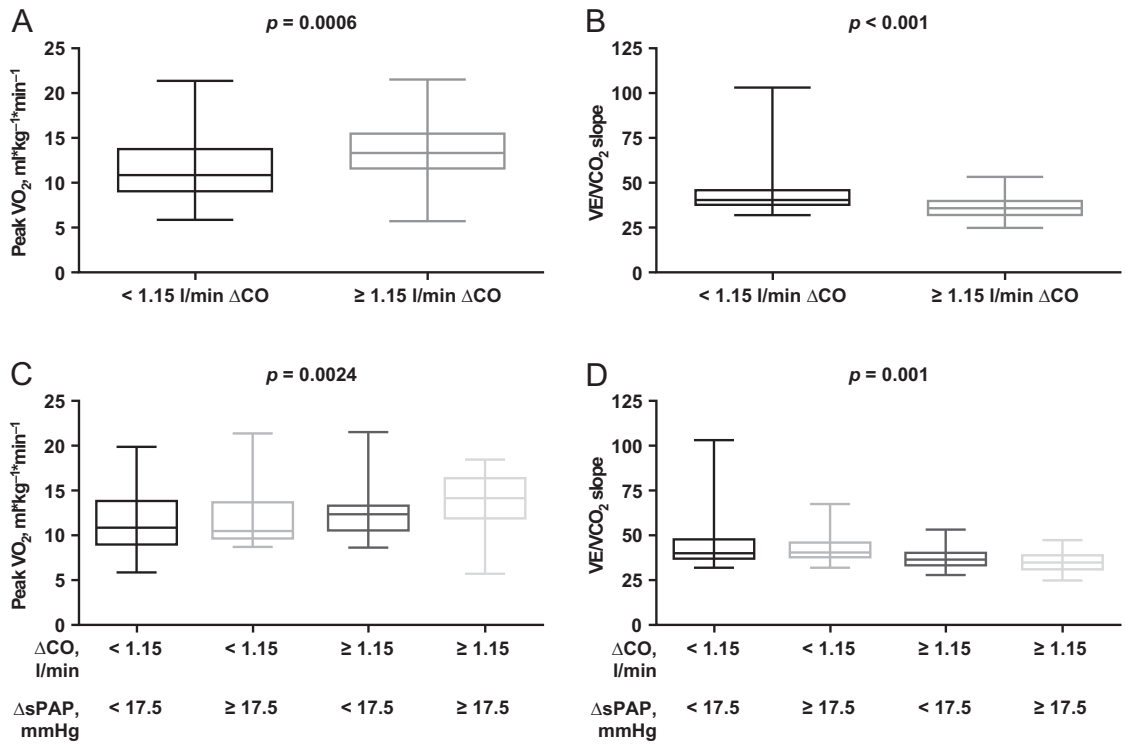


Figure 4 Peak V_{O_2} and rate of increase in V_E/V_{CO_2} slope according to ΔCO and hemodynamic phenotype based on ΔCO/ΔsPAP in patients with HFrEF. ΔCO and ΔsPAP were dichotomized at cutoffs derived from receiver operating characteristic analyses (Figures S3 and S7, available in the online version of this article at www.jhltonline.org). (A) Peak V_{O_2} differed significantly between the groups with ΔCO <1.15 liter/min and ΔCO ≥ 1.15 liter/min (mean $\pm$ SD, 11.5 $\pm$ 3.0 vs 13.6 $\pm$ 3.0; *t*-test $p = 0.0006$), (B) as did V_E/V_{CO_2} slope (44.1 $\pm$ 13.0 vs 36.1 $\pm$ 6.0; *t*-test $p < 0.001$). (C) Peak V_{O_2} also differed significantly between hemodynamic phenotypes (ΔCO <1.15 liter/min/ΔsPAP <17.5 mm Hg vs ΔCO <1.15 liter/min/ΔsPAP ≥ 17.5 mm Hg vs ΔCO ≥ 1.15 liter/min/ΔsPAP <17.5 mm Hg vs ΔCO ≥ 1.15 liter/min/ΔsPAP ≥ 17.5 mm Hg, 11.3 $\pm$ 3.1 vs 11.6 $\pm$ 2.9 vs 12.6 $\pm$ 3.1 vs 14.1 $\pm$ 2.8; one-way analysis of variance $p = 0.0024$), (D) as did V_E/V_{CO_2} slope (45.5 $\pm$ 16.5 vs 42.8 $\pm$ 7.9 vs 38.0 $\pm$ 7.3 vs 35.1 $\pm$ 5.2; one-way analysis of variance $p = 0.001$).

supine position leads to complete pulmonary vascular recruitment,[50] increases venous return at rest, and negatively influences the increase of stroke volume during exercise.[27] Therefore, the body position and exercise protocol must be considered when interpreting the hemodynamic results. We performed exercise measurements at a steady state rather than during a continuously increasing workload. Hemodynamic assessment during steady-state conditions is long established, and a steady state of CO is achieved after 2 to 3 minutes.[51,52] A supine exercise hemodynamic protocol with exercise stages lasting 3 to 5 minutes and measurements beginning during the last 1 to 2 minutes of each exercise step has been used in recent studies.[28,53,54] Mild to moderate exercise seems sufficient to challenge the capacity of the circulatory system, and measuring the cardiac index at S_{VO_2} of 30% is considered appropriate to detect cardiac dysfunction.[52] As average S_{VO_2} during exercise was near 30% in our cohort, we believe that the exercise level reached was sufficient. However, we cannot rule out an influence of exercise inhomogeneity (probably resulting in a submaximal rather than maximal exercise status), and our exercise test findings might not be directly extrapolated to maximal exercise testing.[27] In addition, our study focused exclusively on invasive hemodynamic parameters, and we did not perform a parallel CPET. Moreover, the previously observed "plateau and take-off" pattern of mPAP vs V_{O_2}[6] warrants further investigation, especially in patients with IpC-PH and combined pre-capillary and post-capillary PH. However, the hemodynamic phenotypes identified in our study were related to important CPET parameters such as peak V_{O_2} and V_E/V_{CO_2} slope measured a short time (several days) before the RHC assessment. Further studies are warranted to clarify the clinical role of invasive hemodynamic parameters in relation to indirect measurements of CO and CPET. Our study also did not measure ventricular elastance, pulmonary arterial elastance, and RV-arterial coupling during exercise. Previous studies have indicated that cardiac magnetic resonance imaging or conductance catheter measurements during exercise would have provided reliable and robust data regarding load-independent RV contractility[55]; this must be investigated further in clinical trials.

In conclusion, ΔCO was an independent prognostic factor in our HFrEF cohort. The differentiation of exercise hemodynamic phenotypes, with patients able to increase CO by ≥ 1.15 liter/min and sPAP by ≥ 17.5 mm Hg showing the best outcome, could expand the choice of available prognostic tools. Clinical decisions cannot be made based on registry data alone, and the results of our observational study require further investigation in prospective clinical trials (e.g., in combination with CPET and therapeutic intervention). If our findings are confirmed, one might speculate that risk stratification for heart transplantation

could be supported by results of exercise hemodynamic measurements in addition to standard parameters.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org.

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ORIGINAL PAPER

Exercise hemodynamics in heart failure patients with preserved and mid-range ejection fraction: key role of the right heart

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Abstract

Objective We sought to explore whether classification of patients with heart failure and mid-range (HFmrEF) or preserved ejection fraction (HFpEF) according to their left ventricular ejection fraction (LVEF) identifies differences in their exercise hemodynamic profile, and whether classification according to an index of right ventricular (RV) function improves differentiation.

Background Patients with HFmrEF and HFpEF have hemodynamic compromise on exertion. The classification according to LVEF implies a key role of the left ventricle. However, RV involvement in exercise limitation is increasingly recognized. The tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure (TAPSE/PASP) ratio is an index of RV and pulmonary vascular function. Whether exercise hemodynamics differ more between HFmrEF and HFpEF than between TAPSE/PASP tertiles is unknown.

Methods We analyzed 166 patients with HFpEF (LVEF ≥ 50%) or HFmrEF (LVEF 40–49%) who underwent basic diagnostics (laboratory testing, echocardiography at rest, and cardiopulmonary exercise testing [CPET]) and exercise with right heart catheterization. Hemodynamics were compared according to echocardiographic left ventricular or RV function.

Results Exercise hemodynamics (e.g. pulmonary arterial wedge pressure/cardiac output [CO] slope, CO increase during exercise, and maximum total pulmonary resistance) showed no difference between HFpEF and HFmrEF, but significantly

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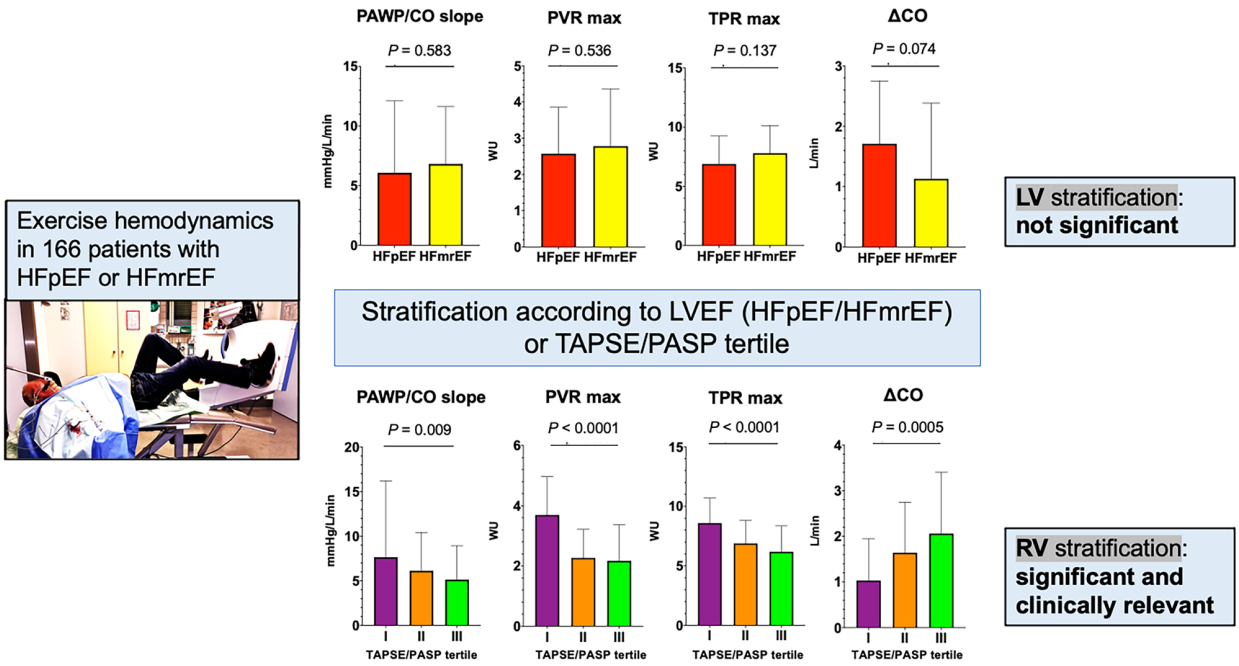
differed across TAPSE/PASP tertiles and were associated with CPET results. N-terminal pro-brain natriuretic peptide concentration also differed significantly across TAPSE/PASP tertiles but not between HFpEF and HFmrEF.

Conclusion In patients with HFpEF or HFmrEF, TAPSE/PASP emerged as a more appropriate stratification parameter than LVEF to predict clinically relevant impairment of exercise hemodynamics.

Graphic abstract



Stratification of exercise hemodynamics in patients with HFpEF or HFmrEF according to LVEF or TAPSE/PASP, showing significant distinctions only with the RV-based strategy. All data are shown as median [upper limit of interquartile range] and were calculated using the independent-samples Mann–Whitney *U* test or Kruskal–Wallis test. *PVR* pulmonary vascular resistance; *max* maximum level during exercise.

Keywords Exercise hemodynamics · Heart failure with preserved ejection fraction · Heart failure with mid-range ejection fraction · Right heart · TAPSE/PASP ratio

Introduction

Since its introduction in the "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" [1], the term "heart failure with mid-range ejection fraction" (HFmrEF, left ventricular ejection fraction (LVEF) 40–49%) has been the subject of broad discussion and controversy. There is still no general consensus as to whether HFmrEF truly represents a distinct entity or whether it should be grouped with "heart failure with preserved ejection fraction" (HFpEF; LVEF ≥ 50%) or "heart failure with reduced ejection fraction" (HFrEF; LVEF < 40%). Patients with HFmrEF show a high prevalence of coronary artery disease (similar to patients with HFrEF) and benefit from HFrEF drug therapies (in contrast to patients with HFpEF), leading some authors to propose categorizing HFmrEF together with HFrEF [2, 3]. However, HFmrEF shows greater similarity to HFpEF in other characteristics such as long-term prognosis [2]. Not least because of these inconsistencies, the concept of classifying patients with heart failure (HF) merely by their LVEF has been challenged fundamentally, and a more pathophysiological approach (e.g. based on hemodynamic characteristics) has been proposed [4–7].

However, both HFpEF and HFrEF often share progressive right ventricular (RV) impairment at rest and during exercise [8]. In this regard, the ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary arterial pressure (PASP) has been validated as an echocardiographic surrogate of right ventricular to pulmonary artery (RV-PA) coupling in HFpEF [9] and pulmonary hypertension (PH) [10], and further explored as an important determinate of afterload, symptomatology, and

Table 1 Baseline characteristics of patients with HFpEF and patients with HFmrEF

	N	HFpEF	HFmrEF	*P* value*
Patients, *n* (%)	166	125 (75.3)	41 (24.7)	
Male/female, (*n*/*n*)	166	54/71	28/13	0.005[a]
Age, years	166	74 [71–77]	73 [65–78]	0.216[b]
BMI, (kg/m^2)	166	28 ± 5	29 ± 5	0.487[c]
NYHA functional class, *n* (%)	166			0.347[a]
II		32 (25.6)	6 (14.6)	
III		90 (72.0)	34 (82.9)	
IV		3 (2.4)	1 (2.4)	
Clinical characteristics				
Hypertension, *n* (%)	165	100 (80.0)	36 (90.0)	0.148[a]
Diabetes mellitus, *n* (%)	162	23 (18.7)	17 (43.6)	0.002[a]
Coronary artery disease, *n* (%)	164	41 (33.1)	19 (47.5)	0.099[a]
Atrial fibrillation/flutter, *n* (%)	166	95 (76.0)	31 (75.6)	0.960[a]
Pacemaker or ICD, *n* (%)	166	23 (18.4)	18 (43.9)	0.001[a]
ICD		3 (2.4)	9 (22.0)	
Pacemaker		20 (16.0)	9 (22.0)	
Permanent RV pacing, *n* (%)	164	11 (8.8)	6 (14.6)	0.301[a]
CRT, *n* (%)	155	4 (3.2)	7 (17.1)	0.005[d]
Duration of HF diagnosis, months	166	0 [0–8]	9 [0–57]	< 0.001[b]
History of HF hospitalization, *n* (%)	148	49 (39.2)	22 (61.1)	0.085[d]
Medications, *n* (%)				
ACEI/ARB	165	82 (66.1)	32 (78.0)	0.115[a]
≥ 50% of target dose			21 (65.6)	
Beta-blockers	164	102 (82.3)	34 (82.9)	0.697[a]
≥ 50% of target dose			25 (73.5)	
Mineralocorticoid receptor antagonists	141	38 (38.4)	29 (70.7)	< 0.001[d]
≥ 50% of target dose			23 (88.5)	
Diuretics	163	100 (80.6)	36 (92.3)	0.087[a]
Digitoxin	163	18 (14.5)	9 (23.1)	0.210[a]
Laboratory tests				
NT-proBNP, (pg/mL)	88	1187 [679–1990]	1742 [908–4124]	0.124[b]
BNP, (pg/mL)	78	174 [130–295]	196 [144–377]	0.459[b]
GFR, (L/min/m^2)	163	70 ± 25	61 ± 23	0.05[c]
Echocardiography				
LVEF, (%)	165	60 [55–65]	45 [40–45]	< 0.001[b]
LVMI, (g/m^2)	86	120 ± 33	139 ± 27	0.004[c]
E/e'	71	16 [13–19]	13 [11–18]	0.156[b]
TAPSE, (mm)	166	19 [17–23]	15 [13–19]	< 0.001[b]
PASP, (mmHg)	166	45 [37–54]	48 [39–61]	0.455[b]
TAPSE/PASP, (mm/mmHg)	166	0.44 [0.35–0.58]	0.30 [0.24–0.54]	< 0.001[b]
Mitral regurgitation grade (1–3)	166			0.324[a]
0 (no mitral regurgitation)		42 (33.6)	19 (46.3)	
1		42 (33.6)	12 (29.3)	
2		41 (32.8)	10 (24.4)	
Tricuspid regurgitation grade (1–3)	166			0.559[a]
0 (no tricuspid regurgitation)		8 (6.4)	1 (2.4)	
1		59 (47.2)	24 (58.5)	
2		40 (32.0)	11 (26.8)	
3		18 (14.4)	5 (12.2)	
CPET				
Workload, (W)	79	65 ± 38	58 ± 26	0.461[c]

Table 1 (continued)

	N	HFpEF	HFmrEF	*P* value*
Peak V´O_2, (mL/min/kg)	79	12.3 [10.6–15.4]	11.6 [10.2–14.0]	0.227[b]
V´E/V´CO_2 slope	53	35 [31–40]	41 [34–47]	0.111[b]

Values represent mean ± standard deviation or median [interquartile range] except where otherwise indicated. *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CPET* cardiopulmonary exercise testing, *CRT* cardiac resynchronization therapy, *E/e'* ratio of mitral inflow velocity to annular relaxation velocity, *GFR* glomerular filtration rate, *ICD* implantable cardiac defibrillator, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *NT-proBNP* N-terminal fragment of pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PASP* systolic pulmonary arterial pressure, *RV* right ventricular, *TAPSE* tricuspid annular plane systolic excursion, *V´E/V´CO*$_2$ minute ventilation/carbon dioxide production, *V´O*$_2$ oxygen uptake

*HFpEF vs HFmrEF

[a]Pearson Chi-square test

[b]Mann–Whitney *U* test

[c]Independent Student's *t* test

[d]Fisher´s exact test

Table 2 Resting and exercise pulmonary hemodynamics in patients with HFpEF compared with patients with HFmrEF

Parameters	At rest				During exercise			
	n	HFpEF	HFmrEF	*P* value*	*n*	HFpEF	HFmrEF	*P* value*
mPAP, (mmHg)	166	24 [20–30]	23 [20–36]	0.680[a]	166	41 [35–50]	44 [36–53]	0.341[a]
PAWP, (mmHg)	166	15 [12–20]	16 [12–22]	0.503[a]	166	28 ± 6	27 ± 7	0.901[b]
TPG, (mmHg)	166	9 [7–12]	10 [7–14]	0.312[a]	166	15 [10–20]	16 [12–24]	0.208[a]
RAP, (mmHg)	165	7 [4–10]	7 [4–11]	0.794[a]	114	15 ± 7	17 ± 7	0.352[b]
CO, (L/min)	166	4.2 [3.5–4.8]	4.4 [3.4–5.3]	0.351[a]	166	6.1 [4.7–7.7]	6.1 [4.7–7.2]	0.535 [a]
PAC, (mL/mmHg)	165	2.4 [1.9–3.4]	2.4 [1.7–3.1]	0.862[a]	165	1.6 [1.3–2.1]	1.5 [1.2–2.0]	0.521 [a]
PAPi, (mmHg)	165	3.5 [2.7–6.9]	3.7 [2.8–6.1]	0.824[a]	114	2.8 [2.0–4.1]	2.5 [2.1–3.3]	0.381 [a]
RVSWI, (g/m^2/beat)	165	8.0 [6.3–9.9]	7.9 [5.7–11.0]	0.814[a]	116	13 ± 6	13 ± 6	0.932[b]
PVR, (WU)	166	2.0 [1.2–2.9]	2.1 [1.2–3.2]	0.644[a]	165	2.6 [1.8–3.9]	2.8 [1.8–4.4]	0.536 [a]
TPR, (WU)	166	6.0 [4.7–7.5]	5.6 [4.5–8.3]	0.983[a]	166	6.9 [5.5–9.3]	7.8 [6.1–10.1]	0.137 [a]
Heart rate, (beats/min)	165	65 [59–75]	66 [62–72]	0.673[a]	165	90 [76–105]	86 [75–96]	0.324 [a]
Systolic blood pressure, (mmHg)	165	129 ± 20	127 ± 19	0.483[b]	164	151 ± 26	145 ± 24	0.224[b]
Ea, (mmHg/mL)	165	0.50 [0.38–0.70]	0.52 [0.33–0.86]	0.836[a]	165	0.92 [0.68–1.3]	0.97 [0.72–1.3]	0.616 [a]
Total RV power, (watts)	166	0.29 [0.23–0.39]	0.31 [0.23–0.46]	0.301[a]	166	0.74 [0.56–0.95]	0.78 [0.59–0.91]	0.785[a]
mPAP/CO slope, (mmHg/L/min)	–	–	–	–	160	9.4 [5.9–16.5]	11.8 [7.2–21.7]	0.119[a]
PAWP/CO slope, (mmHg/L/min)	–	–	–	–	159	6.1 [3.5–12.1]	6.8 [3.9–11.6]	0.583[a]
ΔCO, (L/min)	–	–	–	–	166	1.7 [1.0–2.8]	1.1 [0.6–2.4]	0.074[a]
Workload, (W)	–	–	–	–	145	30 [25–50]	25 [25–50]	0.431[a]
Atrial fibrillation/flutter during RHC, *n* (%)	–	–	–	–	165	72 (57.6)	26 (63.4)	0.545[c]

Values represent mean ± standard deviation or median [interquartile range]

CO cardiac output, Δ*CO* change in cardiac output in response to exercise, *Ea* arterial elastance, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *mPAP* mean pulmonary arterial pressure, *PAC* pulmonary arterial capacitance, *PAPi* pulmonary artery pulsatility index, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RHC* right heart catheterization, *RV* right ventricular, *RVSWI* right ventricular stroke work index, *TPR* total pulmonary resistance, *WU* Wood Units

*HFpEF vs HFmrEF

[a]Mann–Whitney *U* test

[b]Independent Student's *t* test

[c]Pearson Chi-square test

outcome [11–13]. Our hypothesis was that classification of patients with HFpEF or HFmrEF according to LVEF is not suitable to predict exercise hemodynamic profile, and that classification using tertiles of the TAPSE/PASP ratio could be more appropriate for this purpose. Therefore, the primary objective of our study was to compare exercise hemodynamics during right heart catheterization (RHC) in a cohort of patients with HFpEF or HFmrEF stratified by LVEF or the TAPSE/PASP ratio. The secondary objective was to compare the exercise hemodynamic profile of patients with HFmrEF with that of patients with HFrEF.

Methods

Patients

We retrospectively analyzed data from the prospectively recruiting Kerckhoff-Klinik HF Registry and the Giessen PH Registry [14]. First, consecutive patients registered from 04/2009 to 03/2017 with available exercise RHC data were identified within the two databases (online resource 1). The main indication for RHC was suspected PH or evaluation of dyspnea (76%); other common indications were controls in patients already diagnosed with post-capillary PH (11%) and evaluation of valve defects of unknown significance (10%). We then excluded patients without a final diagnosis of HFpEF or HFmrEF according to current guidelines [1]. Patients without adequate medical treatment (i.e. patients with volume overload and [in patients with HFmrEF] lack of guideline-directed drug treatment), patients with severe valvular defects (left-sided stenosis and regurgitation more than moderate), ventricular assist devices, or acute untreated HF, and those without available measurements of TAPSE and/or PASP were also excluded.

Echocardiographic evaluation included standard acquisition of LVEF, baseline left ventricular mass index (LVMI), the ratio of mitral inflow velocity to annular relaxation velocity (E/e'), PASP derived from continuous wave Doppler assessment of the peak tricuspid regurgitant velocity, and TAPSE. In patients with atrial fibrillation, measurements of PASP and TAPSE were repeated until consistent measurements could be achieved. Baseline laboratory measurements, cardiopulmonary exercise testing (CPET) parameters, and New York Heart Association (NYHA) functional class were included in the analysis as available.

In addition, we analyzed patients with HFrEF (LVEF < 40%) from a previously published cohort [7]; patients with LVEF 40–45% ($n = 12$) and without available TAPSE and/or PASP measurements ($n = 47$) were excluded.

Exercise RHC

RHC was performed under local anesthesia with insertion of a Swan-Ganz catheter (7F Thermodilution Catheter, Biosensors International, Singapore) via the internal jugular vein or a cubital vein. The exercise protocol of the Kerckhoff-Klinik was published in detail previously [7]. Briefly, exercise was performed on a standard cycle ergometer in the supine position with an adjusted external workload, and workload was adapted stepwise until the patient was exhausted. The exercise protocol of the Giessen PH Division involved an incremental exercise test (step protocol with 3-min steps) in the semi-supine position with repeated hemodynamic measurements. The zero reference levels for the pressure transducer were placed as recommended for the supine position and the semi-supine position [15]. In both centers, workload was determined based on the workload achieved during CPET and/or adjusted on an individual, clinical basis to allow measurement of hemodynamic parameters for a total duration of < 10 min. In both centers, exercise was started 30 min after catheter insertion and all pulmonary pressures were averaged over several respiratory cycles [15].

The following parameters were measured: mean pulmonary arterial pressure (mPAP); right atrial pressure (RAP); pulmonary arterial wedge pressure (PAWP); and cardiac output (CO) by the thermodilution technique. The single CO measurements were repeated at least three times, until three measurements with < 10% deviation could be obtained, which were then averaged. The slopes of hemodynamic parameters/CO were calculated as recommended [16]. The pulmonary artery pulsatility index (PAPi), pulmonary arterial capacitance (PAC), total pulmonary resistance (TPR), pulmonary vascular resistance (PVR), transpulmonary gradient (TPG), right ventricular stroke work index (RVSWI), arterial elastance ($Ea = 1.65 \times mPAP - 7.79$/stroke volume), and total RV power were calculated as described previously [17–23]. The presence/absence of atrial fibrillation or flutter (AF) during RHC was also noted.

Statistical analysis

Statistical analysis was performed using SPSS, version 22.0 (IBM, Armonk, NY). Data are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] for normally or non-normally distributed parameters, respectively. Adherence to a Gaussian distribution was determined using the Kolmogorov–Smirnov test. Missing values were not imputed. Numbers of patients with available data for each parameter are provided.

Patients were stratified by tertile of TAPSE/PASP ratio as previously proposed [11, 13] (tertile 1: < 0.35 mm/mmHg; tertile 2: 0.35–0.51 mm/mmHg; tertile 3: > 0.51 mm/mmHg).

For independent samples, comparison was made with the independent-samples Kruskal–Wallis test or Mann–Whitney *U* test for non-normally distributed parameters, the Student's *t* test or analysis of variance for normally distributed parameters, and the Pearson Chi-square test or Fisher's exact test for categorical parameters as appropriate, with $P < 0.05$ considered statistically significant. Associations between parameters were assessed using simple linear regression.

Results

Comparison of patients with HFpEF vs HFmrEF

The analysis included 125 patients with HFpEF and 41 patients with HFmrEF. In comparison with the HFmrEF group, the patients with HFpEF presented with significantly lower rates of diabetes mellitus, markedly higher LVEF and TAPSE, and lower left ventricular (LV) mass index. Diastolic LV dysfunction was present in both the HFpEF and HFmrEF groups. Of note, the ratio of TAPSE/PASP was significantly higher in the HFpEF group compared with the HFmrEF group, despite both groups having similar PASP. The majority of patients in both groups were in NYHA functional class III, and the two groups showed no significant difference in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Both groups achieved similar levels of workload and peak oxygen uptake ($V´O_2$) during CPET, with no significant difference observed in the minute ventilation/carbon dioxide production ($V´E/V´CO_2$) slope. High rates of AF and systemic hypertension were reported. Use of devices (pacemaker/implantable cardiac defibrillator) was more common in the group with HFmrEF than the group with HFpEF. The degree of mitral or tricuspid regurgitation did not differ between the two groups (Table 1).

There was no difference in resting or exercise hemodynamics between the HFpEF and HFmrEF groups (Table 2). Of note, the increase of CO during exercise (ΔCO) showed no significant difference between the two groups. Starting from median resting pulmonary pressures below the definition of PH (mPAP ≥ 25 mmHg) [24], patients with HFpEF and HFmrEF showed a comparable pattern of concomitant increases in mPAP, PAWP, and RAP during exercise. These increases were accompanied by only a moderate increase of CO, resulting in steep mPAP/CO and PAWP/CO slopes. PAC decreased and RVSWI increased during exercise to a similar extent in the HFpEF and HFmrEF groups. Resting TPG and PVR were low in both groups. Interestingly, PAPi substantially decreased (i.e. worsened) from rest to exercise in both the HFpEF and HFmrEF groups (for both groups: $P < 0.001$; related-samples Wilcoxon signed rank test).

Impact of RV function

Echocardiography at rest revealed significantly better longitudinal RV function in patients with HFpEF versus HFmrEF (TAPSE 19 [17–23] vs 15 [13–19] mm, $P < 0.001$). LVEF and TAPSE were moderately correlated (Spearman $r = 0.41$, $P < 0.001$). However, these findings did not translate into differences in symptoms or hemodynamics between the HFpEF and HFmrEF groups at rest and during exercise. By contrast, stratification of the patients by TAPSE/PASP tertile revealed that those in the lowest tertile had higher NT-proBNP levels, steeper $V´E/V´CO_2$ and mPAP/CO slopes, and a substantially higher degree of LV backward failure (higher PAWP/CO slope and PAWP during exercise), pulmonary vascular disease and thus RV afterload (higher PVR, TPR, and Ea, and lower PAC during exercise), and impairment of CO reserve (reduced maximum CO and ΔCO) than those in the intermediate and highest tertiles (Tables 3 and 4 and graphic abstract). However, hemodynamic indices of RV contractile function during exercise (RVSWI and PAPi) were not significantly different between the TAPSE/PASP tertiles. NYHA functional class showed a difference between TAPSE/PASP tertiles which was borderline significant ($P = 0.053$; Table 3), and TAPSE/PASP showed a significant decrease with increasing NYHA functional class ($P = 0.035$; Fig. 1).

PAWP/CO slope, maximum TPR and PVR, and ΔCO showed associations with exercise capacity (peak $V´O_2$) and ventilatory inefficiency ($V´E/V´CO_2$ slope) during CPET (Fig. 2).

In summary, key hemodynamic and CPET parameters as well as NT-proBNP concentration were markedly more different between TAPSE/PASP tertiles than between patients with HFpEF and those with HFmrEF.

Comparison of patients with HFmrEF vs HFrEF

Patients with HFrEF ($n = 108$) showed no differences in NYHA functional class and age, lower rates of AF and hypertension, higher rates of implantable cardiac defibrillator and ß-blocker use, and markedly higher NT-proBNP levels compared with patients with HFmrEF (online resource 2). Interestingly, TAPSE, PASP, and the TAPSE/PASP ratio did not show significant differences between the two groups. Exercise hemodynamics showed important differences: patients with HFrEF had lower CO at rest and during exercise, lower ΔCO, and higher TPR, Ea, and total RV power than patients with HFmrEF (online resources 3 and 4).

Table 3 Baseline characteristics in patients with HFpEF and HFmrEF stratified by TAPSE/PASP tertile

	TAPSE/PASP tertile			
	I	II	III	*P* value*
Patients, *n* (%)	55	56	55	
Male/female, (*n*/*n*)	34/21	26/30	22/33	0.063[a]
Age, years	75 [71–79]	74 [69–77]	74 [65–77]	0.167[d]
BMI, (kg/m^2)	28 ± 7	27 ± 5	29 ± 6	0.501[b]
NYHA class, *n* (%)				0.053[a]
II	6 (10.9)	18 (32.1)	14 (25.5)	
III	47 (85.5)	36 (64.3)	41 (74.5)	
IV	2 (3.6)	2 (3.6)	0	
Clinical characteristics				
Hypertension, *n* (%)	44 (80.0)	45 (80.4)	47 (85.5)	0.761[a]
Diabetes mellitus, *n* (%)	24 (43.6)	10 (17.9)	6 (10.9)	< 0.001[a]
Coronary artery disease, *n* (%)	29 (52.7)	17 (30.4)	14 (25.5)	0.003[a]
Atrial fibrillation/flutter, *n* (%)	48 (87.3)	44 (78.6)	34 (61.8)	0.007[a]
Pacemaker or ICD, *n* (%)	14 (25.5)	14 (25.0)	12 (23.6)	0.974[a]
Permanent RV pacing, *n* (%)	6 (10.9)	7 (12.5)	4 (7.3)	0.665[a]
CRT, *n* (%)	5 (9.1)	1 (1.8)	5 (9.1)	0.508[c]
Duration of HF diagnosis, months	1 [0–16]	1.5 [0–18.5]	0 [0–10]	0.672[d]
History of HF hospitalization, *n* (%)	24 (43.6)	24 (42.9)	23 (41.8)	0.874[a]
Medications, *n* (%)				
ACEI/ARB	40 (72.7)	40 (71.4)	35 (63.6)	0.466[a]
Beta-blockers	44 (80.0)	45 (80.4)	47 (85.5)	0.761[a]
Mineralocorticoid receptor antagonists	27 (49.1)	17 (30.4)	23 (41.8)	0.327[a]
Diuretics	47 (85.5)	47 (83.9)	42 (76.4)	0.148[a]
Digitoxin	7 (12.7)	12 (21.4)	8 (14.5)	0.476[a]
Laboratory tests				
NT-proBNP, (pg/mL)	1849 [1152–3739]	1132 [668–1768]	1000 [521–1748]	0.005[d]
BNP, (pg/mL)	216 [174–377]	187 [110–282]	154 [121–282]	0.060[d]
GFR, (L/min/m^2)	62 ± 24	73 ± 25	70 ± 25	0.062[b]
Echocardiography				
LVEF, (%)	50 [45–60]	55 [55–60]	60 [50–65]	< 0.001[d]
LVMI, (g/m^2	135 ± 28	114 ± 25	124 ± 39	0.012[b]
E/e'	18 [13–22]	16 [13–18]	14 [12–17]	0.107[d]
TAPSE, (mm)	14 [13–17]	19 [17–22]	22 [19–26]	< 0.001[d]
PASP, (mmHg)	58 [50–69]	48 [40–52]	35 [31–40]	< 0.001[d]
TAPSE/PASP, (mm/mmHg)	0.26 [0.21–0.30]	0.42 [0.38–0.46]	0.62 [0.57–0.72]	< 0.001[d]
Mitral regurgitation grade (1–3)				0.642[a]
0 (no mitral regurgitation)	20 (36.4)	20 (35.7)	21 (38.2)	
1	15 (27.3)	22 (39.3)	17 (30.9)	
2	20 (36.4)	14 (25.0)	17 (30.9)	
Tricuspid regurgitation grade (1–3)				0.380[a]
0 (no tricuspid regurgitation)	2 (3.6)	2 (3.6)	5 (9.1)	
1	26 (47.3)	25 (44.6)	32 (58.2)	
2	20 (36.4)	19 (33.9)	12 (21.8)	
3	7 (12.7)	10 (17.9)	6 (10.9)	
CPET				
Workload, (W)	50 [40–58]	50 [40–90]	60 [46–90]	0.075[d]
Peak V´O_2, (mL/min/kg)	11.5 [9.8–13.6]	11.6 [10.3–16.3]	13 [11.4–15.3]	0.163[d]

Table 3 (continued)

	TAPSE/PASP tertile			
	I	II	III	*P* value*
V´E/V´CO_2 slope	42 [35–53]	32 [30–47]	37 [32–40]	0.015[d]

Values represent mean ± standard deviation or median [interquartile range] except where otherwise indicated

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CPET* cardiopulmonary exercise testing, *CRT* cardiac resynchronization therapy, *E/e'* ratio of mitral inflow velocity to annular relaxation velocity, *GFR* glomerular filtration rate, *ICD* implantable cardiac defibrillator, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *NT-proBNP* N-terminal fragment of pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PASP* systolic pulmonary arterial pressure, *RV* right ventricular, *TAPSE* tricuspid annular plane systolic excursion, *V´E/V´*CO_2 minute ventilation/carbon dioxide production, *V´*O_2 oxygen uptake

*Comparison across all TAPSE/PASP tertiles

[a]Pearson Chi-square test

[b]Analysis of variance

[c]Fisher´s exact test, tertile I + II vs III

[d]Independent-samples Kruskal–Wallis test

Discussion

We here present an analysis of invasive hemodynamics at rest and during exercise in patients with HFpEF, HFmrEF, and HFrEF. Our cohort of patients had manifest HF, as indicated by their NYHA functional class and NT-proBNP levels. The relevant findings of our study are as follows: (1) patients with HF classified based on LVEF (mid-range vs preserved) do not show relevant differences in their exercise hemodynamic and clinical profile; (2) patients with HF stratified according to the TAPSE/PASP ratio as an echocardiographic surrogate of RV-PA coupling show several important differences in their hemodynamic, CPET, and clinical profile, supporting a key role of the right ventricle in determining the severity of both HFpEF and HFmrEF; and (3) in terms of exercise hemodynamic phenotype, HFmrEF shares greater similarity with HFpEF than with HFrEF.

LVEF is universally accepted as an index of contractility, but it is known to have low specificity [25], and a more detailed phenotyping is desirable [26]. Recent analyses of outcomes and the effect of specific medications in HF indicate that LVEF may be more useful as a continuum than as a categorical variable with rigid cutoffs [4, 27]. Moreover, an index derived using a pathophysiological approach is expected to correlate better with HF symptoms and exercise capacity than LVEF, although the use of such an approach to guide HF therapy has not yet been validated [5]. Our results support these findings, since hemodynamic profiles at rest and during an exercise challenge showed very little association with LVEF classified as mid-range (40–49%) or preserved (≥ 50%) in our cohort [15, 25, 28]. However, comparison between patients with HFmrEF and patients with HFrEF showed more severe failure to increase CO during exercise and more advanced pulmonary vasculopathy with RV afterload elevation in the latter group, while maximum PAWP and PAWP/CO slope were not different. A cautious interpretation could suggest the right ventricle as a key factor for disease severity also in patients with HFrEF. Paradoxically, echocardiographic RV parameters were not different between HFrEF and HFmrEF; one possible explanation is that those were measured only at rest. All in all, HFmrEF shares more exercise hemodynamic characteristics with HFpEF than with HFrEF.

We used the TAPSE/PASP ratio as the key criterion to stratify our cohort of patients with preserved and mid-range ejection fraction. This stratification led to a clinically relevant differentiation of our cohort, as those with greater impairment of RV function according to the TAPSE/PASP ratio showed a depressed ability to increase CO and a higher degree of RV afterload during exercise. By contrast, indices of RV contractility during exercise showed no difference across TAPSE/PASP tertiles, possibly indicating a predominant role of afterload. Although TAPSE is known to reflect RV longitudinal contractility and to give prognostic information [29, 30], its value for a more comprehensive description of RV function is limited [31, 32]. Measuring contractility without respect to the related afterload may be insufficient to describe circulatory function. We interpret the marked differences in RV load in the absence of differences in hemodynamic indices of RV contractility across TAPSE/PASP tertiles in this context. Patients with a more favorable relationship of RV load to contractility have an increased CO reserve, which is ultimately the most important factor and has a positive impact on prognosis [7].

Surprisingly at first sight, those patients with a reduced TAPSE/PASP ratio also showed more pronounced LV dysfunction expressed by a steeper PAWP/CO slope and higher maximum PAWP. However, this is consistent with the left ventricle being the origin and driver of the dysfunctional RV-pulmonary circulation unit [33, 34].

Table 4 Resting and exercise pulmonary hemodynamics in patients with HFpEF and HFmrEF stratified by TAPSE/PASP tertile

Parameters	At rest				During exercise			
	I	II	III	*P* value*	I	II	III	*P* value*
mPAP, (mmHg)	30 [22–37]	24 [20–30]	22 [19–24]	< 0.001	47 [39–55]	42 [35–48]	39 [34–47]	< 0.001
PAWP, (mmHg)	18 [15–22]	15 [12–22]	13 [11–17]	0.001	29 [25–33]	28 [24–32]	25 [22–30]	0.036
RAP, (mmHg)	8 [6–10]	6 [3–10]	6 [4–9]	0.128	17 [12–22]	15 [10–20]	15 [10–19]	0.328
CO, (L/min)	4.3 [3.4–5.0]	4.2 [3.5–5.0]	4.1 [3.4–5.0]	0.905	5.5 [4.3–6.9]	6.3 [4.8–7.6]	6.3 [4.8–8.3]	0.041
PAC, (mL/mmHg)	2.0 [1.5–2.7]	2.4 [2.0–3.5]	2.7 [2.0–3.5]	< 0.001	1.4 [1.1–1.7]	1.7 [1.4–3.5]	1.8 [1.4–2.8]	< 0.001
PAPi, (mmHg)	3.5 [2.9–6.0]	3.7 [2.2–8.0]	3.8 [2.8–5.3]	0.866	2.8 [2.2–3.6]	2.8 [1.9–4.5]	2.8 [2.0–3.6]	0.820
RVSWI (g/m^2/beat)	9.5[6.8-12.0]	10.0 ± 4.1	8.0 ± 3.1	0.012	13.0 ± 6.1	15.0 ± 6.6	13.0 ± 6.0	0.392[b]
PVR, (WU)	2.9 [2.0–3.7]	1.7 [1.2–2.4]	1.7 [1.1–2.5]	< 0.001	3.7 [2.4–5.0]	2.3 [1.6–3.2]	2.2 [1.6–3.4]	< 0.001
TPR, (WU)	6.7 [5.2–9.3]	5.8 [4.3–7.3]	5.2 [4.2–7.2]	0.002	8.6 [6.7–10.7]	6.7 [5.4–8.8]	6.2 [4.9–8.4]	< 0.001
Ea, (mmHg/mL)	0.65 [0.45–0.96]	0.49 [0.34–0.70]	0.47 [0.33–0.61]	< 0.001	1.1 [0.85–1.5]	0.90 [0.63–1.3]	0.85 [0.59–1.0]	< 0.001
Total RV power, (watts)	0.35 [0.25–0.53]	0.28 [0.20–0.40]	0.27 [0.22–0.34]	0.007	0.79[0.59–0.94]	0.75 [0.57–0.98]	0.71 [0.53–0.85]	0.711
Heart rate (beats/min)	66 [60–75]	65 [59–75]	65 [57–71]	0.292	89 [75–102]	89 [78–101]	90 [71–102]	0.901
mPAP/CO slope, (mmHg/L/min)	–	–	–	–	14.1 [8.9–26.9]	8.7 [5.7–13.6]	7.5 [4.9–13.8]	< 0.001
PAWP/CO slope, (mmHg/L/min)	–	–	–	–	7.6 [4.5–16.2]	6.1 [3.6–10.4]	5.1 [2.8–8.9]	0.009
ΔCO, (L/min)	–	–	–	–	1.0 [0.5–2.0]	1.6 [1.0–2.7]	2.1 [1.1–3.4]	< 0.001
Workload, (W)	–	–	–	–	25 [25–40]	35 [25–50]	43 [25–50]	0.086
Atrial fibrillation/flutter during exercise RHC, *n* (%)	–	–	–	–	42 (76.4)	34 (60.7)	22 (40.0)	< 0.001[a]

Values represent mean ± standard deviation or median [interquartile range] except where otherwise indicated

CO cardiac output, Δ*CO* change in cardiac output in response to exercise, *Ea* arterial elastance, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *mPAP* mean pulmonary arterial pressure, *PAC* pulmonary arterial capacitance, *PAPi* pulmonary artery pulsatility index, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RC time* constant of the pulmonary circulation, *RV* right ventricular, *RVSWI* right ventricular stroke work index, *TPG* transpulmonary gradient, *WU* Wood units

*Independent-samples Kruskal–Wallis test for comparison across all TAPSE/PASP tertiles, unless otherwise specified

[a]Pearson Chi-square test

[b]Analysis of variance

The clinical relevance of the hemodynamic key parameters we found related to TAPSE/PASP is underlined by their correlation to CPET parameters with proven prognostic impact [6].

Therefore, we see these hemodynamic differences across TAPSE/PASP tertiles as a strong hint for a key role of RV failure—as a consequence of LV dysfunction causing increased RV afterload—in depressed CO response and the heart failure syndrome, independent from the resting LVEF category (mid-range or preserved). Our findings are consistent with numerous previous reports indicating the dominance of RV dysfunction for the prediction of symptoms and risk stratification in patients with HFpEF [35] and HFrEF [36, 37]. Although the noninvasively measured index of TAPSE/PASP has been shown to indicate risk in all patients with HF [37], concerns have been raised about the use of echocardiography values alone because of broad confidence intervals [38]. Hemodynamic characteristics measured by RHC could complement echocardiographic measurements and provide the basis for clinical management and entry criteria for clinical trials [39]. How to improve RV loading conditions in patients with HF is an unsolved clinical issue and should be investigated in future studies. The TAPSE/PASP ratio and ΔCO could be used as selection criteria among others to test therapeutic strategies.

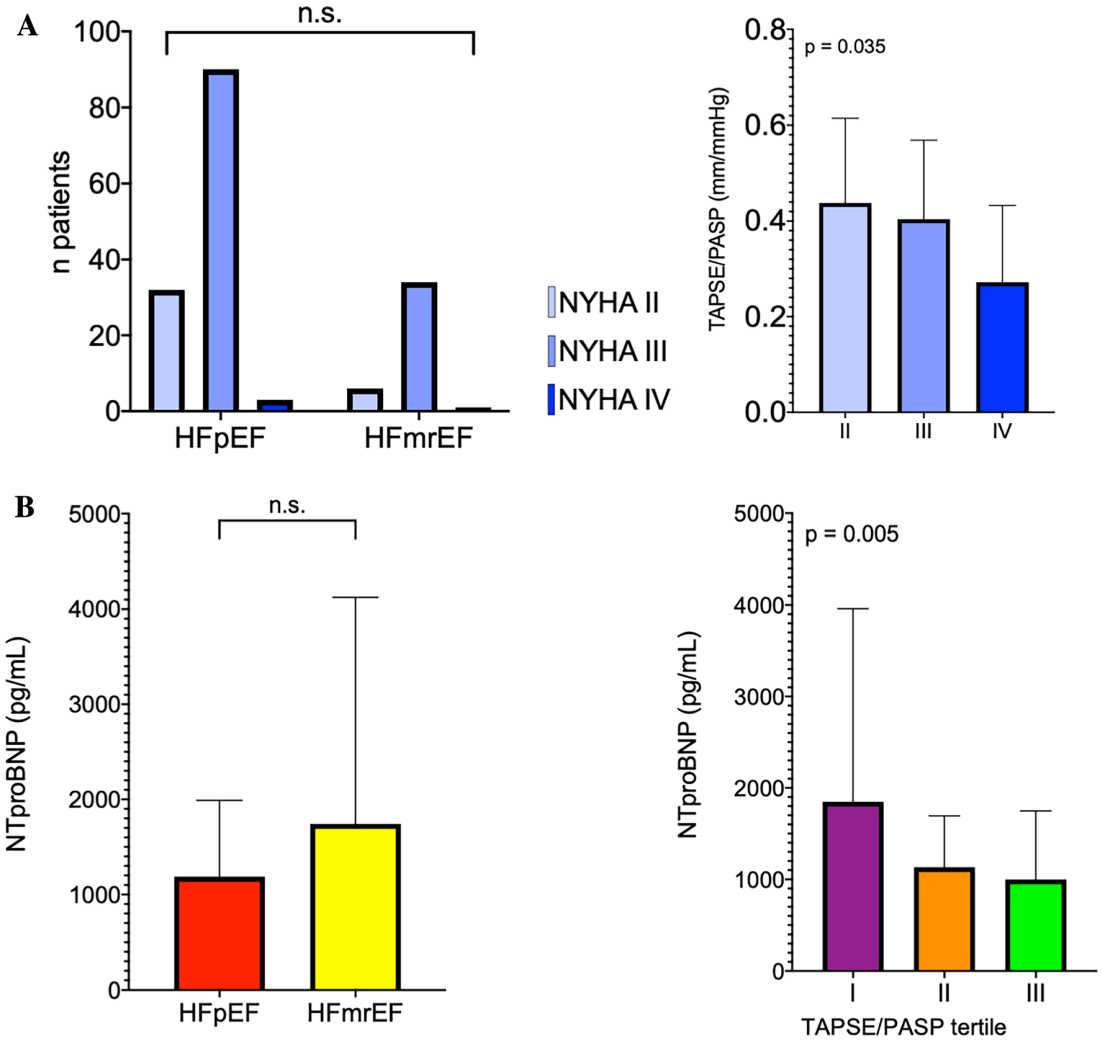


Fig. 1 **a** Stratification of New York Heart Association functional class according to heart failure with preserved or mid-range ejection fraction and TAPSE/PASP stratified by NYHA class. **b** Stratificaton of NT-proBNP levels according to HFpEF/HFmrEF or TAPSE/PASP. The first display shows numbers of patients, otherwise median values are shown, with error bars indicating the upper limit of the interquartile range. Statistical significance was assessed using the Chi-square test, the Kruskal–Wallis and the Mann–Whitney U test. *HFpEF* heart failure with preserved ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *NYHA* New York Heart Association, *PASP* systolic pulmonary arterial pressure, *TAPSE* tricuspid annular plane systolic excursion, *NT-proBNP* N-terminal pro-brain natriuretic peptide

Limitations

Limitations of our study include its two-center design and the lack of additional echocardiographic parameters, such as deformation imaging of the left and right ventricle and RV fractional area change. The different exercise protocols in the Kerckhoff-Klinik and the Giessen PH Division (supine vs semi-supine exercise) may be a source of bias. In addition, the high rate of atrial fibrillation in our cohort carries a risk of error for CO measurement; however, repetitive measurements as described in our methods section have the potential to minimize this risk. Echocardiographic parameters during exercise would also have been of interest but were not available. In addition, CPET data were not available in all patients. Outcome data were not registered systematically; analyses of the available data on hospitalization for HF did not show associations with the TAPSE/PASP ratio, which is in contrast to previously published data [11]. Concerning mortality, the number of registered events was too low for meaningful analysis of prognostic relevance.

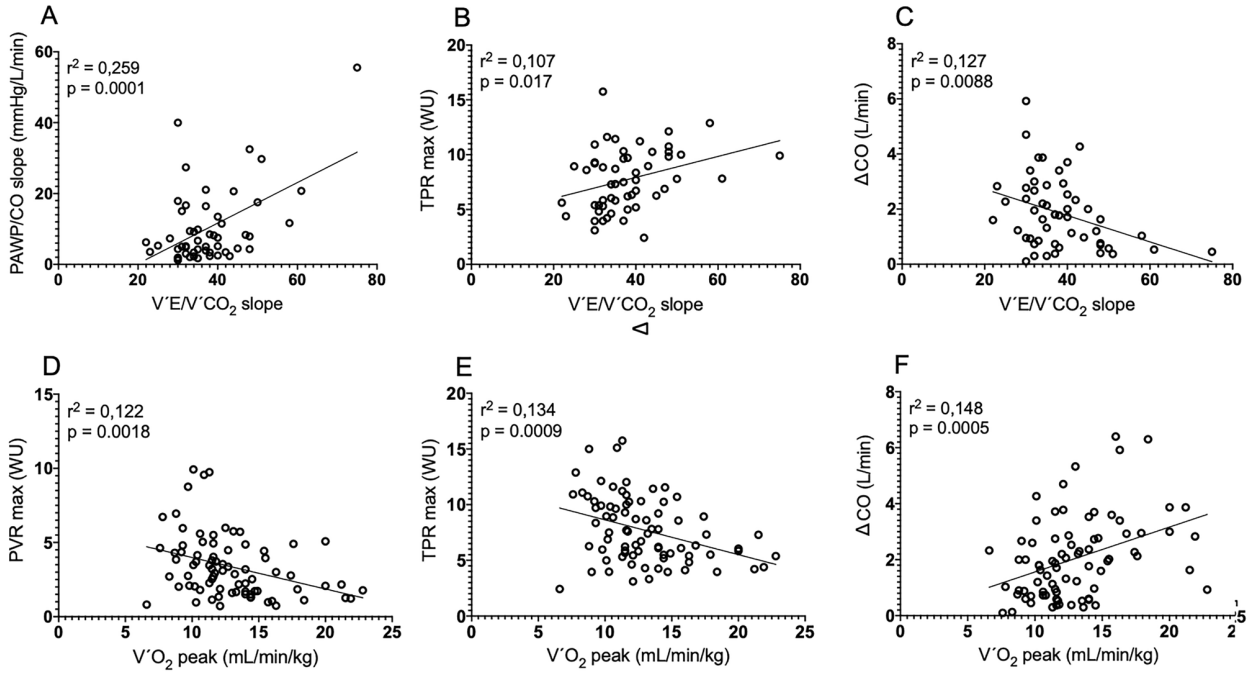


Fig. 2 Association of exercise hemodynamics with cardiopulmonary exercise test parameters. The association of ventilatory inefficiency ($V´E/V´CO_2$ slope) with **A** PAWP/CO slope, **B** TPR max, and **C** ΔCO, and the association of exercise capacity ($V´O_2$ peak) with **D** PVR max, **E** TPR max, and **F** ΔCO are shown. Data were calculated using simple linear regression. *CO* cardiac output, *ΔCO* change in cardiac output in response to exercise, *Max* maximum level during exercise, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *TPR* total pulmonary resistance, *$V´E/V´CO_2$* minute ventilation/carbon dioxide production, *$V´O_2$ peak* peak oxygen uptake, *WU* Wood Units

Conclusion

In conclusion, the categorization of HF as HFpEF and HFmrEF did not correspond to exercise hemodynamic profiles or exercise limitation in our cohort. Stratification based on an echocardiographic surrogate of RV-PA coupling demonstrated important differences within the exercise hemodynamic, CPET, and clinical profile of patients with HFpEF and HFmrEF. Our study underlines the right side of the heart as a key determinant of the heart failure syndrome in both HF entities and challenges the current HF classification based solely on the left side of the heart.

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Author contributions Each author has contributed significantly to this work: AJR, MJR, KT: conception and design, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript submitted. HG, HAG, SG, CBW, WS, SDK, VM, PCS, CWH: analysis and interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted.

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Declarations

Conflict of interest All authors report that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Ethical approval The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients enrolled into the registries gave written informed consent, and data collection and analyses were approved by the ethics committee of the Faculty of Medicine at the University of Giessen (Approval No. 186/16, 266/11, 117/16).

Consent to participate All patients enrolled into the registries gave written informed consent.

Consent for publication All patients enrolled into the registries gave written informed consent.

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Exercise MR-proANP unmasks latent right heart failure in CTEPH

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KEYWORDS:
MR-proANP;
cardiac biomarkers;
right heart failure;
exercise testing;
CTEPH

OBJECTIVE: The present study was designed to investigate the dynamics of right atrial pressure (RAP) and mid-regional pro-atrial natriuretic peptide (MR-proANP) during physical exercise in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and to determine whether these parameters might serve as a tool to measure exercise-dependent atrial stress as an indicator of right heart failure.

METHODS: This prospective observational cohort study included 100 CTEPH patients who underwent right heart catheterization during physical exercise (eRHC). Blood samples for MR-proANP measurement were taken prior, during, and after eRHC. MR-proANP levels were correlated to RAP levels at rest, at peak exercise (eRAP), and during recovery. RAP at rest ≤7 mmHg was defined as normal and eRAP >15 mmHg as suggestive of right heart failure.

RESULTS: During eRHC mean RAP increased from 6 mmHg (standard deviation, SD 4) to 16 mmHg (SD 7; $p < 0.001$). MR-proANP levels and dynamics correlated with RAP at rest ($r_s = 0.61$; $p < 0.001$) and at peak exercise ($r_s = 0.66$; $p < 0.001$). Logistic regression analysis revealed the peak MR-proANP level (B = 0.058; $p = 0.004$) and the right atrial area (B = 0.389; $p < 0.001$) to be associated with eRAP dynamics. A peak MR-proANP level ≥139 pmol/L (AUC = 0.81) and recovery level ≥159 pmol/L (AUC = 0.82) predicted an eRAP >15 mmHg. Physical exercise unmasked right heart failure in 39%

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Abbreviations: CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; CTEPD, chronic thromboembolic pulmonary disease; mPAP, mean pulmonary artery pressure; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; (e)RAP, (exercise) right atrial pressure; (e)RHC, (exercise) right heart catheterization; RHF, right heart failure; RV, right ventricle; RVSWI, right ventricular stroke work index; SvO2, mixed venous oxygen saturation; TPR, total pulmonary resistance

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of patients with normal RAP at rest; these patients were also characterized by a more distinct increase in MR-proANP levels ($p = 0.005$) and higher peak ($p < 0.001$) and recovery levels ($p < 0.001$).
CONCLUSIONS: RAP and MR-proANP dynamics unmask manifest and latent right heart failure in CTEPH patients.
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In chronic thromboembolic pulmonary hypertension (CTEPH) chronic pressure overload burdens the right heart,[1-3] and the gradual failure of compensatory adaption mechanisms leads to secondary right heart failure (RHF).[1,3] A crucial component of this process is impaired right ventricular (RV) filling, which is a result of systolic dysfunction and myocardial stiffness and thus increased filling pressures.[1] The resulting right atrial pressure (RAP) overload is accompanied by increased right atrial wall tension.

RAP at rest has shown to be a predictor of outcome in pulmonary hypertension (PH) and other cardiac disorders[4-9]; it is used for individual risk stratification and as a target of therapy in PH.[10] Right heart catheterization (RHC) at rest is the gold-standard procedure for hemodynamic assessment[10] but does not take into account dynamics in response to exercise. The assessment of RHC during physical exercise (eRHC) has evolved as a supplementary approach to unmask isolated exercise PH and an exercise-dependent deterioration of hemodynamics.[1,11] Despite an increasing recognition of exercise hemodynamics, exercise RAP (eRAP) has been widely neglected in this context. In healthy individuals, the RAP moderately increases in response to exercise, if at all.[12-16] Mehra et al. defined RHF as "elevated venous pressures—at rest or with exercise."[17] Further hemodynamic parameters, such as the pulmonary artery pulsatility index (PAPi), also include RAP and were suggested as indices of right heart function.[18] In patients with left heart failure, a greater increase in RAP with exercise was found to be associated with pulmonary vasculopathy and RHF.[19]

Less is known about RAP dynamics and its clinical implications in PH. However, considering that a disproportionate rise in RAP during exercise might be a sign of RHF, its quantification is of interest.

Atrial natriuretic peptide (ANP) and mid-regional pro-atrial natriuretic peptide (MR-proANP) are protein biomarkers that reflect atrial stress levels.[20,21] Both correlate with atrial pressure under resting conditions in left heart failure and isolated RHF.[21-23] Whether atrial natriuretic peptides also reflect short-term changes in RAP during physical exercise is unknown. Data concerning the dynamics of natriuretic peptides during diagnostic exercise testing in CTEPH or PH are scarce and have not been linked to exercise hemodynamics.[24-26] The present study was designed to investigate the dynamics of RAP and MR-proANP during physical exercise in CTEPH patients and to determine whether these parameters might serve as a tool to measure exercise-dependent atrial stress as an indicator of RHF.

Methods

Study design and population

This observational cohort study included patients with CTEPH (N = 88) or chronic thromboembolic pulmonary disease (CTEPD, N = 12) who underwent diagnostic eRHC as a part of the routine diagnostic work-up[27,28] at the Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany. The diagnosis of CTEPH was made at baseline prior to any interventional or surgical therapy and in accordance with the current guidelines[10] in all patients. Accordingly, the criteria for the diagnosis of CTEPH were oral anticoagulation therapy ≥3 months, typical radiographic signs of CTEPH (pulmonary perfusion deficits and/or typical vascular obstructive lesions), and the finding of precapillary PH. The diagnosis of CTEPD is similar but lacks the finding of precapillary PH.

All patients were asked to limit physical activity to a minimum on the day of eRHC and to fully rest for 2 hours prior to and after eRHC. Blood samples for biomarker measurement were taken at

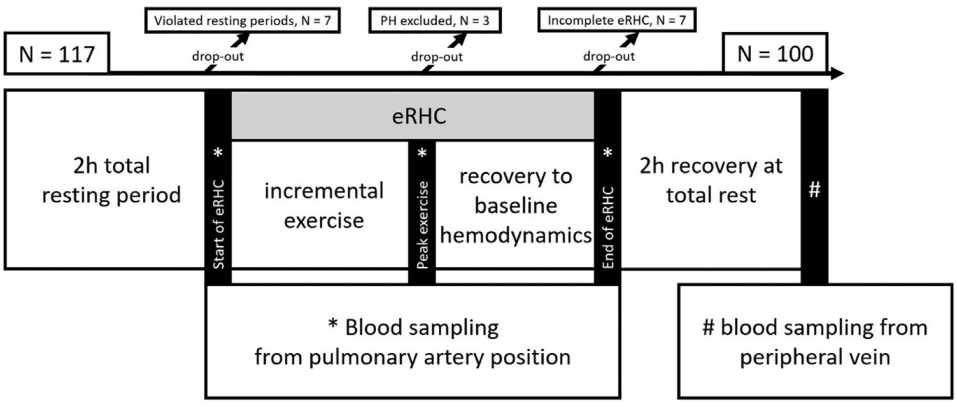

Figure 1 Workflow of the study. Seventeen patients were excluded to give a final cohort of N=100 patients. Abbreviations: eRHC = exercise right heart catheterization, PH = pulmonary hypertension.

rest before initiation of eRHC, immediately after peak exercise, after return to resting hemodynamics, and after a recovery period of 2 hours of full rest (Figure 1).

All patients gave written informed consent. The study was approved by the ethics board of the Justus Liebig University of Giessen (AZ 43/14), conforms to the ethical guidelines of the Declaration of Helsinki, and is compliant with the ISHLT Ethics statement.

A total of 117 patients were considered for inclusion. After the exclusion of patients with protocol violations (N = 7), incomplete eRHC (N = 7), and patients without CTEPD-specific imaging findings (N = 3), a study cohort of 100 patients (88 CTEPH, 12 CTEPD) remained. The eRHC was a part of the baseline diagnostic work-up in 60 patients and follow-up eRHC in 40 patients 6 (after balloon pulmonary angioplasty) or 12 (after surgical pulmonary endarterectomy) months after completed specific CTEPH therapy with surgical pulmonary endarterectomy (N = 9) or interventional balloon pulmonary angioplasty (N = 31).

Exercise right heart catheterization

Medication was not modified prior to or during the procedure. In accordance with the standard RHC procedure, a triple-lumen Swan-Ganz catheter (7F 2.3 mm Thermodilution Catheter, Bioptimal, Germany) was inserted via the right jugular vein and connected to a hemodynamic measurement system (General Electric, Freiburg, Germany). The mid-thoracic level in the supine position was fixed as the zero reference level for the pressure transducer. Pressure parameters were measured continuously and cardiac output was measured by the thermodilution technique by averaging the results of three out of five determinations. eRHC was performed during physical exercise on a supine cycle ergometer (eBike, General Electric, Freiburg, Germany). The exercise protocol of the Kerckhoff Heart and Thorax Center has been published in detail previously.[29,30] Briefly, exercise was performed in the supine position with an adjusted external workload, and the workload was adapted stepwise every 5 minutes until the patient was exhausted. Workload was determined based on the workload achieved during cardiopulmonary exercise testing and/or adjusted on an individual, clinical basis to allow measurement of hemodynamic parameters. Exercise was started 30 min after catheter insertion, and all pulmonary pressures were averaged over several respiratory cycles to compensate for respiratory fluctuations.[29-31] Hemodynamic parameters were measured at baseline during full rest, during the last 30 sec of each workload step, and during recovery to detect the return to baseline hemodynamics. The mixed venous blood oxygenation was measured at rest and during the last 30 sec of each workload step.

Biomarker measurement

The first 3 samples during RHC were taken from the pulmonary artery, and the 2-hour recovery sample was taken from a peripheral vein (Figure 1). The blood samples were processed immediately (centrifugation, aliquoting, and freezing at minus 80°C). All biomarker measurements were carried out batch-wise on thawed samples by experienced staff blinded to patient characteristics. MR-proANP was measured in serum by TRACE (time-resolved amplified cryptate emission) technology (MR-proANP KRYPTOR assay, Kryptor Compact Plus, B·R·A·H·M·S GmbH, Hennigsdorf, Germany).

Statistical analysis

All continuous variables are expressed as mean and standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical variables are reported as number and percentage. Normal distribution was assessed using the Shapiro-Wilk test. Parameters gathered at one point of time were compared using the Student t-test or ANOVA for normally distributed parameters and the Mann-Whitney-*U* test or the Kruskall-Wallis Test for other continuous variables. The χ^2 test and Fisher-Yates test were used for categorical variables. Parameters from different timepoints were subjected to paired sample testing. Paired t-test was applied for normally distributed parameters and the Wilcoxon signed-rank test for other continuous variables. Correlations were analysed using bivariate Pearson correlation.

A value of RAP ≤7 mmHg was defined as normal.[10,12,13] Considering this and the risk stratification model of the European guidelines on pulmonary hypertension,[10] patients were classified as subgroup 1 (normal RAP at rest ≤7 mmHg), subgroup 2 (moderately increased RAP at rest = 8-14 mmHg), and subgroup 3 (severely increased RAP at rest >14 mmHg). There is no approved definition of physiological RAP dynamics during physical exercise. Considering the existing evidence,[12-16,32] an eRAP of 15 mmHg was defined as the upper limit of normal in the current study.

Univariate and multiple linear regression analysis with forward stepwise entry was performed to analyse the association between noninvasive diagnostic parameters (independent variable) and eRAP (dependent variable). Standardisation of raw values was performed automatically by the statistical analysis software. The results show both the non-standardised (B) and the standardised coefficients (ß). Unstandardized coefficients refer to the change of the depend variable per 1 unit increase in the independent predictor variable. Standardized coefficients refer to how many standard deviations a dependent variable will change, per standard deviation increase in the independent variable.

The diagnostic performance of exercise MR-proANP levels as an indicator of a pathological increase of RAP during exercise (eRAP >15 mmHg) was analysed using binary logistic regression analysis and receiver operating characteristics (ROC). Results are presented as area under the curve (AUC). ROC curves were compared by the DeLong test. The optimal biomarker cut-off value to indicate eRAP >15 mmHg was calculated using Youden index quantification.

To assess the prognostic performance of the cut-off value with regard to eRAP >15 mmHg, odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated. Statistical analysis was carried out with SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). A 2-tailed p value <0.05 was considered to be statistically significant.

Results

Clinical characteristics and hemodynamic findings

The demographic and clinical data of the study cohort are presented in Table 1, with data displayed for the whole cohort (N = 100; 53 women; age 61.7 y with a SD of 14.9) and separately for patients with eRAP≤ or >15 mmHg. Supplementary Table 1 provides clinical data and diagnostic findings separately for patients who were included at baseline or at a follow-up timepoint of their work-up.

Table 1 Demographic and clinical characteristics

Parameter	Whole cohort (N = 100)	eRAP ≤15 mmHg (N = 49)	eRAP >15 mmHg (N = 51)	*p*= (eRAP groups)
Age, years	61.7 ± 14.9	59.6 ± 14.7	63.8 ± 15.0	0.16
Female sex	53	28 (57)	25 (49)	0.42
BMI, kg/m^2	27.0 ± 5.6	26.4 ± 5.5	27.6 ± 5.7	0.28
CTEPH / CTEPD	88 / 12	42/7 (86/14)	46/5 (90/10)	0.49
Patients at baseline	60	23 (47)	37 (73)	-
Patients at follow-up	40	26 (53)	14 (27)	-
Diabetes mellitus	14	4 (8)	10 (20)	0.1
Arterial hypertension	60	20 (41)	40 (78)	<0.001
Current or ex-smoker	39	19 (39)	20 (39)	0.1
Dyslipidemia	24	7 (14)	17 (33)	0.03
CAD	21	7 (14)	14 (27)	0.11
Atrial fibrillation	5	1 (2)	4 (8)	0.18
History of acute PE	92	47 (96)	45 (88)	0.16
History of DVT	35	17 (35)	18 (35)	0.1
COPD	6	2 (4)	4 (8)	0.43
History of cancer	12	6 (12)	6 (12)	0.94
CID	0	0 (0)	0 (0)	-
History of splenectomy	5	2 (4)	3 (6)	1.0
Chronic renal failure	11	2 (4)	9 (18)	0.52
eGFR, mL/min	89.1 ± 27.6	96.5 ± 27.2	82.0 ± 26.3	0.01
Creatinine, μmol/L	0.88 ± 0.3	0.81 ± 0.28	0.95 ± 0.3	0.02
NT-proBNP, ng/L	203 (90-989)	114 (56 − 225)	798 (167 − 1462)	<0.001
Medication				
NOAC	87	40 (82)	47 (92)	0.12
VKA	13	9 (18)	4 (8)	0.14
ERA	3	2 (4)	1 (2)	0.61
PDE5i	5	3 (6)	2 (4)	0.68
GCS	53	24 (49)	29 (67)	0.55
WHO -FC I	8	4 (8)	4 (8)	
II	36	25 (51)	11 (22)	0.02
III	52	19 (39)	33 (65)	
IV	4	1 (2)	3 (6)	
Echocardiography				
LVEF, %	55 (55-55)	55 (55-55)	55 (55-55)	0.62
RV diameter, mm	40 ± 9	35 ± 7	43 ± 10	<0.001
TAPSE, mm	18 ± 5	19 ± 5	17 ± 4	0.03
RA area, cm^2	21 ± 8	17 ± 4	24 ± 8	<0.001
6-MWD, m	385 ± 95	427 ± 98	347 ± 79	0.08
CPET				
Duration, min	6 (5-8)	7 (5-9)	5 (6-7)	0.16
Peak workload, W	70 (50-110)	75 (50-113)	70 (50-105)	0.38
Peak VO_2, ml/kg/min	15.4 ± 5.2	16.5 ± 5.1	14.1 ± 5.1	0.06

Values represent N, N (%), mean ± SD, or median (IQR). Baseline refers to prior to specific therapy, follow-up refers to after BPA or PEA therapy.

Abbreviations: BMI, body mass index; BPA, balloon pulmonary angioplasty; CAD, coronary artery disease; CID, chronic inflammatory disease; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; CTEPD, chronic thromboembolic pulmonary disease without pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; eRAP, exercise right atrial pressure; eRHC, exercise right heart catheterization; GCS, guanylate cyclase stimulator; LVEF, left ventricular ejection fraction; NOAC, new oral anticoagulant NT-proBNP, N-terminal pro-B-type natriuretic peptide; PEA, pulmonary endarterectomy; PE, pulmonary embolism; PDE5i, phosphodiesterase 5 inhibitor; RA area (end-systolic), right atrial end-systolic area; RV diameter, right ventricular diameter (basal); VKA, vitamin K antagonist; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization functional class; 6-MWD, 6-minute walking distance.

eRHC was performed over a median duration of 8 (7-11) minutes with a median workload of 50 (25-75) W. In 30 patients the mixed venous oxygen saturation (SvO2) reached a value <30%. Table 2 illustrates the RHC findings at rest and their dynamics during exercise for the whole cohort and separately for the subgroups of patients with eRAP≤ or >15 mmHg.

In response to exercise, RAP increased in all patients but one. The mean RAP increased from 6 mmHg (SD 4; range [min-max] 1-23 mmHg) at rest to 16 mmHg (SD 7; range 4-43 mmHg) during peak exercise ($p < 0.001$), with a percent increase of 160 (100-260) %. In accordance with these findings, the median PAPi decreased (6.4 [4.6-9.4] to 4.2 [3.1-5.4], $p < 0.001$) and the RAP/PCWP (0.6 [0.4-0.8] to

Table 2 Hemodynamic and functional findings from exercise right heart catheterization

Parameter		Rest	Peak exercise	*p*-value*
HR, beats/min;	All	74 ± 12	119 ± 20	<0.001
	eRAP ≤ 15mmHg	72 ± 12	121 ± 19	<0.001
	eRAP > 15mmHg	76 ± 11	117 ± 21	<0.001
	#	*p* = 0.16	*p* = 0.35	
MAP, mmHg	All	96 ± 13	122 ± 19	<0.001
	eRAP ≤ 15mmHg	97 ± 12	122 ± 18	<0.001
	eRAP > 15mmHg	96 ±14	121 ± 20	<0.001
	#	*p* = 0.65	*p* = 0.72	
mPAP, mmHg	All	33 ± 12	59 ± 14	<0.001
	eRAP ≤ 15mmHg	26 ± 9	52 ± 13	<0.001
	eRAP > 15mmHg	40 ± 12	65 ± 12	<0.001
	#	*p* < 0.001	*p* < 0.001	
mPAP increase, %	All	84 (54-130)		
	eRAP ≤ 15mmHg	100 (76-137)		
	eRAP > 15mmHg	69 (40-89)		
	#	p<0.001		
PVR, WU	All	5.3 ± 3.5	5.9 ± 3.9	<0.001
	eRAP ≤ 15mmHg	3.7 ± 2.6	4.1 ± 2.6	<0.001
	eRAP > 15mmHg	6.8 ± 3.5	7.6 ± 4.1	0.002
	#	*p* < 0.001	*p* < 0.001	
PVR increase, %	All	11 (0-25)		
	eRAP ≤ 15mmHg	11 (-1-26)		
	eRAP > 15mmHg	12 (-2-25)		
	#	*p* = 1.0		
RAP, mmHg	All	6 ± 4	16 ± 7	<0.001
	eRAP ≤ 15mmHg	4 ± 2	10 ± 3	<0.001
	eRAP > 15mmHg	7 ± 4	21 ± 5	<0.001
	#	*p* < 0.001	*p* < 0.001	
RAP increase, %	All	160 (100-260)		
	eRAP ≤ 15mmHg	150 (71-212)		
	eRAP > 15mmHg	200 (133-300)		
	#	*p* = 0.007		
PAPi	All	6.4 (4.6-9.4)	4.2 (3.1-5.4)	<0.001
	eRAP ≤ 15mmHg	6.5 (4.5-9.5)	5.2 (3.9-6.5)	0.001
	eRAP > 15mmHg	6.4 (4.6-9.4)	3.4 (2.7-4.5)	<0.001
	#	*p* = 0.94	*p* < 0.001	
PCWP, mmHg	All	9 ± 3	16 ± 5	<0.001
	eRAP ≤ 15mmHg	8 ± 3	15 ± 3	<0.001
	eRAP > 15mmHg	9 ± 4	17 ± 6	< 0.001
	#	*p* = 0.14	*p* = 0.21	
CI, L/min/m^2	All	2.6 ± 0.6	4.6 ± 1.5	<0.001
	eRAP ≤ 15mmHg	2.7 ± 0.5	5.3 ± 1.2	< 0.001
	eRAP > 15mmHg	2.5 ± 0.6	3.9 ± 1.5	<0.001
	#	*p* = 0.06	*p* < 0.001	
CI increase, %	All	69 (38-112)		
	eRAP ≤ 15mmHg	88 (61-140)		
	eRAP > 15mmHg	50 (27-77)		
	#	*p* < 0.001		
RVSWI,	All	11.9	24.6	<0.001
g x m/m^2/beat		(8.4-16.7)	(17.6-29.6)	<0.001
	eRAP ≤ 15mmHg	10.8	26.4	<0.001
	eRAP > 15mmHg	(7.3-14.1)	(19.8-31.2)	
		12.7	20.6	
		(9.9 − 19.5)	(15.1 − 28.8)	
	#	p=0.01	p=0.007	
TPR, WU	All	7.2 ± 3.7	7.9 ± 4.3	<0.001
	eRAP ≤ 15mmHg	5.4 ± 2.8	5.7 ± 3.0	0.024
	eRAP > 15mmHg	8.9 ± 3.7	10.0 ± 4.3	<0.001
	#	p<0.001	p<0.001	

(*continued on next page*)

Table 2 (*Continued*)

Parameter		Rest	Peak exercise	*p*-value*
TPR increase, %	All	7 (-2-18)		
	eRAP ≤ 15mmHg	2 (-4-14)		
	eRAP > 15mmHg	14 (1-23)		
	#	*p* = 0.008		
RAP / PCWP	All	0.6 (0.4 − 0.8)	0.9 (0.7 − 1.2)	<0.001
	eRAP ≤ 15mmHg	0.6 (0.4 − 0.7)	0.7 (0.5 − 0.8)	0.001
	eRAP > 15mmHg	0.7 (0.5 − 1.0)	1.2 (1.0 − 1.7)	<0.001
	#	p=0.002	p<0.001	
SvO2 saturation, %	All	71 ± 6	36 ± 11	<0.001
	eRAP ≤ 15mmHg	72 ± 5	42 ± 10	<0.001
	eRAP > 15mmHg	69 ± 6	30 ± 9	<0.001
	#	*p* = 0.002	*p* < 0.001	

P-values are reported for the comparison of resting and exercise findings (*) and for the comparison of the two subgroups with an eRAP ≤ or > 15mmHg (#)

Abbreviations: CI, cardiac index; HR, heart rate; MAP, mean systemic blood pressure; mPAP, mean pulmonary artery pressure; PAPi, Pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, Right ventricular stroke work index; SvO2 saturation, mixed venous O_2 saturation; TPR, total pulmonary resistance;

0.9 [0.7-1.2], $p < 0.001$) increased in response to exercise. The RVSWI increased from 11.9 (8.4-16.7) g x m/m^2 to 24.6 (17.6-29.6) g x m/m^2 ($p < 0.001$). The RAP correlated with the RAP/PCWP ratio ($r_s = 0.61$; $p < 0.001$) and the PAPi ($r_s = -0.50$; $p < 0.001$) at rest, and the eRAP correlated with the RAP/PCWP ($r_s = 0.69$; $p < 0.001$) and the PAPi ($r_s = -0.67$; $p < 0.001$) at peak exercise. The correlations of RAP ($r_s = 0.47$; $p < 0.001$) and eRAP ($r_s = 0.44$; $p < 0.001$) with the mPAP were moderate.

In response to exercise, 51 patients showed pathological eRAP values (>15 mmHg). These patients were further characterized by worse findings for several baseline characteristics, such as WHO functional class, echocardiographic right heart parameters, renal function, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at rest (Table 1).

Biomarker levels in correlation with hemodynamic findings

The median MR-proANP level increased during physical exercise and returned to baseline values after 2 hours of recovery in the majority of patients (Figure 2). The resting and peak MR-proANP levels correlated with RAP at rest ($r_s = 0.61$; $p < 0.001$; Figure 3a) and eRAP at peak exercise ($r_s = 0.66$; $p < 0.001$; Figure 3b), respectively. Furthermore, the relative percent increase in MR-proANP correlated with the relative percent increase in eRAP ($r_s = 0.52$; $p < 0.001$; Figure 3c).

Patients with eRAP >15 mmHg had higher peak MR-proANP levels (226 [163-347] pmol/L vs 123 [77-196] pmol/L; $p < 0.001$]) and higher 2-hour recovery levels (204 [141-290] pmol/L vs 94 [65-150] pmol/L; $p < 0.001$) than those with eRAP ≤15 mmHg.

Univariate linear regression analysis included diagnostic findings that differed between patients with eRAP≤ and >15 mmHg and selected parameters with a potential impact on biomarker levels (age, arterial hypertension, see Table 1). In the final model after multiple linear regression analysis the peak MR-proANP level (B = 0.058; $p = 0.004$) and the right atrial area (B = 0.389; $p < 0.001$) remained significant and the MR-proANP level at rest (B = −0.041; $p = 0.05$) as borderline significant regarding the association with eRAP dynamics (Supplementary Table 2).

ROC analysis revealed a peak MR-proANP level ≥139 pmol/L (AUC = 0.81 [95% CI 0.73-0.89]; OR 14.5 [95% CI 4.9-43.1]; $p < 0.001$) and a 2-hour recovery level ≥159 pmol/L (AUC = 0.82 [95% CI 0.73-0.89]; OR 9.1 [CI 3.6-22.9]: $p < 0.001$) as strong predictors of an eRAP >15 mmHg. The performance of these 2 models−−the peak MR-proANP ($p = 0.05$) and the 2-hour recovery MR-proANP ($p = 0.015$)−−was superior to that of MR-proANP

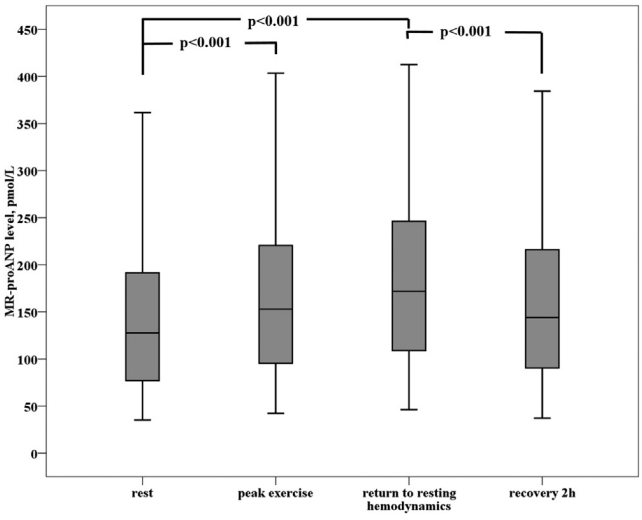

Figure 2 Development of MR-proANP levels during exercise right heart catheterization. Box-and-whiskers plot showing significant changes in median biomarker levels. Abbreviations: MR-proANP = mid-regional pro-atrial natriuretic peptide.

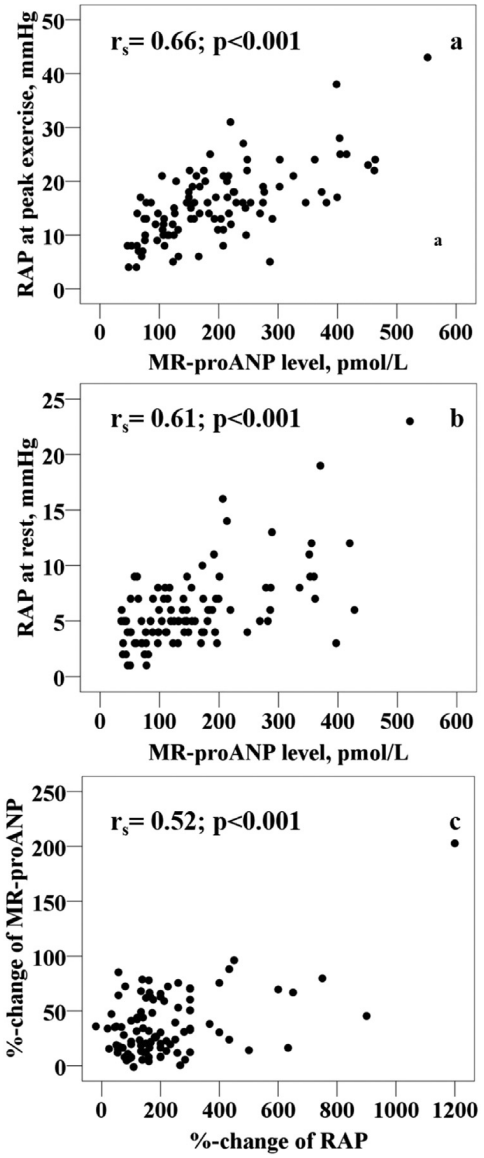

Figure 3 a-c Correlation of MR-proANP levels and right atrial pressure. Parameters compared at rest (a) and at peak exercise (b) with bivariate Pearson correlation of relative changes (c). Abbreviation: MR-proANP = mid-regional pro-atrial natriuretic peptide.

levels at rest (AUC = 0.78 [95% CI 0.69-0.87]). The fitted models after binary logistic regression analysis are reported in supplement Table 3.

Changes in eRAP and MR-proANP in RAP-specific subgroups

The RAP at rest was ≤7 mmHg in 77 patients (subgroup 1), 8 to 14 mmHg in 20 patients (subgroup 2), and >14 mmHg in 3 patients (subgroup 3). Figure 4 illustrates the individual dynamics of eRAP per patient in these subgroups. In subgroup 1, 39% of the patients had an eRAP >15 mmHg; in subgroup 2 this was 90%, and in subgroup 3 100%. The median MR-proANP levels at rest in the subgroups 1 to 3 were 112 (70-171) pmol/L, 207 (124-348) pmol/L, and 371 (206-521) pmol/L, respectively ($p < 0.001$). In subgroup 1, patients with eRAP ≤15 mmHg and those with eRAP >15 mmHg had similar RAP at rest ($p = 0.11$). However, among those with eRAP >15 mmHg the percent increase in MR-proANP levels was more distinct (p = 0.005), and the peak MR-proANP levels ($p < 0.001$) as well as the levels after 2 hours of recovery ($p < 0.001$) were higher (Figure 5). In subgroup 1, the cut-off values identified for the peak MR-proANP level (>139 pmol/L; OR 10.5 [95% CI 3.1-35.0]; $p < 0.001$) and the 2-hour recovery level (>159 pmol/L; OR 4.8 [95% CI 1.8-13.2]; $p = 0.003$) were predictive of eRAP >15 mmHg. Patients with eRAP >15 mmHg in subgroup 1 also had a slightly lower eGFR ($p = 0.04$), a larger right atrial area ($p = 0.007$) and right ventricular diameter ($p = 0.04$), and worse pulmonary hemodynamics (mPAP, PVR, TPR) at rest. There were no differences between the subgroups regarding established hemodynamic risk stratification parameters (CI, RAP, and SvO2) at rest (Table 3).

Discussion

This study investigated the dynamics of RAP and MR-proANP levels in response to physical exercise testing during eRHC in CTEPH patients. The major findings are that (1) physical exercise frequently provokes an increase in RAP that is suggestive of RHF, even if resting RAP levels are normal; (2) MR-proANP levels correlate with RAP in this scenario; (3) MR-proANP levels during exercise testing and recovery may serve as surrogates for altered right atrial hemodynamics. It should be noted that we do not believe that the dynamics of eRAP obtained during exercise is specific to CTEPH. We decided to choose a CTEPH cohort for the current proof-of-concept study, since this pathology provides a unique constellation of isolated RHF.

Dynamics of right atrial pressure and MR-proANP during exercise testing

Progressive RHF is a crucial landmark of disease deterioration in CTEPH and other subtypes of PH and should thus be detected as early as possible.[4,6,33-37] eRHC has evolved as a diagnostic tool that can unmask the true severity of hemodynamic impairment and RHF in PH patients, particularly in those with normal or borderline findings at rest[1,11]An increase in RAP, detected by invasive measurement, may be a sensitive parameter of RV dysfunction.[17,19] In healthy individuals, RAP at rest ranges from 1 to 7 mmHg[12,13]; however, there is no generally accepted definition of physiological eRAP. In healthy individuals, RAP dynamics during exercise testing has been reported to increase to 15 mmHg.[12–16,38] In different settings of heart failure and PH, median eRAP levels during peak exercise range from 13 to 17 mmHg.[14,39,40] In our cohort, the exposure to a median workload of 50 (25-75) W led to a significant increase in the mean RAP to 16 mmHg (SD 7) during peak exercise, which conforms with the observations of Lichtblau et al. in a mixed PH cohort.[14] Relative to the chosen eRAP cut-off value of 15 mmHg, 51% of the patients in the present

Table 3 Comparison of Clinical Characteristics of Patients With eRAP ≤ 15 mmHg vs >15 mmHg in Subgroup 1

Parameter	Subgroup 1 (N = 77)		eRAP ≤ 15 mmHg (N = 47)		eRAP > 15 mmHg (N = 30)		P-Value (eRAP groups)	
Age, years	61.7 ± 13.6		59.3 ± 14.6		65.5 ± 10.9		0.05	
BMI, kg/m^2	26.8 ± 5.3		26.2 ± 4.8		27.9 ± 5.8		0.16	
Biomarkers								
eGFR, mL/min	92.0 ± 27.4		97.2 ± 27.6		83.8 ± 25.6		0.04	
NT-proBNP, ng/L	157 (62-406)		114 (55-241)		338 (115-896)		0.001	
WHO -FC I	8		4 (9)		4 (13)		0.10	
II	33		25 (53)		8 (27)			
III	35		17 (36)		18 (60)			
IV	1		1 (2)		0 (0)			
Echocardiography								
RV diameter, mm	37 ± 7		36 ± 7		39 ± 7		0.04	
TAPSE, mm	19 ± 5		19 ± 5		18 ± 5		0.30	
RA area, cm^2	18 ± 5		17 ± 4		20 ± 4		0.007	
6-MWD, m	413 ± 81		427 ± 98		390 ± 42		0.45	
CPET								
Peak VO_2, ml/kg/min	16.1 ± 5.3		16.6 ± 5.2		15.3 ± 5.6		0.41	
Right heart catheter	rest	exercise	rest	exercise	rest	exercise	rest	exercise
mPAP, mmHg	30 ± 11	58 ± 14	26 ± 9	53 ± 13	36 ± 12	65 ± 12	<0.001	<0.001
PVR, WU	4.5 ± 3	5.0 ± 3.1	3.7 ± 2.6	4.1 ± 2.7	5.7 ± 3.2	6.3 ± 3.3	0.003	0.002
CI, L/min/m^2	2.7 ± 0.6	5.0 ± 1.3	2.7 ± 0.5	5.3 ± 1.2	2.6 ± 0.6	4.5 ± 1.4	0.07	0.004
RAP, mmHg	5 ± 2	14 ± 5	4 ± 2	11 ± 3	5 ± 1	18 ± 3	0.11	<0.001
TPR, WU	6.2 ± 3.2	6.8 ± 3.5	5.4 ± 2.8	5.7 ± 3.0	7.6 ± 3.4	8.6 ± 3.6	0.002	0.001
SvO2 saturation, %	71 ± 5	38 ± 10	72 ± 5	41 ± 10	70 ± 4	32 ± 9	0.05	<0.001
RAP/PCWP	0.7 (0.4-0.7)	0.8 (0.6-1.0)	0.6 (0.4-0.7)	0.7 (0.5-0.8)	0.5 (0.4-0.6)	1.0 (0.9-1.3)	0.91	<0.001
PAPi	7.5 (4.8-11.0)	4.6 (3.4-5.9)	6.8 (4.7-9.5)	5.2 (4.0-6.5)	8.3 (5.1-12.4)	4.0 (2.8-4.7)	0.01	<0.001
RVSWI, g x m/m^2/beat	11.9 (8.0-16.6)	26.3 (19.2-31.3)	11.0 (7.2-14.3)	26.5 (20.0-31.2)	12.4 (10.3-20.5)	24.7 (18.0-31.6)	0.02	0.44

Values represent N (%), mean ± SD, or median (IQR).

Abbreviations: BMI, body mass index; CI, cardiac index; SvO2 saturation, mixed venous O2 saturation; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAPi, Pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA area, right atrial end-systolic area; (e)RAP, (exercise) right atrial pressure; RV diameter, right ventricular diameter (basal); RVSWI, Right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance; WHO-FC, World Health Organization functional class; 6-MWD, 6-minute walking distance.

cohort had a pathological eRAP level, which is suggestive of exercise-dependent RHF.

The current study used eRAP as a target parameter to define exercise-dependent RHF. Several other hemodynamic parameters, such as PAPi, have been suggested as indices of right heart dysfunction.[18] We believe that a pathological RAP response to exercise reflects the failure of the RV to empty the RA adequately. This condition is partly driven by an exercise-dependent increase in RV afterload (mPAP) but is certainly not limited to this. Other mechanisms such as impaired RV contractility contribute to this process. From our point of view, eRAP dynamics mirrors contractile RV failure in combination with an increased afterload. In our study, those patients with an eRAP >15 mmHg apparently showed a maladaptive response to exercise despite a lower or similar relative increase in afterload, quantified by the relative increase in mPAP. The use of eRAP to define exercise-dependent RHF in the present study is certainly a matter of debate, since it might oversimplify the assessment of pathological RV response to exercise. It should be mentioned, however, that eRAP correlated well with PAPi in our study. Moreover, there are no data available on parameters such as exercise PAPi in the literature, which makes the definition of a pathological exercise response unfeasible.

The current study investigated the concept of using MR-proANP levels measured during exercise as a surrogate for eRAP dynamics. Natriuretic peptides are released from the myocardium in response to volume or pressure overload.[20] Raine et al. precisely illustrated the atrial origin of atrial natriuretic peptides and their outstanding correlation with atrial pressure levels at rest.[21] In patients with left heart failure, Kato et al. observed an increase in ANP levels in response to diagnostic exercise testing that was greater than that of healthy controls.[41,42] Evidence on natriuretic peptide dynamics during exercise in PH or CTEPH patients is

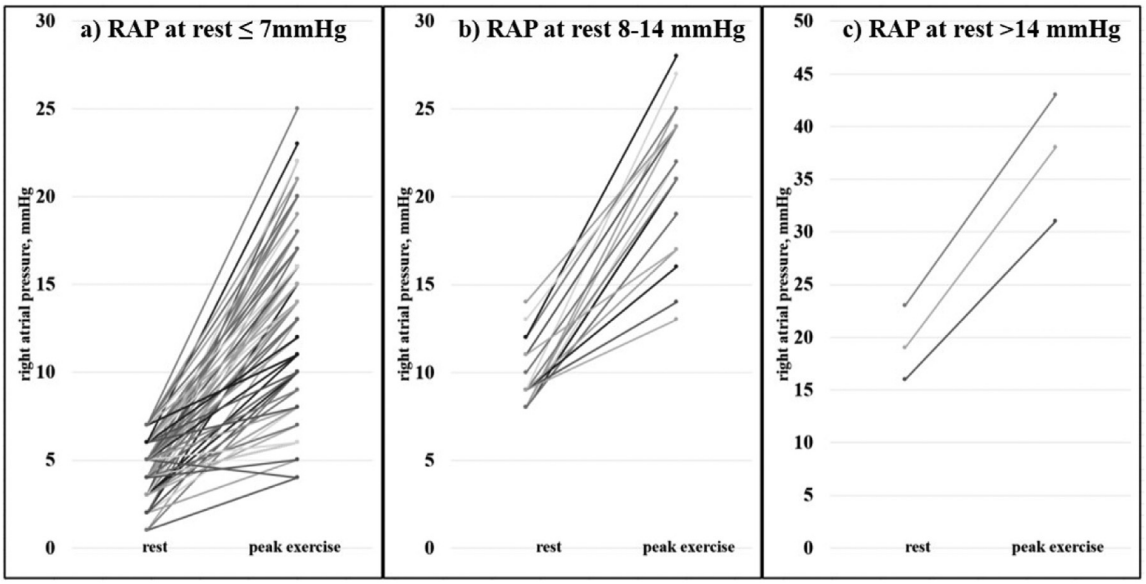

Figure 4 a-c: Dynamics of right atrial pressure during exercise right heart catheterization. Data for individual patients stratified according to right atrial pressure at rest: normal ≤7 mmHg (a); moderately elevated 8-14 mmHg (b); severely elevated >14 mmHg (c).

sparse,[24-26] and there are no reports to date that correlate biomarker levels with simultaneously measured invasive hemodynamic parameters. Such data would be crucial if one considers that hemodynamic stress appears to be the main driver of natriuretic peptide release.[20] The current study observed an increase in MR-proANP levels during physical exercise testing and a variable, individual decrease during recovery. MR-proANP levels showed a strong correlation with the right atrial pressure at all time points measured. This strong association of the two parameters was further supported by multiple linear regression analysis that revealed an increase of 0.6 mmHg eRAP per 10 pmol/L peak MR-proANP.

Patients with pathological levels of eRAP >15 mmHg showed consistently higher peak MR-proANP levels and persistently higher levels after 2 hours of recovery than those with physiologically normal dynamics. ROC analysis demonstrated that measurement of peak MR-proANP and 2-hour recovery levels may serve as a diagnostic tool to identify patients with pathological levels of eRAP. It should be mentioned that patients with eRAP> or ≤15 mmHg differed regarding several baseline characteristics that may have a possible impact on eRAP dynamics. A history of arterial hypertension was reported more frequently in patients with eRAP >15 mmHg. However, mean arterial blood pressure values at rest and during eRHC did not differ between the subgroups. Likewise, there was no difference in the two subgroups regarding PAWP at rest and during peak exercise, which makes the left heart as a driver of eRAP and MR-proANP dynamics unlikely. Parameters that differed between patients with an eRAP> or ≤15 mmHg and the patients' age were included in the multiple logistic regression model in addition to MR-proANP levels. Only the right atrial area and the peak MR-proANP level remained as significant independent parameters associated with eRAP.

Our choice of the eRAP cut-off value of 15 mmHg is certainly a matter for discussion. Lichtblau et al. reported any RAP increase in response to exercise to be a negative predictor of adverse outcome in PH.[14] However, our data strengthen the concept of measuring eRAP and exercise MR-proANP levels as a means of identifying exercise-dependent RHF.

Clinical use of eRAP and MR-proANP to unmask latent right heart failure

eRHC may provide an additional diagnostic benefit in PH patients, particularly in those with normal or borderline

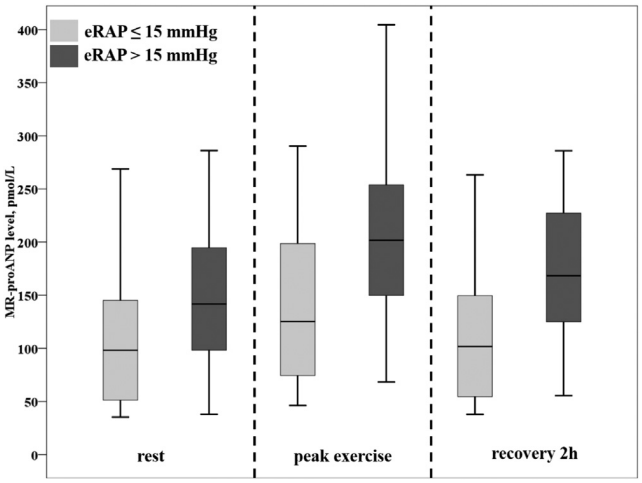

Figure 5 Comparison of MR-proANP dynamics between patients with a physiological or pathophysiological increase in right atrial pressure during exercise in subgroup 1. Box-and-whiskers plot showing the median levels of biomarker stratified according to eRAP at various stages of testing. Abbreviations: eRAP = exercise right atrial pressure; MR-proANP = mid-regional pro-atrial natriuretic peptide.

hemodynamic findings at rest.[11] The multimodal risk-stratification model of the European guidelines includes RAP, CI, and SvO2 at rest as hemodynamic parameters[10] but neglects exercise hemodynamic parameters. In our cohort, 77% of the patients (subgroup 1) showed a normal RAP at rest. Based on the findings for RAP, CI, and SvO2, these patients would have been classified as low-risk patients. However, exercise hemodynamics showed a remarkably heterogeneous pattern in our study cohort. Not surprisingly, the parameters of patients with manifest RHF at rest (subgroups 2 and 3) were consistently exacerbated during exercise, but 39% of the patients in the low-risk RAP group (subgroup 1) developed eRAP >15 mmHg. They were also characterized by a higher RAP/PCWP ratio and a lower PAPi. In addition, despite equal findings at rest, patients with eRAP >15 mmHg were characterized by significantly worse SvO2 and CI during peak exercise in comparison to those with eRAP ≤15 mmHg. Furthermore, the patients of subgroup 1 with high eRAP had an intermediate risk profile based on their mean RA area, median NT-pro BNP, and mean 6-minute walking distance, whereas the patients with low eRAP had low risk based on RA area and NT-pro BNP. Thus, eRAP measurement might allow further discrimination of the low-risk subgroup by unmasking latent RHF in some patients, which would suggest the need for intensifying their therapy.

The results of MR-proANP measurements reflect these hemodynamic findings. The median MR-proANP level at rest was low (112 [70-171] pmol/L) in patients from subgroup 1, which is comparable to the levels in the BACH study (≤120 pmol/L) that ruled out left heart failure.[43] However, the patients with a pathological increase in eRAP to >15 mmHg had higher MR-proANP levels during exercise and a more attenuated slope during recovery than patients with eRAP <15 mmHg. The cut-off values for the peak MR-proANP level (>139 pmol/L) and the 2-hour recovery level (>159 pmol/L) identified here were highly predictive of eRAP >15 mmHg in this subgroup.

Limitations

There are certain limitations of the present study that must be mentioned. The sample size is relatively small, which particularly limits the power of hemodynamic and biomarker cut-off values. Furthermore, as a proof-of-concept project, the study focused on the technical feasibility of using MR-proANP as a noninvasive surrogate of eRAP and does not provide any outcome data. The diagnostic concept requires physical exercise testing, which is always susceptible to individual covariates of the patient such as musculoskeletal disorders. Finally, it needs to be mentioned that the current study included exclusively CTEPH/CTED patients. The resulting homogeneity of the cohort is a strength of the study, but limits the ultimate translation of the diagnostic concept to other cohorts and pathologies, for example, other subtypes of PH.

Conclusions

The present study characterized RAP and MR-proANP dynamics in CTEPH patients during standardized diagnostic exercise testing with eRHC. Both parameters unmasked manifest and latent RHF. Further investigation using standardized exercise protocols and eRHC as a reference will be needed to find valid cut-off values for these 2 parameters and to demonstrate the reliability of their diagnostic application.

Author contributions

SDK - study conception, interpretation of data and management, first draft of the manuscript. JB - interpretation of data and management, proofreading of the manuscript. CBW - treatment of patients, interpretation of data, proofreading of the manuscript. MSDA - treatment of patients, interpretation of data, proofreading of the manuscript. DG - statistics, interpretation of data, proofreading of the manuscript. JV - interpretation of data, proofreading of the manuscript. MJR - statistic, interpretation of data, proofreading of the manuscript. SG - treatment of patients, interpretation of data, proofreading of the manuscript. FR - interpretation of data, proofreading of the manuscript. MR - treatment of patients, interpretation of data, proofreading of the manuscript. UFR - interpretation of data, proofreading of the manuscript. AR - interpretation of data, proofreading of the manuscript. CL - interpretation of data, proofreading of the manuscript. CWH - interpretation of data, proofreading of the manuscript. TK - conception of the study, interpretation of data, proofreading of the manuscript. AJR - conception of the study, interpretation of data, proofreading of the manuscript.

Disclosure statement

CBW received consultant honoraria and/or speaker fees from Actelion, AOP Orphan Pharmaceutical, Bayer AG, MSD, and Pfizer. SG received speaker or consulting honoraria from Actelion, Bayer, GSK and Pfizer. MRa received speaker honoraria from Actelion and Novartis. CL received lecture or consulting honoraria from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer-Bristol-Myers Squibb. CWH received lecture or consulting honoraria from Astra Zeneca, Bayer, Boehringer Ingelheim, GSK, Daiichi-Sankyo and Pfizer-Bristol-Myers Squibb. TK received speaker fees from Abbott. AJR received financial grant/travel support from Johnson&Johnson and Servier, consultant honoraria and/or speaker fees from Astra Zeneca and Bayer. SDK, JB, MSDA, DG, JV, MJR, FCR, UFR, AR have no disclosures.

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Supplementary materials

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Prognostic Power of Pulmonary Arterial Compliance Is Boosted by a Hemodynamic Unloading Test With Glyceryl Trinitrate in Heart Failure Patients With Post-capillary Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) is an established risk factor in patients with heart failure (HF). However, right heart catheterisation (RHC) and vasoreactivity testing (VRT) are not routinely recommended in these patients.

Methods: The primary objective of the present study was to explore the impact of VRT using sublingual glyceryl trinitrate (GTN) on transplant/ventricular assist device-free survival in HF patients with post-capillary PH. RHC parameters were correlated retrospectively with the primary outcome.

Results: The cohort comprised 154 HF patients with post-capillary PH undergoing RHC with GTN-VRT at a tertiary heart failure centre. Multiple parameters were associated with survival. After adjustment for established prognosis-relevant clinical variables from the MAGGIC Score, variables with the most relevant odds ratios (OR) obtained after GTN-VRT were: calculated effective pulmonary arterial (PA) elastance (adjusted OR 2.26, 95%CI 1.30–3.92; $p = 0.004$), PA compliance (PAC-GTN; adjusted OR 0.45, 95%CI 0.25–0.80; $p = 0.006$), and total pulmonary resistance (adjusted OR 2.29, 95%CI 1.34–3.93; $p = 0.003$). Forest plot analysis including these three variables as well as PAC at baseline, delta PAC, and the presence of combined post- and pre-capillary PH revealed prognostic superiority of PAC-GTN, which was confirmed by Kaplan-Meier analysis.

Conclusions: In our cohort of symptomatic HF patients with post-capillary PH, improved PAC after administration of GTN was associated with survival independent

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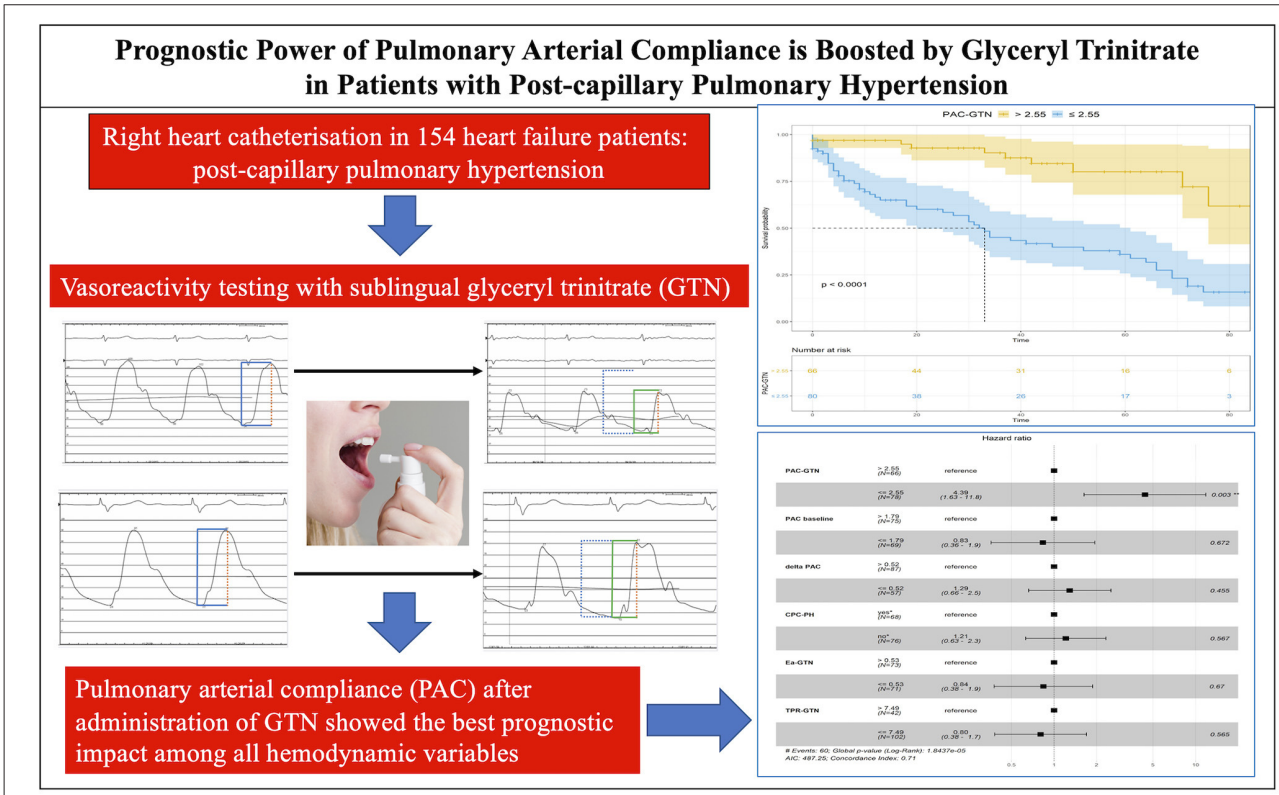
of established hemodynamic and clinical risk factors. VRT using GTN may be better described as unloading test due to GTN's complex effects on the circulation. This could be used for advanced prognostication and should be investigated in further studies.

Keywords: pulmonary arterial compliance, glyceryl trinitrate (GTN), vasoreactivity testing, post-capillary pulmonary hypertension, hemodynamics, prognosis



GRAPHICAL ABSTRACT |

INTRODUCTION

Post-capillary pulmonary hypertension (PH) is an established risk factor in patients with left heart failure (LHF), and those with advanced pulmonary vascular remodeling are known to have worse prognosis than those without. Increased vascular stiffness as a consequence of specific changes in the pulmonary vasculature leads to enhanced right ventricular afterload and right heart failure, which drives mortality in these patients (1). However, there is an ongoing debate concerning which hemodynamic parameters best mirror the extent of fixed pulmonary arterial stiffening and thus best identify patients with poor prognosis. Pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAC) seem to be the strongest prognostic indices in patients with PH associated with LHF (2–5). However, current guidelines define the subgroup of post-capillary PH with worse prognosis using a combination of PVR >3 wood units (WU) and/or diastolic pressure gradient (DPG) ≥7 mmHg, denoted combined post- and pre-capillary pulmonary hypertension (CpcPH), in contrast to isolated post-capillary pulmonary hypertension (Ipc-PH), which is associated with a slightly better prognosis (6). Recently, a modified classification was proposed, with PVR ≥ 3 WU as a single indicator of CpcPH (7).

Abbreviations: PH, pulmonary hypertension; HF, heart failure; RHC, right heart catheterisation; VRT, vasoreactivity testing; GTN, glyceryl trinitrate; LHF, left heart failure; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; DPG, diastolic pressure gradient; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; TD, thermodilution; SV, stroke volume; TPR, total pulmonary resistance; PA, pulmonary arterial; PP, pulmonary arterial pulse pressure; Ea, effective PA elastance; PAPi, PA pulsatility index; RV, right ventricular; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.

Isolated hemodynamic measurements are subject to significant spontaneous variations. The use of serial measurements, e.g., after acute vasoreactivity testing (VRT), likely improves hemodynamic prognostication (8, 9). However, in patients with post-capillary PH, VRT is recommended only as a part of the evaluation for heart transplantation, with fixed PH being a potential contraindication because of a particularly high risk for postoperative right heart failure (6, 10). Beyond this scenario, information gained from an acute vasodilator challenge is of uncertain clinical significance, possibly owing to the heterogeneity of vasodilators used for testing in LHF patients, missing standard protocol and the lack of studies on prognostic implications (11). Despite these facts, VRT is part of the standard hemodynamic workup of patients with LHF in several heart failure centres; according to local customs, sublingual glyceryl trinitrate (GTN) may be used as vasodilator (12). GTN as an arterial and venous vasodilator may be advantageous in LHF patients compared with selective pulmonary vasodilators such as inhaled nitric oxide or iloprost, because the latter may lead to an increase of left ventricular filling pressures and pulmonary edema (11).

The purpose of the present study was to explore the association of VRT results using sublingual GTN with outcomes in LHF patients with post-capillary PH. We hypothesized that application of GTN could provide incremental prognostic information by unmasking substantial pulmonary vascular disease.

MATERIALS AND METHODS

Study Population

The study cohort comprised the ongoing, prospectively recruiting Kerckhoff-Klinik HF Registry. The dataset included 154 consecutive patients registered from 10/2009 to 02/2016 who were assessed for heart failure by right heart catheterization (RHC) that included vasoreactivity testing with GTN. Inpatients (n = 85, 55%) were hospitalized because of worsening heart failure (31.8%), acutely decompensated heart failure (28.2%), diagnostic workup for evaluation of dyspnea (23.5%), and suspected pulmonary hypertension (16.5%). Inclusion criteria were a diagnosis of LHF with preserved or reduced left ventricular (LV) function according to current guidelines, availability of sufficient hemodynamic data, mean pulmonary artery pressure (mPAP) >20 mmHg and pulmonary artery wedge pressure (PAWP) >15 mmHg. PAWP between 10 and 15 mmHg at rest was accepted in a few cases (n = 12) if PAWP increased >25 mmHg during exercise or if clear features of left heart disease such as LV hypertrophy, reduced LV function, and/or significant left atrial enlargement were present. All patients included underwent guideline-compliant treatment for HF excluding PH targeted drugs. Exclusion criteria were loss to follow-up (at least one follow-up visit was required apart from the evaluation visit with RHC), severe heart valve stenosis, congenital heart defects, and constrictive pericarditis (**Supplementary Figure 1**).

The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients enrolled in the registry gave written informed consent. Data collection and analyses were approved by the ethics committee of the Faculty of Medicine at the University of Giessen (approval no. 220/15; 26 January, 2016).

Outcomes

The primary outcome measure was defined as survival free from heart transplantation (HTX) and left ventricular assist device (LVAD) implantation. Survival data were obtained through clinically indicated follow-up visits or telephone contact.

Basic Diagnostics

All patients underwent transthoracic echocardiography according to recommendations of the respective guidelines as part of the clinical work-up with determination of left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), estimated systolic pulmonary artery pressure (sPAP), and valve assessment. Baseline laboratory examinations including N-terminal brain natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR), based on serum creatinine, were carried out by the respective in-house central laboratory as part of the clinical routine care.

Hemodynamic Assessment and Vasodilator Challenge

RHC was performed in recompensated, stable patients under local anesthesia with insertion of a Swan-Ganz catheter (7F Thermodilution Catheter, Biosensors International, Singapore or Edwards Lifesciences) via the internal jugular vein or a cubital vein as described previously (13). The zero reference level for the pressure transducer was placed at the mid-thoracic level as recommended for the supine position, and all pulmonary pressures were taken at end-expiration and averaged over a minimum of 3 cardiac cycles. Baseline measurements were repeated after 20 min of rest. Those patients able to perform bicycle exercise (n = 90, 58%) were measured again during exercise. Instead of bicycle exercise, volume challenge (passive leg raise) was performed in 17 patients (11%) for additional measurements. After exercise / volume challenge, return to resting values was required for continuation of the examination. If mPAP was >20 mmHg and systolic blood pressure >100 mmHg, GTN was administered sublingually at an initial standard dose of 1.2 mg. GTN administration was repeated according to in-house standard operating procedures. The waiting time for repetition of measurements was a minimum of 5 min. A definition of positive response to GTN challenge was not determined in advance.

Cardiac output (CO) was determined by the thermodilution (TD) technique. The calculated parameters were: stroke volume (SV = CO/heart rate); total pulmonary resistance (TPR = mPAP/CO); pulmonary arterial (PA) pulse pressure (PP = sPAP–dPAP); PA compliance (PAC = SV/PP); effective PA elastance (Ea = (1.65 x mPAP−7.79)/SV) (14); PA pulsatility index (PAPi = PP/RAP); mean right ventricular (RV) power (mPAPxCO); total RV power (1.3 x mean RV power); oscillatory RV power (total–mean RV power) (15). Measurements before GTN administration are referred to as "baseline," after administration as "-GTN," and the difference between the two as "delta."

Statistical Analysis

Data are expressed as mean ± standard deviation or median [interquartile range] for normally or non-normally distributed parameters, respectively. Adherence to a Gaussian distribution was determined using the Shapiro test.

For independent samples, comparison was made with the Independent-Samples Kruskal-Wallis test for non-normally distributed parameters, the Student *t* test for normally distributed parameters, and Fisher's exact test for categorical parameters, as appropriate. For dependent samples, the paired *t* test was used for normally distributed parameters, and otherwise the Wilcoxon signed rank test.

We selected variables with the best predictive value for transplant/LVAD-free survival based on their ability to improve the predictive value of the MAGGIC score variables, an established score for risk prediction in patients with heart failure (16–18). Odds ratios (OR) were calculated based on the z-scores of each variable and are referenced as risk per standard deviation. Receiver operator characteristic (ROC) analysis with the calculated area under the curve (AUC) were used to describe an association of a variable with survival. Based on the results of ROC analysis, optimal cutoff values for prediction of mortality were calculated using the Youden index. Furthermore, based on these cutoff values multivariable Cox proportional hazards models and the Kaplan-Meier method were used for survival analyses. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using either R version 3.6.0 (survival package 3.2-3, survminer package 0.4.8) or GraphPad Prism version 8.4.3 (471).

RESULTS

Baseline Characteristics

This mono-centric analysis included 154 patients (39% female). Median age was 71 (IQR 62–76) years and 75% of the patients presented with symptoms according to NYHA class III. NT-proBNP levels [median 1890 (IQR 973-4182) pg/ml] were markedly elevated. Median LVEF was 45 [25–55]%, and the median TAPSE was 15 mm [12–19]. Classification according to heart failure type was as follows: 74 patients with preserved EF (≥50%), HFpEF; 12 with mid range reduced EF (40–49%), HFmrEF; and 68 with reduced EF (<40%), HFrEF). Duration of heart failure ≥ 18 months was present in 27% of HFpEF, 75% of HFmrEF and 79% of HFrEF patients. In HFpEF patients, 84% had a history of hypertension, 36% had coronary artery disease, 28% suffered from diabetes, 81% had atrial fibrillation, and 2 patients had hypertrophic cardiomyopathy. In HFmrEF patients, the etiology of HF was hypertensive in 33% and ischemic in 25%; 2 patients had dilated and 3 valvular cardiomyopathy. In HFrEF patients, 54% had ischemic etiology, and 34% had dilated cardiomyopathy, 7% valvular cardiomyopathy, 3% hypertensive cardiomyopathy; 1 patient had congenital heart disease.

Nearly all patients (94%) were treated with diuretics; guideline-directed medical therapy was present as indicated. Patients had a high frequency of atrial fibrillation/flutter (73%) and device therapy (51%). Baseline characteristics, also stratified by our PAC-GTN cutoff, are provided in **Table 1**.

Effects of GTN Administration

Median administered GTN dose was 2.4 (IQR 1.6-3.2) mg. GTN vasodilator challenge led to a significant change in most hemodynamic parameters, except heart rate and the PVR/SVR ratio (**Supplementary Table 1**). There were no significant side effects of GTN, especially no serious hypotension. Hemodynamics before and after GTN administration, stratified by our PAC-GTN cutoff, are provided in **Table 2**. Comparing survivors with those who died or underwent HTX/LVAD, survivors showed a smaller increase in SV (median +3.11 vs. +6.52 ml) but a markedly larger decrease in PP (−9.0 vs. −3.5 mmHg) and a subsequent larger increase (improvement) in PAC (+0.89 vs. +0.30 ml/mmHg) than those meeting the end point (**Figure 1**). Furthermore, there were numerous differences in response to GTN between these groups.We compared the hemodynamic parameters before and after GTN administration in different types of LHF (HFpEF, HFmrEF and HFrEF). There were no significant differences in baseline PAP. After GTN administration, patients with HFpEF showed the lowest increase in CO and decrease of Ea and systemic vascular resistance, but the largest reduction of PP. Patients with HFrEF had the lowest increase of PAC and decrease of PP, and also lowest fall in systolic blood pressure (**Supplementary Table 2**).

Association of GTN-Dependent Hemodynamics and Outcome

The median follow-up was 30 [8–57] months in our cohort. Within this period 62 (40.3%) patients died, 3 (1.9%) underwent HTX, and 1 (0.6%) underwent LVAD implantation. Overall survival free from HTX and LVAD implantation was 57.2%.

Univariate regression analysis revealed multiple associations between hemodynamic parameters and survival, both at baseline and post-GTN testing. Variables with the best ability to improve the predictive value of the MAGGIC score variables were selected. The components of the MAGGIC-Score are tagged within **Table 1**, and data on the univariate associations and the MAGGIC score are given in **Supplementary Table 3**. The three hemodynamic measures showing the strongest association (lowest adjusted *p*-values in combination with highest AUC) with outcome were Ea-GTN, TPR-GTN, and PAC-GTN, all after GTN challenge.

The areas under the curve (AUC) in the ROC analysis of these parameters (adjusted for the MAGGIC score variables) to discriminate patients with poor outcome were 0.89 (95% CI 0.83-0.95) for Ea-GTN, 0.89 (0.84–0.95) for TPR-GTN, and 0.89 (0.84–0.95) for PAC-GTN. The respective odds ratios (OR) adjusted for the MAGGIC score variables were 2.26 (1.30–3.92) per SD increase ($p = 0.004$) for Ea-GTN, 2.29 (1.34–3.93) per SD increase ($p = 0.003$) for TPR-GTN, and 0.45 (0.25–0.80) per SD increase ($p = 0.006$) for PAC-GTN.

Optimal cut-off values for mortality, calculated using the Youden index, were 0.53 mmHg/ml for Ea-GTN, 7.49 WU for TPR-GTN and 2.55 ml/mmHg for PAC-GTN. The predictive value of these derived cut-off values was compared with the

TABLE 1 | Baseline characteristics.

	Data availability	All $n = 154$	PAC-GTN > 2.55 $n = 66^{\S}$	PAC-GTN ≤ 2.55 $n = 82^{\S}$	*p*-Value*
All-cause mortality/HTX/LVAD Median Survival, months	154/154	66 (43)		33	<0.001
GTN dose, mg	151/154	2.4 [1.6–3.2]	2.4 [1.2–3.2]	2.4 [1.6–3.2]	0.324[a]
Female sex[#]	154/154	60 (39)	28 (42)	29 (35)	0.400
Age[#], years	154/154	71.0 [62.0–76.0]	73.0 [63.3–77.0]	68.0 [59.0–75.0]	0.095[a]
Body mass index[#], kg/m^2	154/154	28.9 [25.3–33.4]	31.0 [27.2–34.3]	27.8 [24.1–32.4]	0.003[a]
Smoker[#] (current or within last 6 months)	154/154	12 (7.8)	6 (9.1)	6 (7.3)	0.767
Hypertension[#]	154/154	125 (81.2)	55 (83.3)	65 (79.3)	0.673
Coronary artery disease	154/154	69 (44.8)	26 (39.4)	42 (51.2)	0.185
Atrial fibrillation/flutter	154/154	113 (73.4)	45 (68.2)	62 (75.6)	0.358
Diabetes mellitus[#]	154/154	56 (36.4)	19 (28.8)	35 (42.7)	0.089
Diagnosis of CHF ≥ 18 months[#]	154/154	83 (53.9)	29 (43.9)	53 (64.6)	0.013
COPD[#]	154/154	25 (16.2)	16 (24.2)	9 (11.0)	0.046
Device therapy (ICD or pacemaker)	154/154	78 (50.7)	23 (34.9)	54 (65.9)	<0.001
Aldosterone blocker use	153/154	82 (53.6)	28 (42.4)	48 (59.3)	0.069
ß-Blocker use[#]	153/154	132 (86.3)	59 (89.4)	69 (85.2)	0.470
ACE inhibitor/ARB use[#]	153/154	136 (88.9)	57 (86.4)	73 (90.1)	0.624
Calcium channel blocker use	153/154	27 (17.7)	12 (18.2)	13 (16.1)	0.826
Cardiac glycoside use	153/154	34 (22.2)	8 (12.1)	26 (32.1)	0.006
Diuretic use	153/154	144 (94.1)	63 (95.5)	76 (93.8)	0.732
NYHA class[#]	153/154				
I		4 (2.6)	3 (4.5)	1 (1.2)	
II		27 (17.5)	13 (19.7)	10 (12.2)	
III		114 (74.0)	47 (71.2)	65 (79.3)	0.337
IV		8 (5.2)	2 (3.0)	6 (7.3)	
V'O_2 peak, ml/min/kg	78/154	11.0 [9.6–13.2]	11.9 [10.7–14.3]	9.9 [8.9–12.5]	0.002[a]
Maximum workload, W	78/154	50 [40–60]	60 [40–70]	40 [30–50]	<0.001[a]
GFR[#], ml/min/1.73 m^2	145/154	62.0 [48.1–81.0]	68.6 [53.8–94.7]	58 [44.5–72.0]	0.009[a]
Urea, mg/dl	126/154	54.0 [38.0–78.5]	42.0 [34.8–66.8]	59.0 [44.0–81.0]	0.005[a]
Sodium, mmol/l	145/154	139 [136–141]	140 [138–141]	138 [135–140]	0.008[a]
NT-proBNP, pg/ml	141/154	1,890 [973–4182]	1,137 [602–2405]	3,281 [1732–5165]	<0.001[a]
LVEF[#], %	154/154	45 [25–55]	55 [39–55]	35 [20–55]	<0.001[a]
TAPSE, mm	109/154	15 [12–19]	18 [16–20]	13 [11–16]	<0.001[a]
RVSP, mmHg	131/154	54 [43–66]	49 [39–60]	58 [47–70]	0.004[a]

*Data are displayed as count (percentage), or median [interquartile range] except where otherwise indicated. GTN, glycerol trinitrate; HTX, heart transplantation; LVAD, left ventricular assist device; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; V'O_2 peak, oxygen uptake measured by cardiopulmonary exercise testing; GFR, glomerular filtration rate; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RVSP, right ventricular systolic pressure derived from tricuspid regurgitation velocity. *PAC-GTN > 2.55 vs. PAC-GTN ≤ 2.55. §Stroke volume and thus PAC after GTN administration was not available in 6 patients. [a]Mann–Whitney U test. All categorical variables were compared using Fisher's exact test. [#]Tagging of the variables used for the MAGGIC-Score.*

predictive information of the difference between baseline PAC and PAC-GTN (delta PAC), and established parameters such as PAC (baseline) and the presence of CpcPH (defined by PVR >3 WU and/or DPG ≥ 7 mmHg). In this multivariable analysis, considering several clinical important factors, PAC-GTN was the only independent significant factor associated with survival (**Figure 2**).

Correlation analyses were performed additionally to demonstrate independence of PAC-GTN related to known risk markers. In patients with PAC-GTN >2.55 ml/mmHg, there were the following correlations of PAC-GTN: vs. NT-pro BNP: $r = -0.10$; vs. LVEF: $r = 0.08$; vs. TAPSE: $r = 0.17$ (all p-values > 0.05); and in patients with PAC-GTN ≤ 2.55 ml/mmHg: vs. NT-pro BNP: $r = -0.16$; vs. LVEF: $r = -0.09$; vs. TAPSE: $r = 0.22$; all p-values > 0.05.

This significant finding was the basis for further analyses. PAC-GTN was able to improve the AUC in the ROC analysis of the MAGGIC score to differentiate patients with an unfavorable outcome (**Figure 3**). PAC-GTN and delta PAC were not correlated to the GTN dose administered (Spearman r

TABLE 2 | Hemodynamics at baseline and after GTN administration.

	BASELINE					GTN				
Data availability (D.a.)	**D.a.**	**PAC-GTN > 2.55** ***n = 66*** [§]	**D.a.**	**PAC-GTN ≤ 2.55** ***n = 82*** [§]	***p*-Value***	**D.a.**	**PAC-GTN > 2.55** ***n = 66*** [§]	**D.a.**	**PAC-GTN ≤ 2.55** ***n = 82*** [§]	***p*-Value***
Systolic BP, mmHg	66	134.0 (±25.0)	82	119 [106-136]	0.006[a]	66	124.0 (±22.0)	82	112 [101-128]	0.003[a]
Mean BP, mmHg	66	93 [84–106]	81	88 [80–97]	0.016[a]	65	88.0 (±14.0)	81	82.0 (±12.0)	0.003[b]
Heart rate, beats/min	66	67.0 (±10.0)	82	70.0 (±9.5)	0.098[b]	66	67 [61–73]	82	69 [62–75]	*0.286*[a]
PAWP, mmHg	66	21.0 [18–24]	82	26.0 (±5.0)	<0.0001[a]	66	13.0 [9.0–18.0]	82	20.0 [16.0–24.0]	<0.0001[a]
sPAP, mmHg	66	51.0 (±11.0)	82	68.0 [56–73]	<0.0001[a]	66	35.0 [29–45]	82	55.0 (±13.0)	<0.0001[a]
mPAP, mmHg	66	33.0 (±6.3)	82	41.0 (±6.7)	<0.0001[b]	66	23.0 (±6.0)	82	32.0 (±7.3)	<0.0001[b]
dPAP, mmHg	66	20.0 (±4.8)	82	25.0 (±5.6)	<0.0001[b]	66	*15.0 (±4.7)*	82	19.0 (±5.8)	<0.0001[b]
PP, mmHg	66	30.0 [25.0–37.0]	82	40.0 [32.0–47.0]	<0.0001[a]	66	20.0 [17.0–25.0]	82	36.0 [29.0–42.0]	<0.0001[a]
RAP, mmHg	66	11.0 [7.0–13.0]	82	12.0 [9.0–17.0]	0.009[a]	63	7.0 [5.0–10.0]	71	9.0 (±4.9)	0.056[a]
TPG, mmHg	66	11.0 [8.0–14.0]	81	15.0 [11.0–19.0]	<0.0001[a]	66	9.6 (±3.7)	81	14.0 (±5.3)	<0.0001[b]
DPG, mmHg	66	−0.92 (±4.1)	81	−1.0 [−4.0-3.0]	0.572[a]	66	1.4 (±3.9)	81	0.28 (±5.3)	0.169[b]
CO-TD, l/min	66	5.0 [4.1–5.9]	82	3.7 [3.1–4.5]	<0.0001[a]	66	5.4 (±1.3)	82	4.2 [3.5–5.1]	<0.0001[a]
CI-TD, l/min/m^2	66	2.5 [2.2–2.8]	82	2.0 [1.7–2.3]	<0.0001[a]	66	2.7 (±0.63)	82	2.2 [2.0–2.6]	<0.0001[a]
SV-TD, mL	66	72.0 [62.0–92.0]	82	54.0 [45.0–69.0]	<0.0001[a]	66	77.0 [64.0–91.0]	82	61.0 [49.0–77.0]	<0.0001[a]
PVR, WU	66	2.3 (±0.9)	81	3.6 [2.9–5.4]	<0.0001[a]	66	1.9 (±0.74)	81	3.0 [2.2–4.2]	<0.0001[a]
SVR, WU	66	19.0 [16.0–22.0]	82	24 (±6.5)	<0.0001[a]	66	17.0 [13.0–20.0]	81	20 (±5.3)	0.002[a]
PVR/SVR	66	0.12 [0.08–0.16]	80	0.16 [0.13–0.22]	<0.0001[a]	65	0.11 (±0.05)	80	0.17 (±0.07)	<0.0001[b]
TPR, WU	66	6.6 (±1.5)	82	11.0 [8.8–13.0]	<0.0001[a]	66	4.5 (±1.2)	82	7.6 [6.0–8.9]	<0.0001[a]
PAC, mL/mmHg	66	2.4 [2.1–3.0]	82	1.4 [1.1–1.7]	<0.0001[a]	66	3.5 [3.0–4.5]	82	1.9 [1.4–2.2]	<0.0001[a]
Ea, mmHg/mL	66	0.63 (±0.18)	82	1.0 [0.89–1.4]	<0.0001[a]	66	0.40 (±0.14)	82	0.73 [0.57–0.87]	<0.0001[a]
PAPi	66	3.0 [2.2–4.0]	82	3.3 [2.2–4.8]	0.263[a]	63	3.0 [2.3-4.2]	71	4.3 [3.2–6.3]	<0.0001[a]
RAP/PAWP	66	0.53 [0.40–0.64]	80	0.53 [0.36–0.62]	0.906[a]	63	0.56 [0.42–0.65]	74	0.43 (±0.21)	0.006[a]
RV power$_{oscill}$, W	66	0.11 [0.08–0.13]	82	0.10 [0.08–0.13]	0.524[a]	66	0.08 [0.06–0.11]	82	0.09 [0.07–0.12]	0.093[a]

*Data are displayed as median [interquartile range] or mean (± standard deviation) except where otherwise indicated. GTN, glycerol trinitrate; BP, blood pressure; PAWP, pulmonary arterial wedge pressure; sPAP, systolic pulmonary arterial pressure; mPAP, mean PAP; dPAP, diastolic PAP; PP, pulse pressure; RAP: mean right atrial pressure; TPG, transpulmonary gradient; DPG, diastolic pulmonary gradient; CO, cardiac output; TD, Thermodilution method; CI, cardiac index; SV, stroke volume; PVR, pulmonary vascular resistance; WU, Wood units; SVR, systemic vascular resistance; TPR, total pulmonary resistance; PAC, pulmonary arterial compliance; Ea, pulmonary effective arterial elastance (calculated); PAPi, pulmonary artery pulsatility index; RV, right ventricle; oscill, oscillatory; W, watt. *PAC-GTN > 2.55 vs. PAC-GTN ≤ 2.55. [§]Stroke volume and thus PAC after GTN administration was not available in 6 patients. [a]Mann–Whitney U test. [b]Student's t-test.*

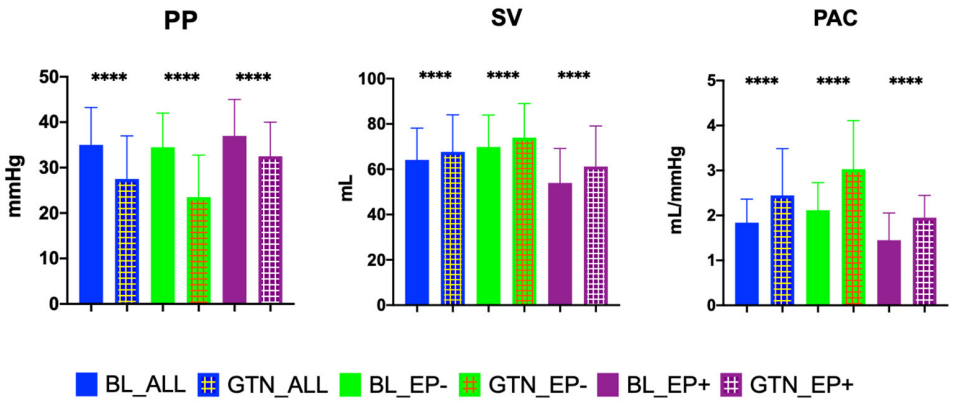


FIGURE 1 | Key hemodynamic parameters at baseline and after glyceryl trinitrate (GTN) application in all patients, in patients who did not reach the endpoint transplant/LVAD free survival (EP-), and in patients reaching the endpoint (EP+). PP, pulse pressure; SV, stroke volume; PAC, pulmonary arterial compliance; BL, baseline. ****$P < 0.00001$.

$= -0.14$; $p = 0.09$, and $r = -0.04$; $p = 0.60$). Kaplan-Meier survival analyses confirmed the prognostic power of PAC-GTN. Although presence of CpcPH and baseline PAC were both associated with survival, PAC-GTN was superior in prognostication (**Figure 4**). Kaplan-Meier subgroup analysis in patients with HFpEF and in patients with HFmrEF/HFrEF demonstrated that PAC-GTN was associated with survival in both groups, and the association appeared stronger in HFpEF patients (**Supplementary Figures 2**, **3**). Delta PAC and percentage increase in PAC after GTN administration were also significantly associated with survival (delta PAC: cutoff 0.52 ml/mmHg, $p < 0.0001$; percentage increase in PAC: cutoff 0.23%, $p < 0.0001$; **Supplementary Figures 4**, **5**).

Interestingly, reduction of RV oscillatory power and thus oscillatory load was more pronounced in PAC-GTN >2.55 than ≤2.55 ml/mmHg (median −0.025 vs. −0.010 W; $p < 0.0001$), whereas the extent of PVR reduction was even smaller in PAC-GTN >2.55 than ≤2.55 ml/mmHg (-0.39 vs.−0.78 WU; $p = 0.031$).

To explore whether classification according to PAC-GTN instead of CpcPH would lead to a significant change in prognostication, we performed a reclassification analysis. Seventy-one patients were classified as high risk according to CpcPH criteria; they all had PVR >3 WU, and 8 of them additionally had DPG ≥ 7 mmHg. Hence, DPG did not influence risk stratification. Fourteen of those patients with PVR >3 WU had PAC-GTN > 2.55 ml/mmHg (thus changing from high to low risk), and 24 patients with PVR ≤3 WU had PAC-GTN ≤2.55 ml/mmHg (thus changing from low to high risk). All in all, 38 patients (25%) had different hemodynamic prognostication by either PVR (CpcPH) or PAC-GTN (cut-off).

DISCUSSION

Here we present a comprehensive analysis of the prognostic value of invasive hemodynamics at baseline and after challenge with sublingual GTN in HF patients with post-capillary PH. The relevant findings of our study are as follows: (i) three hemodynamic parameters (PAC, Ea, TPR) obtained after administration of GTN, all of them derived from pressure/flow relationships, showed significant prognostic value; (ii) PAC-GTN was the best prognostic marker, which was superior to established parameters such as PAC (19) and the presence of CpcPH; (iii) PAC-GTN may be a surrogate for a successful reduction of RV oscillatory load.

There are few reports available concerning prognostic implications of VRT in pre-capillary PH (20, 21). In candidates for cardiac transplantation, reversibility of post-capillary PH and thus a better outcome post-transplantation is assumed if TPG decreases to <15 mmHg and/or pulmonary vascular resistance decreases to <3 WU. In other heart failure patients, VRT is currently not recommended, and a consistent protocol is lacking as well as the definition of a positive test result (22, 23). Ghio et al. (24) conducted VRT using intravenous nitrates in 156 heart failure patients with a reduced LVEF and PH and found that survival was significantly reduced in non-responders in contrast to responders. In a study by Al-Naamani et al. (25) VRT did not predict outcome in 73 patients with PH and heart failure with preserved LVEF. Lim et al. (26) described an association of PVR reduction (at least 20%) with survival, and baseline PAC was associated with survival in 98 patients with "mixed" PH. To the best of our knowledge, however, our study is the first to demonstrate a prognostic value of VRT in post-capillary PH independent of the "CpcPH" definition and a predefined, albeit arbitrary definition of "response."

Three factors may have contributed to these new findings: the vasodilator used and its dosage, the measurement methods, and the most suitable hemodynamic parameter. Most drugs used for VRT are more or less selective pulmonary vasodilators that cause a small decrease or even an increase in PAWP, which is undesired in LHF (but nevertheless may result in PVR reduction). GTN decreases PAP and PAWP markedly by provoking venous and also arterial vasodilation, thus lowering pre- and afterload and indirectly increasing subendocardial blood

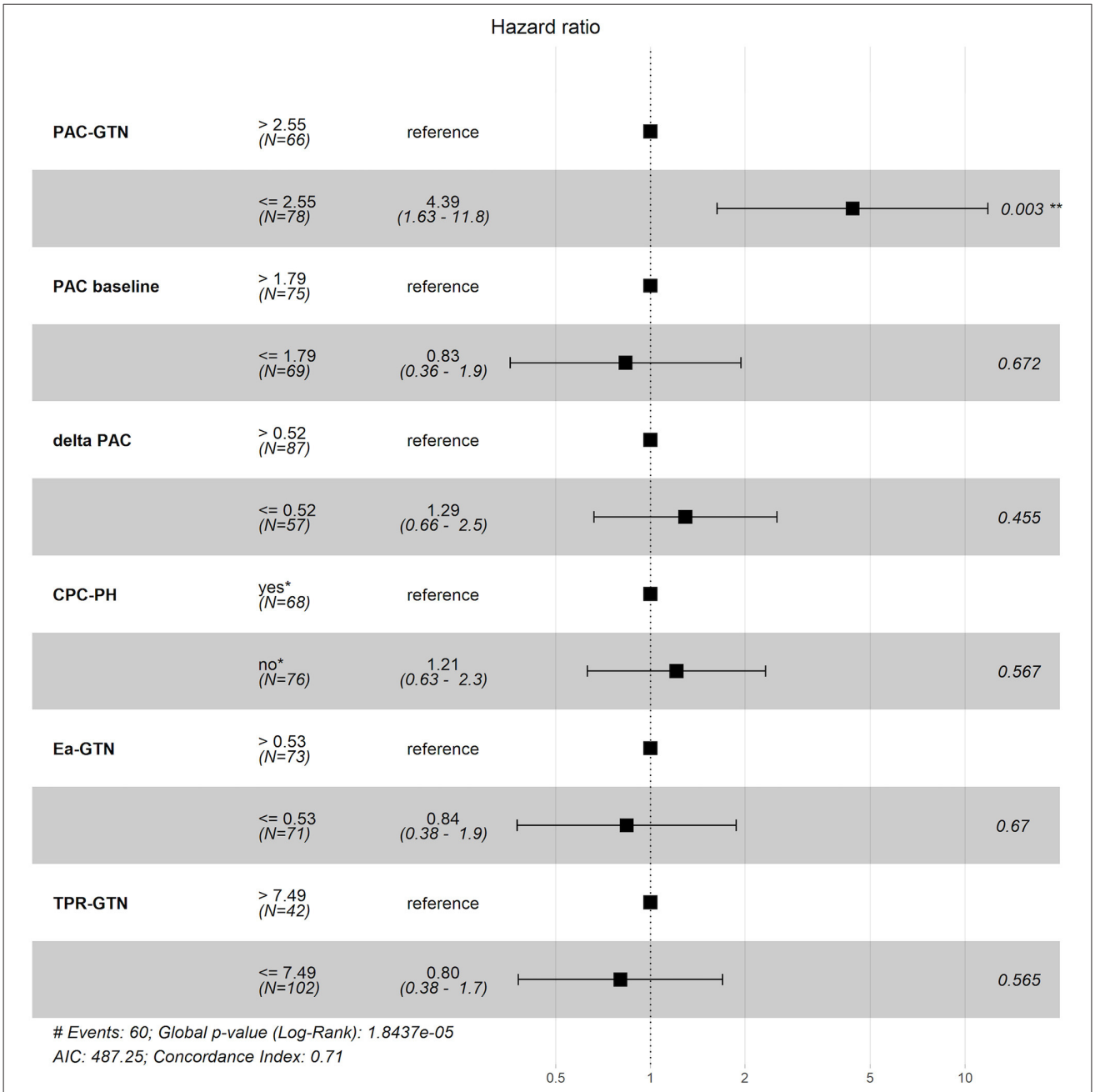


FIGURE 2 | Forest plot of different hemodynamic variables and their impact on prognosis. PAC, pulmonary arterial compliance; CpcPH, combined post- and pre-capillary pulmonary hypertension ("yes," if pulmonary vascular resistance >3 wood units and/or diastolic pulmonary gradient ≥7 mmHg); GTN, glyceryl trinitrate; Ea, pulmonary effective arterial elastance (calculated); TPR, total pulmonary resistance.

flow (11, 27). Therefore, GTN causes much more than pulmonary vasodilation: the whole RV-PA-LV unit is unloaded in a dose-dependent manner. The term "unloading test" would describe these combined effects better than "vasoreactivity test." However, the primary component contributing to improved PAC by GTN in the survivors of our cohort was the decrease in PA pulse pressure rather than an increase in stroke volume. In line with this, PAPi as an index of right ventricular contractility independent of CO measurement (28) did not show prognostic relevance. Pulse pressure after GTN alone was also prognostic, but weaker than PAC-GTN. In our cohort, patients with preserved LVEF showed a larger reduction of pulse pressure in response to GTN than those with reduced LVEF, but a smaller increase of cardiac output.

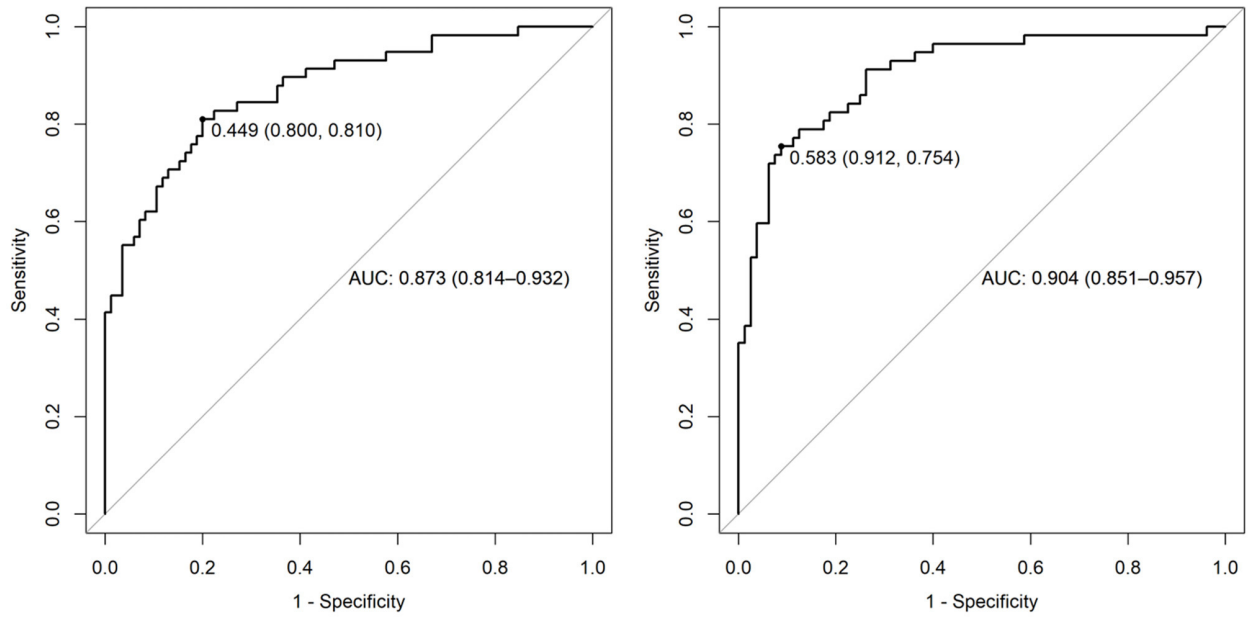


FIGURE 3 | AUC of ROC analysis for prediction of survival. Left panel: variables of the MAGGIC score; right panel: MAGGIC variables and PAC-GTN.

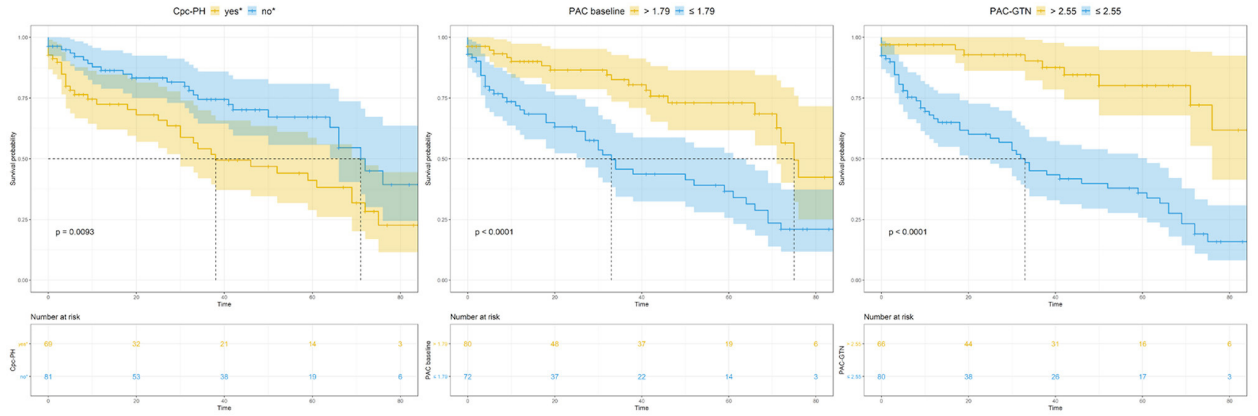


FIGURE 4 | Kaplan-Meier analysis of key variables CpcPH, baseline PAC, and PAC-GTN. CpcPH, combined post- and pre-capillary pulmonary hypertension ("yes," if pulmonary vascular resistance >3 wood units and/or diastolic pulmonary gradient ≥7 mmHg); PAC, pulmonary arterial compliance; GTN, glyceryl trinitrate.

Single hemodynamic measurements may be subject to the bias of situational influences such as vasoconstriction and may mitigate the prognostic power of established hemodynamic indices such as CpcPH. Repeated measurements after vasodilatory challenge and thus ventricular unloading may be advantageous in this context. If unloading does not lead to markedly improved pressure-flow relationships (which are the basis for calculation of the abovementioned three key variables), structural pulmonary vasculopathy may be present.

Our analysis took multiple established prognostic hemodynamic factors into account, and Ea, TPR, and PAC as indicators of RV afterload (29) measured after GTN challenge showed the best associations with prognosis. Among them, PAC-GTN stood out and yielded a clear cut-off value. PAC may be superior to PVR because it "bundles the effects of PVR and left-sided filling pressures on RV afterload." (19) Furthermore, PAC integrates resistive, pulsatile, and passive components of RV afterload and therefore may reflect remodeling of the PA (30). Reduction of the RV oscilllatory load is likely to be the dominant effect of PAC increase in our cohort, for the fall of RV oscilllatory load was markedly more pronounced in the PAC-GTN >2.55 group, and reduction of the steady component of RV load (delta PVR) was relatively weak. RV dysfunction or RV-PA coupling may be better defined by Ea and PAC than by

other parameters (29). However, cut-off values proposed for PAC as a risk marker vary widely (19, 31, 32); repeated measurements after vasodilatory challenge could be a method to obtain a more consistent cut-off value.

Limitations

We included patients with different types of heart failure (HFpEF, HFmrEF and HFrEF), which may be a source of bias. However, the effects of all types are elevated left-sided filling pressures, resulting in post-capillary PH (8). Our analysis of patients with HFpEF vs. HFmrEF/HFrEF confirmed our main results in both groups. Furthermore, 23 patients (12, 5 % of the cohort assessed for eligibility) were lost to follow up, which seems to be within an acceptable range (33).

Conclusions

A hemodynamic unloading test using GTN may improve the prognostic power of PAC in patients with post-capillary PH and should be investigated in further prospective studies. Implications for therapeutic options of patients defined as high risk by this method remain elusive.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Faculty of Medicine at the University of Giessen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR, DG, and TK: conception and design, statistical analysis, interpretation of data, and drafting of the manuscript, GZ: acquisition of data. SK, SW, MR, KT, UK, VM, CH, and SR: analysis and interpretation of data and revising the manuscript critically for important intellectual content. All authors: final approval of the manuscript submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.838898/full#supplementary-material

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Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Exercise Hemodynamic Profiling Is Associated With Outcome in Patients Undergoing Percutaneous Mitral Valve Repair

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BACKGROUND: Percutaneous mitral valve repair (PMVR) in high-risk patients is currently controversial, especially in those with secondary mitral regurgitation (MR). Exercise pulmonary hemodynamics may help to unmask cardiac dysfunction as well as the dynamic impact of MR. The present study sought to explore the clinical impact of preprocedural exercise right heart catheterization (RHC) for the selection of patients who could most benefit from PMVR.

METHODS: Sixty-eight patients with symptomatic primary and secondary MR and exercise RHC before PMVR were included in this retrospective analysis of the association of exercise RHC parameters with survival and improvement in New York Heart Association class within 12 months.

RESULTS: Median patient age was 77 years (±8.5), 37% were female, and 81% presented with New York Heart Association class III. A total of 65% of the patients had left ventricular ejection fraction <55%. MR was severe in 49% and moderate-to-severe in 51%. Twenty-two patients (32%) died within the follow-up period of 19 months (interquartile range, 9–32); they had a lower rise (Δ) in the V-wave on pulmonary artery wedge pressure tracings. Patients with ΔV-wave ≥17 mm Hg had a reduced risk of death after PMVR (hazard ratio, 0.11 [95% CI, 0.04–0.33], $P<0.001$), independent of age, frailty index, and workload during RHC. A higher ΔV-wave was also associated with New York Heart Association improvement (odds ratio, 1.14 [95% CI, 1.07–1.24]; $P<0.001$), and 79% of patients with ΔV-wave ≥15 mm Hg were in New York Heart Association class I or II at follow-up (<15 mm Hg: 28%). These results were for the most part confirmed in the subgroup of patients with secondary MR (65%).

CONCLUSIONS: In our cohort of patients with indication for PMVR, preprocedural exercise RHC was able to identify patients with an unfavorable outcome. Further studies with larger patient numbers are warranted before this approach can be implemented in a structured diagnostic workup of patients under evaluation for PMVR.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: exercise ■ heart failure ■ hemodynamics ■ mitral valve ■ prognosis

In patients with severe secondary mitral regurgitation (MR) and high surgical risk, selection criteria that predict when percutaneous mitral valve repair (PMVR) will lead to positive long-term outcomes are currently under debate. The MITRA-FR trial (Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation)[1] and the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation)[2] revealed that the results

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WHAT IS KNOWN

- Death or continued heart failure symptoms are described in up to one-half of the patients treated with percutaneous mitral valve repair after 1 year; echocardiography and clinical profile alone may not always be sufficient to select suitable candidates for percutaneous mitral valve repair among patients with mitral regurgitation.
- Exercise-induced changes in pulmonary hemodynamics may reflect the severity of heart failure and mitral regurgitation.

WHAT THE STUDY ADDS

- A reduced rise in the V-wave on pulmonary artery wedge pressure tracings during exercise and a smaller increase in cardiac output before intervention was associated with increased mortality and lack of clinical improvement after percutaneous mitral valve repair.
- These parameters identified patients in whom mitral valve repair did not show a benefit for individual hemodynamic pathophysiology.
- Exercise hemodynamic profiling before percutaneous mitral valve repair may extend the spectrum of diagnostic tools and improve candidate selection in cases of doubt.

Nonstandard Abbreviations and Acronyms

ΔCO	rise of cardiac output during exercise
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
exRHC	exercise right heart catheterization
FI	frailty index
HF	heart failure
LA	left atrial
MITRA-FR	Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation
MVARC	Mitral Valve Academic Research Consortium
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAWP	pulmonary arterial wedge pressure
PMVR	percutaneous mitral valve repair

of percutaneous treatment of secondary MR greatly depend on candidate selection: death or continued heart failure (HF) symptoms occurred in about one-third to one-half of the patients treated with PMVR at the 1-year follow-up.[3] This may also apply to patients with primary MR, who comprise up to 28% in national registries (rates of death at 1 year 20.3%–23.0%, continuing functional class III-IV 21.9%–36.7%).[4,5] The great heterogeneity in functional improvement achieved by PMVR is an indicator of the need for refined selection criteria.[6,7]

To date, the indication for PMVR is based mainly on echocardiography in combination with clinical findings.[8] The use of exercise right heart catheterization (exRHC) is an attractive approach for evaluation of hemodynamic MR severity due to the retrograde transmission of left atrial (LA) hemodynamics in the pulmonary arterial wedge pressure (PAWP).[9,10] Exercise hemodynamic assessment can unmask not only dynamic MR but also the severity of HF.[11,12] This could be of special importance for the identification of patients with an optimal risk-benefit balance, which is crucial to avoiding futile interventions in high-risk patients treated by PMVR.

Therefore, the aims of our study were (1) to identify new parameters derived from exRHC indicating hemodynamic severe MR requiring intervention and (2) to identify high-risk patients who do not benefit from PMVR.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

Patients undergoing exRHC while being evaluated for PMVR were enrolled in our single-center Kerckhoff-Klinik HF registry. They were included retrospectively if they underwent PMVR according to the heart team decision that was based on echocardiography, clinical data, and exRHC results. The analysis included consecutive PMVR patients registered from May 2013 to April 2017 with moderate-to-severe and severe MR, as judged by echocardiography at rest. Mandatory inclusion criteria were absence of combined mitral valve defects or more than moderate defects of other valves; MR suitable for PMVR; guideline-directed medical treatment; exRHC <6 months before PMVR; complete hemodynamic data; successful PMVR defined as reduction of MR by ≥1 degree; follow-up data including survival (Figure I in the Data Supplement).

Patients without successful valve repair were excluded because procedural failure was not the point of interest; for this proof-of-concept study, successful repair was the basis for judgment of appropriate candidate selection.

Data collection and analysis were approved by the ethics committee of the Landesärztekammer Hessen (Approval No. FF79/2010) and the Faculty of Medicine at the University of Giessen (Approval No. 36/14). All patients provided written informed consent for their participation in the study. The study conformed to the principles outlined in the Declaration of Helsinki.

Echocardiography

All patients underwent transthoracic and transoesophageal echocardiography in a left decubital position. MR was

classified as primary if left ventricular ejection fraction was normal (≥55%), or as secondary/mixed, if left ventricular ejection fraction was reduced (<55%). The degree of MR was graded into mild, moderate, or severe according to recent guidelines.[8,13] As traditional grading into 4 degrees (mild, moderate, moderate-to-severe, and severe) is common in the context of PMVR,[2] the corresponding degrees derived from the PMVR implantation protocols are given in Roman numerals (I–IV°).

Exercise RHC

Hemodynamic measurements were performed as described in detail previously.[12,14] Briefly, patients underwent exRHC by insertion of a Swan-Ganz catheter (7F Thermodilution Catheter, Biosensors International, Singapore) via the internal jugular vein or a cubital vein under local anesthesia; the procedure was performed by investigators not blinded to clinical records. Exercise was performed on a standard cycle ergometer in the supine position with an adjusted external workload of 0 (freewheel), 10, 15, 25, or 50 W to allow measurement of hemodynamic parameters at steady-state conditions after 2 minutes of exercise at the respective workload level. If the patient was able to continue cycling, the workload was increased to an adjusted higher level to reach at least submaximal exercise. During exercise, 2 to 3 measurements of cardiac output (CO) were taken at each workload level. Pressure tracings were averaged over 3 to 5 cycles and reviewed for plausibility before the measurements were used.

Frailty Index

A frailty index (FI) was calculated using validated deficits in health.[15] Of 40 deficits described originally, 16 were available from the medical records (or 15, if peak flow was not available). The FI is expressed by the ratio of deficits present to the total number of deficits considered. The deficits considered are displayed in Table I in the Data Supplement.

Outcome Measures

The primary outcome was all-cause mortality after PMVR according to MVARC recommendations.[16] The secondary outcome was clinical benefit from PMVR, defined as improvement in New York Heart Association (NYHA) HF class within 12 months by a minimum of 1 class. Death within 12 months was counted as a failure to improve.

Statistical Analysis

Normally distributed data are expressed as mean±SD; nonnormally distributed data are expressed as median (interquartile range). Between-group differences were analyzed with the Student *t* test or the Mann-Whitney *U* test.

Cox regression, receiver operating characteristic curve analysis, and the Youden index were used to identify exercise hemodynamic parameters with significant prediction of all-cause mortality, which was further evaluated by the Kaplan-Meier analysis with a log-rank test and a Cox proportional-hazards regression model.

NYHA improvement was related to exercise hemodynamic parameters by simple logistic regression and receiver operating characteristic analysis and differences between groups by the Fisher exact test.

For all analyses, $P<0.05$ was considered to indicate statistically significant differences.

R version 3.6.0 and Prism 8, version 8.4.3 (471) were used for statistical analyses.

RESULTS

Baseline Characteristics

The analysis included 68 patients with moderate-to-severe (III° of IV°) or severe (IV°) MR treated with PMVR. Sixty-six patients underwent the MitraClip procedure (Abbott Vascular, Inc, Santa Clara, CA), and 2 were treated with the Cardioband (Edwards Lifesciences, Irvine, CA). Primary MR was present in 24 patients and secondary MR in 44. The echocardiography and HF characteristics of the latter group were nearly identical to those of patients included in the COAPT trial.[2] They showed substantially elevated NT-proBNP (N-terminal pro-brain natriuretic peptide) serum levels, a high percentage of NYHA class III, systolic left ventricular dysfunction, pulmonary hypertension, elevated pulmonary vascular resistance, elevated PAWP, reduced CO, atrial fibrillation/flutter, and several comorbidities. All patients received guideline-directed HF medical therapy (Table).

RHC at Rest and During Exercise

Pulmonary hypertension at rest (mean pulmonary artery pressure >24 mm Hg) was present in 74% of the patients, and 47% had pulmonary vascular disease with pulmonary vascular resistance >3.0 WU. Median workload was 15 (0–25) W, and the median duration of exercise was 5.0 (4.5–7.5) minutes. During exercise, patients had steep pressure-flow slopes resulting from substantial increases in LA and pulmonary pressures accompanied by inadequate increases in CO (Table).

Impact of Exercise RHC Parameters on the Primary Outcome

There was one periprocedural death, and within a median follow-up period of 19 (interquartile range, 9–32) months, 22 patients (32%) died. One patient committed suicide 4 years after PMVR, which was not counted as death. Several invasive hemodynamic parameters during exercise were significantly associated with all-cause death (Figure 1). Upon univariate Cox regression analysis, a smaller rise (Δ) in the PAWP V-wave, smaller Δ mean pulmonary artery pressure, smaller ΔPAWP, higher maximum right atrial pressure, lower maximum exercise cardiac index, and a smaller rise of CO (ΔCO) were associated with higher mortality. The most significant single parameter with the highest area under the receiver operating characteristic curve (AUC) was ΔV-wave (hazard ratio, 0.91 [95% CI, 0.87–0.96]; $P<0.001$; AUC, 0.79 [95% CI, 0.67–0.92]; Table II in the Data Supplement) with a cutoff of ≥17 mm Hg (Youden).

Table. Baseline Characteristics of All Patients

Variable	Patients, n (%)			*P* value*
	All, 68 (100)	Primary MR, 24 (35)	Secondary MR, 44 (65)	
Baseline				
Male/female, n/n (%)	43/25 (63/37)	10/14	33/11	0.009
Age, y	77±8.5	82±8.3	74±7.5	<0.001†
BMI, kg/m^2	26 [23–27]	25 [23–27]	26 [23–27]	0.8‡
Frailty index§	0.4 [0.3–0.5]	0.4 [0.3–0.5]	0.4 [0.3–0.5]	0.7‡
NYHA class				0.15
II, n (%)	3 (4)	0 (0)	3 (7)	
III, n (%)	55 (81)	18 (75)	37 (84)	
IV, n (%)	10 (15)	6 (25)	4 (9)	
Clinical characteristics				
Hypertension, n (%)	57 (84)	22 (92)	35 (80)	0.3
Diabetes, n (%)	15 (22)	3 (13)	12 (27)	0.2
COPD, n (%)	9 (13)	4 (17)	5 (11)	0.7
CAD, n (%)	37 (54)	15 (63)	22 (50)	0.4
PAD, n (%)	5 (7)	4 (17)	1 (2)	0.049
Stroke, n (%)	7 (10)	3 (13)	4 (9)	0.7
Atrial fibrillation/flutter, n (%)	42 (62)	18 (75)	24 (55)	0.12
Laboratory results				
eGFR, mL/min per m^2	53 [35–75]	59 [47–84]	48 [33–66]	0.051‡
NT-proBNP, pg/mL	3878 [1826–8400]	2649 [886–6314]	3996 [1866–9379]	0.2‡
Echocardiography				
LVEF, %	40 [25–59]	60 [55–65]	30 [25–39]	<0.001‡
LVEDD, mm	61±17	50±6	66±9	<0.001†
LVESD, mm	50±13	37±7	57±10	<0.001†
RVSP, mm Hg	48 [42–57]	60±22	47±11	0.008†
Mitral regurgitation degree (I–IV)				0.2
Moderate-to-severe (III°), n (%)	35 (51)	15 (62)	20 (45)	
Severe (IV°), n (%)	33 (49)	9 (38)	24 (55)	
Medication				
ACE inhibitor/ARB/ARNI, n (%)	63 (93)	20 (83)	43 (98)	0.6
β-blocker, n (%)	58 (85)	19 (79)	39 (89)	0.3
MRA, n (%)	37 (54)	6 (25)	31 (70)	<0.001
Diuretics, n (%)	67 (99)	23 (96)	44 (100)	0.4
Device therapy				
CRT, n (%)	17 (25)	1 (4)	16 (36)	0.003
ICD, n (%)	26 (38)	0 (0)	26 (59)	<0.001
Pacemaker, n (%)	10 (15)	6 (25)	4 (9)	0.5
Follow-up				
Death during follow-up, n (%)	22 (32)	6 (25)	16 (36)	0.4
Survival follow-up time, mo	19 [9–32]	17 [5–26]	19 [10–40]	0.2‡
MR degree (I–IV)				1
None, n (%)	1 (2)	0 (0)	1 (2)	
Mild (I°), n (%)	37 (54)	13 (54)	24 (55)	
Moderate (II°), n (%)	27 (40)	10 (42)	17 (39)	
Severe (IV°), n (%)	3 (4)	1 (4)	2 (5)	
Mean mitral gradient, mm Hg	4.0 [2.0–5.0]	4.5 [3.0–6.0]	3.0 [2.0–4.8]	0.004‡

(*Continued*)

Table. Continued

Variable	Patients, n (%)			*P* value*
	All, 68 (100)	Primary MR, 24 (35)	Secondary MR, 44 (65)	
Hemodynamics (baseline)				
mPAP rest, mm Hg	32±9	30±10	32±9	0.4†
mPAP ex, mm Hg	49 [42–55]	49 [44–54]	49 [41–55]	1‡
PAWP rest, mm Hg	20±6	18±7	20±6	0.2†
PAWP ex, mm Hg	33±8	32±7	33±9	0.4†
PAWP V-wave rest, mm Hg	28±10	26±12	29±10	0.2†
PAWP V-wave ex, mm Hg	48 [40–54]	47 [40–51]	49 [39–55]	0.4‡
ΔV-wave, mm Hg	17 [8–28]	21 [12–28]	17 [8–26]	0.5‡
RAP rest, mm Hg	8 [6–11]	8 [6–11]	8 [6–12]	1‡
RAP ex, mm Hg	19 [14–24]	20±8	19±7	0.8†
TPR rest, WU	8.4 [6.1–11.0]	8.0 [5.3–10.0]	9.2 [6.6–12.0]	0.2‡
TPR ex, WU	11.0 [8.6–14.0]	11.0 [7.8–15.0]	12.0 [9.1–13.0]	0.5‡
CO rest, L/min	3.7±1.1	3.8 [9–14	3.7±1.0	0.6†
CO ex, L/min	4.6 [3.2–5.5]	4.7 [3.3–6.3]	4.4 [3.2–5.4]	0.5‡
ΔCO, L/min	0.69 [0.10–1.60]	0.78 [0.03–1.90]	0.67 [0.25–1.60]	0.8‡
PVR rest, WU	2.9 [2.1–3.9]	2.8 [2.2–3.8]	3.0 [2.0–4.1]	1‡
PVR ex, WU	3.2 [2.3–5.1]	3.3 [2.7–5.5]	3.2 [1.9–4.7]	0.4‡
SvO_2 ex, %	35±9	37±10	34±9	0.3†
Workload, W	15 [0–25]	5 [0–25]	15 [0–25]	0.3‡

Values represent n (%), mean±SD or median [interquartile range]. Δ indicates change in response to exercise; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ex, maximum measured pressure during exercise; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; mPAP, mean pulmonary arterial pressure; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; PAWP, mean pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSP, right ventricular systolic pressure (estimated by echocardiography); SvO_2, mixed venous oxygen saturation; TPR, total pulmonary resistance; and WU, Wood units.

*P values are given for comparisons between primary and secondary MR.

†Unpaired *t* test.

‡Mann-Whitney *U* test. All categorical variables were compared using the Fisher exact test.

§Frailty index was calculated approximately as described in the text.

Cox regression revealed that ΔV-wave ≥17 mm Hg was associated with reduced risk of death (hazard ratio, 0.11 [95% CI, 0.04–0.33], *P*<0.001), which was confirmed by Kaplan-Meier analysis (Figure 2A). Upon multivariable analysis, ΔV-wave was independent of age, FI, and workload during RHC (Figure II in the Data Supplement).

In the subgroup with secondary MR, those results were confirmed (Figure 2B and Figure III in the Data Supplement).

In both primary and secondary MR, ΔV-wave remained significantly associated with death after adjusting for echocardiographic grading of MR severity into moderate-to-severe or severe before PMVR, and mean pressure gradient and degree of residual MR at the time of echocardiographic follow-up (Figures IV and V in the Data Supplement).

Secondary Outcome

NYHA class after PMVR within 12 months was available in 52 patients, and the median follow-up time was 13 (8–16) weeks. Seven patients died within 12 months without clinical follow-up, and they were counted as a failure to improve NYHA class. Out of these 59 patients, a total of 32 (54%) achieved NYHA improvement. Out of 38 patients with secondary MR and available clinical follow-up or death (n=5) within 12 months, 21 (55%) achieved NYHA improvement. Univariate logistic regression analysis of invasive hemodynamic parameters during exercise revealed similar associations with the secondary outcome as with mortality (Table II in the Data Supplement). A higher ΔV-wave was associated with NYHA improvement in all patients (odds ratio, 1.14 [95% CI, 1.07–1.24]; *P*<0.001; AUC, 0.84 [95% CI, 0.74–0.95]) and in patients with secondary MR (odds ratio, 1.19 [95% CI, 1.08–1.37]; *P*=0.003; AUC, 0.87 [95% CI, 0.75–0.98]). A cutoff value of ≥15 mm Hg was identified (Youden) and applied to all patients and the subgroup with secondary MR (Figure 3A and 3B). NYHA class distributions at baseline and at follow-up were dichotomized based on the ΔV-wave cutoff. The majority (79%) of patients with ΔV-wave ≥15 mm Hg

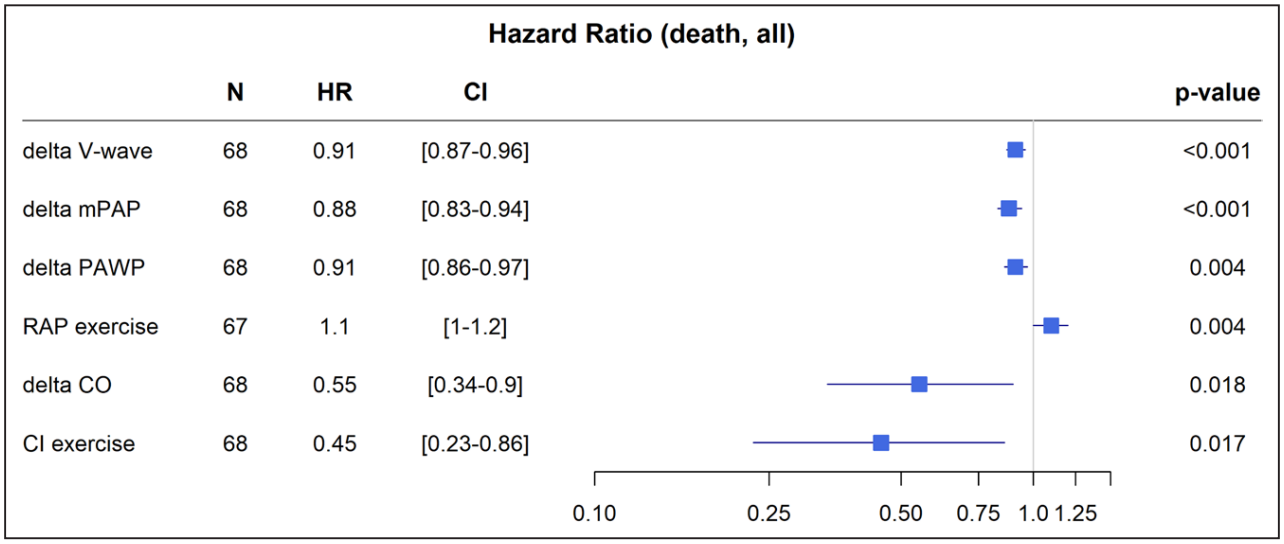

Figure 1. Comparison of univariate hazard ratios (HR) for all-cause mortality of significant invasive hemodynamic parameters during exercise in all patients (Cox regression).
CI indicates cardiac index (L/min/m²); CO, cardiac output (L/min); delta, difference between rest and exercise; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; and RAP, right atrial pressure.

were in class I and II at follow-up, in contrast to those <15 mm Hg (28%; Figure 4).

Apart from pressure parameters, a higher ΔCO was related to NYHA improvement in all patients (odds ratio, 1.86 [95% CI, 1.10–3.43]; *P*=0.031; AUC, 0.69 [95% CI, 0.55–0.82]) and in the subgroup (odds ratio, 2.94 [95% CI, 1.32–8.13]; *P*=0.018; AUC, 0.72 [95% CI, 0.55–0.89]). A ΔCO cutoff ≥0.9 L/min predicting a >50% probability of NYHA improvement was identified and applied to all patients and the subgroup (Figure 5A and 5B).

ΔV-wave and Δ CO remained significantly associated with improvement after adjustment for FI, age, and RHC workload and also adjusted for residual MR and mean pressure gradient at the time of echocardiographic follow-up in all patients and in the subgroup with secondary MR.

DISCUSSION

In high-risk patients with MR of unclear significance, specific hemodynamic evaluation provides important

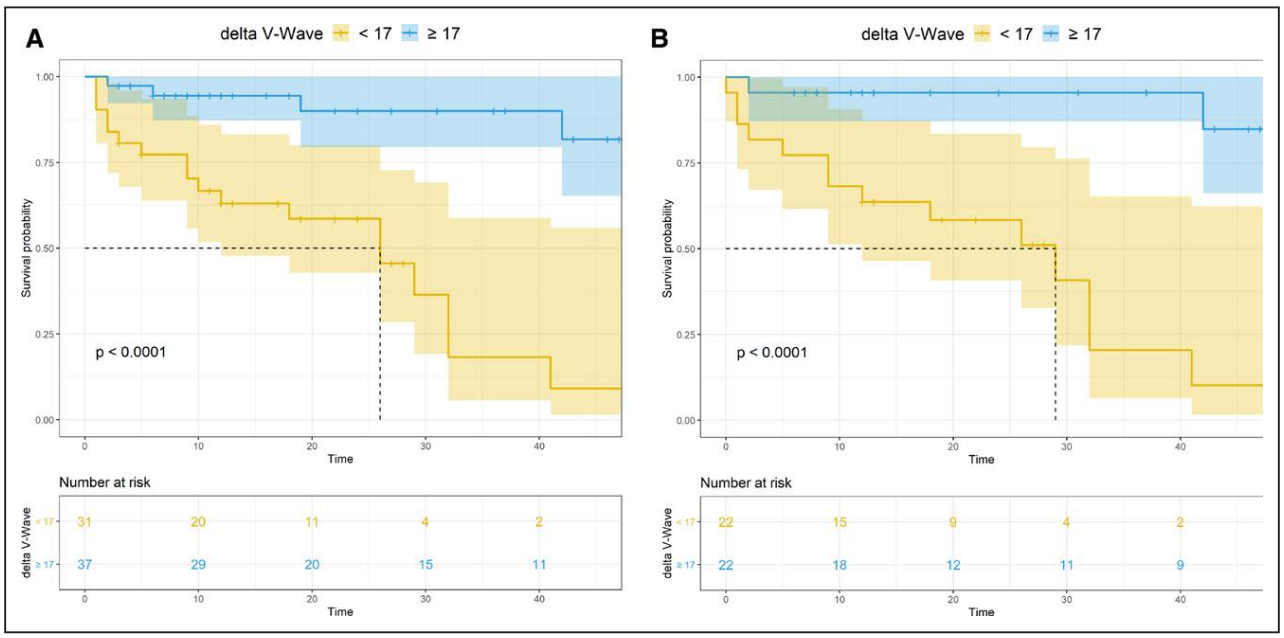

Figure 2. Kaplan-Meier survival curves as a function of hemodynamic profile based on ΔV-wave dichotomized at a cutoff derived from receiver operating characteristic analysis (time axis truncated at 48 mo).
A, All patients and (**B**) only secondary mitral regurgitation.

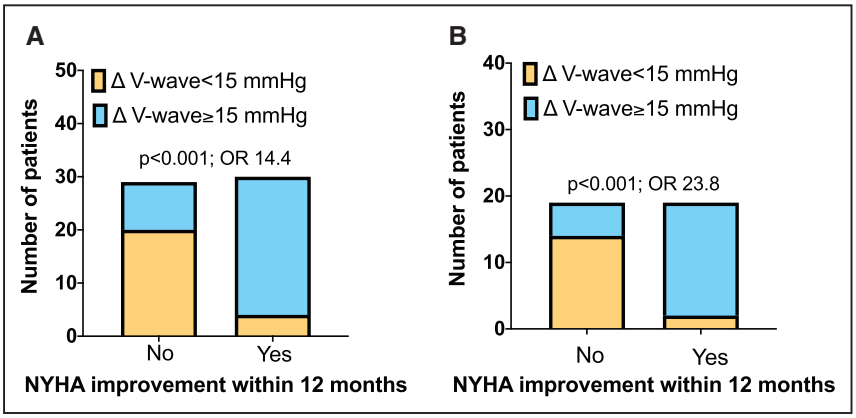

Figure 3. Patients with or without New York Heart Association (NYHA) class improvement within 12 mo (death within 12 mo = failure to improve) dichotomized based on ΔV-wave at a cutoff derived from receiver operating characteristic analysis.
A, All patients and (**B**) only secondary mitral regurgitation.

information for an individualized heart team approach to interventional valve repair. Novel findings of our study include the following: (1) ΔV-wave was associated with survival after PMVR independent of age, FI, and workload during RHC; (2) ΔV-wave and ΔCO were associated with improvement of NYHA class within 12 months; and (3) exercise hemodynamic stratification was significant in the subgroup with secondary MR.

Dynamic MR

The concept of dynamic MR was developed decades ago.[17] In our patients, an exaggerated increase in V-waves during exercise is suggestive of severe dynamic MR. This concept is supported by the improved survival and clinical improvement after PMVR in those presenting with higher ΔV-waves, as valve repair obviously had a pathophysiological benefit in these patients. To the best of our knowledge, characterization of severe dynamic MR by invasive exercise hemodynamic profiling beyond case reports has not been reported previously.

Prominent V-waves in PAWP pressure tracings at rest have been described historically as being suggestive of severe MR,[18] but they can also be observed in stiff LA syndrome and other states of LA volume overload, and absence of significant V-waves at rest does not exclude significant MR.[9] Our patients showed no evidence of significant volume overload at the time of measurements (mean RAP 9 [±4] mm Hg) and no criteria indicative of a stiff LA syndrome.

Heart Failure and MR

One leading cause of PMVR failure seems to be very advanced HF.[19–22] Thus, appropriate hemodynamic conditions for beneficial ventricular unloading by interventional reduction of MR are hard to define in patients with HF.[23] In our patients, exercise hemodynamics revealed that an insufficient CO response may be a reason for clinical PMVR failures because of poor cardiac reserve. Recently, the concept of disproportionate MR severity in relation to left ventricular dilatation has been presented. According to this idea, patients with secondary MR may be suitable for PMVR when MR severity is more than expected from left ventricular end-diastolic volume.[24] As a kind of hemodynamic equivalent, our exercise hemodynamic approach reveals disproportionate MR that is

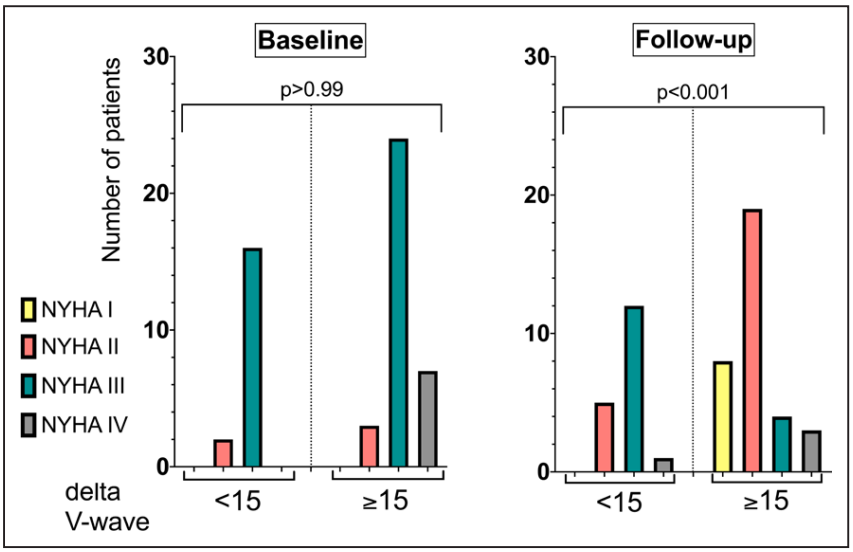

Figure 4. New York Heart Association (NYHA) class distributions (n=52) at baseline and follow-up, dichotomized based on ΔV-wave at a cutoff derived from receiver operating characteristic analysis.

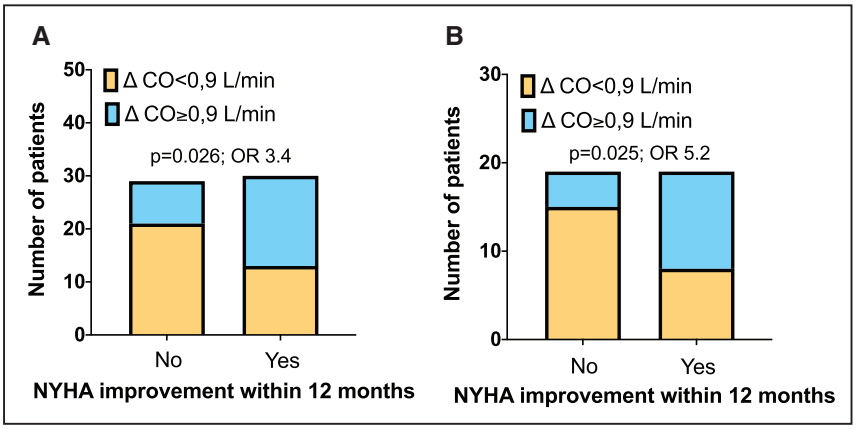

Figure 5. Patients with or without New York Heart Association (NYHA) class improvement within 12 mo (death within 12 mo = failure to improve) dichotomized based on Δ cardiac output (CO) at a cutoff derived from receiver operating characteristic analysis.
A, All patients and (**B**) only secondary mitral regurgitation.

suitable for repair: the combination of ΔV-wave indicating severe dynamic MR and ΔCO indicating less left ventricular dysfunction.

Limitations

Limitations of our study include its single-center design and the fact that we investigated a cohort of patients with mainly secondary MR but also with primary MR, which may be a cause of bias. However, our results were largely congruent between all patients and the subgroup with secondary MR.

Conclusions

Exercise RHC may provide additional information about prognostic and clinical benefit from PMVR in patients with echocardiographic moderate-to-severe and severe MR. Here, we propose an exercise hemodynamic approach that provides selected hemodynamic parameters as an aid for decision making in cases of uncertainty. For the incorporation of this approach into a structured diagnostic workup of patients evaluated for PMVR, further studies with larger patient numbers will be necessary.

ARTICLE INFORMATION

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Disclosures

Dr Liebetrau has received speaker fees from Abbott. The other authors report no conflicts.

Supplemental Materials

Online Figures I–V
Online Tables I–II

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ORIGINAL CLINICAL SCIENCE

Hemodynamic markers of pulmonary vasculopathy for prediction of early right heart failure and mortality after heart transplantation

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KEYWORDS:
pulmonary arterial elastance;
heart transplantation;
risk stratification;
hemodynamics;
mortality

BACKGROUND: Elevated pulmonary vascular resistance (PVR) is broadly accepted as an imminent risk factor for mortality after heart transplantation (HTx). However, no current HTx recipient risk score includes PVR or other hemodynamic parameters. This study examined the utility of various hemodynamic parameters for risk stratification in a contemporary HTx population.

METHODS: Patients from seven German HTx centers undergoing HTx between 2011 and 2015 were included retrospectively. Established risk factors and complete hemodynamic datasets before HTx were analyzed. Outcome measures were overall all-cause mortality, 12-month mortality, and right heart failure (RHF) after HTx.

[†]These authors contributed equally to this work.

Abbreviations: Ea, pulmonary arterial elastance; IMPACT, Index for Mortality Prediction After Cardiac Transplantation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PHM, Predicted heart mass; RHF, right heart failure; VRT, vasoreactivity testing

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RESULTS: The final analysis included 333 patients (28% female) with a median age of 54 (IQR 46-60) years. The median mean pulmonary artery pressure was 30 (IQR 23-38) mm Hg, transpulmonary gradient 8 (IQR 5-10) mm Hg, and PVR 2.1 (IQR 1.5-2.9) Wood units. Overall mortality was 35.7%, 12-month mortality was 23.7%, and the incidence of early RHF was 22.8%, which was significantly associated with overall mortality (log-rank HR 4.11, 95% CI 2.47-6.84; log-rank $p < .0001$). Pulmonary arterial elastance (Ea) was associated with overall mortality (HR 1.74, 95% CI 1.25-2.30; $p < .001$) independent of other non-hemodynamic risk factors. Ea values below a calculated cutoff represented a significantly reduced mortality risk (HR 0.38, 95% CI 0.19-0.76; $p < .0001$). PVR with the established cutoff of 3.0 WU was not significant. Ea was also significantly associated with 12-month mortality and RHF.

CONCLUSIONS: Ea showed a strong impact on post-transplant mortality and RHF and should become part of the routine hemodynamic evaluation in HTx candidates.

J Heart Lung Transplant 000;000:1−10

Multiple factors have been shown to be associated with increased 1-year mortality after adult heart transplantation (HTx), including pulmonary hypertension "as measured by pulmonary vascular resistance and mean pulmonary artery (PA) pressure".[1] This is the basis for the "2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation" recommendations to perform diagnostic right heart catheterization (RHC) "on all candidates in preparation for listing for cardiac transplantation and annually until transplantation". If "the systolic PA pressure is ≥ 50 mm Hg and either the transpulmonary gradient (TPG) is ≥ 15 mm Hg or the PVR is > 3 Wood units", a vasodilator challenge is recommended. Irreversible pulmonary hypertension (PH) is thought to be present when neither vasodilator challenge nor other therapies, including use of a left ventricular assist device, are successful to achieve "acceptable hemodynamics."[2]

Although several studies have investigated the impact of increased recipient PVR on post-transplant outcomes, results concerning mortality after HTx were inconclusive due to variation in study design, sample size, follow-up, and definition of an elevated pre-transplant PVR.[3-7] Moreover, recipient PVR has not shown prognostic significance in the acknowledged IMPACT score dataset, a commonly used recipient risk score, and other transplant risk scores.[8-10] Furthermore, right heart failure (RHF) as a cause of morbidity and mortality following HTx is not even mentioned in the recent ISHLT report 2021.[1] Whether this problem has been solved by strict adherence to the cited guidelines, and thus exclusion of all patients with advanced pulmonary vascular disease from HTx, remains unclear.

Recent data show that the PVR threshold representing initial pulmonary vascular disease may be even lower than 3 Wood units (WU), as an increased mortality risk was found to be associated with PVR values of 2.2 WU and higher in patients with PH.[11,12] Several newer, "advanced" hemodynamic indices have been proposed to define pulmonary vasculopathy in HF patients better than PVR and TPG.[13] However, the impact of such potentially more sensitive thresholds and indices on post-transplant survival has not yet been investigated.

The aim of the present study was to determine whether various parameters of advanced pre-transplant hemodynamics are associated with right heart failure and all-cause mortality after HTx in a contemporary cohort and whether they may be useful in estimating prognosis.

Materials and methods

Patient population

We performed a multicentric, retrospective analysis of HTx patients from seven German HTx centers (Bad Nauheim, Düsseldorf, Hanover, Heidelberg, Jena, Munich, and Münster). The dataset included all adult patients undergoing HTx between 2011 and 2015 at these centers with available RHC hemodynamic measurements obtained within 365 days before HTx and a follow-up time of at least 12 months post-HTx (Figure S1).

The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients enrolled in this study were extensively informed about HTx and gave written informed consent to the procedure and the use of related data. Retrospective data analyses were approved by the local institutional review boards. The ethics committee of the Faculty of Medicine at the University of Giessen, as the leading institution, gave its approval (protocol no. 200/16; 23 January, 2017). The ethics approval did not require additional consent as only routine clinical data were used.

Study protocol

Comprehensive hemodynamic variables and risk factors were extracted from the recipients' medical records. The risk factors recorded were derived from the "Thirty-second Official Adult Heart Transplantation Report-2015"[14] and the IMPACT score.[8] Furthermore, the following variables were recorded: presence of mechanical circulatory support (MCS) including extracorporeal membrane oxygenation (ECMO), left ventricular assist device (LVAD), biventricular assist device (BiVAD), or catecholamine therapy (including levosimendan within 14 days) at the time of RHC; MCS at the time of HTx; MCS after HTx; performance of vasoreactivity testing (VRT) at RHC and hemodynamic variables after testing; performance of induction therapy; immunosuppressive regimen post-HTx. The IMPACT score was calculated as described elsewhere.[8] Donor and recipient right ventricular predicted heart mass (RV-PHM) and their difference were calculated as described before, and undersizing was defined as a ≥30% donor-recipient difference.[15,16]

Outcomes

The primary outcome was all-cause mortality after HTx. Secondary outcomes were 12-month mortality and postoperative RHF as defined by INTERMACS criteria (elevated CVP, reduced RV function by echocardiogram, and clinical manifestations suggestive of RHF plus: right ventricular assist device *or* inotropes *or* inhaled nitric oxide *or* intravenous vasodilators continued beyond postoperative day 7),[17] registered retrospectively from the medical records.

Right heart catheterization

RHC was performed under local anesthesia with insertion of a Swan-Ganz catheter into the internal jugular vein, a cubital vein, or a femoral vein. A complete list of measured and calculated parameters is given in Table 1. Cardiac output (CO) was measured by the thermodilution technique or the indirect Fick method. Other parameters, including PVR and pulmonary arterial elastance (Ea = 1.65 × mPAP−7.79/SV), were calculated as described elsewhere.[18-25]

Statistical analysis

Data are expressed as mean ± standard deviation or median [interquartile range] for normally or non-normally distributed parameters, respectively. Adherence to a Gaussian distribution was determined using the Shapiro-Wilk test. $p < .05$ was considered statistically significant.

Cox proportional hazards models and the Kaplan-Meier method were used for survival analyses, and hazard ratios (HR) and Harrel's C-statistics were calculated. Associations between parameters and secondary outcomes were assessed using simple logistic regression, odds ratios (OR) were calculated, and receiver operating characteristics (ROC) analysis with the calculated area under the curve (AUC) was used to describe an association of a variable with secondary endpoints.

For independent samples, comparison was made with the Mann −Whitney U test for non-normally distributed parameters, the Student's *t* test for normally distributed parameters, and the Pearson Chi-square test or Fisher's exact test for categorical parameters, as appropriate. Statistical analyses were performed using either R version 3.6.0 (survival package 3.2-3, 15 survminer package 0.4.8) or GraphPad Prism version 9.4.1 (458).

Table 1 Hemodynamic Parameters

Parameter	All (n = 333)	Eamissing value(n = 81)	Ea≤1.45 mm Hg/ml(n = 218)	Ea>1.45 mm Hg/ml(n = 34)	p value[a]
Ea (mm Hg/ml), median [IQR]	0.87 [0.55−1.23]	n. a.	0.79 [0.49−1.06]	1.68 [1.57−1.96]	< .0001[b]
SAP (mm Hg), median [IQR]	100.00 [90.00−110.00]	106.00 [93.50−113.00]	100.00 [90.00−110.00]	100.00 [90.00−106.00]	.5[b]
MAP (mm Hg), median [IQR]	77.00 [70.00−85.00]	80.00 [73.00−85.75]	75.50 [70.00−85.00]	75.00 [68.50−81.00]	.6[b]
HR (beats per minute), median [IQR]	73.00 [67.00−84.00]	62.00 [52.00−85.00]	72.00 [66.00−80.00]	90.00 [73.25−98.75]	< .0001[b]
sPAP (mm Hg), median [IQR]	45.00 [34.00−55.00]	45.00 [34.50−56.00]	41.00 [32.00−52.00]	58.00 [50.00−60.00]	< .0001[b]
dPAP (mm Hg), median [IQR]	22.00 [16.00−28.00]	21.00 [16.00−28.00]	20.00 [15.00−26.00]	30.00 [29.00−34.00]	< .0001[b]
PP (mm Hg), median [IQR]	22.00 [17.00−29.00]	24.00 [16.00−29.00]	21.00 [16.00−28.00]	26.00 [20.00−30.00]	.02[b]
mPAP (mm Hg), median [IQR]	30.00 [23.00−38.00]	31.00 [24.00−38.00]	28.50 [22.00−35.00]	41.00 [36.25−43.50]	< .0001[b]
TPG (mm Hg), median [IQR]	8.00 [5.00−10.50]	9.00 [5.75−12.25]	7.00 [5.00−10.00]	9.00 [6.00−12.00]	.1[b]
DPG (mm Hg), median [IQR]	0.00 [-3.00−2.00]	-1.00 [-3.75−3.00]	0.00 [-3.00−2.00]	0.00 [-3.00−2.50]	.9[b]
PVR (WU), median [IQR]	2.11 [1.47−2.89]	2.48 [1.51−3.18]	2.00 [1.41−2.68]	2.83 [2.14−4.46]	< .0001[b]
PVRI (WU*m^2), median [IQR]	3.95 [2.92−5.63]	4.14 [2.86−6.08]	3.75 [2.82−5.12]	5.33 [3.91−8.17]	.0002[b]
TPR (WU), median [IQR]	8.60 [5.86−11.14]	8.87 [6.17−11.41]	7.80 [5.24−10.03]	13.86 [12.44−16.05]	< .0001[b]
RAP (mm Hg), median [IQR]	12.00 [7.00−15.00]	12.00 [8.00−17.75]	10.00 [7.00−15.00]	15.00 [11.00−15.00]	.007[b]
PAWP (mm Hg), median [IQR]	23.50 [16.00−28.00]	23.50 [15.00−28.00]	22.00 [15.00−27.00]	30.00 [28.00−33.00]	< .0001[b]
RAP/PAWP (no unit), median [IQR]	0.50 [0.36−0.67]	0.60 [0.37−0.74]	0.50 [0.38−0.65]	0.44 [0.34−0.50]	.02[b]
CO (l/min), median [IQR]	3.60 [3.12−4.22]	3.65 [3.00−4.44]	3.77 [3.30−4.34]	2.80 [2.43−3.10]	< 0.0001[b]
SV (ml), median [IQR]	50.03 [40.19−59.88]	n. a.	52.52 [43.32−61.47]	33.60 [24.91−38.16]	< 0.0001[b]
SVI (g*m/m^2), median [IQR]	25.78 [21.84−30.63]	n. a.	26.82 [23.61−32.30]	19.02 [13.85−22.20]	< 0.0001[b]
RVSWI (g*m/m^2), median [IQR]	7.43 [4.87−9.31]	n. a.	7.50 [4.87−9.31]	6.79 [4.82−8.97]	.8[b]
CI (l/min/m^2), median [IQR]	1.91 [1.70−2.18]	1.90 [1.65−2.17]	2.00 [1.74−2.20]	1.50 [1.33−1.88]	< .0001[b]
CPO (W), median [IQR]	0.62 [0.50−0.76]	0.64 [0.50−0.80]	0.64 [0.52−0.76]	0.43 [0.40−0.53]	< .0001[b]
CPI (W/m^2), median [IQR]	0.32 [0.27−0.39]	0.35 [0.28−0.41]	0.33 [0.28−0.39]	0.25 [0.19−0.35]	.0002[b]
PAPI (mm Hg), median [IQR]	2.00 [1.39−3.14]	1.96 [1.32−3.38]	2.14 [1.47−3.06]	1.91 [1.40−2.25]	.2[b]
PAC (ml/mm Hg), median [IQR]	2.13 [1.68−3.14]	n. a.	2.43 [1.79−3.44]	1.28 [1.08−1.64]	< .0001[b]
Total RV power (W), median [IQR]	0.31 [0.25−0.39]	0.32 [0.27−0.43]	0.31 [0.24−0.39]	0.32 [0.27−0.37]	.7[b]
Oscillatory RV load (W), median [IQR]	0.07 [0.06−0.09]	0.07 [0.06−0.10]	0.07 [0.05−0.09]	0.07 [0.06−0.09]	.7[b]
RC-time (s), median [IQR]	0.29 [0.22−0.37]	n. a.	0.30 [0.22−0.37]	0.24 [0.19−0.31]	.03[b]

[a] Ea≤1.45 vs. Ea >1.45 mm Hg/ml.
[b] Mann-Whitney-*U* test.
n.a., not available; Ea, pulmonary effective arterial elastance (calculated); IQR, interquartile range; SAP, systemic arterial pressure; MAP, mean SAP; HR, heart rate; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic PAP; PP, pulse pressure; mPAP, mean PAP; TPG, transpulmonary pressure gradient; DPG, diastolic PG; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; CO, cardiac output; CI, cardiac index; CPO, cardiac power output; CPI, CP index; SV, stroke volume; SVI, SV index; RVSWI, right ventricular stroke work index; PAPI, pulmonary artery pulsatility index; PAC, pulmonary arterial capacitance; RV, right ventricle; RC, resistance and compliance.

Results

Clinical characteristics and hemodynamic findings

The final analysis included 333 HTx recipients. The cohort comprised 28% women, the median age was 54 (46-60) years, and the body mass index was 25 (22-28) kg/m2 (Table 2). Among all patients, 46 (13.8%) received targeted PH medications, mostly sildenafil or tadalafil (84.8% of the used PH drugs). More data are given in Table S1.

Resting RHC was performed 52 (26-129) days before HTx. At the time of RHC, 45 (13.5%) patients were on MCS (LVAD), and 149 (44.7%) were on catecholamines or had received levosimendan within the preceding 14 days. Mean pulmonary artery pressure (mPAP) was moderately elevated (30 [23-38] mm Hg), and in 55 (16.5%) patients, PH was not present, as recently redefined (mPAP <21 mm Hg).[19] TPG was 8 (5-11) mm Hg, and PVR was 2.1 (1.5-2.9) WU. MCS at the time of HTx was present in 84 (25.2%) patients (6 ECMO, 65 LVAD, 13 BiVAD). Donor data were available for 326 (97.9%) of our patients. Median Donor RV-PHM was 22.7 (20.4-26.1), and median recipient RV-PHM 23.3 (20.7-25.2). The median difference was 0.32 (1.4% / IQR −14%-9.8%), and only five patients fulfilled the criterion of donor heart undersizing (difference ≥30%). Ischemic time was 240 (206-274) min, and 135 (40.5%) patients underwent induction therapy with anti-thymocyte globulin. Post-HTx, the majority of patients (92.8%) was treated with tacrolimus, mycophenolate mofetil, and corticosteroids.

Association of nonhemodynamic risk factors with the primary outcome

Median follow-up time was 52 (16-74) months; within the observed period, 119 of 333 patients died, and within a 12-month timeframe 79 of 333 patients died. Associations of all assessed non-hemodynamic risk factors with all-cause mortality and hazard ratios are given in Table S2. Significant associations were found for MCS at HTx, infection requiring IV drug therapy within 2 weeks before HTx,

Table 2 Baseline Characteristics

Parameter	All (n = 333)	Eamissing value(n = 81)	Ea≤1.45 mm Hg/ml(n = 218)	Ea>1.45 mm Hg/ml(n = 34)	p value[a]
Age (years), median [IQR]	54.00 [46.00−60.00]	53.00 [46.00−61.00]	54.00 [47.00−60.00]	50.50 [38.50−59.75]	.05[f]
Male sex, n (%)	239 (71.77)	58 (71.60)	160 (73.39)	21 (61.76)	.2[c]
Height (cm), median [IQR]	174.00 [168.00−180.00]	172.00 [165.00−178.00]	175.00 [169.00−181.00]	169.50 [165.00−176.00]	.01[f]
Weight (kg), mean ± SD	76.52 ± 15.36	77.62 ± 16.04	77.04 ± 15.28	70.54 ± 13.20	.01[e]
BMI (kg/m^2), median [IQR]	25.06 [22.10−27.78]	26.03 [22.49−29.05]	24.71 [21.97−27.72]	24.25 [22.91−25.77]	.5[f]
BSA (m^2), mean ± SD	1.91 ± 0.23	1.92 ± 0.23	1.93 ± 0.22	1.82 ± 0.22	.01[e]
Diabetes mellitus, n (%)	61 (18.32)	14 (17.28)	40 (18.35)	7 (20.59)	.8[c]
Dialysis, n (%)	31 (9.31)	4 (4.94)	19 (8.72)	8 (23.53)	.02[d]
Creatinine (mg/dl), median [IQR]	1.30 [1.00−1.60]	1.10 [0.91−1.40]	1.30 [1.07−1.70]	1.40 [1.20−1.59]	.4[f]
Bilirubin (mg/dl), median [IQR]	0.70 [0.48−1.20]	0.70 [0.46−1.18]	0.70 [0.45−**1**.10]	1.07 [0.70−1.40]	.003[f]
Ventilator, n (%)	15 (4.50)	1 (1.23)	10 (4.59)	4 (11.76)	.1[d]
Infection with IV drug therapy, n (%)	53 (15.92)	10 (12.35)	32 (14.68)	11 (32.35)	.01[c]
Transfusion, n (%)	44 (13.21)	3 (3.70)	30 (13.76)	11 (32.35)	.006[c]
Malignancy, n (%)	18 (5.41)	4 (4.94)	12 (5.50)	2 (5.88)	1.0[d]
Congenital CMP, n (%)	9 (2.70)	3 (3.70)	5 (2.29)	1 (2.94)	.6[d]
Acquired CMP, n (%)	324 (97.30)	78 (96.30)	213 (97.71)	33 (97.06)	.6[d]
Re-transplant, n (%)	5 (1.50)	1 (1.23)	2 (0.92)	2 (5.88)	.09[d]
MCS at HTx[b], n (%)	84 (25.23)	26 (32.10)	45 (20.64)	13 (38.24)	.02[c]
ECMO at HTx, n (%)	6 (1.80)	1 (1.23)	3 (1.38)	2 (5.88)	
LVAD at HTx, n (%)	65 (19.52)	24 (29.63)	36 (16.51)	5 (14.71)	
BiVAD at HTx, n (%)	13 (3.90)	1 (1.23)	6 (2.75)	6 (17.65)	
Ischemic time (min), median [IQR]	240.00 [205.75−273.25]	225.00 [194.50−245.50]	241.50 [209.25−274.75]	284.00 [242.50−315.50]	.008[f]
ATG induction, n (%)	135 (40.54)	1 (1.23)	113 (51.83)	21 (61.76)	.3[c]
Standard immunosuppression, n (%) (TAC, MMF, and corticosteroids)	309 (92.79)	69 (85.19)	209 (95.87)	31 (91.18)	.2[d]
Overall mortality, n (%)	119 (35.74)	32 (39.51)	67 (30.73)	20 (58.82)	.003[d]
12-month mortality, n (%)	79 (23.72)	25 (30.86)	38 (17.43)	16 (47.06)	.0004[d]

[a] Ea≤1.45 vs. Ea >1.45 mm Hg/ml.
[b] Not identical to MCS at RHC.
[c] Pearson's Chi-square test.
[d] Fisher's exact test.
[e] Independent Student's t test.
[f] Mann-Whitney-U test.

IQR, interquartile range; BMI, body mass index; BSA, body surface area; IV, intravenous; CMP, cardiomyopathy; MCS, mechanical circulatory support; HTx, heart transplantation; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; BiVAD, biventricular assist device; ATG, anti-thymocyte globulin; TAC, tacrolimus; MMF, mycophenolate mofetil.

mechanical ventilation, height, and body surface area. Upon multivariable analysis, only mechanical ventilation and height remained independently associated with mortality (each $p < .001$). The IMPACT score was associated with 1-year mortality (OR 1.14, 95%CI 1.07-1.21, $p < .0001$; AUC 0.65) and overall mortality (HR 1.08, 95% CI 1.03-1.12, $p = .0003$; Harrel's C-statistic 0.60). Upon multivariable analysis with other significant non-hemodynamic and hemodynamic variables from univariate analysis, it was no longer significant (Table S3). There were no associations between the presence of PH medication and mortality / RHF or the hemodynamic key parameters TPR, PVR and Ea. We found no associations between RV-PHM differences and undersizing with mortality and RHF.

Impact of hemodynamic variables on primary and secondary outcomes

Early RHF was present in 76 patients (22.8%) and was found to be associated with all-cause mortality within the first 12 months post-HTx ($p < .0001$). Fifty-eight (17.4%) patients required post-transplant MCS. The presence of RHF also significantly increased overall mortality (log-rank HR 4.11, 95% CI 2.47-6.84; log-rank $p < .0001$) (Figure 1).

Associations of all assessed hemodynamic variables with all-cause mortality and HR are given in Table S4. TPG, PVR, TPR, and Ea were significantly associated with mortality (p = .04, 0.005, 0.005, and <0.001, respectively) (Figure 2). All of these associations were independent of systolic PA pressure. The greatest HR was observed for Ea (1.74, 95% CI 1.25-2.30). If an alternative method for

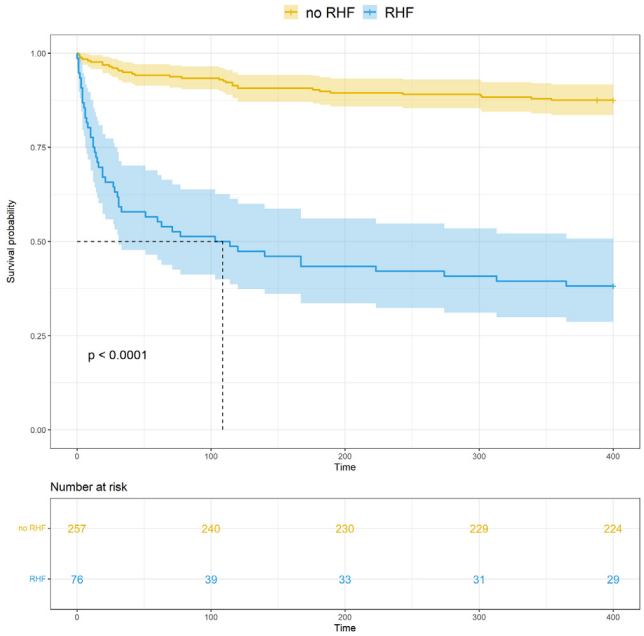

Figure 1 Kaplan-Meier analysis of right heart failure and survival after heart transplantation.

The effects of the presence of right heart failure (RHF) on overall, all-cause mortality.

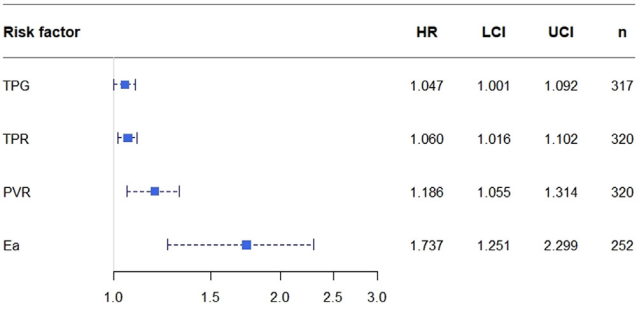

Figure 2 Forest plot of univariate Cox regression analysis of hemodynamic parameters and overall, all-cause mortality after heart transplantation.

TPG, transpulmonary pressure gradient; TPR, total pulmonary resistance; PVR, pulmonary vascular resistance; Ea, calculated pulmonary arterial elastance; LCI, UCI, lower and upper confidence intervals.

calculation of Ea[26] was used (sPAP/SV), similar results were found (HR 1.68, 95% CI 1.17-2.27). Upon multivariable analysis including Ea or TPR or PVR or TPG and the significant non-hemodynamic parameters mentioned above, Ea (Figure S2) and TPR were independently associated with mortality (HR 1.75, 95% CI 1.26-2.34; $p < .001$ and HR 1.05, 95% CI 1.01-1.10; $p = .01$, respectively), whereas PVR and TPG were not ($p = .6$ and $p = .1$). Furthermore, Ea was independently associated with mortality in different multivariable models including age, sex, bilirubin, creatinine, and BSA ($p = .001$); this was also the case when MCS and catecholamine therapy during RHC were included ($p = .001$). The results of further multivariable analyses are shown in Table S3.

To evaluate the impact of the time interval between HTx and hemodynamic measurements, the study cohort of 333 patients was divided into those with RHC closer in time to HTx (<52 days, $n = 163$; group A) and those with RHC farther from HTx (≥52 days, $n = 170$; group B). Overall mortality rates were comparable between groups (A: 36.8%; B: 34.7%). Univariate analysis showed that Ea was associated with mortality in group A (overall mortality: OR 2.46, 95%CI 1.26-5.69, $p = .02$; 1-year mortality: OR 2.47, 95%CI 1.28-5.76, p = .02), but not in group B.

To separate patients with low mortality risk after HTx from those with high risk, a cutoff value for Ea was calculated using the log-rank test with the aim of optimizing specificity. The resulting cutoff value for Ea was 1.45 mm Hg/ml (negative predictive value 0.69, positive predictive value 0.59), and the corresponding survival analysis is shown in Figure 3. Ea values below the cutoff translated into a significantly reduced mortality risk (log-rank HR 0.38, 95% CI 0.19-0.76; $p < .0001$). Patients with Ea >1.45 ($n = 34$) displayed a 12-month mortality of 47% and an overall mortality of 59% (Table 2). In comparison, survival analysis based on PVR (using the traditional cutoff value ≤3 WU) did not show significant results (log-rank $p = .2$); using a recently proposed new cutoff (<2.2 WU)[7] instead resulted in a slightly significant result (log-rank HR 0.68, 95% CI 0.46-0.99; $p = .04$). TPG using the cutoff <15 mm Hg was not significant (log-rank $p = .08$).

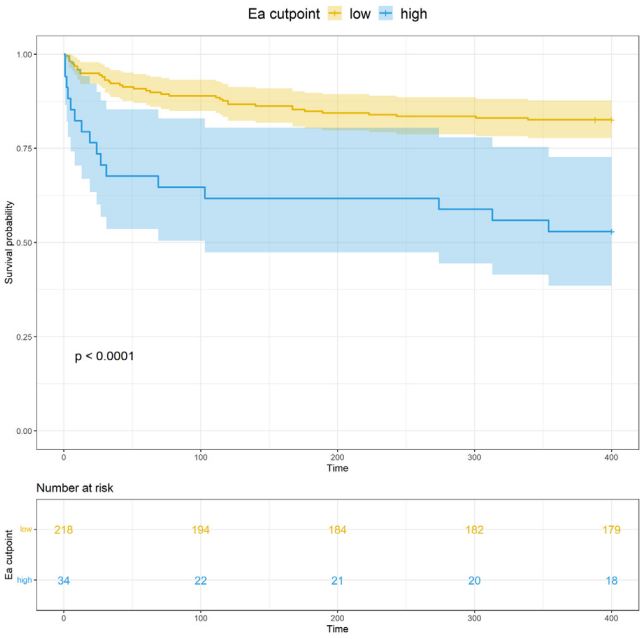

Figure 3 Kaplan-Meier analysis of calculated pulmonary arterial elastance and survival after heart transplantation.

The effects of pulmonary arterial elastance (Ea) cutoff value (≤ or >1.45 mm Hg/ml) on overall, all-cause mortality.

To illustrate how risk stratification based on "PVR 2.2 WU" or "Ea 1.45 mm Hg/ml" instead of traditional stratification might change clinical practice, we performed a reclassification analysis (Table S5). In summary, up to 129 patients would have been reclassified from low to high risk by applying the PVR 2.2 WU (Ea 1.45 mm Hg/ml) thresholds.

Vasoreactivity testing

Only 21 patients underwent vasoreactivity testing (VRT), according to the relatively low level of pulmonary pressures and PVR in our study population; the results are described and displayed in Table S6.

Secondary endpoints

Twelve-month mortality after HTx was associated with PVR (OR 1.21, 95% CI 1.03-1.45; p = .03), TPR (OR 1.08, 95% CI 1.02-1.14; p = .007), and Ea (OR 2.01, 95% CI 1.25-3,43; p = .006) (Table S7). Only Ea was significant upon ROC analysis (AUC 0.60, p = .02) and upon groupwise comparisons (Figure 4).

RHF was associated with several hemodynamic variables (Figures 5 and S3, Table S8). TPR had the lowest p value (OR 1.1, 95% CI 1.04-1.17; p < .001) and the largest AUC (0.62, p = .002), whereas Ea again had the largest impact (OR 1.77, 95% CI 1.12-2.92; p = .02; AUC 0.61, p = .01). Upon multivariable analysis (Ea, PVR, TPR), only TPR was independently associated with RHF (p = .02). The combined risk of 12-month mortality and RHF post-HTx in different hemodynamic subgroups is displayed in Figure 6;

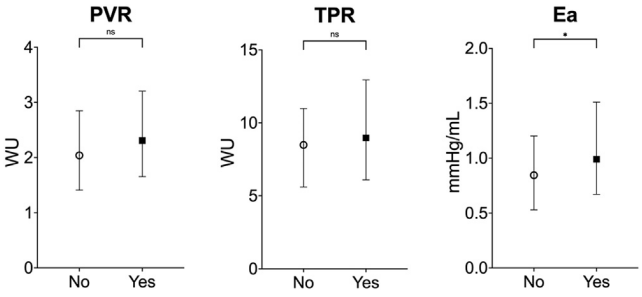

Figure 4 Hemodynamic parameters in patients censured as alive or deceased 12 months after transplantation.

Pulmonary vascular resistance (PVR), total pulmonary resistance (TPR) and calculated pulmonary arterial elastance (Ea) in patients alive ("No") or dead ("Yes") within 12 months after heart transplantation. ns, not significant; * p <.05.

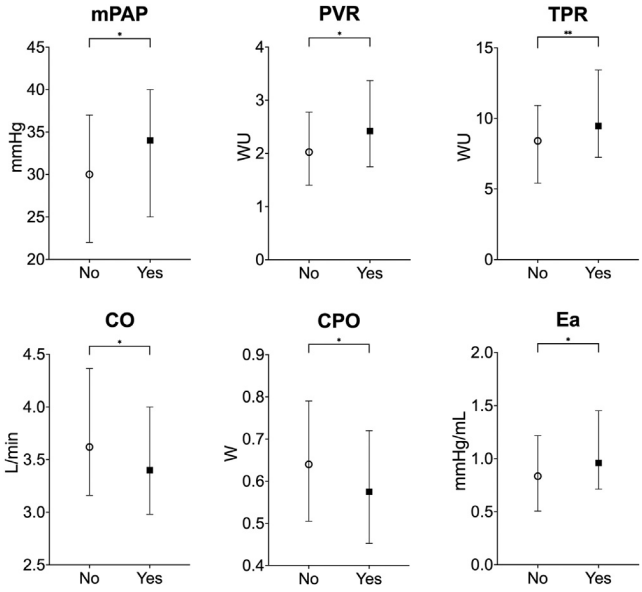

Figure 5 Hemodynamic parameters in patients without or with right heart failure after transplantation.

Mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), cardiac output (CO), cardiac power output (CPO), and calculated pulmonary arterial elastance (Ea) in patients without ("No") or with ("Yes") right heart failure after heart transplantation. * p < 0.05; ** p < .01.

the highest proportion of patients reaching the combined endpoint (35.3%) was in subgroup "Ea >1.45" and the lowest proportion (6.3%) in subgroup "TPR <5.8".

Discussion

We present a comprehensive analysis of routinely and non-routinely measured hemodynamic parameters for evaluation of mortality risk and RHF after HTx in a contemporary German cohort. The relevant findings of our study are as follows: (1) despite broad adherence to hemodynamic pretransplant guidelines, post-HTx RHF might be underestimated as a major cause of death; (2) in the present cohort with mainly "mild" PH, the established parameters PVR and TPG were not significantly associated with mortality if traditional cutoff values

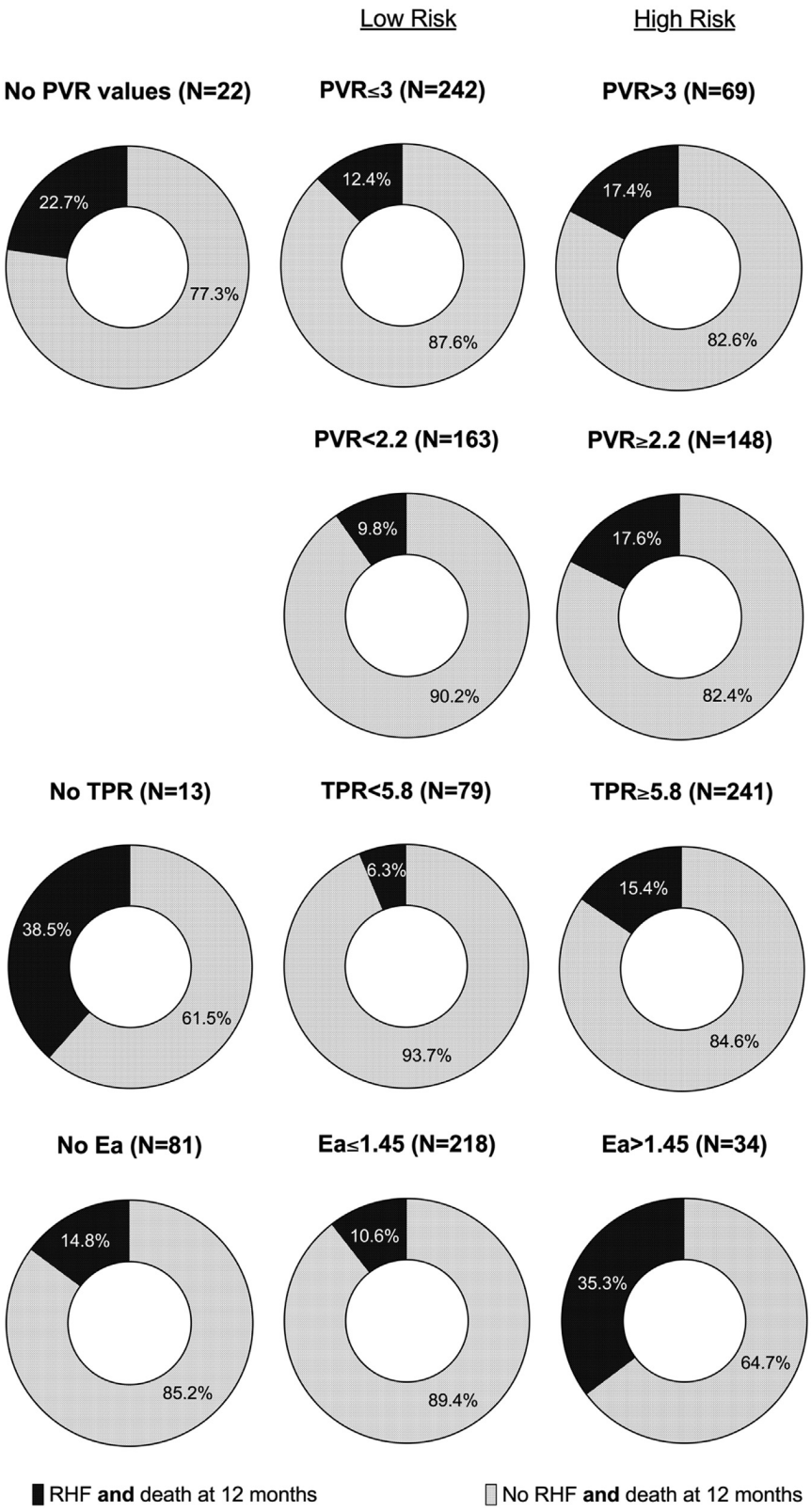

Figure 6 Effects of using different cutoffs on RHF and prognosis after heart transplantation in hemodynamic subgroups.

Pulmonary vascular resistance (PVR) with different cutoff values; total pulmonary resistance (TPR) with cutoff value 5.8 WU (1st tertile); calculated pulmonary arterial elastance (Ea) with combined risk of 12-month mortality and right heart failure (RHF).

were used; (3) use of a lower PVR threshold improved the result of Kaplan-Meier analysis; (4) among all hemodynamic parameters, Ea, as a measure of pulmonary vasculopathy and right ventricular afterload, had the strongest impact on post-transplant survival and this was independent of other non-hemodynamic risk factors; (5) Ea and TPR were significantly associated with post-transplant RHF.

Attempts to establish recipient risk scores to improve post-HTx results are ongoing in times of progressively increasing organ shortage, and successful HTx is strongly dependent on optimized candidate selection. In a recent meta-analysis, most risk prediction scores did not perform particularly well, with C-statistic or area under the receiver operating characteristics curve values of 0.54-0.77; the IMPACT score was the most widely validated.[27] Hemodynamic risk factors do not play a role in any of these risk scores and may be underestimated, despite the need for an individual stratification.[6,27,28] The low impact of PVR based on the traditional cutoff value of 3.0 WU was confirmed in our cohort; lowering the cutoff to 2.2 WU as recently proposed for patients with PH and left heart disease[11] might be a step towards a more sensitive risk analysis.

Our study demonstrated that calculation of other parameters derived from routinely performed RHC in HTx candidates[29] might improve risk stratification: in particular, pulmonary arterial elastance (Ea) showed the strongest association with overall and 12-month mortality among the hemodynamic parameters investigated. Several other markers of disease severity such as elevated bilirubin, dialysis or infections were also increased in those patients with elevated Ea values in our cohort. However, multivariable evaluation considering non-hemodynamic risk factors revealed that Ea was independently associated with mortality.

Ea is easy to obtain if heart rate for the calculation of stroke volume is recorded. The increase in RV afterload due to pulmonary vasculopathy, which is the main challenge for the transplanted right heart, may be incompletely described by PVR, whereas Ea takes into account both resistive and pulsatile loading.[22] Ea has been shown to predict mortality more consistently than PVR or TPG in patients with PH and left heart disease.[13,30]

RHF following HTx was associated with several hemodynamic variables in our cohort. Among them, Ea showed the highest OR, and TPR showed the highest AUC and was independent of other hemodynamic parameters. Despite its independent association with RHF, TPR is closely intertwined with Ea. TPR represents the mPAP/CO ratio and is − as well as Ea - independent of PA wedge pressure (PAWP), which is necessary for PVR calculation, and accurate measurement of PAWP may be challenging in some patients. Overestimation of PAWP leads to underestimation of PVR, and lowering the PVR threshold improved its predictive value in our study. One may speculate that independency of PAWP measurement might be associated with a predictive superiority of TPR and Ea. In one study, Ea was the only significant hemodynamic predictor of RHF after LVAD implantation.[31] One other study assessed the development of RV load adaptation during temporary mechanical support before LVAD implantation; those patients who developed RHF after LVAD insertion had smaller improvements of RV load (among them Ea) and Ea-related indices during temporary support, suggestive of a more advanced pulmonary vasculopathy.[32] Recently, hemodynamically described RV dysfunction has been shown to be associated with mortality after HTx[33]; in our cohort, hemodynamic parameters of contractile RV function were not associated.

The analysis of subgroups with RHC within 52 days of HTx or earlier than 52 days implies that the information value of hemodynamic measurements may decline already after a few months. The RHC intervals in high-risk patients should be chosen accordingly, for example, every 2 to 3 months. To further improve risk prediction and to uncover the extent of pulmonary vascular disease, hemodynamic exercise testing or other provocation tests may be useful.[11,18,34,35]

Our approach to dealing with hemodynamic high-risk patients would be to not exclude them categorically from HTx but to promote further therapy intensification for improvement of their pulmonary vascular profile.[36,37] Furthermore, LVAD implantation earlier than usual could be a way to prevent severe end-organ failure as well as to reverse advanced pulmonary vasculopathy and thus improve poor outcomes of HTx performed in high-risk patients. This concept, however, needs to be confirmed by randomized studies such as the currently recruiting VAD-DZHK3 study (ClinicalTrials.gov Identifier: NCT02387112).

Limitations

Given the retrospective, non-randomized study design, our findings should be interpreted with caution. Data on medical therapies for HF and pulmonary hypertension before HTX were not available for all patients (8.1% missing data). In a significant portion of patients (24%), heart rate during RHC and consequently derived parameters like stroke volume and Ea were not available; moreover, right atrial pressure and derived parameters were missing in 16.8% of patients, which could be a source of bias. Furthermore, the mode of CO measurement (thermodilution or Fick's method) was not recorded; differences in these two methods may have caused the relatively broad confidence interval of Ea values. Calculation of right ventricular primary graft dysfunction as defined by ISHLT consensus[38] was not possible. However, the INTERMACS definition for RHF we used is broadly established, and its specificity for the right heart is independent of the presence of an LVAD.

Despite its limitations, our results were derived from a large multicenter study with a contemporary population of 333 HTx patients, and the final analysis provided important and clinically needed information. Finally, our findings should be regarded as hypothesis generating, especially in terms of mortality after HTx, as several factors may affect post-transplant survival. Therefore, to confirm our results, further large, prospective multicenter studies are required.

Conclusions

The current practice of hemodynamic evaluation of HTx candidates is not used to its full potential, as the established PVR cutoff value of 3.0 WU is not part of any pre-transplant risk score and seems of minor prognostic impact compared with other hemodynamic variables. Lowering the PVR threshold and considering advanced markers of pulmonary vasculopathy such as Ea may improve risk stratification and enable individualized therapy optimization to improve HTx outcomes; therefore, such a strategy should be integrated into routinely performed RHC in HTx candidates. However, prediction of death and RHF remains challenging and should be investigated in further prospective studies.

Author contributions

AJR, RR, UB: conception and design, acquisition of data, statistical analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript submitted. DG, TK: conception and design, drafting of the manuscript, statistical analysis and interpretation of data; final approval of the manuscript submitted. KT, MJR: drafting of the manuscript, revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. TL, CG, DS, CB, MH, TS, JS, HW: acquisition of data, final approval of the manuscript submitted. NF, CS, SK, JV, AL, Y-HC, MR, CWH: revising the manuscript critically for important intellectual content; final approval of the manuscript submitted.

Disclosure statement

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.10.002.

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