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Biomarkerdiagnostik der reversiblen pulmonalen Hypertonie und Rechtsherzinsuffizienz – Die inoperable chronisch thromboembolische pulmonale Hypertonie (CTEPH) als Modell

Habilitationsschrift
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<u>Diese kumulative Habilitationsschrift basiert auf den folgenden Publikationen:</u>
(Originalversionen der Publikationen im Abschnitt 12.)

1. N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Wolter JS, Hütz R, Haas M, Breithecker A, Roller FC, Keller T, Guth S, Rolf A, Hamm CW, Mayer E, Liebetrau C. J Heart Lung Transplant. 2018 May;37(5):639-646. **(Erstautorenschaft)**

2. Dynamics of high-sensitivity cardiac troponin T during therapy with balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Keller T, Wolter JS, Ajnwojner R, Peters K, Haas MA, Roller FC, Breithecker A, Rieth AJ, Guth S, Rolf A, Bandorski D, Hamm CW, Mayer E, Liebetrau C. PLoS One. 2018 Sep 25;13(9):e0204683 **(Erstautorenschaft)**

3. Mid-regional pro-atrial natriuretic peptide and copeptin as indicators of disease severity and therapy response in CTEPH. **Kriechbaum SD**, Scherwitz L, Wiedenroth CB, Rudolph F, Wolter JS, Haas M, Fischer-Rasokat U, Rolf A, Hamm CW, Mayer E, Guth S, Keller T, Konstantinides SV, Lankeit M, Liebetrau C; ERJ Open Res. 2020 Nov 2;6(4):00356-2020. **(Erstautorenschaft)**

4. Galectin-3, GDF-15, and sST2 for the assessment of disease severity and therapy response in patients suffering from inoperable chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Peters K, Barde MA, Ajnwojner R, Wolter JS, Haas M, Roller FC, Guth S, Rieth AJ, Rolf A, Hamm CW, Mayer E, Keller T, Liebetrau C. Biomarkers. 2020 Nov;25(7):578-586. **(Erstautorenschaft)**

5. Pregnancy-associated plasma protein A - a new indicator of pulmonary vascular remodeling in chronic thromboembolic pulmonary hypertension? **Kriechbaum SD**, Rudolph F, Wiedenroth CB, Mielzarek L, Haas M, Guth S, Hamm CW, Mayer E, Liebetrau C, Keller T. Respir Res. 2020 Aug 3;21(1):204. **(Erstautorenschaft)**

6. Development of renal function during staged balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Hesse ML, Ajnwojner R, Keller T, Sebastian Wolter J, Haas M, Roller FC, Breithecker A, Rieth AJ, Guth S, Rolf A, Hamm CW, Mayer E, Liebetrau C. Scand J Clin Lab Invest. 2019 Jul;79(4):268-275. **(Erstautorenschaft)**

7. Cardiac biomarkers as indicators of right ventricular dysfunction and recovery in CTEPH – a cardiac magnetic resonance imaging cohort study; **Kriechbaum SD,** Julia M. Vietheer; Christoph B. Wiedenroth; Felix Rudolph; Marta Barde; Jan-Sebastian Wolter; Moritz Haas; Ulrich Fischer-Rasokat; Maren Weferling; Andreas Rolf; Christian W. Hamm; Eckhard Mayer; Stefan Guth; Till Keller; Fritz C. Roller; Christoph Liebetrau; Pulm Circ. 2021 Dec 10;11(4):20458940211056500. **(Erstautorenschaft)**

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

9. Exercise right heart catheterization before and after balloon pulmonary angioplasty in inoperable patients with chronic thromboembolic pulmonary hypertension. CB Wiedenroth, AJ Rieth, **SD Kriechbaum**, HA Ghofrani, A Breithecker, M Haas, F Roller, MJ Richter, M Lankeit, L Mielzarek, A Rolf, CW Hamm, E Mayer, S Guth, C Liebetrau; Pulm Circ 2020 Aug 18;10(3):2045894020917884 **(Koautorenschaft)**

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

1 Einleitung

1.1 Rechtsherzinsuffizienz im Kontext einer Nachlasterhöhung

Die Rechtsherzinsuffizienz beschreibt die Manifestation eines klinischen Syndroms, bei dem eine Rechtsherzdysfunktion zu einer insuffizienten Hämodynamik und/oder erhöhten rechtskardialen Füllungsdrucken in Ruhe und/oder bei Belastungszuständen führt[1]. Als Kardinalsymptome zeigen sich eine systemische Volumenstauung, inadäquate Dyspnoe und Abgeschlagenheit[1].

Die Rechtsherzdysfunktion kann dabei aus einer primär rechtskardialen Pathologie (Kardiomyopathie, Myokardischämie, Klappenvitium o.a.) resultieren, tritt jedoch meist als Sekundärfolge einer pulmonalen Hypertonie (PH) auf[2]. In Abhängigkeit von der zugrundeliegenden Genese werden verschiedene Subgruppen der PH unterschieden: Pulmonalarterielle Hypertonie (Gruppe 1), PH als Folge einer Linksherzpathologie (Gruppe 2), PH bei Lungenerkrankungen und/oder Hypoxie (Gruppe 3), chronisch thromboembolische pulmonale Hypertonie (CTEPH, Gruppe 4) und sonstige Genesen (Gruppe 5)[3]. Definitionsgemäß besteht bei allen Formen der PH eine pathologische Veränderung der pulmonalen Hämodynamik mit einer Erhöhung des mittleren pulmonalarteriellen Druckes (mPAP), welche mit einer Nachlaststeigerung für den rechten Ventrikel (RV) einhergeht[4]. Während eine akute Nachlasterhöhung nur in sehr begrenztem Rahmen toleriert werden kann, besteht seitens des rechten Herzens ein immenses Kompensationspotential gegenüber einer chronischen, sich sukzessiv entwickelnden Nachlasterhöhung[5]. Diese löst am rechten Herzen vielfältige morphologische, metabolische und funktionelle Anpassungsmechanismen aus[1,5,6]. Initial führt die intrinsische Fähigkeit von Kardiomyozyten über eine Mechanotransduktion zu strukturellen Anpassungen mit Zunahme der kontraktilen Elemente und konsekutiver makroskopischer Myokardhypertrophie[7,8]. Diese phänotypische Veränderung ist auch Folge der Aktivierung eines fetalen Genexpressionsmusters[6] und ist, konträr zum linken Herzen, kein grundsätzlich pathologischer Vorgang[5]. Im Sinne eines adaptiven Remodelings führt die Zunahme der RV-Wandstärke zu einer Reduktion der Wandspannung und zum Erhalt der

Auswurfleistung bei normwertigen RV-Füllungsdrucken[8,9]. Ein Fortbestehen der Nachlasterhöhung kann jedoch auch nur transient kompensiert werden und führt im Verlauf zum maladaptiven Remodeling. Führend zeigt sich eine progrediente RV-Dilatation mit konsekutivem Anstieg der Wandspannung und feinstrukturell eine zunehmende Fibrosierung des Myokards[5,8,9] An dieser Sequenz sind vielfältige metabolische, zellmigratorische, neurohumorale und inflammatorische Prozesse beteiligt[5,8,9]. Funktionell gehen diese Veränderungen mit einer diastolischen Dysfunktion und Reduktion der antegraden RV-Auswurfleistung einher[8,9]. Ein retrograder Volumenstau und eine reduzierte linksventrikuläre Füllung mit konsekutiver systemischer Hypotension sind die Folge[8,9]. Der Übergang vom druckbelasteten, hypertrophierten jedoch adaptierten hin zu einem volumenüberlasteten, dilatierten und maladaptierten rechten Ventrikel mit zunehmender Myokardfibrose ist fließend und zeitlich sehr variabel[5,8,9].

Das Versagen der Kompensationsmechanismen mit konsekutiver Rechtsherzinsuffizienz ist bei allen Formen der PH, unabhängig von der Genese, ein starker Indikator der Krankheitsschwere und der führende Prognoseparameter[3,10–12]. Eine exakte diagnostische Erfassung der individuellen rechtskardialen Beeinträchtigung ist insofern von zentralem klinischem Interesse.

In der klinischen und wissenschaftlichen Praxis erschwert die häufige Assoziation der Rechtsherzinsuffizienz zu einer primären Linksherzerkrankung oder irreversiblen Systemerkrankungen eine isolierte Betrachtung respektive die Aufarbeitung regenerativer Prozesse. Die jüngsten Leitlinien der europäischen Fachgesellschaft verweisen für das klinische Management auf Erkenntnisse zur Rechtsherzinsuffizienz bei Patienten/-innen mit einer Linksherzinsuffizienz mit erhaltener linksventrikulärer Pumpfunktion (HFpEF)[2,11]. Jedoch sind die Anforderungen an die Modellsituation einer isolierten Rechtsherzinsuffizienz auch hier nicht erfüllt. Die Leitlinien zur Diagnostik und Therapie der PH empfehlen einen multimodalen Ansatz zur diagnostischen Aufarbeitung des rechtskardialen Status bei PH[3]. Dieser integriert umfassende, ressourcenintensive (nicht-)invasive Diagnostik[3].

Die hier vorgelegte Habilitationsschrift stellt die (inoperable) CTEPH als Modellerkrankung zur diagnostischen Aufarbeitung einer reversiblen sekundären Rechtsherzinsuffizienz bei reversibler PH ohne Linksherzbezug vor.

1.2 Die (inoperable) CTEPH als Modell der reversiblen PH und Rechtsherzinsuffizienz

Definition der Erkrankung

Der Nachweis pulmonaler Perfusionsdefizite, sowie typischer pulmonalarterieller Obstruktionen trotz einer kontinuierlichen therapeutischen Antikoagulation über 3 Monate und der zusätzliche Befund einer präkapillären PH definieren eine CTEPH. Zeigen sich die o.g. Befunde ohne eine PH, wird dies als „Chronic Thromboembolic Pulmonary Disease (CTEPD), vor 2021 als „Chronic Thromboembolic Disease“ (CTED), bezeichnet[3,13]. Die präkapilläre PH wird durch eine Erhöhung des mPAP >20mmHg seit 2021, zuvor 25mmHg, und des pulmonalvaskulären Widerstandes (PVR) > 3 Wood Units (WU) bei normwertigem pulmonalarteriellen Wedgedruck (PAWP) ≤ 15 mmHg definiert[3,13]. Die Publikationen dieser Habilitationsschrift folgen der Krankheitsdefinition der europäischen Leitlinie aus dem Jahr 2015[3].

Epidemiologie & Pathophysiologie

Die CTEPH wird als seltene Spätkomplikation bei Patienten/-innen mit einer oder mehreren akuten Lungenarterienembolien (LAE) angesehen[14,15]. Eine Metaanalyse von 16 Studien mit 4047 eingeschlossenen Patienten/-innen zum Verlauf nach einer akuten LAE berichtete eine Inzidenz von ~ 3%[16]. Die Fehlinterpretation einer CTEPH als akute LAE, ein eingeschränktes klinisches Bewusstsein gegenüber dieser Spätkomplikation, sowie populationsabhängige Unterschiede limitieren jedoch eine abschließende Beschreibung der Inzidenz[13,15].

Bei Patienten/-innen mit einer CTEPH kommt es im Anschluss an das akute thromboembolische Ereignis, bedingt durch eine insuffiziente Thrombusresolution, eine gestörte Angiogenese und Endothelfunktion sowie inflammatorische Prozesse zur Fixierung fokaler pulmonalarterieller Obstruktionen[9,13,15]. Trotz der Identifikation einzelner Prädilektionsfaktoren sind die pathophysiologischen Prozesse, welche individuell zur Entwicklung einer CTEPH führen, nicht abschließend geklärt[15].

Die makroskopischen Gefäßläsionen imponieren als netzartig, ringförmig einengend oder als komplette Gefäßverschlüsse (Abbildung 1) und sind der primäre Auslöser für

eine Erhöhung des PVR[9]. Als additionaler Mechanismus der PH findet sich eine Kleingefäßvaskulopathie mit Remodeling des Endothels und der fibromuskulären Gefäßwand in variabler Ausprägung[9]. Als zugrundeliegende Prozesse werden u.a. eine Hyperperfusion nicht-okkludierter Gefäßbettareale, eine Rekrutierung systemisch-pulmonalarterieller Shunts und distale Mikrothrombosen sowie Alterationen des Stickoxid-Guanylatcyclase-Stoffwechsels diskutiert[9]. Die hieraus resultierende Beeinträchtigung der pulmonalen Hämodynamik hat eine Erhöhung der rechtsventrikulären Nachlast mit den oben beschriebenen Konsequenzen zur Folge[9].

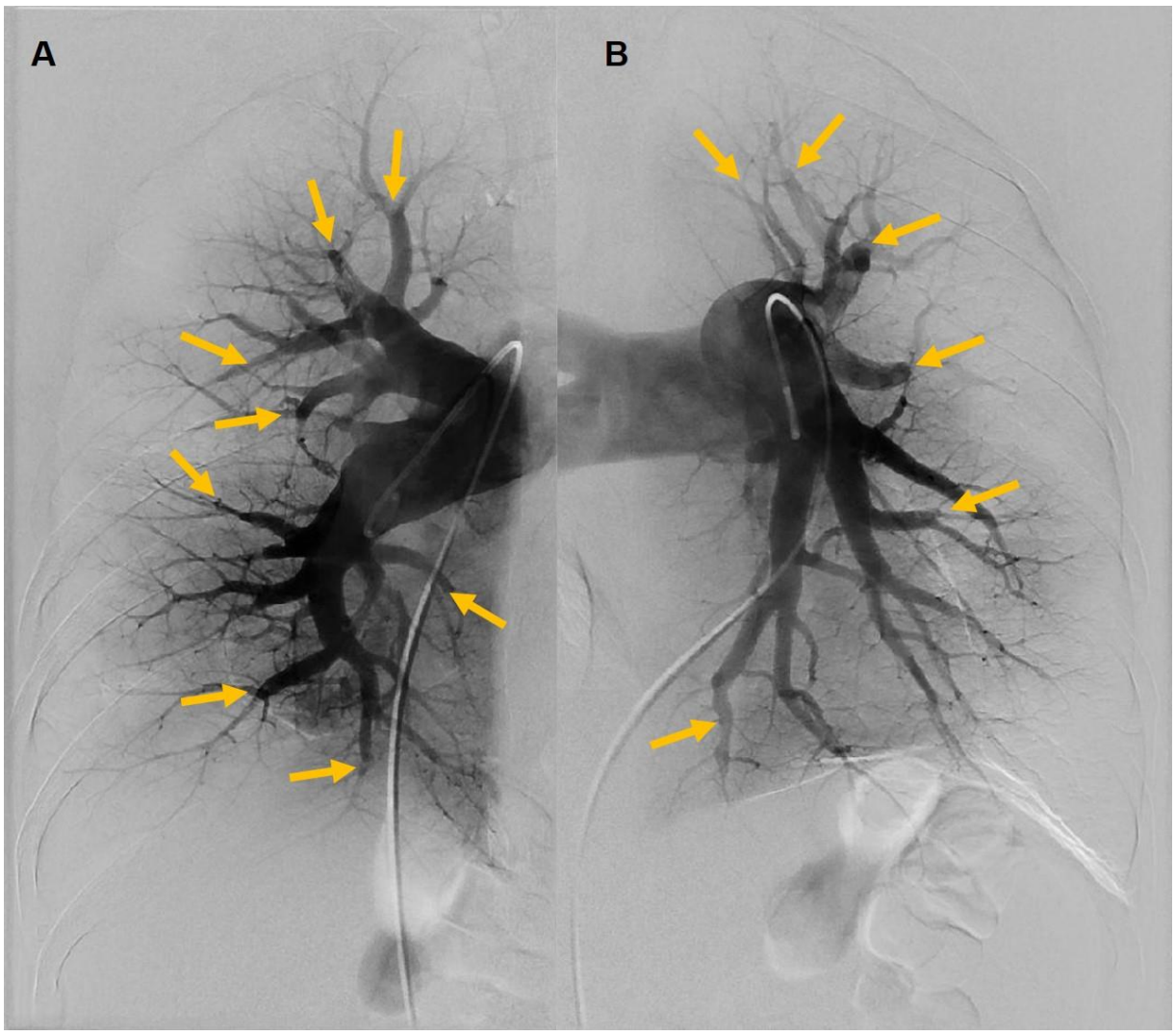

Abbildung 1: Pulmonalisangiographie mit kontrastmittelbasierter Darstellung der Lungenarterien; Die Markierungen verweisen auf die typischen obstruktiven Gefäßläsionen bei einer CTEPH, A= rechte Lunge, B = linke Lunge; (Aus der Kerckhoff-Klinik Bad Nauheim)

Therapiekonzepte

Die Veränderungen des pulmonalen Gefäßbettes sind der Ansatzpunkt für die derzeit empfohlenen Therapiekonzepte[3,13]. Die Basistherapie beinhaltet eine lebenslange therapeutische Antikoagulation sowie supportive Maßnahmen mittels Diuretika und Sauerstoffgabe zur Symptomkontrolle. Der Hauptfokus der Therapie liegt im Weiteren auf der Sanierung der Gefäßläsionen.

Die chirurgische pulmonale Endarteriektomie (PEA) ist die einzige kausale Therapie der CTEPH und ist deshalb die Therapie der Wahl bei allen operablen Patienten/-innen[13]. Das Verfahren beschreibt das chirurgische Ausschälen des betroffenen pulmonalen Gefäßbaumes von zentral bis (sub-) segmental mit möglichst vollständiger Entfernung des obstruktiven Materials[13] (Abbildung 2).

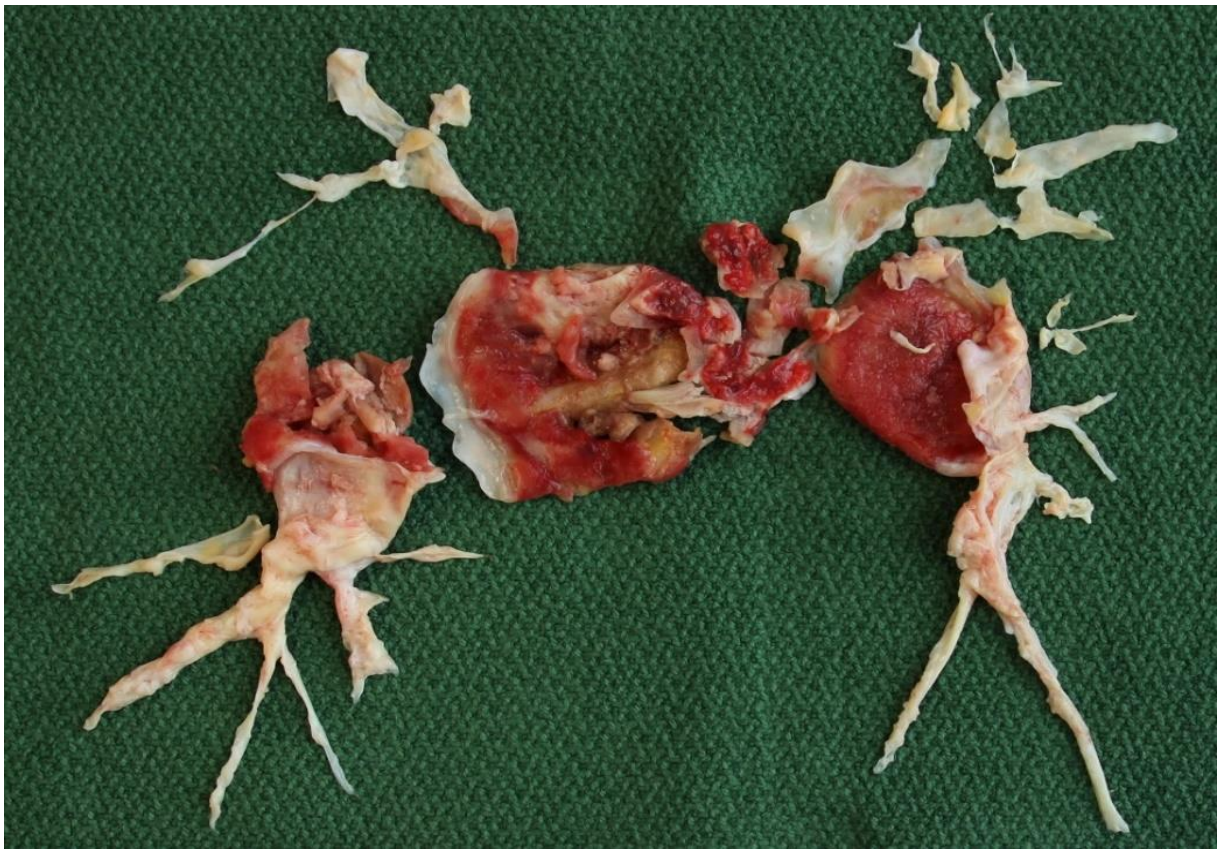

Abbildung 2: Operationspräparat einer PEA; Das dargestellte Material entspricht dem zuvor innerhalb der stammnahen Lungenarterien befindlichen obstruktiven Material; (Mit freundlicher Genehmigung der Abt. für Thoraxchirurgie der Kerckhoff-Klinik)

Internationale Registerdaten dokumentieren die Verbesserung der pulmonalen Hämodynamik (Mittlerer Abfall des PVR von 8,75 WU auf 2,95 WU) und des klinischen Status [Zunahme der mittleren 6-Minuten-Gehtest-Strecke (6-MWD) von 362 m auf

459 m] ein Jahr nach der operativen Therapie, bei hoher prozeduraler Sicherheit (PEA-assoziierte Mortalität < 5%). Die Registerdaten zeigen auch die signifikant verbesserte Überlebensprognose im Vergleich zu einem konservativen Therapieregime (89 % vs. 70% nach 3 Jahren)[17,18].

Ungefähr ein Drittel der CTEPH-Patienten/-innen ist jedoch, zumeist wegen peripher lokalisierten Gefäßläsionen, nicht für eine chirurgische Therapie geeignet[19]. Nachdem sich die Therapie dieses Kollektivs über lange Zeit auf symptomatische Maßnahmen beschränkte, sind inzwischen zwei spezifische Therapiemodalitäten verfügbar.

Der oral zu verabreichende Stimulator der löslichen Guanylatzyklase Riociguat modifiziert den Stickoxid-Guanylatzyklase-Stoffwechsel und adressiert damit insbesondere die sekundäre Mikrovaskulopathie[20]. Im Jahr 2013 präsentierten die Resultate der CHEST-1 Studie den Wirkstoff als erste spezifische Medikation mit klinischem und funktionellem Nutzen bei inoperabler CTEPH. Ghofrani und Kollegen berichteten hier u.a. über eine Reduktion des PVR um 2,83 WU und eine Verbesserung der World-Health-Organisation-Funktionsklasse (WHO-FC) bei 33% der Patienten/-innen bei gleichzeitiger Dokumentation einer hohen therapeutischen Sicherheit[20]. Der erstmalige Nachweis einer medikamentös bedingten Verbesserung der körperlichen Leistungsfähigkeit führte zur Aufnahme dieser Medikation in die Leitlinien als erste spezifische medikamentöse Therapiesäule (Ib)[3,20]. Als weiteres spezifisches Medikament erhielt im Verlauf, begründet durch dessen positive Effekte auf die 6-MWD, den PVR und die klinische Symptomatik, ausschließlich das vasodilatative und thrombozytenaggregationshemmende Prostacyclinanalogon Treprostenil eine Zulassung für die Therapie der CTEPH[13]. PH Medikamente unterschiedlicher anderer Wirkstoffklassen[21,22] zeigten im Kontext der CTEPH keine substantiellen Effekte.

Zur Sanierung der chirurgisch nicht zugänglichen Gefäßobstruktionen wurde die interventionelle pulmonale Ballonangioplastie (BPA) entwickelt[23]. Hier werden die Gefäßobstruktionen, entgegen der PEA, nicht entfernt, sondern durch gezielte Ballondilatationen aufgebrochen, wodurch eine verbesserte Perfusion des stromabwärts liegenden Gefäßbettes erreicht werden soll[13,24]. Nach der Erstbeschreibung 1988 wurde die BPA wegen der hohen Rate fataler Komplikationen, insbesondere massiver Reperfusionsschäden und Blutungen, vorrübergehend wieder

verworfen[23]. Grundsätzliche prozedurale Modifikationen führten später zur erneuten Anwendung, primär in japanischen, folgend auch in westlichen Fachzentren mit einer deutlichen Verbesserung der prozeduralen Sicherheit[25,26]. Die BPA wurde inzwischen als Abfolge mehrerer, durch mehrwöchige Intervalle getrennte, Therapiesitzungen mit jeweiliger Behandlung von nur wenigen betroffenen Gefäßsegmenten, durchgeführt. Sowohl japanische als auch westliche Zentren konnten positive Effekte der Therapie auf die pulmonale Hämodynamik dokumentieren, wobei sich signifikante regionale Unterschiede bzgl. der Reduktion des mPAP und PVR zeigten[26–29]. Während in japanischen Zentren regelhaft eine Normalisierung der pulmonalen Hämodynamik mit einer mittleren PVR-Reduktion von bis zu 65% erreicht wurde, fielen die Effekte in nicht-japanischen Zentren positiv, jedoch deutlich weniger ausprägt aus[29]. Unterschiede bei der Selektion der Therapieverfahren sowie der chirurgischen Expertise wurden als Erklärung für diese Inhomogenität gesehen. Vor dem Hintergrund der vielversprechenden, jedoch stark limitierten Datenlage erhielt die BPA in den Leitlinien 2015 eine Empfehlung als zu erwägende Therapieoption (IIb) bei Patienten/-innen ohne chirurgischen Therapieansatz und persistierend symptomatischer PH unter einer spezifischen Medikation mit Riociguat[3]. Die BPA Therapie sollte jedoch ausdrücklich nicht als Alternative zur PEA, sondern als ergänzende Therapiesäule bei CTEPH verstanden werden[13]. Im Verlauf konnten die positiven Effekte der einzelnen Bestandteile (spezifische Medikation, BPA Therapie) der medikamentös-interventionellen Therapiesequenz, sowie deren kumulativer Effekt differenziert dargestellt werden[30].

1.3 Die diagnostische Erfassung des rechtskardialen Status

Die Diagnostik der CTEPH ist, angesichts der vielfältigen Pathomechanismen, mit einer hohen quantitativen und qualitativen Ressourcenintensität verbunden[3,13]. Die Quantifizierung der pulmonalen Hämodynamik und Charakterisierung des rechtskardialen Status ist dabei ein zentraler Aspekt und erfordert den Einsatz multimodaler (nicht-)invasiver Diagnostik [5,24]. Der invasive Rechtsherzkatheter (RHK) ist der Goldstandard zur Quantifizierung der (pulmonalen) hämodynamischen Verhältnisse sowohl in Ruhe, als auch unter körperlicher Belastung[31]. Zur morphologischen und funktionellen Diagnostik des rechten Herzens ist in Anpassung an die individuellen Patientencharakteristika und Fragestellungen der Einsatz

bildgebender Verfahren, insbesondere der Echokardiographie und der Magnetresonanztomographie, empfohlen[11,13,32]. Die kardiale Magnetresonanztomographie (Kardio-MRT) ermöglicht, zusätzlich zur makroskopischen und funktionellen Beurteilung, eine nichtinvasive Gewebecharakterisierung[33,34] mit entsprechenden Informationen über rechtskardiale Remodelingprozesse[34–37]. In einigen Vorarbeiten konnte das kardiale Remodeling und die konsekutive Rechtsherzdysfunktion im Rahmen einer CTEPH sowie deren Regeneration nach einer PEA oder BPA Therapie im Kardio-MRT dokumentiert werden[38–43].

Biomarker sind körpereigene, messbare und quantifizierbare Parameter, welche als Folge (patho-)physiologischer Prozesse im Körper entstehen und die standardisierte Quantifizierung dieser Prozesse möglich machen[44]. Die Bestimmung von Biomarkern im Blut wird bei zahlreichen kardialen Erkrankungen u.a. als Indikator für hämodynamischen Myokardstress und myokardiale Zellschädigung zur Diagnosestellung, Risikostratifizierung und zum Therapiemonitoring erfolgreich eingesetzt[2]. Zahlreiche neue Biomarker werden als Indikatoren vielfältiger Prozesse des chronischen kardialen Remodelings diskutiert[44,45]. Das Expressionsverhalten kardialer und nicht-kardialer Biomarker im Rahmen einer CTEPH, deren Assoziation zu zentralen Krankheitsparametern, insbesondere der pulmonalen Hämodynamik und der rechtskardialen Funktion, ist nicht umfassend untersucht. Nichtinvasiv bestimmbare Biomarker spielen daher zum aktuellen Zeitpunkt in der Diagnostik der CTEPH nur eine untergeordnete Rolle. Ausschließlich die natriuretischen Peptide erhielten in den europäischen Leitlinien eine Empfehlung zur Bestimmung im Rahmen des initialen Screenings und zur Risikostratifizierung[3].

Der Fokus dieser kumulativen Habilitationsschrift liegt auf der Evaluation des diagnostischen Potentials nichtinvasiver (kardialer) Biomarker zur Erfassung (mal-)adaptiver und regenerativer Prozesse im Kontext der reversiblen PH und Rechtsherzinsuffizienz unter Verwendung der (inoperablen) CTEPH als Modellerkrankung.

1.4 Wissenschaftlicher Kontext des CTEPH-Programms am Studienzentrum

Die Teilprojekte dieser kumulativen Habilitationsschrift wurden an der Kerckhoff-Klinik Bad Nauheim, einem europäischen CTEPH-Referenzzentrum, in Kooperation mit dem assoziierten Franz-Grödel-Institut umgesetzt. Die diagnostische und therapeutische Versorgung von Patienten/-innen mit einer CTEPH erfolgt dort durch ein spezielles interdisziplinäres CTEPH-Team nach am Studienzentrum etablierten Standardprotokollen[25,46]. Die PEA, als therapeutischer Goldstandard der CTEPH, wird am Studienzentrum langjährig durchgeführt[46,47]. Zur Therapie von Patienten/-innen mit einer inoperablen CTEPH wurde im Jahr 2014 an der Kerckhoff-Klinik ein BPA-Programm etabliert, welches von Beginn an durch die Initiierung des CTEPH-Registers „BioCTEPH“ wissenschaftlich begleitet wurde.

Der Fokus der wissenschaftlichen Arbeit lag auf der Analyse prozeduraler Aspekte und der Therapieeffekte aller beschriebenen chirurgischen, medikamentösen und interventionellen Therapiemodalitäten. Dabei konnten die ausgeprägten positiven Effekte CTEPH-spezifischer Therapieverfahren auf hämodynamische, kardiale und klinische Zielparameter der CTEPH bei gleichzeitig hoher therapeutischer Sicherheit gezeigt werden[25,30,36,43,46,48,49].

2 Biomarker als Indikatoren verschiedener Aspekte der reversiblen PH und Rechtsherzinsuffizienz

Im Blut zirkulierende Biomarker sind ein diagnostischer Zugangsweg zur Darstellung und Quantifizierung (patho-)physiologischer Prozesse im Körper. Dabei liegen die Vorzüge der Biomarkerdiagnostik im Blut insbesondere in der vergleichsweise einfachen, risikoarmen Erfassungsprozedur, der Standardisierung und Wiederholbarkeit sowie der Vielfältigkeit der adressierbaren in vivo Prozesse. Im Kontext der CTEPH ist die Biomarkerdiagnostik deshalb sowohl für ein weiterführendes Verständnis der beteiligten Krankheitsprozesse als auch zur Vereinfachung des ressourcenintensiven diagnostischen Algorithmus interessant.

2.1 Dynamik des N-terminalen pro-BNPs unter der CTEPH-Therapie (Publikation 1)

Studienrationale und Studiendesign

Die CTEPH ist durch einen Anstieg von mPAP und PVR gekennzeichnet. Die damit verbundene rechtsventrikuläre Nachlasterhöhung geht mit einem Anstieg der myokardialen Wandspannung einher[15]. Dieser Dehnungsreiz ist u.a. der Auslöser für die vermehrte myozytäre Expression natriuretischer Peptide[50]. Effekte natriuretischer Peptide werden vorrangig durch den natriuretic peptide receptor-A und den Messenger zyklisches Guanosinmonophosphat vermittelt und lassen sich grundsätzlich als kardioprotektiv und antagonistisch zum Renin-Angiotensin-Aldosteron-System zusammenfassen[50]. Der tierexperimentelle Knockout des natriuretic peptide receptor-A führt zu Hypersensibilität gegenüber einer Nachlasterhöhung mit vermehrter Myokardhypertrophie und -fibrose[50].

Brain-natriuretisches Peptid (BNP) liegt größtenteils im ventrikulären Myokard vor und wird von dort als Antwort auf eine erhöhte Wandspannung sezerniert[50]. Die Nutzung als diagnostischer Marker für hämodynamisch induzierten kardialen Stress gelingt durch den direkten serologischen Nachweis oder den des äquimolar sezernierten

metabolisch inaktiven Spaltprodukts N-terminales pro-BNP (NT-proBNP)[51]. NT-proBNP ist im Kontext zahlreicher kardialer Erkrankungen, insbesondere der akuten und chronischen Linksherzinsuffizienz, als Biomarker etabliert und dient hier zur individuellen Risikostratifikation, Verlaufsbeurteilung und Therapiemonitoring[2,51,52]. Natriuretischer Peptide erhielten als einzige Biomarkergruppe eine diagnostische Empfehlung in den Leitlinien zur Behandlung und Diagnostik der PH[3]. In einzelnen Arbeiten zur CTEPH zeigten sich die Serumspiegel natriuretischer Peptide assoziiert zur Schwere der rechtsventrikulären Dysfunktion und rückläufig nach einer PEA- respektive BPA-Therapie[53,54]. Insgesamt existierte jedoch eine limitierte Datenlage zum Expressionsprofil des NT-proBNP bei Patienten/-innen mit einer inoperablen CTEPH. Insbesondere die exakte Dynamik während einer interventionellen Stufentherapie mittels BPA und der damit verbundenen sukzessiven hämodynamischen Entlastung des rechten Herzens war nicht untersucht. Dies war der Anlass für die wissenschaftliche Aufarbeitung (Publikation 1).

Insgesamt wurden 51 konsekutive Patienten/-innen, welche an der Kerckhoff-Klinik wegen einer inoperablen CTEPH mittels BPA-Therapie behandelt wurden und am Studienzentrum eine 6-Monats-Nachsorge absolvierten, in die Studie eingeschlossen. Die diagnostische und therapeutische Versorgung erfolgte entsprechend des am Studienzentrum etablierten Standardprozedere[25,30]. Zum Einschlusszeitpunkt, vor jeder BPA-Sitzung, nach der letzten BPA-Sitzung und im Rahmen der 6-Monats-Nachsorge wurde der NT-proBNP Konzentration im Serum der Patienten/-innen bestimmt. Die Messung erfolgte mittels Elektro-Chemilumineszenz-ImmunoAssay (NT-proBNP Assay, Elecsys Analyzer2010, Roche Diagnostics, Mannheim, Germany). Alle Patienten/-innen gaben ihr schriftliches Einverständnis zur Studienteilnahme und dem Einschluss in das BioCTEPH-Register. Die Studie wurde durch die Ethikkommission der Justus-Liebig-Universität Gießen (Aktenzeichen 43/14) bewilligt.

Ergebnisse

Die soziodemographischen und klinischen Daten charakterisierten eine typische Kohorte inoperabler CTEPH-Patienten/-innen. Im Hinblick auf die erfolgte Analyse des NT-proBNP ist zu betonen, dass alle Patienten/-innen eine regelrechte

Linksherzfunktion und eine uneingeschränkte Nierenfunktion anhand der geschätzte glomeruläre Filtrationsrate (eGFR) mit 79,2 ± 26,7 ml/min/1,73m² aufwiesen.

Die BPA-Therapie wurde im Mittel in fünf Sitzungen pro Patient mit einer Behandlung von im Mittel 8 Gefäßsegmenten durchgeführt. Die Überlebensrate nach 6 Monaten lag bei 96,1%. Die BPA Therapie führte bei den Patienten/-innen zu einer signifikanten Verbesserung des klinischen Status, quantifiziert durch eine Reduktion der Patientenanzahl in WHO-FC ≥ III von 91,1% auf 11,8% (p<0,001) und eine Verlängerung der medianen Gehstrecke im 6-Minuten-Gehttest [375 m (IQR 281 – 446 m) vs. 409 m (IQR 332 – 446 m); (p=0.017)]. Der mittlere PVR fiel von 6,47 ± 2,74 WU auf 4,97 ± 2,29 WU (p<0.001) und der mPAP von 40 ± 12 mmHg auf 33 ± 13mmHg (p<0.001). Die mediane NT-proBNP Konzentration fiel von 821 ng/L (IQR 153-1872 ng/L) vor der BPA-Therapie auf 159 ng/L (IQR 84 – 464 ng/L) in der 6-Monats-Nachsorge (p<0,001). Abbildung 3 illustriert den sukzessiven Abfall der NT-proBNP Konzentration während der BPA-Stufentherapie. Dabei fällt auf, dass der NT-proBNP-Spiegel unmittelbar nach Abschluss der BPA-Sequenz bis hin zum Nachsorgezeitpunkt stabil bleibt.

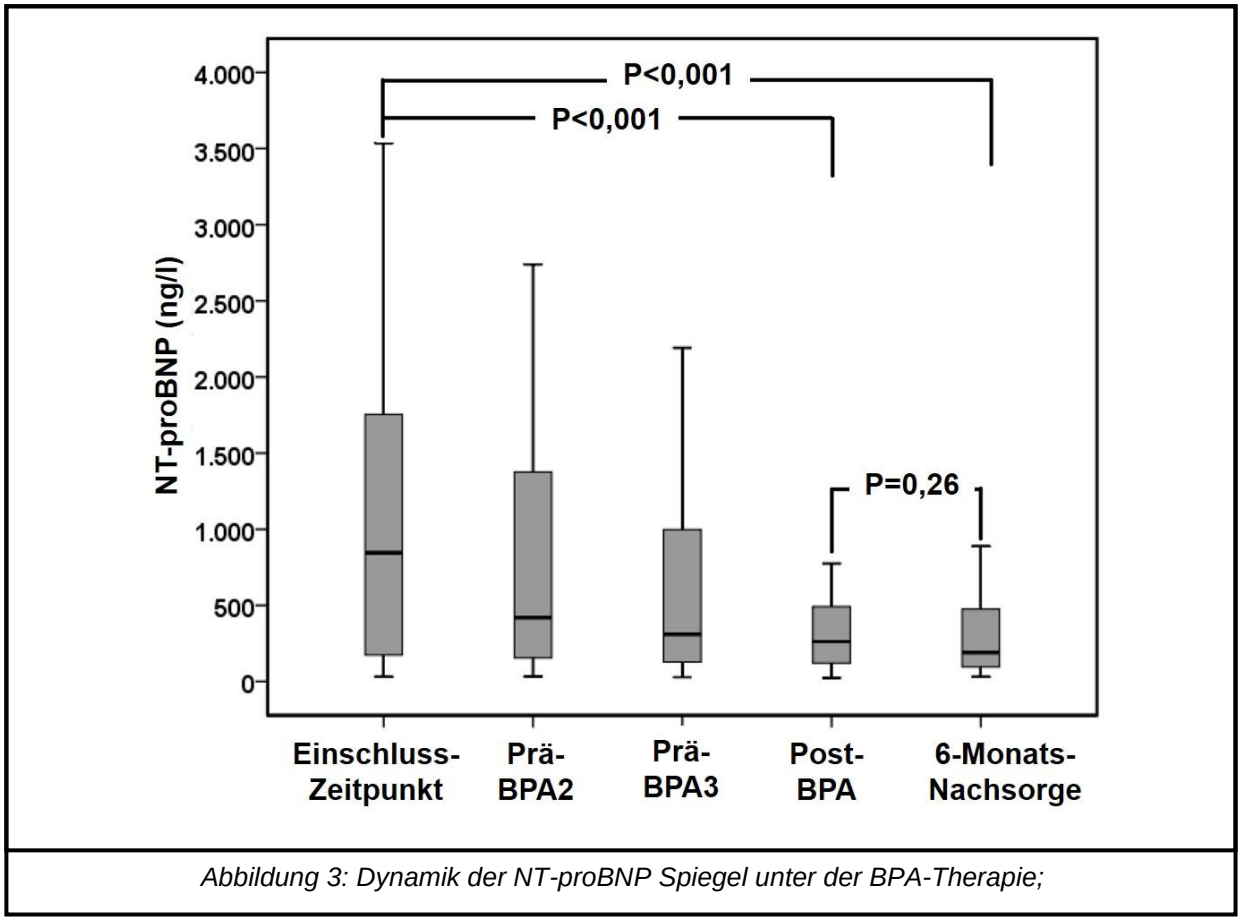

Abbildung 3: Dynamik der NT-proBNP Spiegel unter der BPA-Therapie;

Die NT-proBNP Konzentration korrelierte mit der WHO-FC (Einschluss: r_{rs} = 0,49, p<0,001; Nachsorge: r_{rs} = 0,44, p<0,001), dem mPAP und dessen Dynamik (Einschluss: r_{rs} = 0.65, p<0,001; Nachsorge: r_{rs} = 0,49, p<0,001; Dynamik: r_{rs} = 0,43, p=0,002) sowie dem PVR und dessen Dynamik (Einschluss: r_{rs} = 0,31, p=0,032; Nachsorge: r_{rs} = 0,37, p=0,016; Dynamik: r_{rs} = 0,50, p=0,001).

Zum Studienzeitpunkt und auch heute existiert keine anerkannte Definition einer erfolgreichen BPA-Therapie, gemessen am hämodynamischen Effekt. Grund hierfür ist u.a. die große Spanne der berichteten hämodynamischen Therapieeffekte in unterschiedlichen BPA-Programmen[25,27–29,55]. In der vorgelegten Studie wurde ein Abfall des mPAP um ≥25% oder des PVR um ≥35% als Therapieerfolg definiert. Ein Abfall des NT-proBNP Spiegels nach Therapie um ≥ 46% [Area under the curve (AUC) = 0,71] wurde als Indikator für einen Abfall des mPAP um ≥25% und eine Reduktion um ≥ 60% (AUC = 0,77) als Indikator für einen Abfall des PVR um ≥35% identifiziert. Eine signifikante kardiale Entlastung wurde in der Studie als Reduktion des NT-proBNP Ausgangswertes um ≥25% definiert. Patienten/-innen ohne signifikante Reduktion der NT-proBNP Konzentration waren durch einen vergleichsweise geringeren prozentualen Abfall des mPAP [2,1 (IQR -8,5 bis 20,3) % vs. 21,7 (IQR 8,1 bis 29,9), p=0,007] und des PVR [4,6 (IQR -14,9 bis 22,2) % vs. 28,9 (IQR 16,6 bis 40,5) %, p=0,002] charakterisiert.

Schlussfolgerung

Die Ergebnisse dieser Studie illustrierten erstmalig den sukzessiven Abfall des NT-proBNP, und somit den Rückgang des hämodynamisch induzierten kardialen Stresslevels, unter einer BPA-Stufentherapie. Bei einem Großteil der Patienten/-innen ließen sich unmittelbar nach der Therapie normwertige NT-proBNP Werte messen, welche darüber hinaus in der 6-Monats-Nachsorge konstant niedrig blieben und insofern für eine anhaltende Reversibilität der Rechtsherzbelastung sprechen. Die Bestimmung des NT-proBNP-Spiegels im Therapieverlauf erlaubte auch die Diskriminierung von Patienten/-innen mit einem Therapieerfolg oder -versagen.

2.2 Dynamik des kardialen Troponins T unter der CTEPH-Therapie (Publikation 2)

Studienrationale und Studiendesign

Als zugrundeliegende Mechanismen der myokardialen Fibrose im Rahmen des maladaptiven Rechtsherzremodelings werden u.a. die durch Dehnungsstress induzierte Stimulation kardialer Fibrozyten, aber auch ischämisch getriggerte Schädigungsprozesse diskutiert[5]. Mögliche Auslöser einer direkten Myokardschädigung bei PH sind eine systemische Hypoperfusion, Myozytenschäden durch eine erhöhte Wandspannung, eine kompressionsbedingte Beeinträchtigung der Koronarperfusion und eine Kapillarrarefizierung[5,56,57].

Kardiale Troponine sind in kardialen Myozyten als struktureller Bestandteil des kontraktilen Sarkomers und ungebunden im Zytoplasma zu finden[57]. Der serologische Nachweis ermöglicht den sensitiven Nachweis bereits geringfügiger Myokardschädigung. Ursprünglich als Biomarker zur Diagnostik des akuten Myokardinfarktes ohne ST-Streckenhebung etabliert, haben kardiale Troponine auch bei anderen kardialen und extrakardialen Erkrankungen und sogar bei mutmaßlich gesunden Individuen prognostische Aussagekraft[57]. Die Entwicklung hochsensitiver Messverfahren führte insbesondere auch zum Nachweis kardialer Troponine im Kontext chronischer Krankheitskonstellationen[58] und zur Frage nach deren klinischen Implikationen. Im Kontext der PH konnten kardiale Troponine als Indikator der Krankheitsschwere und als Prognoseparameter identifiziert werden[59,60]. Die Expression kardialer Troponine bei CTEPH und deren Dynamik unter einer Therapie sind nicht umfassend untersucht.

Die vorgelegte Studie untersuchte die Expressionskinetik des hochsensitiv-gemessenen kardialen Troponin T (hs-cTnT) bei Patienten/-innen mit einer inoperablen CTEPH unter einer BPA-Therapie mit der Zielsetzung die etwaige Dynamik einer sekundären, chronischen Myokardschädigung zu erfassen. Die Studienkohorte aus 51 Patienten/-innen war identisch zu der zuvor berichteten Kohorte aus Publikation 1. Das hs-cTnT wurde mittels eines hochsensitiven Assays (hs-cTnT Assay, Elecsys Analyzer 2010, Roche Diagnostics) zum Einschlusszeitpunkt, vor jeder BPA-Sitzung und im Rahmen der 6-Monats-Nachsorge im Serum der Patienten/-innen

bestimmt. Die 99. Perzentile dieses Assays in der gesunden Normalbevölkerung liegt bei 14 ng/L[61] und wird als Grenzwert zur Detektion für Myokardschäden im Rahmen eines akuten Koronarsyndroms empfohlen. Es wurde die Assoziation des hs-cTnT einerseits zu den hämodynamischen Zielparametern und andererseits zum NT-proBNP untersucht.

Ergebnisse

Zum Einschlusszeitpunkt lag der mediane hs-cTnT Konzentration bei 11 (6-16) ng/L, wobei 16 (31,4%) der Patienten/-innen einen das hs-cTnT oberhalb der 99. Perzentile aufwiesen. Der Ausgangswert fiel im Rahmen der 6-Monats-Nachsorge signifikant auf 7 (5-12) ng/L ($p<0,001$). Die Entwicklung reichte von einem maximalen Anstieg um 39% bis zu einem Abfall um 86%. Bei 8 Patienten/-innen (15,7%) stieg das hs-cTnT unter der Therapie an. Diese Patienten/-innen unterschieden sich bezüglich ihrer Einschlusscharakteristika nicht von den anderen Patienten/-innen: Alter ($p = 0,69$), Body Mass Index ($p = 0,77$), LVEF ($p = 0,43$), Tricuspid annular plane systolic excursion (TAPSE) ($p = 0,21$), mPAP ($p = 0,63$), PVR ($p = 0,38$), WHO-FC ($p = 0,40$), 6-Minuten-Gehstrecke ($p = 0,14$), eGFR ($p = 0,45$) und Serumkreatinin ($p = 0,41$). Zu dieser Gruppe von Patienten/-innen gehörten die zwei Patienten/-innen, welche zum Zeitpunkt der 6-Monats-Nachsorge verstorben waren.

Die hs-cTnT-Konzentration korrelierte zum Einschlusszeitpunkt ($r_{rs} = 0.51$; $p \leq 0.001$) als auch bei der 6-Monats-Nachsorge ($r_{rs} = 0.42$; $p=0.002$) mit der NT-proBNP-Konzentration. Der mittlere pulmonal-arterielle Druck ($r_{rs} = 0.32$; $p=0.029$) und der PVR ($r_{rs} = 0.42$; $p=0.005$) korrelierten lediglich moderat und ausschließlich vor der BPA-Therapie.

Abbildung 4 zeigt detailliert die Dynamik der hs-cTnT-Konzentration unter Therapie. Im Rahmen der 6-Monats-Nachsorge zeigte sich ein progredienter Abfall des hs-cTnT Spiegels.

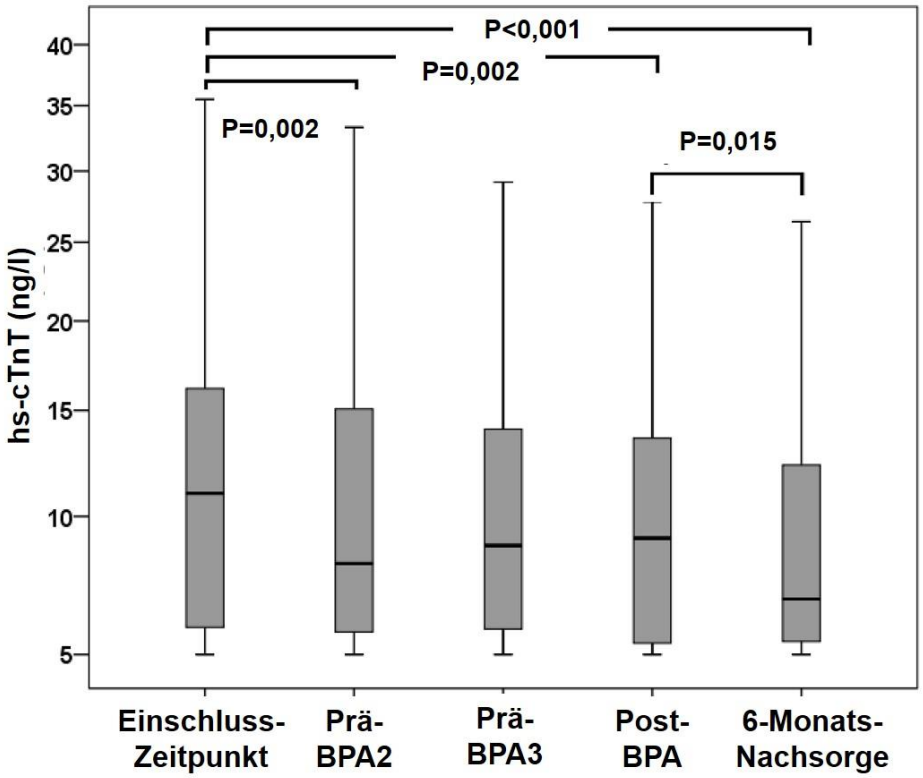

Abbildung 4: Dynamik des hs-cTnT Spiegels unter der BPA-Therapie;

Schlussfolgerung

Die Studienergebnisse zeigten erstmalig den sukzessiven Abfall des hs-cTnT unter einer BPA-Stufentherapie und damit den Rückgang einer chronischen subklinischen Myokardschädigung. Die Korrelation zu den NT-proBNP-Werten legt eine Assoziation der Troponinfreisetzung zu hämodynamisch induzierter RV-Wandspannung als Genese der Myozytenschädigung nahe. Der beobachtete Troponinanstieg bei zwei, im Rahmen der Nachsorge verstorbenen, Patienten/-innen lässt zwar eine erhöhte Krankheitsschwere bei Patienten/-innen mit fehlendem Troponinabfall vermuten, ist aber angesichts der Patientenzahl allenfalls hypothesengenerierend.

2.3 Dynamik des midregionalen pro-atrialen natriuretischen Peptids und des Copeptins unter der CTEPH-Therapie (Publikation 3)

Studienrationale und Studiendesign

Der Progress der Rechtsherzinsuffizienz bei einer CTEPH führt im Verlauf zunehmend zur ante- und retrograden kardialen Dekompensation mit Effekten auf die systemischen Kreislaufverhältnisse[9]. Ein reduzierter kardialer Index (CI) und ein erhöhter rechtsatrialer Druck (RAP) sind Indikatoren des Vorwärts- respektive Rückwärtsversagens und Charakteristika einer Risikokonstellation[3]. Die frühzeitige Erfassung systemischer Kreislaufeffekte ist deshalb essentiell im diagnostischen Monitoring der CTEPH.

Vasopressin ist ein Peptidhormon, welches im Hypothalamus gebildet und als Antwort auf systemischen hämodynamischen Stress, Hypotension und einen Anstieg der Plasmaosmolarität im Hypophysenhinterlappen sezerniert wird[62]. Die Effekte, u.a. eine periphere Vasokonstriktion und die renale Absorption freier Flüssigkeit, zielen auf eine akute Wiederherstellung der Kreislaufhomöostase ab[62]. Atriales natriuretisches Peptid (ANP) ist ein weiterer Vertreter der natriuretischen Peptide mit antagonistischen Effekten zum Renin-Angiotensin-Aldosteron-System[50]. Entgegen dem BNP findet dessen Sekretion jedoch, überwiegend durch den Dehnungsreiz an atrialen Myozyten statt[50] und illustriert deshalb die Wandspannung bzw. den atrialen Stress[63]. Ein Anstieg des RAP und das damit verbundene rechtsatriale Remodeling sind Indikatoren des fortschreitenden Rechtsherzversagens und einer schlechten Prognose[64–67]. Sowohl Vasopressin als auch ANP sind wegen einer geringen Plasmastabilität nicht valide als Biomarker nutzbar[62,68]. Copeptin und Midregionales-proANP (MR-proANP) entstehen bei der Sekretion von Vasopressin und ANP als Spaltprodukte, weisen eine deutlich höhere Plasmastabilität auf und ermöglichen so eine äquimolare labordiagnostische Quantifizierung[62,68]. Copeptin wurde zunächst als Biomarker zum beschleunigten Ausschluss eines akuten Koronarsyndroms prominent[69], im Verlauf aber auch als Prognoseparameter bei der akuten Lungenarterienembolie identifiziert[70,71]. ANP/MR-proANP-Spiegel korrelieren mit der Krankheitsschwere und Prognose bei Linksherzinsufifzienz[68], akuter Lungenarterienembolie[72], und PH[73–75]. Daten über die Rolle von MR-proANP und Copeptin bei CTEPH beschränken sich auf Tiermodelle[76],

kleine Subkohorten und gemischte PH-Kohorten[73,74,77,78]. Die Dynamik unter einer CTEPH spezifischen Therapie wurde bisher nicht untersucht.

Ziele der vorgelegten Studie (Publikation 3) waren die Analyse der Biomarker MR-proANP und Copeptin als Indikatoren der kardialen Dekompensation im Zuge eines progredienten chronischen Rechtsherzversagens und dessen Reversibilität unter Therapie.

Insgesamt wurden 125 Patienten/-innen, welche an der Kerckhoff-Klinik wegen einer CTEPH mittels PEA- (55) oder BPA-Therapie (70) behandelt wurden und am Studienzentrum eine 6- (nach BPA) oder 12- (nach PEA) Monats-Nachsorge absolvierten, in die Studie eingeschlossen. Die diagnostische und therapeutische Versorgung erfolgte nach einem etablierten Standard[25,47]. Alle Patienten/-innen gaben ihr schriftliches Einverständnis zur Teilnahme und die Studie wurde durch die Ethikkommission der Justus-Liebig-Universität Gießen (Aktenzeichen 43/14) bewilligt. Die Biomarker MR-proANP (BRAHMS, MR-proANP KRYPTOR Assay, Kryptor Compact Plus; BRAHMS GmbH, Henningsdorf, Deutschland) und Copeptin (BRAHMS Copeptin proAVP KRYPTOR Assay, Kryptor Compact Plus; BRAHMS GmbH, Henningsdorf, Deutschland) wurden zum Einschlusszeitpunkt, im Rahmen der Nachsorge und bei BPA-Patienten/-innen zusätzlich vor jeder BPA-Sitzung und nach Abschluss der Sequenz bestimmt. NT-proBNP (NT-proBNP Assay, Elecsys Analyzer2010, Roche Diagnostics, Mannheim, Germany) wurde als etablierter Referenzbiomarker zu den gleichen Zeitpunkten bestimmt.

Ergebnisse

Die MR-proANP-Spiegel korrelierten (ρ = Spearman's Rho) zum Einschlusszeitpunkt mit dem PVR (ρ = 0,51; p < 0.001), dem RAP (ρ = 0,51; p < 0,001), dem mPAP (ρ = 0,44; p < 0,001) und invers mit dem CI (ρ = -0,36; p < 0.001). Für das Copeptin zeigten sich keine relevanten Korrelationen zur Hämodynamik. Abbildung 5 und Abbildung 6 zeigen die Biomarkerkonzentrationen der Patientenkohorte, unterteilt in Terzile nach der Schwere der hämodynamischen Beeinträchtigung. Während sich für das MR-proANP eine stetige Erhöhung des Spiegels innerhalb der Terzile zeigt, findet sich eine Erhöhung der Copeptinkonzentration lediglich bei Patienten/-innen der oberen RAP-Terzile.

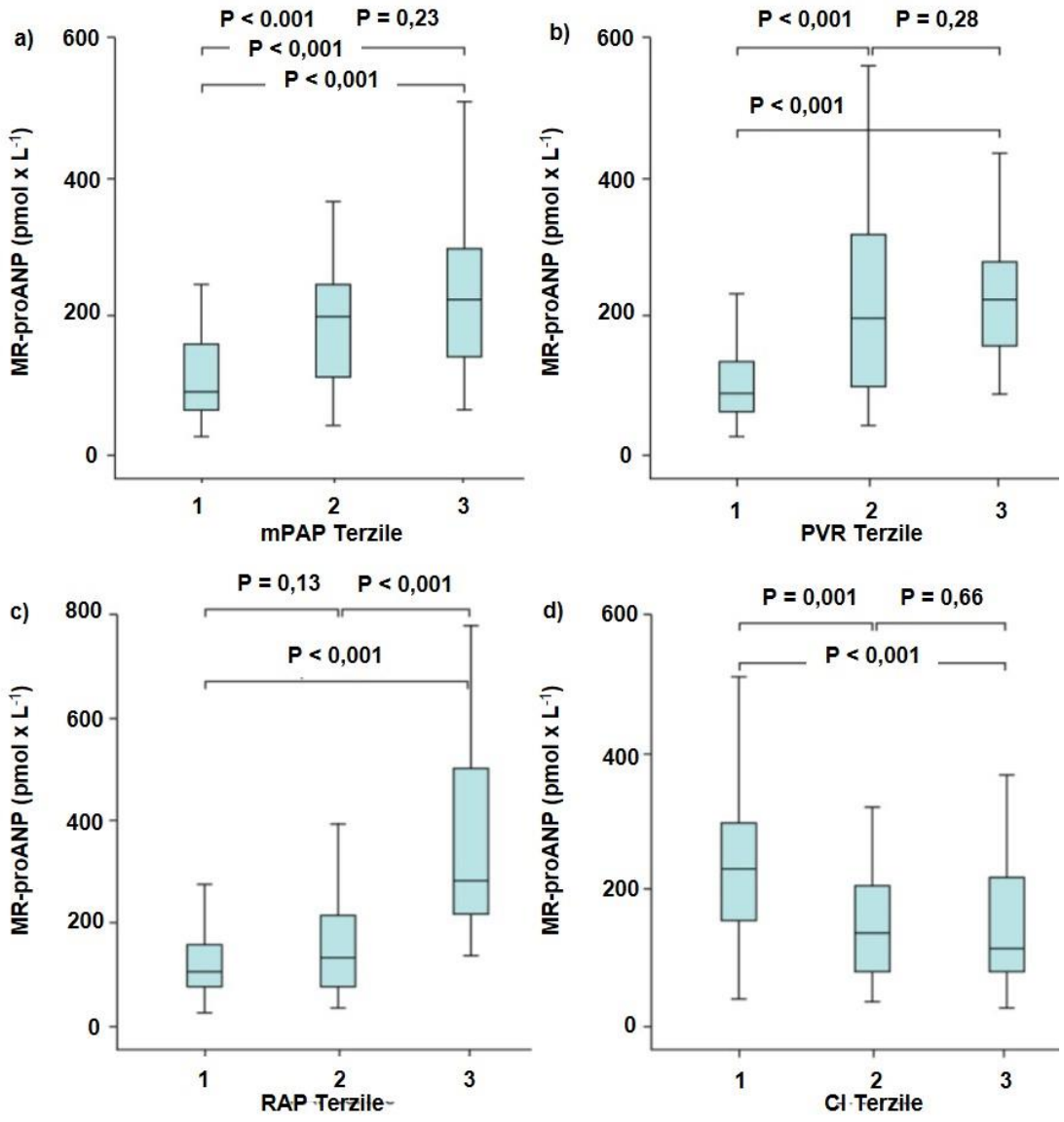

Abbildung 5: MR-proANP-Spiegel in Assoziation zu den hämodynamischen Parametern; Die Kohorte (N= 125) wurde unter Verwendung der folgenden Grenzwerte in Terzile unterteilt: mPAP (≤38/≤47mmHg), PVR (≤5.7/≤8.3WU), RAP (≤5/≤8mmHg), CI (≤2.1/≤2.7 L/min/m²)

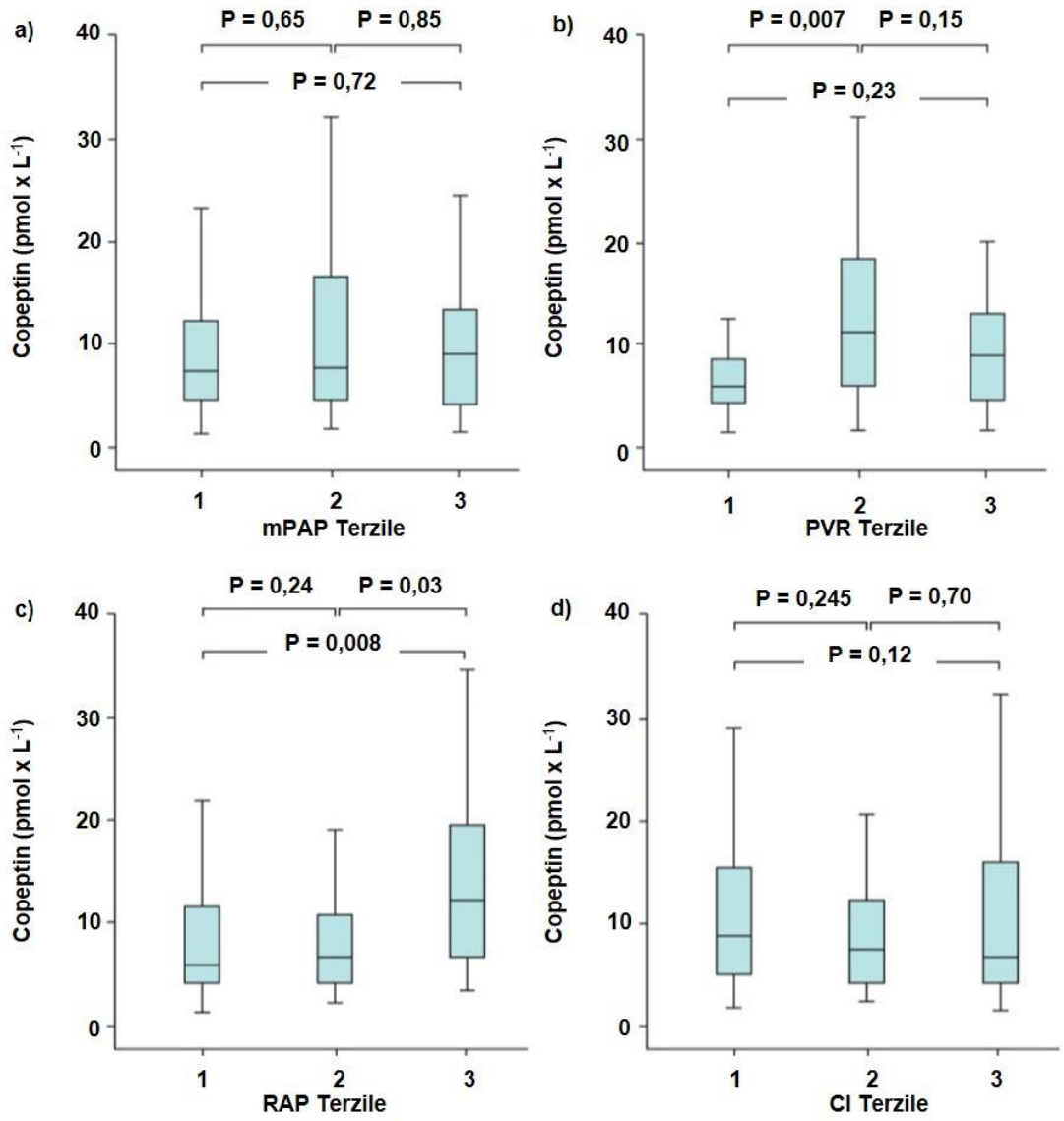

Abbildung 6: Copeptinspiegel in Assoziation zu den hämodynamischen Parametern; Die Kohorte (N= 125) wurde unter Verwendung der folgenden Grenzwerte in Terzile unterteilt: mPAP (≤38/≤47mmHg), PVR (≤5.7/≤8.3WU), RAP (≤5/≤8mmHg), CI (≤2.1/≤2.7 L/min/m²)

Patienten/-innen (N=17) mit einem fortgeschrittenen Erkrankungsstatus (Primärendpunkt: Kombination aus einem RAP ≥8 mmHg und einem CI ≤ 2,4 L/min/m²) wiesen signifikant höhere MR-proANP Spiegel im Median [320 (IQR 246-527) pmol/L vs. 133 (IQR 82-215) pmol/L; p = 0,001] und Copeptin Spiegel im Median [12,7 (IQR 7,3-20,6) pmol/L vs. 6,8 (IQR 4,4-12,8) pmol/L; p = 0,015] auf. Ein MR-proANP Spiegel ≥227 pmol/L [AUC 0,91; Odds ratio (OR) 56 (95% Konfidenzintervall 6,9 - 454,3] konnte als starker Indikator des Primärendpunktes (Kombination aus einem RAP ≥8 mmHg und einem CI ≤ 2,4 L/min/m²) identifiziert werden. Der Biomarker war in diesem

Kontext mindestens gleichwertig zum NT-proBNP und überlegen zu Copeptin, der Nierenfunktion und den klinischen Parametern (WHO-FC, 6-Minuten-Gehstrecke).

Die PEA-Therapie und BPA-Therapie führten zu einer signifikanten Verbesserung der klinischen (WHO-FC, 6-Minutengehstrecke) und hämodynamischen Parameter (PVR, mPAP) im Studienkollektiv. Erwähnenswert ist insbesondere die Reduktion des medianen RAP von 7 (5-9) mmHg auf 5 (4-7) mmHg ($p < 0,001$) und die Verbesserung des medianen CI von 2,4 (2,1 -2,8) L/min/m² auf 2,6 (2,3 -2,9) L/min/m² ($p = 0,009$).

Der mediane MR-proANP [156 (IQR 91-246) pmol/L vs. 99 (IQR 58-145) pmol/L; p< 0, 001] und Copeptin-Spiegel [7,7 (IQR 4,6-14,2) pmol/L vs. 6,3 (IQR 3,7-12,6) pmol/L; p = 0,009] zeigten sich im Rahmen der Nachsorge signifikant reduziert. Die Reduktion des Copeptin beschränkte sich auf die PEA-Kohorte und war im Betrag wenig substantiell. Abbildung 7 illustriert die dezidierte Expressionsdynamik des MR-proANP im Verlauf der sukzessiven Rechtsherzentlastung im Rahmen der BPA-Therapie.

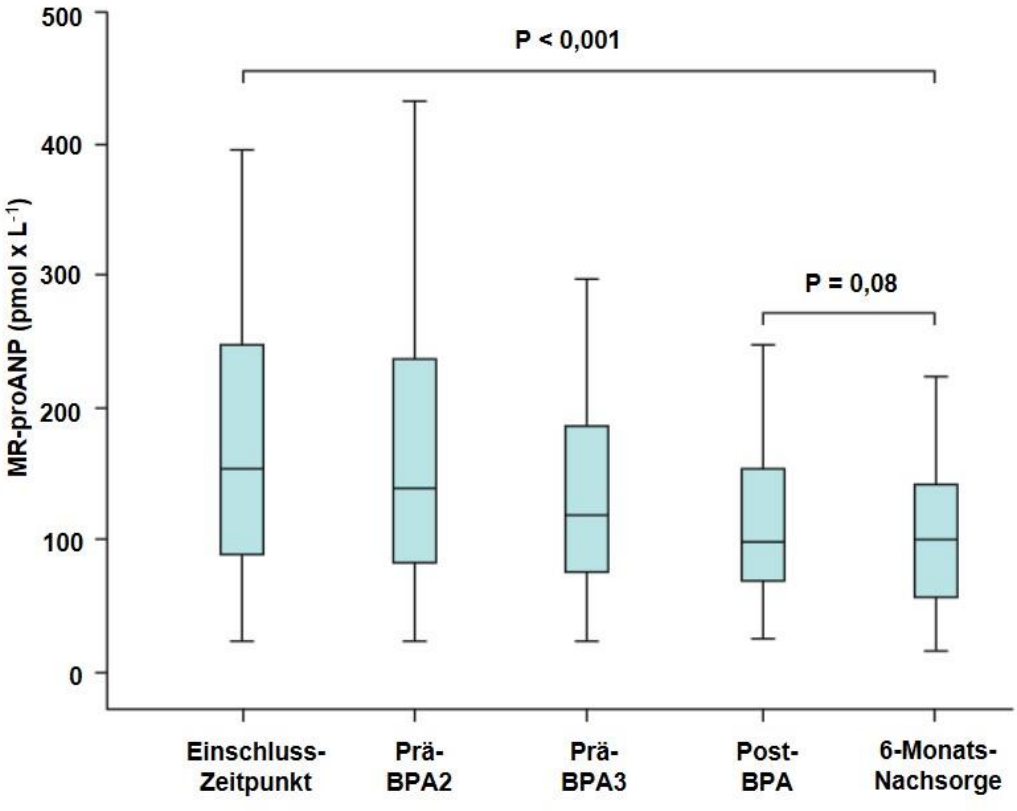

Abbildung 7: Dynamik des MR-proANP Spiegels unter der BPA-Therapie;

Patienten/-innen (N = 53) mit einem optimalen Therapieansprechen [Sekundärendpunkt: Normalisierung der pulmonalen Hämodynamik (mPAP ≤ 25mmHg, PVR ≤ 3 WU) und des RAP ≤ 6 mmHg oder eine signifikante Reduktion dieser Parameter (mPAP ≥ 25 %, PVR ≥ 35 %, RAP ≥ 25 %)] konnten anhand eines MR-proANP Spiegels ≤ 123 pmol/L [AUC 0.70; Odds Ratio 5.2 (95% CI 2.0-13.5)] im Rahmen der Nachsorge identifiziert werden.

Schlussfolgerung

Die Studienergebnisse identifizieren MR-proANP als Indikator der Krankheitsschwere und des Therapieerfolges bei Patienten/-innen mit einer CTEPH, welche eine Therapie mittels PEA oder BPA erhalten. Abgeleitet aus der atrialen Expressionslokalisation[50,63] und der Korrelation zum RAP kann MR-proANP insbesondere als Biomarker zur Quantifizierung der rechtsatrialen Belastung und des retrograden Rechtsherzversagens interpretiert werden. Copeptin zeigte keine relevante Korrelation zu den klinischen, hämodynamischen und funktionellen Parametern und keine substantielle Dynamik unter der Therapie bei CTEPH.

2.4 Dynamik des löslichen Supression-of-tumorigenicity-2, des Galectin-3 und des Growth/Differentiation Faktor-15 unter der CTEPH-Therapie (Publikation 4)

Studienrationale und Studiendesign

In der pathophysiologischen Sequenz der CTEPH kommt es zur Störung der Homöostase gleich mehrerer funktioneller Systeme im Organismus[9]. Die pulmonal vaskulären Veränderungen, die kardialen Anpassungsprozesse und die systemische Kreislaufbeeinträchtigung gehen mit systemischem Gewebestress einher[5,9]. Inflammation, Zellmigration, Zellapoptose und Fibrosierung sind Kernprozesse der maladaptiven Anpassungsprozesse bei der Antwort auf eine chronische Gewebeschädigung[9].

Soluble suppression of tumorigenicity 2 (sST2), Growth differentiation factor-15 (GDF-15) und Galectin-3 sind als Mediatoren an Stoffwechselprozessen in diesem Kontext beteiligt und wurden zuletzt u.a. im Kontext kardialer Erkrankungen als Biomarker analysiert[45,79]. sST2 ist als löslicher Rezeptor für Interleukin-33 an der Vermittlung dessen gewebeprotektiver, antiproliferativer, antifibrotischer sowie antiapoptotischer Effekte beteiligt und wird in Assoziation zu einer inflammatorischen Gewebeschädigung von zahlreichen Zelltypen (Endothel, Kardiomyozyten, glatte Muskelzellen) exprimiert[80–82]. Der Nachweis einer Überexpression von sST2 bei kardialen und pulmonalen Erkrankungen mit herausragenden Spitzenwerten im Rahmen einer Sepsis stützt die Hypothese eines inflammatorischen Sekretionsstimulus auch im Rahmen primär nichtinflammatorischer Erkrankungen[81,83]. GDF-15 gehört zur Superfamilie der transforming-growth-factors-β und wird in nahezu allen Zelltypen auf niedrigem Niveau exprimiert[79]. Eine gesteigerte Expression ist als Reaktion auf inflammatorische, mechanische und ischämische Gewebeschädigung im Rahmen vielfältiger Erkrankungen zu detektieren[79,84,85]. Der plasmatische GDF-15 Spiegel scheint dabei das zelluläre Stresslevel widerzuspiegeln. Ob GDF-15 dabei gewebeprotektive oder –schädigende Effekte hat und über welche Signalkaskaden diese vermittelt werden, ist nicht abschließend geklärt[79]. Galectin-3 ist ein β-Galaktoseidasebindendes Lektin, wird von zahlreichen Zelltypen (u.a. Monozyten und Endothelzellen) exprimiert und vermittelt durch eine Interaktion mit anderen zellulären

und nichtzellulären Bestandteilen der Extrazellulärmatrix dessen fibrotischen Umbau als Antwort auf eine inflammatorische Gewebeschädigung[86,87]. Bei chronischer Herzinsuffizienz sind die drei Biomarker zur Krankheitsschwere und Prognose assoziiert[88–90]. Die entsprechenden Leitlinien der American Heart Association empfehlen sST2 und Galektin-3 als Biomarker zur erweiterten Risikostratifikation[91]. Eine begrenzte Zahl von Studien hat die pathophysiologische Rolle und den diagnostischen Einsatz dieser Biomarker bei PH untersucht[82,92–97]. Deren Assoziation zur Krankheitsschwere und deren Dynamik unter einer Therapie bei CTEPH sind weitgehend unklar.

Die vorgelegte Studie (Publikation 4) analysierte die drei Biomarker im Kontext der CTEPH als Indikatoren einer chronischen, jedoch potentiell reversiblen Gewebeschädigung. In die Studie wurden 57 Patienten/-innen eingeschlossen, welche wegen einer inoperablen CTEPH eine BPA-Therapie erhielten und eine 6-Monats-Nachsorge absolviert haben. Vor dem Hintergrund limitierter Referenzwerte zu den drei Biomarkern bei PH wurde zusätzlich eine Kontrollkohorte gesunder Individuen (N=25) eingeschlossen. Gesund wurde definiert durch normwertige Konzentrationen für hs-cTnT und NT-proBNP, normwertige Befunde in der Echokardiographie sowie kein Diabetes mellitus, keine Lungenerkrankung, keine Tumorerkrankung und keine chronische inflammatorische Erkrankung in der Vorgeschichte. Alle Patienten/-innen gaben ihr schriftliches Einverständnis zur Teilnahme und die Studie wurde durch die Ethikkommission der Justus-Liebig-Universität Gießen (Aktenzeichen 43/14) bewilligt. Die BPA-Therapie und die begleitende Diagnostik erfolgte entsprechend des zuvor berichteten Standards[25,30]. Die Bestimmung der Biomarker erfolgte bei allen Studienteilnehmern zum Einschlusszeitpunkt und bei den CTEPH-Patienten/-innen zusätzlich im Rahmen der 6-Monats-Nachsorge. Die Analyse erfolgte mittels sST2 (Presage ST2 Assay, Critical Diagnostics, San Diego, CA, USA), galectin-3 (Human Galectin-3, Quantikine ELISA, R&D Systems, Abingdon, United Kingdom), GDF-15 (GDF-15 Assay, Quantikine ELISA, R&D Systems, Abingdon, United Kingdom), NT-proBNP (NT-proBNP Assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany).

Ergebnisse

Der Vergleich der Biomarkerkonzentrationen zum Einschlusszeitpunkt zeigte höhere Werte im Median für GDF-15 [CTEPH: 820 (IQR 556-1315) pg/ml vs. Kontrolle: 370 (IQR 314-516) pg/ml; p<0,001] und sST2 [CTEPH: 53,7 (IQR 45,3-74,1) ng/ml vs. Kontrolle: 48,7 (IQR 35,5-57,0) ng/ml; p=0,02] bei CTEPH-Patienten/-innen im Vergleich zur Kontrollgruppe. Kein Unterschied zeigte sich für Galectin-3 [CTEPH: 13,2 (IQR 10,4-16,8) ng/ml; vs. Kontrolle: 13,6 (IQR 10,8-16,0) ng/ml; p=0,91].

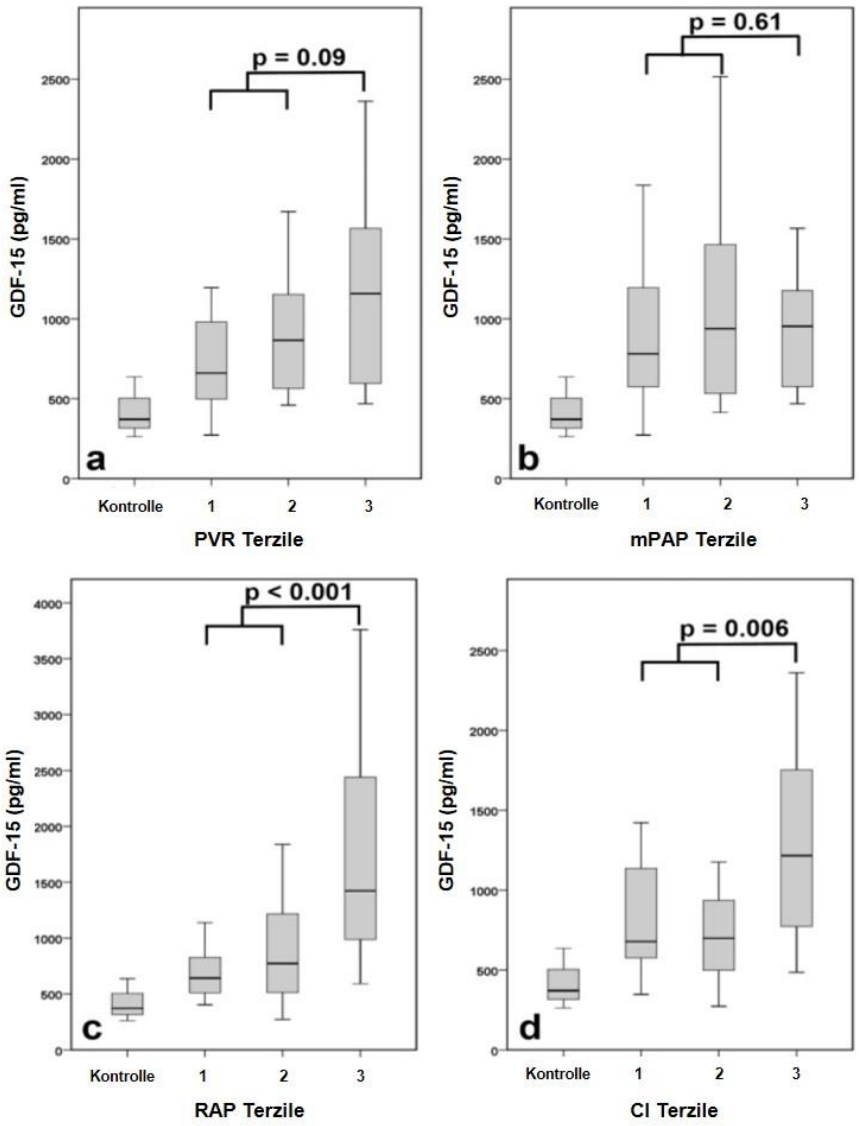

Abbildung 8: GDF-15 Spiegel in Assoziation zu den hämodynamischen Parametern; Die Kohorte (N= 57) wurde unter Verwendung der folgenden Grenzwerte in Terzile unterteilt: a) PVR (≤5,7/≤8,3WU), b) mPAP (≤38/≤47mmHg), c) RAP (≤5/≤8mmHg), d) CI (≤2,4/≤2,8 L/min/m²)

Die Studie untersuchte im nächsten Schritt die Assoziation der Biomarkerkonzentration zur Schwere der hämodynamischen Einschränkung. Abbildung 8 und Abbildung 9 zeigen die Verteilung der Biomarker in Patientensubgruppen mit zunehmender Schwere, unterteilt in Terzile und zusätzlich den Vergleich zur Kontrollkohorte.

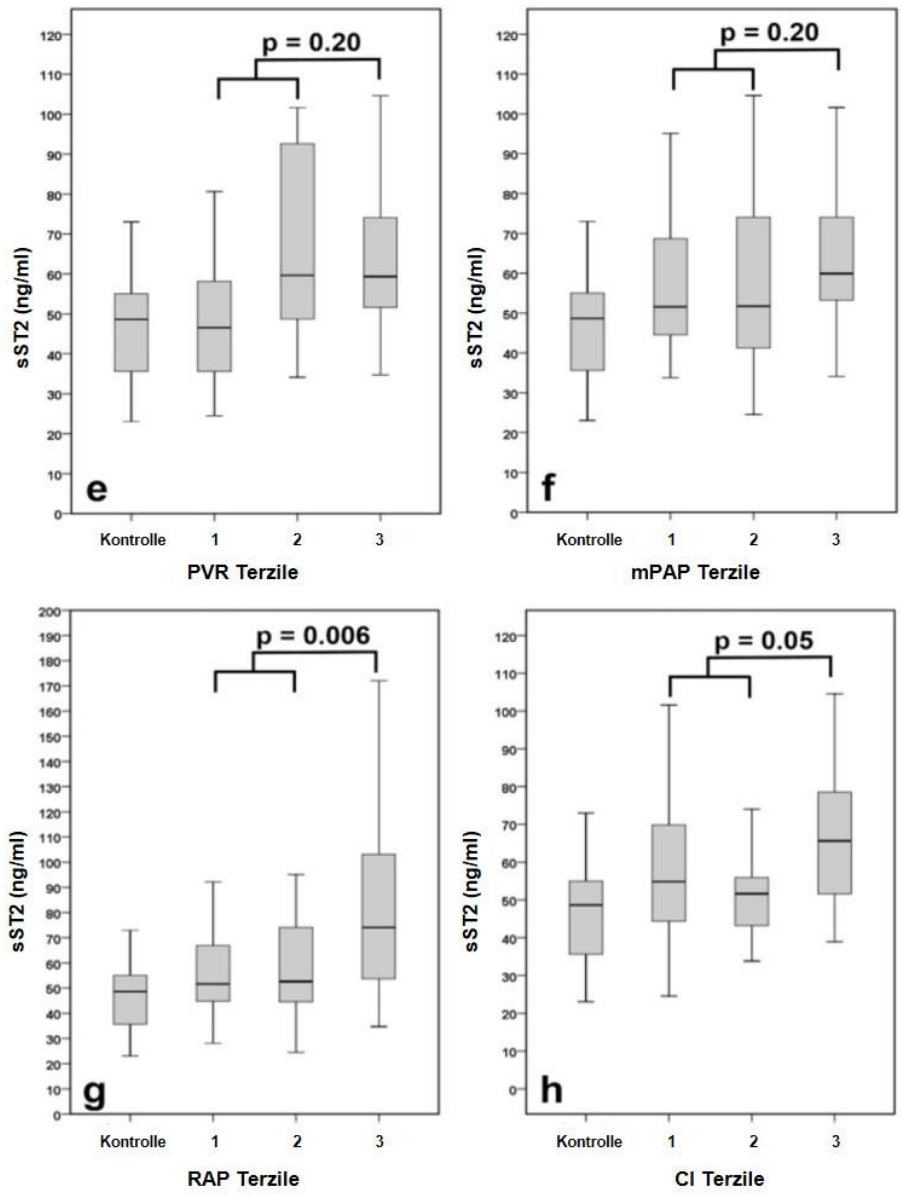

Abbildung 9: sST2 Spiegel in Assoziation zu den hämodynamischen Parametern;
Die *Kohorte (N= 57) wurde unter Verwendung der folgenden Grenzwerte in Terzile unterteilt:*
e) PVR (≤5,7/≤8,3WU), f) mPAP (≤38/≤47mmHg), g) RAP (≤5/≤8mmHg), h) CI (≤2,4/≤2,8 L/min/m²)

Patienten/-innen mit einer fortgeschrittenen Krankheitsschwere (N=6) [Primärendpunkt: RAP (>8mmHg) und CI (< 2,8L/min/m²) in der schlechtesten Terzile]

zeigten vergleichsweise höhere Konzentration des GDF-15 im Median [1964 (IQR 1344-3693) vs. 780 (IQR 533-1138) pg/ml; p=0,001], des sST2 [81,7 (IQR 62,5-109,1) vs. 53,3 (IQR 44,6-71,7) ng/ml; p=0,013] und des NT-proBNP [3445 (IQR 2186-4657) vs. 554 (IQR 147-1273) ng/L; p<0,001] ohne Unterschied bzgl. des Geschlechts (p=0,22) und des Alters (p=0,52).

Tabelle 1a illustriert das diagnostische Potential der Biomarker bei der Identifikation der Patienten/-innen mit fortgeschrittener Einschränkung der Hämodynamik.

Tabelle 1: Diagnostische Kennzahlen der Biomarker bei der Identifikation von Patienten/-innen mit fortgeschrittener hämodynamischer Beeinträchtigung (Primärendpunkt) sowie optimalem Therapieansprechen (Sekundärendpunkt)

a) Identifikation von Patienten/-innen mit fortgeschrittener hämodynamischer Beeinträchtigung (Primärendpunkt); N=6							
Biomarker	**Grenzwert**	**AUC (95% CI)**	**Sensitivität (%, 95% CI)**	**Spezifität (%, 95% CI)**	**NPV (%, 95% CI)**	**PPV (%, 95% CI)**	**OR (95% CI)**
GDF-15, pg/ml	1443	0,88 (0,77-0,99)	83 (36-100)	86 (74-94)	98 (87-100)	43 (26-62)	31 (3-310)
sST2, ng/ml	65	0,80 (0,66-0,95)	83 (36-100)	69 (54-81)	97 (85-100)	25 (16-36)	11 (1-101)
NT-proBNP, ng/L	1449	0,92 (0,85-0,92)	100 (54-100)	82 (69-91)	100	41 (28-55)	∞
b) Identifikation von Patienten/-innen mit optimalem Therapieansprechen (Sekundärendpunkt); N=17							
GDF-15, pg/ml	958	0,74 (0,61-0,89)	94 (71-100)	52 (36-68)	95 (75-99)	46 (38-55)	18 (2-146)
sST2, ng/ml	65	0,51 (0,35-0,68)	nicht berechnet	nicht berechnet	nicht berechnet	nicht berechnet	nicht berechnet
NT-proBNP, ng/L	77	0,71 (0,56-0,85)	59 (33-82)	75 (59-87)	81 (71-89)	50 (34-66)	4 (1-14)

Ein Modell zum Vergleich des NT-proBNP mit GDF-15 (AUC = 0,77) zeigte keinen zusätzlichen diagnostischen Nutzen zum NT-proBNP bei der Identifikation schwer erkrankter Patienten/-innen zum Einschlusszeitpunkt. [NT-proBNP vs. NT-proBNP + GDF-15 (p=0,22)].

Der Vergleich der Biomarkerspiegel zwischen dem Einschlusszeitpunkt und der 6-Monats-Nachsorge zeigte einen signifikanten Abfall des sST2 Spiegels [53,7 (IQR 45,3

-74,1) auf 48,1 (IQR 39,0-58,4) ng/ml; p≤0.001] jedoch nicht des GDF-15 Spiegels [820 (IQR 556 - 1315) vs. 893 (IQR 640-1293) pg/ml; p=0,73] und des Galectin-3 Spiegels [6,6 (IQR 5,2-8,4) vs. 6,6 (IQR 5,0-8,6) ng/ml; p=0.41].
Patienten/-innen welche die Kriterien eines optimalen hämodynamischen Ansprechens auf die BPA-Therapie erfüllten [Sekundärendpunkt: Normalisierung der pulmonalen Hämodynamik (mPAP ≤ 25mmHg, PVR ≤ 3 Wood Units) und des RAP ≤ 6 mmHg oder eine signifikante Reduktion dieser Parameter (mPAP ≥ 25 %, PVR ≥ 35 %, RAP ≥ 25 %)], zeigten niedrigere Spiegel für GDF-15 [646 (IQR 498-884) pg/ml vs. 968 (IQR 732-1474); p= 0.005) und des NT-proBNP [75 (IQR 31-186) ng/L vs. 140 (IQR 73-347) ng/L; p=0.013] als der Rest der CTEPH Kohorte.

Tabelle 1b illustriert die diagnostische Performance der Biomarker bei der Identifikation der Patienten/-innen mit optimalem Therapieansprechen im Sinne einer Normalisierung der pulmonalarteriellen Hämodynamik.

Schlussfolgerung

Die Studie dokumentierte erhöhte Serumspiegel für GDF-15 und sST2 bei CTEPH-Patienten/-innen im Vergleich zu einer gesunden Kontrollkohorte. Beide Biomarker waren darüber hinaus dazu geeignet, Patienten/-innen mit einer fortgeschrittenen Krankheitsschwere vor Therapiebeginn zu identifizieren. GDF-15 war darüber hinaus Indikator eines Therapieansprechens. Beide Biomarker zeigten bzgl. der Assoziation zu den hämodynamischen Zielgrößen keine Überlegenheit zum NT-proBNP. Trotzdem illustrieren die erhöhten Biomarkerspiegel zum Einschlusszeitpunkt und deren Abfall nach Therapie die chronische Gewebeschädigung unter der PH und Rechtsherzinsuffizienz sowie deren Rückgang/Reversibilität.

2.5 Pregnancy-associated plasma protein-A als Biomarker vaskulärer Umbauprozesse bei CTEPH (Publikation 5)

Studienrationale und Studiendesign

PAPP-A fungiert als Regulator des insulin-like growth factor/ insulin-like growth factor -binding-protein Signalweges durch Spaltung des insulin-like growth factor-binding-proteins[98]. Initial wurde PAPP-A als Biomarker im 1.Trimester Screening zur Detektion von Chromosomenanomalien etabliert. Inzwischen konnte insbesondere die Beteiligung an vaskulären inflammatorischen Umbauprozessen u.a. bei Atherosklerose und koronarer Herzerkrankung gezeigt werden[99]. PAPP-A wird in diesem Kontext als Promotor der Plaquebildung und inflammationsbedingten Plaquevulnerabilität vorgestellt[100]. Yang et al zeigten eine Aktivierung des insulin-like growth factor/ insulin-like growth factor -binding-protein Signalweges in glatten Muskelzellen und Endothelzellen bei neonataler PH unter experimenteller Hypoxie[101]. Eine Beteiligung an der Pathophysiologie der adulten PH und CTEPH wurde bisher nicht untersucht. Die vorgelegte Studie analysierte die Expressionscharakteristik des PAPP-A (PAPP-A Thermo Scientific, BRAHMS GmbH, Henningsdorf, Germany) bei 125 Patienten/-innen mit einer CTEPH (CTEPH-Kohorte der Studie in Publikation 3) im Vergleich zu einer Kontrollkohorte von Patienten/-innen (N= 58) mit einer PH anderer Genese. Darüber hinaus wurde die Dynamik des PAPP-A unter einer BPA- (N=70) oder PEA- (N=55) Therapie bis hin zu einer 6(BPA)-/12(PEA)-Monats-Nachsorge im Abgleich mit dem Referenzbiomarker NT-proBNP erfasst.

Ergebnisse

Der mediane PAPP-A Spiegel zum Einschlusszeitpunkt war in der CTEPH-Gruppe [13,8 (11,0-18,6) mU/L] geringfügig höher als in der Kontrollgruppe [12,6 (8,6-16,5) mU/L; p=0,05]. Innerhalb der CTEPH-Kohorte zeigte sich kein Unterschied zwischen Patienten/-innen mit einem operablen oder nicht operablen Befund (p=0,437). Die PAPP-A Werte korrelierten nicht substantiell mit der pulmonalen Hämodynamik [mPAP (r=0.120; p=0.188), PVR (r=0.013; p=0.893)] und dem NT-proBNP (r=0.128; p=0.169) der CTEPH-Patienten/-innen. Es zeigte sich allerdings eine moderate Korrelation zum Inflammationsparameter C-reaktives Protein (r=0.259; p=0.004).

Abbildung 10 a zeigt die Entwicklung der PAPP-A Spiegel mit einer signifikanten Reduktion sowohl in der PEA Gruppe [13,7 (10,4-17,6) vs. 11,4 (9,9-14,6) mU/L (p=0,003)] als auch der BPA Gruppe [14,5 (11,2-18,9) vs. 11,1 (9,8-12,9) mU/L (p<0,001)]. Abbildung 10 b Illustriert die sukzessive Dynamik des PAPP-A während der BPA-Stufen-Therapie im Vergleich zum NT-proBNP. Die Unterschiede in der Dynamik, mit einem signifikanten Abfall des NT-proBNP unmittelbar nach der ersten Prozedur und einem signifikanten PAPP-A Abfall erst nach der vierten Prozedur, legen unterschiedliche zugrundeliegende Auslöser der Sekretion nahe.

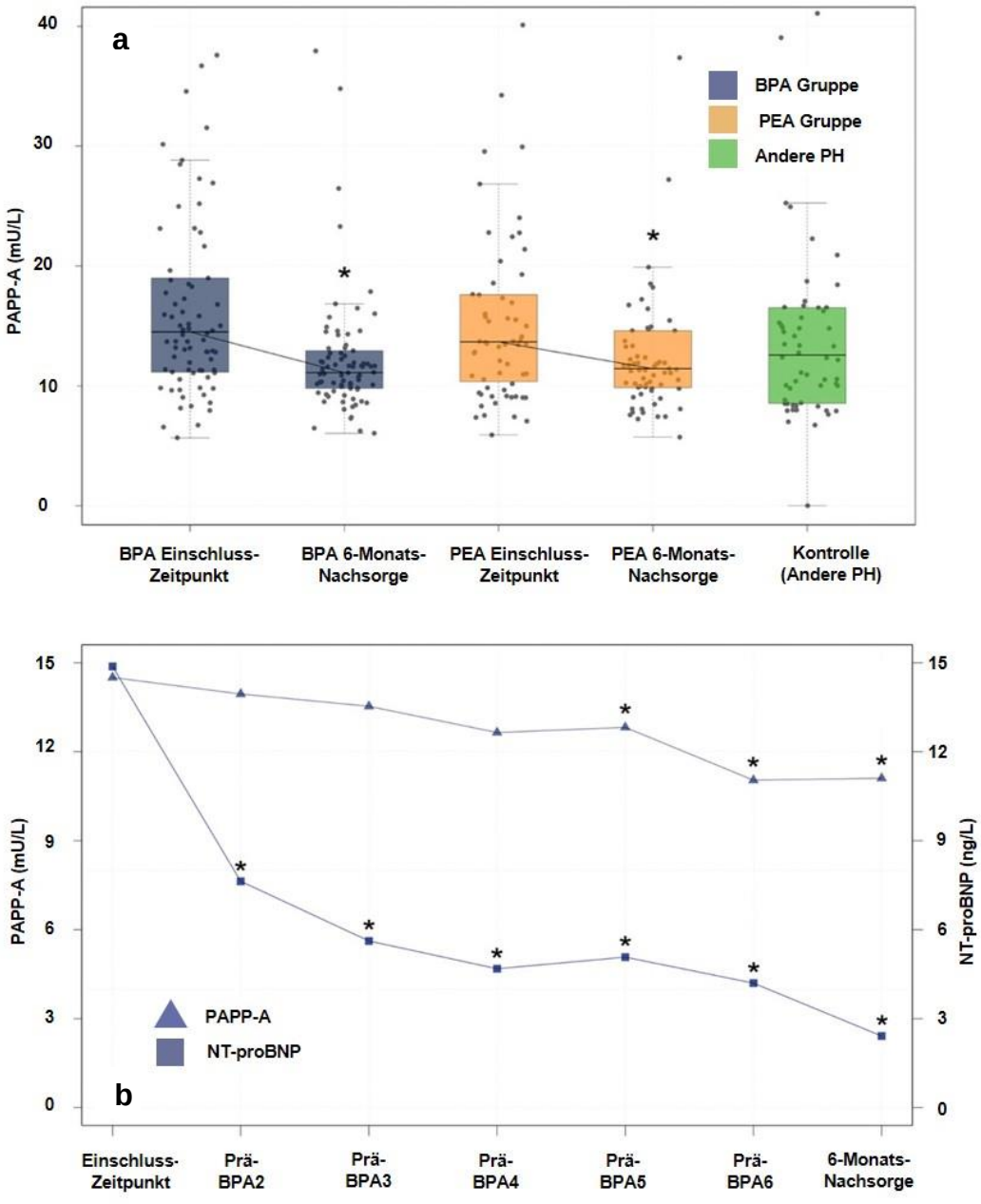

Abbildung 10: Vergleich der PAPP-A Spiegel vor und nach einer BPA-Therapie respektive der PEA-Therapie (a) und Darstellung der Dynamik der PAPP-A Spiegel unter einer BPA-Stufentherapie (b)

Schlussfolgerung

PAPP-A wurde als Promotor inflammationsgetragener vaskulärer Umbauprozesse identifiziert. Grundsätzlich spielen solche Prozesse auch bei der Pathophysiologie der CTEPH eine Rolle. Die gezeigten Daten unterstützen die Hypothese einer vermehrten Expression von PAPP-A bei pulmonaler Hypertonie, jedoch keine Spezifität für die CTEPH selbst. Die spezifische Therapie der CTEPH resultiert in einer Reduktion des PAPP-A Spiegels. Die Unterschiede zwischen der Kinetik des NT-proBNP als valider Indikator hämodynamischen Stresses und der des PAPP-A werfen jedoch Fragen nach den Expressionsmechanismen auf.

2.6 Dynamik der renalen Funktionsparameter unter der CTEPH-Therapie (Publikation 6)

Studienrationale und Studiendesign

Die systemische Malperfusion im Rahmen der progredienten Rechtsherzinsuffizienz bei PH führt zu Endorganschäden und metabolischen Veränderungen[64,102,103]. In diesem Kontext ist die chronische Niereninsuffizienz (CKD) eine häufige Komorbidität[104]. Die Manifestation der CKD ist ein negativer Prognoseprädiktor bei PH[64,103,105,106].

Es besteht eine limitierte Datenlage zu den Effekten einer BPA-Stufentherapie auf die chronische Nierenfunktion. In einzelnen Studien konnte eine BPA Therapie eine umfassende Verbesserung metabolischer Parameter, u.a. der Nierenfunktion, erzielen[102,107]. Im Kontext der BPA-Stufentherapie mit repetitiven Kontrastmittelgaben ist die Nierenfunktion auch aus prozeduraler Sicht von Interesse.
Ein kontrastmittelinduziertes Nierenversagen gehört zu den häufigen Komplikationen interventioneller kardiovaskulärer Eingriffe[108].

Diese Konstellation war der Auslöser für eine Analyse der Nierenfunktionsparameter in einer Kohorte von inoperablen CTEPH-Patienten/-innen, fokussiert auf mittelfristige Therapieeffekte und mögliche kurzfristige renale Komplikationen.
Die Studienkohorte entspricht dem Patientenkollektiv der Publikationen 1 & 2. Das Standardprozedere der BPA-Therapie am Studienzentrum beinhaltet neben einer

sorgfältigen Kontrastmittelrestriktion eine präventive periinterventionelle Nephroprotektion (dosierte Hydrierung, Acteylcystein, Schleifendiuretika, Elektrolytausgleich). Zur Detektion eines akuten Nierenversagens wurden die Nierenfunktionsparameter (Serumkreatinin, Serumharnstoff, eGFR) 24, 48 und 72 Stunden nach jeder Prozedur gemessen. Die Graduierung erfolgte nach den Stadien der Kidney Disease: Improving Global Outcomes (KDIGO). Die chronische Nierenfunktion wurde anhand der eGFR in die Chronic-Kidney-Disease(CKD)-Stadien der KDIGO eingeteilt[109].

Ergebnisse

Während einer BPA-Therapie wurde nach 6 von 265 Prozeduren (2,3%) ein akutes Nierenversagen, jeweils Grad 1 nach KDIGO-Skala, bei fünf verschiedenen Patienten/-innen beobachtet. Die betroffenen Patienten/-innen unterschieden sich nicht vom Rest hinsichtlich ihrer präprozeduralen Hämodynamik [mPAP (p = 0.75), PVR (p = 0,47)] und der Nierenfunktion [eGFR (p = 0,09), Serumkreatinin (p = 0,06), Serumharnstoff p = 0.13)]. Keiner der Patienten/-innen benötigte eine Dialysetherapie.

Die mediane eGFR vor Therapie lag bei 79.3 (IQR 59.0–93.9) mL/min/m². Diese korrelierte mit dem RAP (r_{rs}=0,44; p=0,002) und dem NT-proBNP-Spiegel (r_{rs}=0,50; p<0,001). Der Vergleich der Nierenfunktionsparameter zum Einschlusszeitpunkt und im Rahmen der Nachsorge zeigte keine generelle Dynamik in der Gesamtkohorte. Zum Einschlusszeitpunkt befanden sich 36 (71%) Patienten/-innen in einem CKD-Stadium ≥ 2. Bei diesen Patienten/-innen mit reduzierter Nierenfunktion zum Einschlusszeitpunkt zeigte sich ein signifikanter Anstieg der eGFR [69 (54–80) mL/min/m² vs. 74 (63–90) mL/min/m²; p= 0,004] und ein Abfall des Serumkreatinins [88,4 (79,2–105,6) mmol/L vs. 79,2 (70,4 –96,8) mmol/L; p=0.002] und des Serumharnstoffs [15,7 (12,3–18,4) mmol/L vs. 13,9 (11,8–17,1) mmol/L; p=0.043]. Allerdings gehörten auch beide, bei der 6-Monats-Nachsorge verstorbenen, Patienten/-innen (CKD-Stufe 2 und 3a) vor Therapie dieser Subkohorte an. Unter den Überlebenden zeigte sich die CKD-Stufe bei 41% verbessert, bei 56% statisch und bei 3% verschlechtert.

Schlussfolgerung

Die Studienergebnisse dokumentieren die hohe prozedurale Sicherheit der interventionellen BPA-Therapie in Bezug auf die Nierenfunktion. Dies galt unter dem angewendeten Protektionsregime in der Studienkohorte, insbesondere auch bei Patienten/-innen mit einer vorgeschädigten Nierenfunktion. Strategien zur Prävention eines periprozeduralen Nierenversagens sind nicht validiert. Eine Verbesserung der Nierenfunktion zeigte sich nur bei Patienten/-innen, welche zum Einschlusszeitpunkt vor der Therapie eine reduzierte Nierenfunktion aufwiesen. Die Korrelation der eGFR mit dem NT-proBNP und dem RAP zum Einschlusszeitpunkt stützt die These eines retrograden Rechtsherzversagens als zugrundeliegenden Mechanismus der CKD bei CTEPH.

2.7 Biomarker als Indikatoren der Rechtsherzfunktion bei CTEPH (Publikation 7)

Studienrationale und Studiendesign

In der pathophysiologischen Sequenz der CTEPH resultiert aus einer initial fokal beeinträchtigten pulmonalen Hämodynamik sukzessive eine Beeinträchtigung des gesamten Organismus[9,102]. Der entscheidende Promotor dieser Globalisierung ist die progrediente Dysfunktion und schließlich Dekompensation der Rechtsherzfunktion[9]. Unter der spezifischen Therapie einer PH ist die Regeneration des rechten Herzens der Verbesserung der pulmonalen Hämodynamik als Prognoseparameter überlegen[110]. Im Zuge der individuellen Risikostratifikation muss die Rechtsherzfunktion deshalb immer die führende Ziel- und Indikatorgröße sein.

In der folgenden Studie (Publikation 7) sollte untersucht werden ob nicht-invasive Biomarker eine diagnostische Wertigkeit bei der unmittelbaren Identifikation von Patienten/-innen mit reduzierter Rechtsherzfunktion oder deren insuffizienter Regeneration nach Therapie besitzen. Als Referenzmethode zur Bestimmung der rechtskardialen Dimensionen und Funktion diente das Kardio-MRT, der Goldstandard zur Erfassung der rechtskardialen Morphologie und Funktion[33]. Die Biomarkeranalyse umfasste NT-proBNP, MR-proANP, sST2 und PAPP-A. Insgesamt wurden 22 Patienten/-innen mit inoperabler CTEPH in die Studie eingeschlossen und sowohl zum

Einschluss- vor der BPA-Therapie als auch zum Nachsorgezeitpunkt ein Kardio-MRT erhielten. Die sonstige diagnostische und therapeutische Versorgung erfolgte entsprechend des am etablierten Standards[25,30]. Alle Patienten/-innen gaben ihr schriftliches Einverständnis zur Teilnahme und die Studie wurde durch die Ethikkommission der Justus-Liebig-Universität Gießen (Aktenzeichen 43/14) bewilligt. Zum Einschlusszeitpunkt und im Rahmen der 6-Monats-Nachsorge wurden die Biomarker NT-proBNP (NT-proBNP Assay, Elecsys Analyzer2010, Roche Diagnostics, Mannheim, Germany), MR-proANP (BRAHMS, MR-proANP KRYPTOR Assay, Kryptor Compact Plus; BRAHMS GmbH, Henningsdorf, Deutschland), sST2 (Presage ST2 Assay, Critical Diagnostics, San Diego, CA, USA) und PAPP-A (PAPP-A Thermo Scientific, BRAHMS GmbH, Henningsdorf, Germany) bestimmt. Die Abnahme des Probenmaterials erfolgte in enger zeitlicher Assoziation zum Kardio-MRT.

Ergebnisse

Die BPA-Therapie führte zu einer Verbesserung der pulmonalen Hämodynamik mit einem Abfall des mPAP im Median [41 (IQR 38-47) mmHg auf 32 (IQR28-37) mmHg, p<0,001], des PVR [7,7 (IQR 6,0-9,0) WU auf 4,7 (IQR 3,5-5,5) WU; p<0,001] und des RAP [6 (IQR 5-9) mmHg auf 5 (IQR 4-8) mmHg; p = 0,05]. Die Befunde des Kardio-MRT zum Einschlusszeitpunkt dokumentierten die bestehende morphologische und funktionelle Maladaptation des rechten Herzens (Tabelle 2).

Tabelle 2: Kardio-MRT Befunde vor und nach der BPA-Therapie

MRT-Parameter	**Einschluss**	**Nachsorge**	**p-Wert**
LVEDV, ml (IQR)	87 (81-99)	108 (95-130)	0,001
LVESV, ml (IQR)	33 (22-45)	37 (26-54)	0,08
LVEF, % (IQR)	65 (56-72)	65 (62-70)	0,12
RVEDV, ml (IQR)	192 (141-229)	143 (128-172)	0,002
RVEDV index, ml/m² (IQR)	100 (74-129)	84 (71-97)	0,001
RVESV, ml (IQR)	131 (73-157)	77 (61-99)	0,001
RVESV index, ml/m² (IQR)	76 (44-87)	46 (34-52)	<0,001

RVSV, ml (IQR)	66 (51-74)	73 (67-86)	0,003
RVSV index, ml/m² (IQR)	37 (28-43)	39 (35-51)	0,003
RVEF, % (IQR)	34 (28-41)	52 (41-54)	<0,001

Vor der BPA-Therapie wiesen 64% der Patienten/-innen eine schwer eingeschränkte RVEF, definiert durch einen Wert ≤35% auf. Diese Patienten/-innen zeichneten sich durch signifikant höhere Spiegel von NT-proBNP [RVEF ≤35%: 1427 (IQR 931-3377) ng/L vs. RVEF >35%: 214 (IQR 45-779) ng/L; p= 0,001], sST2 [RVEF ≤35%: 65,3 (IQR 51,7-96,8) ng/mL vs. RVEF >35%: 42,9 (39,0-50,7) ng/mL; p= 0,003], PAPP-A [RVEF ≤35%: 20,6 (IQR 14,9-29,5) mU/L vs. RVEF >35%: 13.0 (IQR 8,7-17,3) mU/L; p= 0,02] und MR-proANP [RVEF ≤35%: 261 (IQR 105-422) pmol/L vs. RVEF >35%: 122 (IQR 58-149) pmol/L; p= 0,04] aus.

Ein NT-proBNP Spiegel von 347 ng/L (AUC 0,91), ein MR-proANP Spiegel von 230 pg/L (AUC 0.,78), ein PAPP-A Spiegel von 14,5 mU/L (AUC 0,81) und ein sST2 Spiegel von 48,0 ng/ml (AUC 0,88) waren starke Indikatoren für eine schwer eingeschränkte RVEF. Kein Patient (N=4), bei dem alle vier Biomarker unter diesen Grenzwerten lag, zeigte eine RVEF ≤35% vor Therapie. Im Zuge der BPA-Therapie zeigte sich eine Reduktion der Spiegel aller vier Biomarker (Tabelle 3).

Tabelle 3: Biomarker Befunde vor und nach der BPA-Therapie

Biomarker	**Einschluss**	**Nachsorge**	**p-Wert**
NT-proBNP, ng/L (IQR)	1122 (295-2365)	149 (71-341)	<0,001
sST2, ng/mL (IQR)	52,6 (43,7-76,1)	44,7 (37,6-58,4)	0,002
PAPP-A, mU/L (IQR)	17,2 (13,1-28,6)	11,7 (10,3- 13,5)	0,006
MR-proANP, pmol/L (IQR)	145 (102-285)	125 (58-155)	0,002

Die relative Veränderung der RVEF nach Therapie korrelierte signifikant mit der relativen Dynamik von NT-proBNP, MR-proANP und sST2 jedoch nicht der des PAPP-A (Abbildung 11).

Insgesamt zeigten 59% der Patienten/-innen nach Therapie eine normalisierte RVEF ≥50%, jedoch auch 36% der Patienten/-innen keine signifikante Verbesserung, definiert als einen Anstieg <25%. Diese Patienten/-innen konnten durch die Dynamik der Biomarker NT-proBNP und MR-proANP identifiziert werden. Eine relative Reduktion der NT-proBNP-Konzentration < 53% (AUC 0,86) respektive des MR-proANP-Spiegels < 24% (AUC 0,82) war Indikator für das insuffiziente Therapieansprechen.

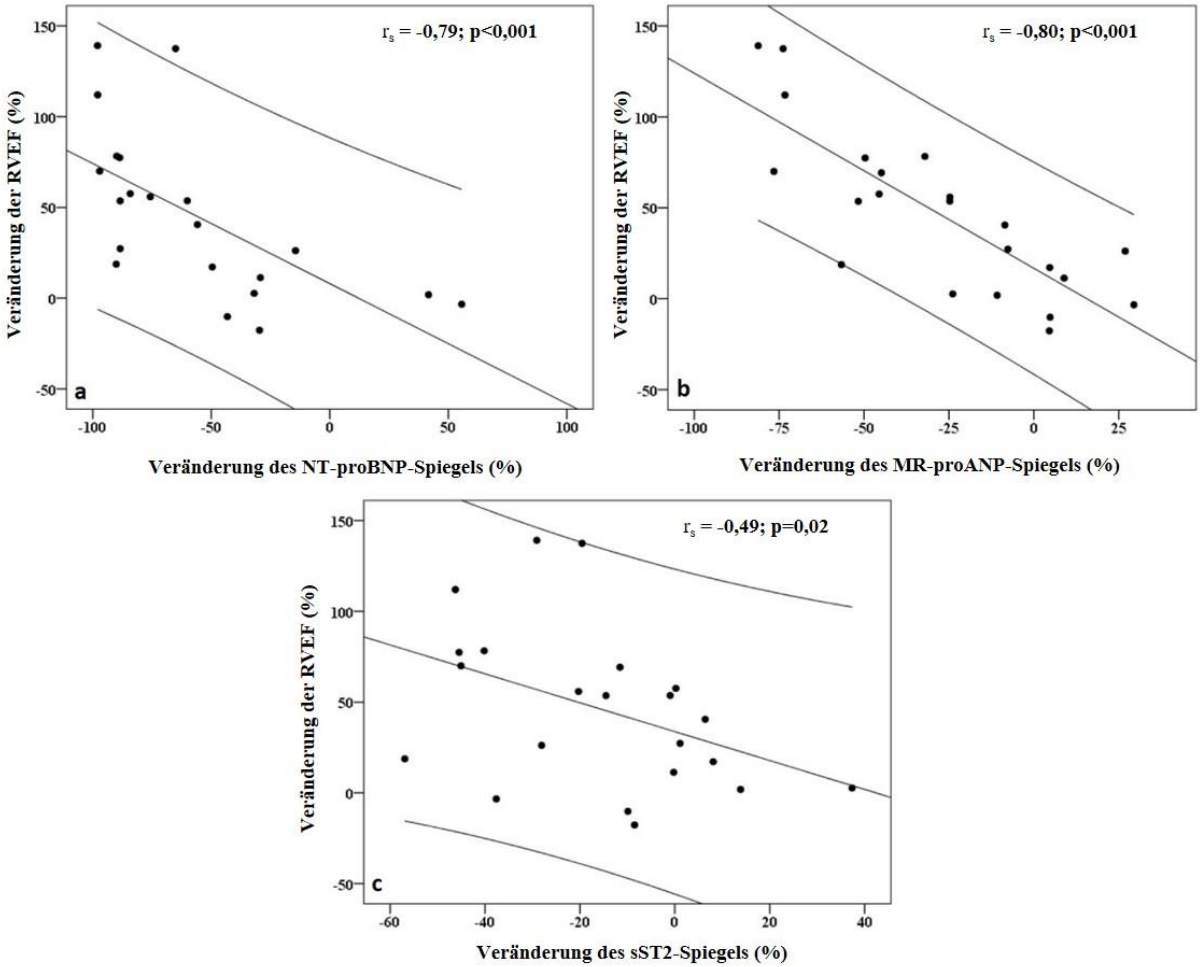

Abbildung 11: Korrelation zwischen der relativen Veränderung der Biomarkerspiegel und der RVEF

Schlussfolgerung

Die Studie bestätigte die morphologische und funktionelle Beeinträchtigung des rechten Herzens bei Patienten/-innen mit einer CTEPH und zeigte deren Regeneration bei einem Großteil der Patienten/-innen unter BPA-Therapie. Eine hochgradig reduzierten RVEF vor Therapie konnte durch die Bestimmung der Biomarker NT-proBNP, MR-proANP, sST2 und PAPP-A identifiziert respektive ausgeschlossen werden. Die Bestimmung der natriuretischen Peptide NT-proBNP und MR-proANP erlaubte die Identifikation von Patienten/-innen mit insuffizientem Therapieansprechen, gemessen an einer insuffizienten Erholung der RVEF.

3 Belastungsdiagnostik als neuer diagnostischer Ansatz

Die diagnostische Beurteilung der kardiopulmonalen Funktion in Ruhe liefert ein nur unvollständiges Bild der Krankheitsschwere kardiopulmonaler Erkrankungen[31]. Die Anwendung diagnostischer Verfahren unter Belastung rückt deshalb seit einigen Jahren zunehmend in den Fokus des klinischen und wissenschaftlichen Interesses. Insbesondere bei Patienten/-innen mit normalen oder grenzwertigen Befunden in Ruhe kann eine Belastungsdiagnostik helfen, funktionelle Einschränkungen zu demaskieren[31].

Der Belastungsrechtsherzkatheter (eRHK) ist der Goldstandard zur Erfassung dynamischer Veränderung der pulmonalen Hämodynamik unter körperlicher Belastung[31]. Nichtstandardisierte Untersuchungsprotokolle, limitierte Daten zu Norm-/Grenzwerten und der prognostischen Bedeutung bei unterschiedlichen Krankheitsentitäten begrenzen derzeit noch den routinemäßigen Einsatz des eRHK[31]. Die European Respiratory Society sieht potentielle Einsatzgebiete bei der Graduierung von Herzklappenvitien sowie bei der Differenzierung, Risikostratifizierung und Monitoring unterschiedlicher PH Formen[31]. Dieser Empfehlung folgend wurde in den folgenden Publikationen der Einsatz des eRHK zum einen im Kontext einer Mitralklappeninsuffizienz und zum anderen bei Patienten/-innen mit einer CTEPH untersucht.

3.1 Belastungsrechtsherzkatheter im Kontext kardiopulmonaler Erkrankungen (Publikation 8)

Studienrationale und Studiendesign

Die erfolgreiche Anwendung einer interventionellen Therapie bei Mitralklappeninsuffizienz setzt eine adäquate Patientenselektion voraus[111,112]. Eine Mitralklappeninsuffizienz kann sich unter körperlicher Belastung dynamisch zeigen und in diesem Rahmen in unterschiedlicher Intensität auch die pulmonale Hämodynamik beinträchtigen[113]. Inwiefern die Erfassung der pulmonalen Hämodynamik unter Belastung bei der Patientenselektion bzgl. einer interventionellen Therapie nützlich sein kann, ist nicht bekannt. Die vorgelegte Studie evaluiert den

Zusammenhang zwischen im eRHK erhobenen Befunden der pulmonalen Hämodynamik und dem Ansprechen auf eine interventionelle Therapie bei Patienten/-innen mit einer schweren Mitralklappeninsuffizienz.

Insgesamt wurden 68 Patienten/-innen in die Studie eingeschlossen, die an der Kerckhoff-Klinik wegen einer hochgradigen MI mit einem interventionellen Therapieverfahren (66 Patienten/-innen mit Edge-to-Edge-Repair, zwei Patienten/-innen mit Cardioband) zwischen 2014 und 2017 behandelt wurden. Die Patienten/-innen erhielten vor der interventionellen Therapie zusätzlich zur standardisierten Diagnostik (u.a. klinische Untersuchung, Labordiagnostik, Echokardiographie) einen eRHK. Die Befunde des eRHK wurden mit den Studienendpunkten Überleben (primärer Endpunkt) und Symptomverbesserung (Abfall der NYHA Klasse um ≥1 Stufe) nach Therapie assoziiert. Alle Patienten/-innen gaben ihr schriftliches Einverständnis zur Teilnahme und die Studie wurde durch die Ethikkommission der Landesärztekammer Hessen (Nr. FF79/2010) und die Justus-Liebig-Universität Gießen (Aktenzeichen 36/14) bewilligt.

Ergebnisse

Die Studienkohorte umfasste 44 Patienten/-innen mit einer sekundären und 24 Patienten/-innen mit einer primären hochgradigen und symptomatischen Mitralklappeninsuffizienz. Insgesamt wiesen 74% der Patienten/-innen eine PH und 47% einen PVR >3 WU auf. Während des Rechtsherzkatheters erfolgte eine körperliche Belastung über im Median 5 (4,5 -7,5) min mit einer Intensität von 12 (0-25) Watt. Unter der Belastung zeigte sich ein deutlicher Anstieg des PAWP (20 ± 6 mmHg auf 33 ± 8 mmHg), der PAWP-V-Welle [28 ± 10 mmHg auf 48 (40-54) mmHg] und aller pulmonalen Druckwerte.

Im Nachsorgezeitraum, von 19 (9-32) Monaten, verstarben 22 (32%) der Patienten/-innen. Abbildung 12 zeigt das Ergebnis der Überlebenszeitanalyse. Zahlreiche hämodynamische Parameter, ein geringer Anstieg der PAWP V-Welle, des mPAP, des PAWP, des CI sowie ein hoher RAP zeigten eine Assoziation zur Mortalität. In der ROC-Analyse zeigte ein Anstieg der PAWP V-Welle ≥ 17mmHg (AUC 0,79 [95%-KI, 0,67–0,92]) unter Belastung die stärkste Assoziation zum Überleben. Dies konnte in der Cox-Regressionsanalyse (hazard ratio, 0,11 [95%-KI, 0,04–0,33], P<0,001) und

der Kaplan-Meier-Analyse bestätigt werden. Ein Anstieg der PAWP V-Welle ≥15mmHg (AUC 0,84 [95%-KI, 0,74–0,95]) und des kardialen Auswurfs (CO) ≥0,9L/min (AUC, 0,69 [95%-KI, 0,55–0,82]) waren darüber hinaus mit einer Verbesserung der NYHA Klasse assoziiert (Abbildung 13).

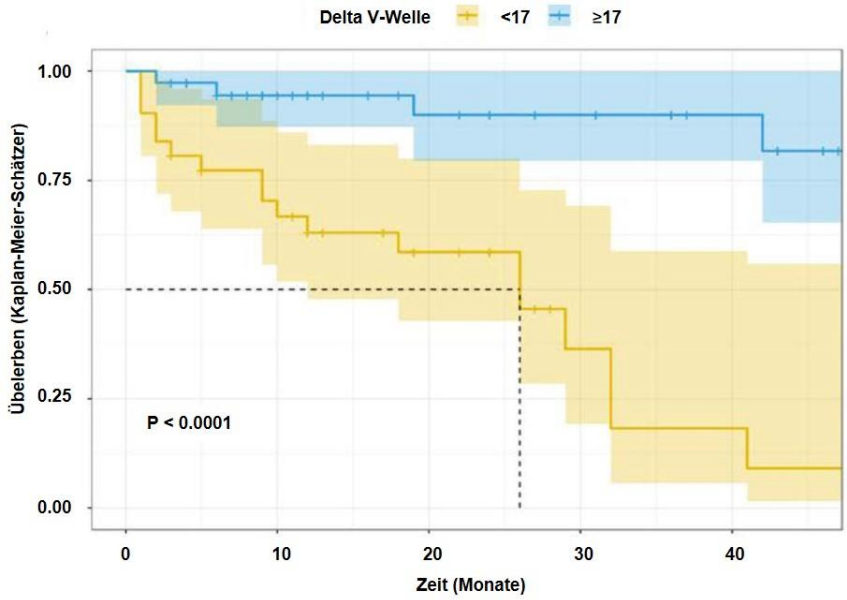

Abbildung 12: Überlebenszeitanalyse für Patienten/-innen mit einem Anstieg der PAWP-V-Welle über 17mmHg im Vergleich zu Patienten/-innen mit einem Anstieg unter 17mmHg (Kaplan-Meier-Analyse)

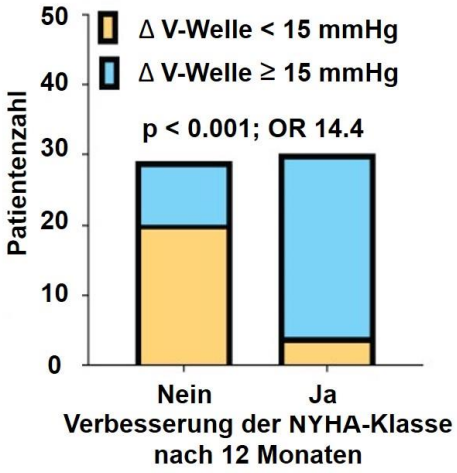

Abbildung 13: Therapieeffekt der interventionellen Mitralklappentherapie, gemessen an der Verbesserung der NYHA-Klasse um min. 1 Stufe – Vergleich zwischen Patienten/-innen mit einem Anstieg der PAWP-V-Welle unter oder über 15mmHg

Schlussfolgerung

Die vorgelegte Studie demonstriert den erfolgreichen Einsatz des eRHK als diagnostisches Verfahren zur Erfassung der Veränderung der pulmonalen Hämodynamik unter einer Mitralklappeninsuffizienz. Der belastungsinduzierte pulmonale Rückstau, einhergehend mit einem Anstieg der pulmonalen Druckwerte zeigt die hämodynamische Relevanz der schweren Mitralklappeninsuffizienz. Der Anstieg der pulmonalen Druckwerte konnte jedoch auch als kontraktile Reserve des linken Ventrikels und als positiver Prognoseprädiktor identifiziert werden.

3.2 Anwendung des Rechtsherzkatheters unter Belastung im Kontext der inoperablen CTEPH (Publikation 9)

Studienrationale und Studiendesign

Die BPA bei inoperabler CTEPH geht mit einer signifikanten Erholung der pulmonalen Hämodynamik in Ruhe einher[25,27–29,55,114]. Die Mehrheit der Patienten/-innen berichtet in diesem Zuge auch eine Reduktion der klinischen Symptomatik. Trotz deutlich verbesserter oder sogar normalisierter hämodynamischer Zielgrößen in Ruhe berichtet ein Teil der Patienten/-innen über fortbestehende Symptome einer PH unter Exposition zur Alltagsbelastung[25,27–29,55,114].

Ob persistierende Symptome bei Patienten/-innen mit regelrechten Befunden in Ruhe, nach abgeschlossener BPA-Therapie womöglich belastungsabhängige Exazerbationen der pulmonalen Hämodynamik unterliegen, ist nicht bekannt. Es existieren keine Daten zu den Effekten einer BPA-Therapie auf die Befunde des eRHK. Dies war Grundlage für die vorgelegte Studie.

In die Studie wurden 64 Patienten/-innen eingeschlossen, wegen einer inoperablen CTEPH eine BPA-Therapie erhalten, dort eine 6-Monats-Nachsorge absolviert und zu beiden Zeitpunkten einen eRHK erhalten haben. Im Rahmen des eRHK wurden die folgenden hämodynamischen Zielgrößen und deren Dynamik erfasst: PVR, CI = Cardiac output (CO) / Körperoberfläche, Totaler pulmonaler Widerstand (TPR) = mPAP/CO, Pulmonalarterielle Compliance (PAC) = (CO/ Herzfrequenz) / (PAPs – PAPd), transpulmonaler Gradient (TPG) = mPAP – PAWP; diastolischer pulmonaler

Gradient (DPG) = PAPd – PAWP; Slope des mPAP/CO Verhältnisses, Slope des Schlagvolumens = CO/Herzfrequenz.

Ein mPAP >30mmHg und ein TPR >3 WU unter Belastung ist als pathologische Reaktion der pulmonalen Hämodynamik bzw. als Belastungs-PH anerkannt[31].

Alle Patienten/-innen gaben ihr schriftliches Einverständnis zur Teilnahme und die Studie wurde durch die Ethikkommission der Justus-Liebig-Universität Gießen (Aktenzeichen 43/14) bewilligt. Die BPA-Therapie und die begleitende Diagnostik erfolgte entsprechend des zuvor berichteten, am Studienzentrum etablierten Standardprozedere.

Ergebnisse

Die BPA-Therapie ging mit einer signifikanten Verbesserung der hämodynamischen Zielgrößen sowohl in Ruhe als auch unter Belastung einher (Tabelle 4)

Tabelle 4: Vergleich der hämodynamischen Befunde in Ruhe und unter Belastung vor und nach einer BPA-Therapie

Hämodynamische Befunde in Ruhe					
	Vor BPA-Therapie		**Nach BPA-Therapie**		
	N = 64	Mittelwert ± SD	N = 64	Mittelwert ± SD	P-Wert
RAP, mmHg	64	7 ± 4	64	5 ± 2	<0,0001
mPAP, mmHg	64	41 ± 9	64	31 ± 9	<0,0001
PAPs, mmHg	64	70 ± 16	64	52 ± 16	<0,0001
PAPd, mmHg	63	23 ± 6	64	16 ± 6	<0,0001
PAWP, mmHg	63	10 ± 2	64	9 ± 3	0,335
DPG, mmHg	62	13,6 ± 6,2	57	6,6 ± 5,8	<0,0001
TPG, mmHg	63	31,8 ± 8,9	64	21,3 ± 8,4	<0,0001
CO, L/min	63	4,9 ± 1,2	64	5,1 ± 1,0	0,068
CI, L/min/m²	64	2,6 ± 0,6	64	2,7 ± 0,5	0,138
PVR, WU	63	6,8 ± 2,3	64	4,3 ± 1,9	<0,0001
TPR, WU	63	8,9 ± 2,5	64	6,2 ± 2,1	<0,0001
PAC, ml/mmHg	63	1,5 ± 0,6	64	2,3 ± 0,9	<0,0001
HF, Schläge/min	63	77 ± 13	64	71 ± 12	<0,0001
SV, ml	63	66 ± 19	64	73 ± 15	<0,0001

Hämodynamische Befunde unter Belastung					
Belastung, W	64	27 ± 14	64	28 ± 15	0,187
RAP, mmHg	64	15 ± 7	64	11 ± 5	<0,0001
mPAP, mmHg	64	62 ± 11	64	52 ± 11	<0,0001
PAPs, mmHg	64	102 ± 22	64	86 ± 20	<0,0001
PAPd, mmHg	63	33 ± 8	64	26 ± 4	<0,0001
PAWP, mmHg	58	14 ± 7	63	15 ± 4	0,164
DPG, mmHg	57	18,5 ± 10,7	63	11,5 ± 7,0	<0,0001
TPG, mmHg	58	48,1 ± 13,7	63	37,3 ± 11,3	<0,0001
CO, L/min	62	7,0 ± 2,0	63	8,3 ± 2,0	<0,0001
CI, L/min/m²	62	3,8 ± 1,1	63	4,4 ± 1,1	<0,0001
PVR, WU	56	8,0 ± 4,4	63	5,0 ± 2,4	<0,0001
TPR, WU	62	9,6 ± 3,0	63	6,7 ± 2,5	<0,0001
PAC, ml/mmHg	62	0,9 ± 0,8	63	1,5 ± 0,6	<0,0001
HF, Schläge/min	63	104 ± 15	64	101 ± 15	0,022
mPAP/CO-slope, WU	62	11,2 ± 25,6	63	7,7 ± 4,1	<0,0001
SV, ml	62	69 ± 22	64	83 ± 21	<0,0001

Insbesondere der TPR und der Slope des mPAP/CO Verhältnisses zeigten sich nach erfolgter BPA-Therapie signifikant reduziert. Die 14 (22%) Patienten/-innen mit einem mPAP <25mmHg in Ruhe nach BPA-Therapie zeigten eine deutliche Reduktion des Slopes des mPAP/CO Verhältnisses von 8,6 (6,3 – 11,3) WU auf 5,7 (4,8 – 8,1) WU. Trotzdem erfüllten alle Patienten/-innen nach abgeschlossener interventioneller Therapie weiterhin die Kriterien einer Belastungs-PH.

Schlussfolgerung

Die vorgelegte Studie beschreibt erstmalig die positiven Effekte der BPA-Therapie auf die Hämodynamik, wiedergegeben durch die Befunde des eRHK bei Patienten/-innen mit einer inoperablen CTEPH. Die Ergebnisse illustrieren aber auch, dass die Erfassung der Hämodynamik in Ruhe den Umfang der hämodynamischen Beeinträchtigung unterschätzt. Die Erkenntnis, dass alle Patienten/-innen nach

abgeschlossener interventioneller Therapie weiterhin eine Belastungs-PH aufweisen, verdeutlicht die Notwendigkeit eines fortgesetzten klinischen Monitorings und wirft die Frage nach Modifikationen des langfristigen Therapieregimes auf.

3.3 Belastungsbiomarker – ein neues Konzept im Kontext der Rechtsherzinsuffizienz (Publikation 10)

Studienrationale und Studiendesign

Der RAP ist ein Indikator für die rechtsventrikuläre Füllung. Ein erhöhter RAP in Ruhe[3,64,115–119] oder dessen Anstieg unter körperlicher Belastung ist ein Indikator für eine Rechtsherzdysfunktion[120,121]. Der eRHK ist das einzige Verfahren zur exakten Quantifizierung des RAP unter körperlicher Belastung[31]. Der Biomarker MR-proANP korreliert bei CTEPH mit dem RAP in Ruhe (Publikation 3). Es existieren keine Daten dazu, ob eine Bestimmung von MR-proANP unter körperlicher Belastung auch eine Dynamik des RAP unter Belastung abbilden kann.

In Publikation 10 wurde bei Patienten/-innen mit einer CTEPH die Dynamik des RAP unter körperlicher Belastung als Indikator eines belastungsinduzierten Rechtsherzversagens evaluiert. Darüber wurde das neue Konzept einer belastungssimultanen Bestimmung des MR-proANP zur Erfassung der RAP Dynamik untersucht. In die Studie wurden, deren schriftliche Einwilligung vorausgesetzt, 100 Patienten/-innen mit einer CTEPH (n = 88) oder einer CTED (n = 12) eingeschlossen, welche an der Kerckhoff-Klinik zwischen 01 und 10/2021 eine Belastungs-RHK Untersuchung erhalten haben. Die Patienten/-innen wurden im Vorfeld und Nachgang der eRHK zu einer zweistündigen Phase körperlicher Ruhe verpflichtet. Die Blutabnahmen zur Biomarkerbestimmung erfolgten in Ruhe unmittelbar vor dem eRHK, während der maximalen Belastung, nach Rückkehr zur Ruhehämodynamik und nach zwei Stunden Erholung in Ruhe. Der Rechtsherzkatheter erfolgte in standardisierter Art, während einer körperlichen Belastung mittels Fahrradergometrie. Die Bestimmung des MR-proANP erfolgte mittels TRACE (time-resolved amplified cryptate emission) Technologie (B·R·A·H·M·S MR-proANP KRYPTOR Assay, Kryptor Compact Plus, B·R·A·H·M·S GmbH, Hennigsdorf, Deutschland).

Ein Ruhe RAP ≤ 7mmHg wurde als normwertig definiert. In Orientierung an das Risikostratifikationsmodell der europäischen Leitlinien zur PH wurde ein RAP zwischen 8 und 14 mmHg als moderat und ein RAP >14mmHg als schwer erhöht eingestuft. Mangels eines allgemeingültigen Grenzwertes jedoch unter Würdigung der existierenden Literatur, wurde ein RAP unter Belastung (eRAP) >15mmHg als pathologisch und hinweisend für ein belastungsinduziertes Rechtsherzversagen gewertet.

Ergebnisse

Während der körperlichen Belastung über 8 (7-11) min stieg der mittlere RAP von 6 ± 4 mmHg auf 16 ± 7 mmHg (p<0.001) an. Dabei zeigten sich unterschiedliche Muster der Dynamik in den Subkohorten mit normwertigem, moderat und schwer erhöhtem Ruhe-RAP (Abbildung 14). In Summe zeigten 51 Patienten/-innen unter der Belastung einen pathologisch erhöhten eRAP.

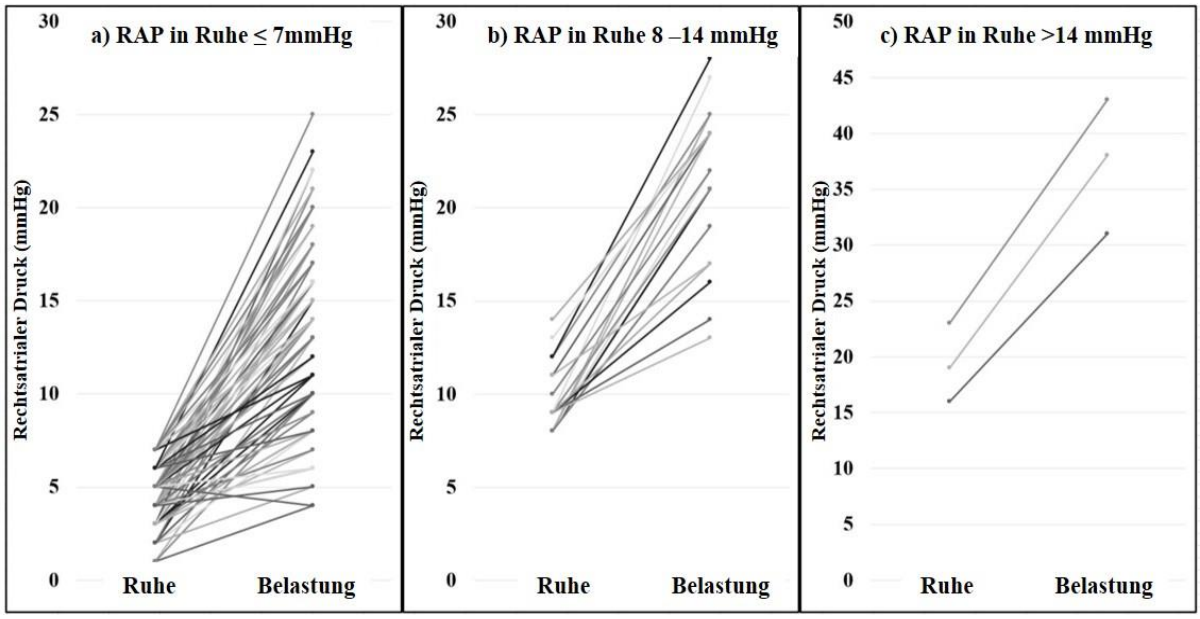

Abbildung 14:Dynamik des RAP unter Belastung bei Patienten/-innen mit normalem (a), moderat erhöhtem (b) und schwer erhöhtem (c) RAP in Ruhe

Der MR-proANP Spiegel zum jeweiligen Zeitpunkt korrelierte mit den Messwerten des RAP in Ruhe (rs =0,61; p <0,001) und dem eRAP während der maximalen Belastung (rs= 0,66; p<0,001), ebenso wie die relative Veränderung des RAP und MR-proANP Spiegels (rs= 0,52; p<0,001) (Abbildung 15).

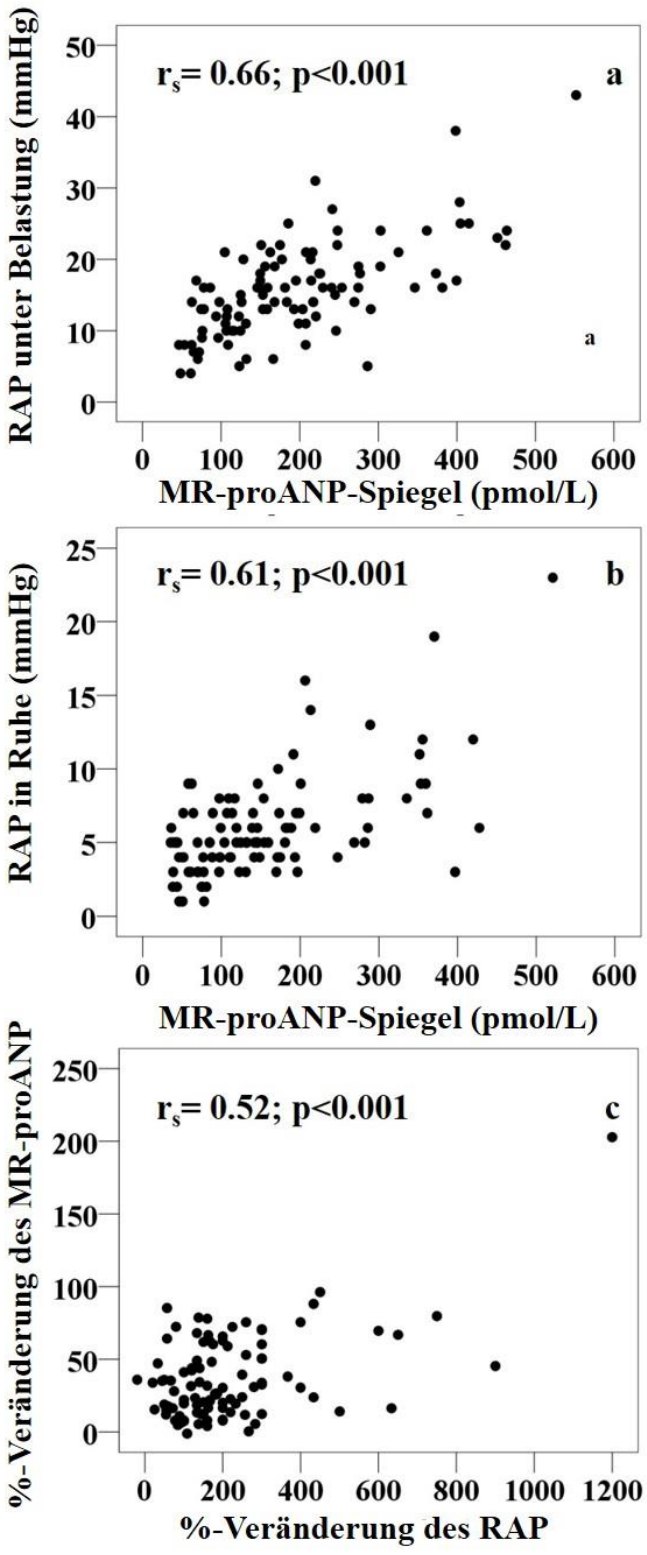

Abbildung 15: Korrelation zwischen dem MR-proANP Spiegel und dem RAP in Ruhe (a) und unter Belastung (b) sowie zwischen der relativen Veränderung der beiden Parameter (c)

Sowohl die Spitzenwerte des MR-proANP [226 (IQR 163-347) pmol/L vs. 123 (IQR 77-196) pmol/L; p<0,001)] als auch die Werte nach zwei Stunden Erholung [204 (IQR 141-290) pmol/L vs. 94 (IQR 65 -150) pmol/L; p<0,001] waren bei Patienten/-innen mit einem pathologischen eRAP >15mmHg deutlich erhöht.

Die Ergebnisse der multiplen linearen Regressionsanalyse zeigten eine starke Assoziation des MR-proANP Spitzenspiegels (B= 0,058; p = 0,004) und der rechtsatrialen Fläche (B= 0,389; p <0,001) mit dem eRAP. Ein MR-proANP Spitzenwert ≥139 pmol/L (AUC = 0,81) und ein Wert nach zweistündiger Erholung ≥159 pmol/L (AUC = 0,82) konnten in der ROC-Analyse als Indikatoren für einen eRAP >15 mmHg identifiziert werden.

Der grundsätzlichen Hypothese folgend, dass Belastungsdiagnostik die Demaskierung pathologischer Zustände bei Patienten/-innen mit normwertigen oder grenzwertig auffälligen Befunden in Ruhe erlaubt, erfolgte eine Subgruppenanalyse der Patienten/-innen mit normwertigem RAP in Ruhe. Während in der Gruppe der Patienten/-innen mit erhöhten RAP Werten in Ruhe nahezu alle Patienten/-innen einen Anstieg des RAP auf pathologisch Werte zeigten, war dies bei den 77 Patienten/-innen mit einem normwertigem RAP in Ruhe nur in 39% der Fall. Diese Patienten/-innen mit einer pathologischen Belastungsreaktion unterschieden sich nicht vom Rest der Subgruppe bzgl. ihrer anderen hämodynamischen Parameter in Ruhe (CI, RAP, SvO2). Die o.g. MR-proANP Grenzwerte waren auch in der Subkohorte der Patienten/-innen mit normwertigem RAP in Ruhe mit einem signifikant erhöhten Risiko einer pathologischen Belastungsreaktion assoziiert.

Schlussfolgerung

Die vorgelegte Studie charakterisierte erstmalig die Dynamik des RAP und des MR-proANP unter körperlicher Belastung bei CTEPH-Patienten/-innen. Die Dynamik des MR-proANP korrelierte dabei mit dem eRAP und damit mit der Veränderung des rechtsatrialen hämodynamischen Stresslevels. Patienten/-innen mit einer belastungsabhängigen Rechtsherzdysfunktion konnten durch die Bestimmung des Belastungs-MR-proANP identifiziert werden. Insbesondere bei Patienten/-innen mit normwertigen RAP-Werten in Ruhe konnte eine belastungsinduzierte Rechtsherzdysfunktion demaskiert werden.

4 Diskussion und Einordnung der Studienergebnisse

Nicht-invasive Biomarker sind ein diagnostisches Mittel zur Erfassung multipler (patho-)physiologischer Prozesse bei (extra-) kardialen Erkrankungen. Der erste Abschnitt dieser Habilitationsschrift (Publikationen 1 bis 7) befasst sich mit der diagnostischen Anwendung verschiedener Biomarker zur Darstellung kardialer und extrakardialer Prozesse im Kontext der CTEPH. Der Fokus lag dabei auf der Erfassung der Krankheitsschwere und kardialer (Mal-)Adaptations- und Regenerationsprozesse. Die hämodynamische Belastung des rechten Herzens in Form einer chronischen Nachlasterhöhung ist einer der zentralen Prozesse in der Pathophysiologie der PH/CTEPH[5]. Diese wird u.a. als führender Auslöser für den fibrotischen Umbau des rechten Herzens diskutiert[5]. Natriuretische Peptide sind Indikatoren von myokardialem Wandstress[2,50] und als diagnostische Parameter im Kontext zahlreicher kardialer Erkrankungen zur Diagnosestellung, Risikostratifikation und zum Therapiemonitoring etabliert[2,3,61,122]. In Publikation 1 konnte anhand der Dynamik des Biomarkers NT-proBNP erstmalig die sukzessive Entlastung des rechten Herzens unter einer sequentiellen BPA-Therapie gezeigt werden. Die Resultate weisen darüber hinaus auf eine anhaltende kardiale Entlastung des rechten Herzens im mittelfristigen Verlauf hin. Andreassen et al. identifizierten erhöhte NT-proBNP Spiegel als Prädiktor für eine reduzierte Überlebensprognose bei präkapillärer PH[123]. Bei Patienten/-innen mit einer CTEPH zeigen sich natriuretische Peptide regelhaft erhöht und korrelieren mit der Schwere der Rechtsherzdysfunktion[29,53,54,123,124]. Kongruent zu dieser Datenlage zeigten die Patienten/-innen in unserer Studienkohorte (Publikation 1) deutlich erhöhte NT-proBNP Spiegel vor Beginn einer BPA-Therapie. Die NT-proBNP-Spiegel korrelierten zum Einschlusszeitpunkt vor der Therapie mit der Schwere der hämodynamischen Beeinträchtigung, der Symptomatik und der physischen Leistungsfähigkeit. In Arbeiten von Surie et al. und Andreassen et al. zeigten sich die BNP-/NT-proBNP Spiegel unter einer Therapie mittels PEA oder BPA bei der Mehrheit der Patienten/-innen reversibel[29,53]. Patienten/-innen mit reduziertem Therapieansprechen und der Entwicklung eines chronischen Rechtsherzversagens waren in deren Kohorten durch höhere Spiegel der natriuretischen Peptide charakterisiert[29,53]. In unserer Kohorte konnte ein Abfall der NT-proBNP Konzentration bei 37 von 51 Patienten/-innen beobachtet werden. Passend zu den Vorstudien,

kennzeichnete ein fehlender oder reduzierter Abfall des NT-proBNP Spiegels jene Patienten/-innen mit einem reduzierten Therapieansprechen, gemessen an der Erholung der hämodynamischen Zielgrößen PVR und mPAP. Bei der BPA-Therapie handelt es sich um eine Stufentherapie mit wiederholten Interventionen über mehrere Monate. Bei Patienten/-innen mit einer Linksherzinsuffizienz konnten natriuretische Peptide effektiv zum Therapiemonitoring eingesetzt werden[125]. Zur Dynamik der NT-proBNP Expression während einer stufenweisen BPA-Therapie existierten keine Vorarbeiten. Die serielle Bestimmung des Biomarkers in unserer Arbeit zeigte eine sukzessive Reduktion der Spiegel, beginnend bereits nach der ersten Intervention des BPA-Zyklus. Der Vergleich der NT-proBNP Spiegel zwischen dem Zeitpunkt unmittelbar nach der BPA-Therapie mit der 6-Monats-Nachsorge zeigten darüber hinaus anhaltend niedrige Werte. Die Befunde zeigen die Entlastung des rechten Herzens als Folge der Nachlastreduktion. Insgesamt legen die Ergebnisse eine Verwendung des NT-proBNP als Parameter zur initialen Evaluation der Krankheitsschwere und zur Beurteilung des hämodynamischen Therapieansprechens nahe.

Neben dem hämodynamisch induzierten myokardialen Dehnungsreiz wird auch die unmittelbare myozytäre Zellschädigung als Mechanismus der rechtskardialen Maladaptation diskutiert[5]. Kardiale Troponine sind als Biomarker der Myozytenschädigung etabliert[126]. In Publikation 2 konnte erstmalig die Dynamik kardialer Troponine im Rahmen einer sequentiellen BPA-Therapie gezeigt werden. Die Messung kardialer Troponine ist fester Bestandteil der Diagnose- und Therapiealgorithmen des akuten Koronarsyndroms[61]. Im Zuge der akuten Myokardischämie erfolgt die Freisetzung als Zeichen der myokardialen Zellnekrose[57]. Erhöhte Spiegel kardialer Troponine sind jedoch auch im Rahmen vielfältiger anderer kardialer und extrakardialer Pathologien als Zeichen einer Myozytenschädigung messbar und hier von prognostischer Relevanz[57]. So zeigen erhöhte Troponinspiegel im Rahmen einer akuten Lungenarterienembolie die sekundäre nachlastbedingte Rechtsherzbelastung an[122]. Hochsensitive Messverfahren erlauben inzwischen auch die Erfassung geringgradiger Änderung der Troponinkonzentration im Rahmen chronischer kardialer Belastungskonstellationen[58]. Auch bei Patienten/-innen mit einer PH sind erhöhte Troponinspiegel als Zeichen einer chronischen Myokardschädigung messbar[29,60]. Vergleichbar zu anderen Kohorten zeigten die CTEPH-Patienten/-innen

der Studienkohorte in Publikation 2 initial eine Erhöhung der hs-cTnT-Konzentration[29,60] mit einem Wert oberhalb der 99. Perzentile bei 31% der Patienten/-innen. Patienten/-innen mit einem hs-cTnT Konzentration oberhalb der 99. Perzentile waren durch eine stärkere Beeinträchtigung der pulmonalen Hämodynamik gekennzeichnet. Andreassen et al. beschreiben im Zuge einer BPA-Therapie bei CTEPH einen Abfall der Troponinspiegel[29]. Kongruent hierzu illustrieren die Ergebnisse der Publikation 2 die sukzessive Reduktion der hs-cTnT Spiegel unter der BPA-Therapie als Zeichen einer rückläufigen chronischen Myokardschädigung. Die Dynamik des Hs-cTnT korrelierte dabei mit der Dynamik des NT-proBNP, was die Hypothese einer wandspannungsinduzierten chronischen Myokardschädigung als Mechanismus der Troponinfreisetzung stützt.

Während das NT-proBNP und kardiale Troponine zu den Routineparametern in der kardialen Biomarkerdiagnostik[2,126] gehören, existiert eine weitaus geringere Datenlage zur Anwendung weiterer Biomarker. Das Fortbestehen einer PH mit sekundärer Rechtsherzinsuffizienz führt zunehmend zur retrograden und antegraden Dekompensation mit einer Beeinträchtigung der systemischen Hämodynamik. Publikation 3 untersuchte die Biomarker MR-proANP und Copeptin als Biomarker zur Erfassung dieses Prozesses. Copeptin ist ein Nebenprodukt der Expression von Vasopressin, welches in vivo als Akutregulator des Volumenhaushalts wirkt[62]. Im Rahmen einer akuten Myokardischämie und einer akuten Lungenarterienembolie zeigten sich erhöhte Copeptinspiegel als Zeichen der akut gestörten Kreislaufhomöostase[69–71]. In unserer Kohorte lagen die Copeptinspiegel deutlich unterhalb der Werte bei akuten Krankheitsbildern[70,71,127,128]. Die gemessenen Spiegel waren vergleichbar mit den Resultaten anderer Arbeiten zu Patienten/-innen mit PH[74,77,78]. In der Literatur existieren inhomogene Daten zur diagnostischen Anwendung des Copeptins bei PH. Während teilweise eine Assoziation zur Schwere der Symptomatik und Beeinträchtigung der körperlichen Leistungsfähigkeit gezeigt wurde, zeigte sich keine konsistente Korrelation mit hämodynamischen Zielgrößen[74,77,78]. Copeptin zeigte in unserer Kohorte keine diagnostische Wertigkeit, weder bei der Identifikation von Patienten/-innen mit fortgeschrittener Krankheitsschwere noch bei der Evaluation eines Therapieansprechens. Entsprechend interpretieren wir Vasopressin als Regulator akuter

Kreislaufveränderungen ohne relevante Rolle bei Patienten/-innen mit einer chronischen Rechtsherzbelastung.

Verschiedene Subtypen natriuretischer Peptide zeigen unterschiedliche Expressionscharakteristika. Während BNP/NT-proBNP überwiegend ventrikulär sezerniert werden, erfolgt die Ausschüttung atrialer natriuretischer Peptide führend als Antwort auf Dehnungsreize des atrialen Myokards[50,63]. Die morphologische und funktionelle Beeinträchtigung des rechten Atriums ist im Rahmen einer PH als Indiz für die Progression des Rechtsherzversagens und entsprechend als negativer Prognoseparameter zu verstehen[67,129–132]. Die Messung des Biomarkers MR-proANP erlaubt einen nichtinvasiven Zugang zur Quantifizierung der atrialen Belastung. Andere Arbeiten berichteten bereits erhöhte MR-proANP Spiegel bei Patienten/-innen mit unterschiedlichen Formen der PH[73,74,78]. Die CTEPH-Patienten/-innen in Publikation 3 zeigten vergleichbar erhöhte MR-proANP Spiegel vor Beginn einer Therapie. Die Interpretation des MR-proANP als Indikator für das atriale Stresslevel wurde durch die starke Korrelation mit dem RAP bestärkt. Im Kontext der chronischen Linksherzinsuffizienz, akuten Lungenarterienembolie, sowie der chronischen PH konnte MR-proANP als Prognoseprädiktor mit diagnostischer Überlegenheit zu anderen natriuretischen Peptiden identifiziert werden[68,74,75,133,134]. Konform mit den Resultaten von Kaiser et al.[73] zeigten Patienten/-innen mit einer fortgeschrittenen hämodynamischen Krankheitsschwere in unserer Kohorte signifikant höhere MR-proANP Spiegel und konnten durch diese mit hoher diagnostischer Aussagekraft von anderen Patienten/-innen differenziert werden. Dabei war MR-proANP mindestens gleichwertig zum etablierten Biomarker NT-proBNP. Zur Dynamik des MR-proANP unter einer spezifischen CTEPH Therapie existierten keine Vorstudien. Die Ergebnisse unsere Publikation 3 zeigen erstmalig den Abfall der MR-proANP Konzentration unter einer spezifischen CTEPH Therapie. Dabei illustrieren die seriellen Messungen unter einer BPA-Therapie die sukzessive kardiale Entlastung. Patienten/-innen mit optimalem Therapieansprechen konnten durch die MR-proANP Bestimmung valide identifiziert werden. Unter Berücksichtigung der prognostischen Bedeutung der rechtsatrialen Belastung bei PH, machen die Ergebnisse MR-proANP als Biomarker im Kontext der CTEPH attraktiv.

Die Rolle von inflammatorischen Prozessen und fibrotischen Gewebeumbaus rückten in den letzten Jahren zunehmend in den Fokus des wissenschaftlichen und klinischen

Interesses, insbesondere im Kontext kardialer Erkrankungen. Bedingt durch die Vielfältigkeit der beteiligten Zelltypen und Stoffwechselprozesse erscheint eine biomarkerbasierte Erfassung jedoch komplex. In Publikation 4 wurden sST2, GDF-15 und Galectin-3, Biomarker mit Assoziation zu inflammatorisch-fibrotischem Gewebeumbau, als Indikatoren der Krankheitsschwere und Therapieeffekte bei CTEPH untersucht. Einzelne Studien haben die pathophysiologische Rolle dieser Biomarker bei PH bereits analysiert[82,92–97].

Die Aktivierung des IL-33/(s)ST2-Stoffwechselweges ist Indikator für inflammatorisch-fibrotischen Gewebeumbau bei zahlreichen Erkrankungen[79,83,93,135], so auch im Kontext des kardialen Remodelings[80,136–138]. Die große Spanne der messbaren sST2-Spiegel sowie eine Überschneidung zu Werten bei gesunden Individuen erschweren jedoch die Interpretation[79,83,93,135,139]. Vergleichbar zu den wenigen vorbestehenden Daten zu sST2 bei PH[93,97,140] zeigten sich die sST2-Spiegel in unserer Studienkohorte vor Therapie erhöht. Erhöhte sST2-Spiegel waren in einzelnen Studien an Patienten/-innen mit einer PH zu einer RV-Dilatation, RV-Dysfunktion und erhöhter Mortalität assoziiert[82,93,141]. In unserer Studienkohorte war ein sST2-Spiegel > 65 ng/ml Indikator für eine fortgeschrittene hämodynamische Beeinträchtigung. Passend hierzu berichteten Placido et al. ein erhöhtes Mortalitätsrisiko bei PH-Patienten/-innen mit einem sST2-Spiegel über 69 ng/ml[140]. Zur Dynamik der sST2-Expression unter einer CTEPH-Therapie existierten keine Daten. In unserer Studienkohorte fiel die sST2-Konzentration nach Therapie in den Bereich der gesunden Kontrollgruppe, jedoch ohne Assoziation zu den hämodynamischen Zielgrößen. Grundsätzlich scheinen die hämodynamischen Effekte der BPA-Therapie inflammatorisch-fibrotische Gewebeumbauprozesse zu reduzieren, jedoch ist eine hohe individuelle Variabilität mit weiteren Einflussgrößen neben der reinen Hämodynamik zu vermuten.

GDF-15 Spiegel zeigen sich als Folge von inflammatorischer, hämodynamischer und ischämischer Gewebeschädigung mit hoher individueller Variabilität erhöht[79,84,85]. Dabei zeigt sich bei unterschiedlichen Krankheitsbildern, aber auch bei gesunden Individuen eine große Konzentrationsspanne. In unserer Studienkohorte zeigten sich die GDF-15 Spiegel im Vergleich zur gesunden Kontrollkohorte signifikant erhöht und bzgl. der Größenordnung vergleichbar zu anderen Kohorten von Patienten/-innen mit einer CTEPH[92,96,97]. GDF-15 wird als unspezifischer Indikator für systemischen Gewebestress angesehen[85]. Kardiomyozyten und Endothelzellen zeigen eine

Überexpression und gewebeprotektive Effekte von GDF-15 als Antwort auf hämodynamisch induzierte Scherkräfte[84,142,143]. Dies könnte auch der auslösende Mechanismus für die vermehrte Expression bei CTEPH sein. In einigen Studien, welche PH-Patienten/-innen untersuchten, zeigte sich eine Assoziation von GDF-15 Spiegeln zum RAP und dem CI[96,144,145]. Im Einklang mit diesen Ergebnissen zeigten Patienten/-innen mit einer fortgeschrittenen Beeinträchtigung der Hämodynamik in unserer Kohorte erhöhte GDF-15 Spiegel und konnten durch diese mit hoher diagnostischer Aussagekraft vom Rest der Kohorte differenziert werden. Es existierten keine Daten zur Dynamik von GDF-15 Spiegeln unter einer CTEPH Therapie. Nickel et al. dokumentierte keine Veränderung von GDF-15 Spiegeln bei Patientin mit einer idiopathischen PH nach Initiierung einer Medikation[144]. Bei Betrachtung unserer Gesamtkohorte zeigten sich die GDF-15 Spiegel nach Therapie unverändert. Jedoch konnten Patienten/-innen mit optimalem Therapieansprechen durch niedrige GDF-15 Spiegel identifiziert werden. Sowohl sST2 als auch GDF-15 zeigten eine diagnostische Anwendbarkeit bei der Beurteilung der hämodynamischen Krankheitsschwere und der Therapieeffekte bei CTEPH, jedoch waren beide Marker hierbei nicht dem etablierten Biomarker NT-proBNP überlegen.

Galectin-3 ist als Mediator im Kontext inflammatorisch-fibrotischen Gewebeumbaus und hierbei insbesondere bei der Organisation des interzellulären Raums beschrieben[86,87]. In einer einzelnen kleinen Kohorte von Patienten/-innen mit PH wurden erhöhte Galectin-3 Spiegel mit einer Assoziation zur Rechtsherzfunktion beschrieben[95]. Unsere Studie lieferte erstmalig Ergebnisse zur Expression von Galectin-3 bei CTEPH. Diese zeigte keine Veränderung der Serumspiegel im Vergleich zur gesunden Kontrollkohorte. Entsprechend konnte keine diagnostische Wertigkeit des Biomarkers bei der Beschreibung der Krankheitsschwere oder des Therapieansprechens gezeigt werden.

Ein weiterer Biomarker mit Assoziation zu inflammatorischem, insbesondere vaskulärem Gewebeumbau ist PAPP-A. In Publikation 5 wurde erstmalig die Expression von PAPP-A und dessen Dynamik bei CTEPH-Patienten/-innen unter einer spezifischen Therapie untersucht. Bisher existierten keine Daten zur Expression von PAPP-A bei CTEPH. In unserer Studie konnten erhöhte PAPP-A Konzentration zum Einschlusszeitpunkt gemessen werden, welche jedoch keine Unterscheidung zwischen CTEPH-Patienten/-innen und jenen mit einer PH anderer Genese zuließ.

Unter der spezifischen CTEPH-Therapie konnte ein stetiger Abfall ohne Assoziation zur Hämodynamik dokumentiert werden. Die Beteiligung des PAPP-A an vaskulären Remodelingprozessen im Kontext der CTEPH erscheint möglich, jedoch sind die aktuellen Ergebnisse lediglich als hypothesengenerierend zu bezeichnen.

Die progrediente systemische Beeinträchtigung der Hämodynamik im Rahmen der Rechtsherzinsuffizienz manifestiert sich auch als kardiorenales Syndrom im Sinne einer Endorganschädigung[64,103,104]. Die Manifestation der CKD ist ein negativer Prognoseprädiktor bei PH[64,103,105,106]. Als zugrundeliegende Mechanismen einer CKD bei kardialen Erkrankungen werden sowohl die reduzierte antegrade kardiale Auswurfleistung als auch die retrograde venöse Stauung diskutiert[104]. Zahlreiche Studien kommen zu unterschiedlichen Schlussfolgerungen, da sich inhomogen eine Korrelation der Nierenfunktion zum RAP als Parameter des venösen Rückstaus, dem CI als Parameter der Auswurfleistung oder beiden Größen zeigt[64,103–105,119,146–148]. In unserer Studienkohorte der Publikation 6 zeigte sich einer Korrelation der eGFR zum RAP und nicht zum CI, was für den venösen Rückstau als führende auslösende Komponente des CKD spricht. Tatebe et al berichteten eine Verbesserung der Nierenfunktion bei CTEPH-Patienten/-innen nach einer BPA-Therapie[102], Kimura et al wiederum nur bei Patienten/-innen mit einer reduzierten Nierenfunktion vor Therapie[107]. Passend zu diesen Ergebnissen zeigte sich eine Verbesserung der Nierenfunktion in unserer Studienkohorte nur bei Patienten/-innen mit einer eingeschränkten Nierenfunktion vor der BPA-Therapie. Die Analyse der Nierenfunktion bei Patienten/-innen, welche wegen einer inoperablen CTEPH mit einer BPA-Therapie behandelt werden, war auch aus prozeduralen Sicherheitsaspekten interessant. Das Auftreten eines akuten Nierenversagens in zeitlicher Assoziation zur Gabe von jodhaltigem Kontrastmittel wurde wiederholt beschrieben[108,149,150]. In unserer Kohorte zeigte sich eine insgesamt niedrige Inzidenz eines periprozeduralen akuten Nierenversagens im Sinne einer Kontrastmittelnephropathie mit zusätzlich nur leichtgradiger Ausprägung in den beobachteten Fällen. Auch Patienten/-innen mit einer fortgeschrittenen CKD vor Therapie zeigten keine erhöhte Rate renaler Komplikationen.

Die Rechtsherzfunktion stellt die zentrale diagnostische und therapeutische Zielgröße der CTEPH dar. Deren Monitoring ist komplex und erfordert den Einsatz multimodaler Diagnostik. Das Kardio-MRT ist die Referenzmethode zur Erfassung der

Rechtsherzmorphologie und –funktion[151]. Das Verfahren dokumentiert sowohl die rechtkardiale Maladaptation im Rahmen einer PH als auch die morphologische und funktionelle Regeneration unter einer Therapie[40,152–155]. Publikation 7 untersuchte den Ansatz CTEPH-Patienten/-innen mit einer fortgeschrittenen Rechtsherzinsuffizienz vor Therapie und solche mit mangelnder Regeneration der Rechtsherzfunktion unter einer spezifischen Therapie mittels nichtinvasiven Biomarkern zu identifizieren und verwendete das Kardio-MRT als Referenzmethode. Basierend auf der existierenden Literatur und den Vorarbeiten in dieser Habilitationsschrift wurden die Biomarker NT-proBNP, MR-proANP, sST2 und PAPP-A analysiert. Vergleichbar zu anderen Arbeiten zeigten die Patienten/-innen in unserer Studienkohorte vor Therapie eine deutliche Dilatation der rechtskardialen Herzhöhlen und eine reduzierte RVEF[38,154,155]. Die RVEF und der das körperoberflächenadjustierte endsystolische RV-Volumen, bestimmt im Kardio-MRT, konnten als herausragende Parameter zur Risikostratifizierung von Patienten/-innen mit einer PH identifiziert werden[156]. Vergleichbar zu anderen Serien zeigte NT-proBNP eine starke Korrelation zu den RV-Dimensionen und zur RVEF[54,157]. Die europäischen Leitlinien beschreiben einen NT-proBNP Spiegel >300ng/L[3] als Risikocharakteristikum. Konsistent dazu war in unserer Kohorte ein NT-proBNP-Spiegel >347ng/L hochprädiktiv für eine RVEF <35%. MR-proANP zeigte als zweites natriuretisches Peptid eine Korrelation zu RV-Dimensionen und der RVEF, jedoch schwächer als das NT-proBNP, was womöglich durch die vorrangig atriale Expressionslokalisation erklärt werden kann[50]. sST2 zeigte in Vorstudien eine Assoziation zur RV-Dilatation, - Dysfunktion und erhöhter Mortalität bei PH[82,93,141]. Im Einklang mit diesen Ergebnissen zeigten Patienten/-innen mit einer RVEF <35% signifikant erhöhte sST2-Spiegel im Vergleich zum Rest der Studienkohorte. PAPP-A zeigte sich in unserer Kohorte bei Patienten/-innen mit einer RVEF <35% signifikant erhöht, korrelierte aber nur schwach mit den rechtskardialen Kardio-MRT Befunden. Der Befund, dass kein Patient mit niedrigen Spiegeln aller vier bestimmten Biomarkern eine schwer reduzierte RVEF aufwies, regt eine Verwendung als Monitoringparameter im Sinne einer Multimarkerstrategie an. Mehrere Bildgebungsstudien dokumentierten eine Erholung morphologischer und funktioneller Rechtsherzparameter nach einer CTEPH-Therapie[153,155,158,159], wie sie sich auch in unserer Studienkohorte zeigte. Bemerkenswerterweise zeigen Patienten/-innen, welche unter Therapie eine Regeneration der RVEF hin zu Normalwerten erreichen,

eine ähnlich gute Prognose wie Patienten/-innen die bereits vor Therapie keine signifikante Einschränkung der RVEF aufweisen[156]. Diese Befunde bestätigen erneut die RV-Funktion als zentralen Zielparameter der CTEPH-Therapie. Die beiden Biomarker NT-proBNP und MR-proANP zeigten eine sehr gute Korrelation mit endsystolischer RV-Volumina und der RVEF vor und nach der BPA-Therapie. Ein fehlender oder nur reduzierter Abfall der beiden Biomarker konnte als starker Indikator für eine fehlende Verbesserung der RVEF identifiziert werden.

Der zweite Abschnitt dieser Habilitationsschrift (Publikation 8 - 10). befasste sich mit der Anwendung von Belastungsdiagnostik zur Erfassung pathologischer Veränderungen der pulmonalen Hämodynamik. Der eRHK erlaubt eine Erfassung und Quantifizierung von Veränderungen der pulmonalen Hämodynamik unter körperlicher Belastung. Ein Zusatznutzen, ergänzend zur Ruhediagnostik, ist bei der Beurteilung von Herzklappenvitien, bei der weiterführenden Abklärung einer PH, zur Demaskierung latenter pathologischer Konstellation sowie zur Erfassung von Therapieeffekten bei kardiopulmonalen Erkrankungen vorgeschlagen[31].

Publikation 8 zeigt die Anwendung des eRHK als Diagnostikum zur Evaluation von Patienten/-innen mit einer schweren Mitralklappeninsuffizienz (MI) im Vorfeld einer interventionellen Therapie. Studien zum interventionellen Mitralklappenrepair betonen stets die Abhängigkeit des Therapieerfolges von der adäquaten Patientenselektion[112,160]. Der eRHK bietet als zusätzliches Diagnostikum zur Echokardiographie die Möglichkeit zur Erfassung dynamischer Veränderungen der MI als auch die Beurteilung einer koinzidenten Herzinsuffizienz, was insbesondere bei der sekundären MI von Bedeutung ist[31,161]. In mehreren Arbeiten konnte eine fortgeschrittene Herzinsuffizienz als Grund für ein Therapieversagen einer interventionellen Mitralklappentherapie identifiziert werden[162–165]. Grayburn et al. stellten das Konzept der unverhältnismäßigen vs. verhältnismäßigen MI vor[111], wonach Patienten/-innen mit einer im Vordergrund stehenden Linksherzinsuffizienz und fehlender funktioneller Reserve des linken Ventrikels nicht mehr von einer Klappentherapie profitieren können. Konsistent mit diesen Daten zeigten Patienten/-innen mit einer hohen V-Welle als Zeichen der schweren MI und gleichzeitig signifikantem belastungsabhängigen CO-Anstieg das beste Therapieansprechen in unserer Studienkohorte.

Die Publikation 9 zeigt erstmals die Anwendung des eRHK bei CTEPH-Patienten/-innen vor und nach einer BPA-Therapie. Zahlreiche Arbeiten beschreiben die positiven Effekte der BPA-Therapie auf die pulmonale Hämodynamik in Ruhe[25,27–29,55,114,159]. Nach abgeschlossener BPA-Therapie zeigten in unserer Studienkohorte alle Patienten/-innen eine Verbesserung der pulmonalen Hämodynamik, in 22% der Patienten/-innen sogar mit einem Abfall des mPAP auf Normwerte <25mmHg. Der bis dato geltende Expertenkonsensus definiert eine Belastungs-PH als einen mPAP >30mmHg mit einem TPR oder mPAP/CO slope >3.0 WU[31]. Der Vergleich der prä- und postprozeduralen eRHK Befunde demonstriert eine konsistente Verbesserung aller Parameter der pulmonalen Hämodynamik. Trotzdem wiesen, der o.g. Definition folgend, alle Patienten/-innen in unserer Studienkohorte nach abgeschlossener BPA-Therapie weiterhin eine Belastungs-PH auf. Der Verbleib obstruktiven Materials in der Lungenstrombahn bei einer BPA-Therapie im Gegensatz zur PEA, sowie eine verbleibende Kleingefäßvaskulopathie könnten diese Befunde erklären. Die Erkenntnis, dass normalisierte Befunde im RHK nicht gleichbedeutend mit einer Normalisierung der pulmonalen Hämodynamik sind, ist essentiell für die Bewertung des Therapieerfolges. Die klinischen Implikationen der Studienergebnisse bleiben zu diskutieren. Cannon et al. zeigte Daten zur negativen prognostischen Relevanz einer persistierenden PH in Ruhe nach einer PEA-Therapie[166]. Inwiefern eine persistierende Belastungs-PH nach BPA bei inoperablen Patienten/-innen eine ähnliche prognostische Relevanz hat und ob beispielweise die Fortsetzung einer spezifischen Medikation indiziert ist, kann derzeit noch nicht beantwortet werden. Sicherlich befürworten die Ergebnisse aber die Integration des eRHK in die Nachsorgeroutine bei Patienten/-innen mit einer inoperablen CTEPH.

In Publikation 10 wurde die Quantifizierung der Dynamik des RAP und des MR-proANP unter körperlicher Belastung als diagnostischer Ansatz zur Erfassung einer Rechtsherzdysfunktion untersucht. Der RAP in Ruhe wurde bei verschiedenen kardialen Erkrankungen und auch der PH als Prognoseprädiktor identifiziert und wird bei PH zur individuellen Risikostratifizierung verwendet[3,64,115–119]. Trotz des zunehmenden Bewusstseins gegenüber dem diagnostischen Nutzen der Belastungshämodynamik im Kontext der PH und der Entwicklung einer Definition der Belastungs-PH, wurde der eRAP als Parameter nahezu ignoriert[31]. Gesunde Individuen zeigen unter körperlicher Belastung keinen oder nur einen moderaten

Anstieg des RAP[167–171]. Bei Patienten/-innen mit einer Linksherzinsuffizienz zeigte sich ein vermehrter Anstieg des RAP unter Belastung assoziiert zu einer pulmonalen Vaskulopathie und einer koinzidenten Rechtsherzinsuffizienz[121]. In unserer Studie zeigten CTEPH-Patienten/-innen einen signifikanten Anstieg des RAP im eRHK, vergleichbar mit den Beobachtungen von Lichtblau et al. in einer Patientenkohorte mit unterschiedlichen Formen der PH[169]. Es existiert keine anerkannte Definition eines physiologischen eRAP, jedoch kann, basierend auf der Literatur ein Wert >15mmHg als pathologisch angenommen werden. In unsere Kohorte zeigten 51% der Patienten/-innen einen Anstieg des RAP auf Werte >15mmHg als Hinweis auf ein belastungsabhängiges Rechtsherzversagen. MR-proANP wurde in dieser Habilitationsschrift bereits als Biomarker mit starker Korrelation zum RAP und der damit verbundenen hämodynamischen Belastung des rechten Atriums vorgestellt. Ob sich eine kurzfristige belastungsinduzierte Dynamik des RAP auch in einer Dynamik des MR-proANP wiederspiegelt, wurde bisher nicht untersucht. Kato et al. fanden heraus, dass Patienten/-innen mit einer Linksherzinsuffizienz unter körperlicher Belastung einen verstärkten Anstieg des ANP im Vergleich zu gesunden Individuen zeigen[172]. In unsere Studie konnte erstmalig die exakte Dynamik des MR-proANP im unmittelbaren Abgleich zu simultan erhobenen hämodynamischen Befunden beschrieben werden. Die MR-proANP Spiegel und deren Dynamik zeigten eine starke Korrelation zur Dynamik des RAP unter Belastung. Patienten/-innen mit einem pathologischen Anstieg des eRAP konnten durch die MR-proANP Spiegel unter Belastung und während der Erholungsphase verlässlich identifiziert werden. Die Resultate stützen das Konzept der Messung des eRAP und Belastungs-MR-proANP als Indikatoren für eine belastungsabhängige Rechtsherzinsuffizienz. Insbesondere bei Patienten/-innen mit norm- oder grenzwertigen Befunden in Ruhe könnte die Belastungsdiagnostik von Nutzen sein[31]. In unserer Studie konnte gezeigt werden, dass Patienten/-innen mit normwertigen RAP Werten in Ruhe unter Belastung eine inhomogene Dynamik des eRAP zeigen. Insgesamt zeigten 39% der Patienten/-innen in dieser vermeintlichen Niedrig-Risiko-Gruppe einen Anstieg des eRAP auf pathologische Werte >15mmHg. Auch bezüglich der anderen hämodynamischen Parameter präsentierten sich diese Patienten/-innen deutlich schlechter als Patienten/-innen mit einer physiologischen Dynamik des eRAP. Die MR-proANP Spiegel unter Belastung und in der Erholungsphase konnten auch in dieser Subkohorte verlässlich

Patienten/-innen mit einem pathologischen Anstieg des eRAP identifizieren. Diese Resultate legen ein Überdenken der bisherigen Risikostratifikation anhand der Ruhehämodynamik bei Patienten/-innen mit PH nahe. Eine Integration von Belastungsparametern könnte insbesondere bei Patienten/-innen mit norm- oder grenzwertigen Befunden in Ruhe die Risikostratifizierung verfeinern.

5 Zusammenfassung

Die PH geht mit einer sekundären Rechtsherzbelastung einher, die bei Persistenz in eine chronische Rechtsherzinsuffizienz mündet. Diese Rechtsherzinsuffizienz ist sowohl die führende Determinante der Krankheitsschwere als auch der entscheidende Prognoseprädiktor. Ein exaktes diagnostisches Monitoring der hämodynamischen und kardialen Veränderungen im Kontext der PH ist deshalb essentiell für eine optimierte Patientenversorgung. Die hier vorgelegte kumulative Habilitationsschrift stellt die inoperable CTEPH zur Aufarbeitung der chronischen, aber reversiblen PH und der assoziierten Rechtsherzinsuffizienz vor. Dabei fokussierte sich die Arbeit auf die diagnostische Erfassung der (Mal-)Adaptations- und Regenerationsprozesse durch die Bestimmung nicht-invasiver Biomarker.

In den Publikationen 1 bis 7 wurde die diagnostische Anwendung verschiedener Biomarker zur Darstellung kardialer und extrakardialer Prozesse im Kontext der CTEPH untersucht. Der Fokus lag auf der Erfassung von kardialen (Mal-)Adaptations- und Regenerationsprozessen. In Publikation 1 konnte an Hand der Dynamik des Biomarkers NT-proBNP erstmalig die sukzessive und nach Therapie anhaltende hämodynamische Entlastung des rechten Herzens unter einer sequentiellen BPA-Therapie gezeigt werden. In Publikation 2 konnte erstmalig die Dynamik des hs-cTnT im Rahmen einer sequentiellen BPA-Therapie gezeigt werden. Der sukzessive Rückgang der Serumspiegel zeigt den Rückgang der chronischen, subklinischen Myozytenschädigung, einem weiteren Mechanismus der rechtskardialen Maladaptation. In Publikation 3 wurde die Dynamik von MR-proANP und Copeptin als Indikatoren für eine progressive Beeinträchtigung der systemischen Hämodynamik im Kontext der CTEPH-Therapie untersucht. Während Copeptin keine diagnostische Wertigkeit zeigte, konnte eine starke Assoziation der MR-proANP Spiegel zur Krankheitsschwere vor Therapie und dem Therapieerfolg gezeigt werden. In Publikation 4 wurde erstmalig die Anwendung der Biomarker sST2, GDF-15 und Galectin-3 als Indikatoren der Krankheitsschwere und Therapieeffekte bei CTEPH untersucht. Es handelt sich dabei um Biomarker mit einer Assoziation zu inflammatorisch-fibrosierenden Gewebeumbauprozessen. Während Galectin-3 keine diagnostische Wertigkeit aufwies, zeigten sich sST2 und GDF-15 bei Patienten/-innen

mit fortgeschrittener Krankheitsschwere deutlich erhöht und stärken damit die Hypothese einer Beteiligung inflammatorisch-fibrosierender Gewebeumbauprozesse an der Pathophysiologie der CTEPH. Ein weiterer Biomarker mit Assoziation zu inflammatorischem, insbesondere vaskulärem, Gewebeumbau ist das PAPP-A. In Publikation 5 konnte erstmalig die Expression von PAPP-A und dessen Dynamik bei Patienten/-innen mit einer CTEPH unter einer spezifischen Therapie gezeigt werden. Auch wenn die diagnostische Wertigkeit wegen fehlender Assoziation zu den etablierten diagnostischen Zielgrößen, zum aktuellen Zeitpunkt unklar ist, stützen die Resultate die Hypothese einer Beteiligung inflammationsgetragener Remodelingprozesse bei CTEPH. In Publikation 6 konnte die sukzessive Verbesserung der renalen Funktion bei CTEPH-Patienten/-innen unter eine BPA Therapie, gemessen an renalen Biomarkern gezeigt werden. Die Befürchtung, die wiederholten Kontrastmittelapplikationen könnten insbesondere in diesem Kollektiv mit einem erhöhten Risiko eines akut-auf-chronischen Nierenversagens und einer dauerhaften Verschlechterung der Nierenfunktion einhergehen, bewahrheitete sich nicht. Die Rechtsherzfunktion stellt die zentrale diagnostische und therapeutische Zielgröße der CTEPH dar. Publikation 7 untersuchte den Ansatz, CTEPH-Patienten/-innen mit einer fortgeschrittenen Rechtsherzinsuffizienz vor Therapie und solche mit mangelnder Regeneration der Rechtsherzfunktion unter einer spezifischen Therapie mittels nichtinvasiven Biomarkern zu identifizieren. Insbesondere die natriuretischen Peptide NT-proBNP und MR-proANP zeigten hierbei eine starke diagnostische Performance.

Die Publikationen im zweiten Abschnitt dieser Habilitationsschrift (Publikation 8 - 10) fokussieren sich auf die diagnostische Anwendung von Belastungsdiagnostik zur Erfassung pathologischer Veränderungen der pulmonalen Hämodynamik. Publikation 8 zeigte erstmalig den erfolgreichen Einsatz des eRHK als Diagnostikum zur Evaluation einer schweren Mitralklappeninsuffizienz und dem Ansprechen auf eine interventionelle Therapie. Publikation 9 zeigt die erste Anwendung des eRHK bei CTEPH-Patienten/-innen vor und nach einer BPA-Therapie. Die Ergebnisse illustrieren, dass eine Normalisierung der hämodynamischen Zielgrößen in Ruhe nicht gleichbedeutend mit einer normalisierten Hämodynamik nach Therapie ist. Das Resultat, dass alle Patienten/-innen nach Therapie, insbesondere auch solche mit einer normalisierten Ruhehämodynamik, eine Belastungs-PH aufwiesen, motiviert

zum routinemäßigen Einsatz von Belastungsdiagnostik zur Erfassung der wahren Krankheitsschwere bei CTEPH.

Ein gänzlich neuer Ansatz ist die Messung kardialer Biomarker unter körperlicher Belastung zur unmittelbaren Abbildung hämodynamischer Veränderungen unter Belastung. In Publikation 10 konnte erstmalig die Dynamik des MR-proANP und des RAP unter körperlicher Belastung beschrieben werden. Die Dynamik des MR-proANP präsentierte sich als starker Indikator für eine pathologische Erhöhung des RAP unter Belastung und damit als Indikator eines belastungsinduzierten Rechtsherzversagens.

Zusammenfassend konnte in dieser Habilitationsschrift die CTEPH als reversible Form der PH mit reversiblem assoziiertem Rechtsherzversagen beschrieben werden. Die Arbeit präsentiert nichtinvasive Biomarker als diagnostisches Werkzeug zur Erfassung (mal-)adaptiver und regenerativer (kardialer) Prozesse im Rahmen der CTEPH.

6 English Summary

Pulmonary hypertension is accompanied by secondary right heart strain, which, if persistent, leads to chronic right heart failure. Right heart failure is not only the dominant determinant of disease severity but also a decisive predictor of prognosis. Therefore, accurate diagnostic monitoring of hemodynamic and cardiac changes in the context of pulmonary hypertension is essential for optimizing patient care. This cumulative habilitation thesis presents (inoperable) CTEPH as a model for the precise investigation of chronic but reversible PH and associated right heart failure. This thesis is focused on the diagnostic assessment of (mal-)adaptation and regeneration processes through the measurement of noninvasive biomarkers.

The first seven publications presented here investigated the diagnostic use of different biomarkers for the assessment of cardiac and non-cardiac processes in the context of CTEPH. The focus was to record cardiac (mal-)adaptation and regeneration processes. The results of publication 1 illustrate the continuous and persistent relief of hemodynamic right heart strain during step-wise BPA therapy with the help of serial NT-proBNP measurements. Publication 2 described for the first time the dynamics of hs-cTnT in the course of step-wise BPA therapy. The continuous decrease in serum levels mirrors the decline of chronic subclinical myocardial damage, a further mechanism of right heart maladaptation.

Publication 3 investigated the dynamics of MR-proANP and copeptin as indicators of the impairment of systemic hemodynamics in CTEPH patients undergoing BPA therapy. Whereas copeptin proved to have no diagnostic benefit, MR-proANP levels were strongly associated with disease severity and treatment effects. Publication 4 constitutes the first report of the use of sST2, GDF-15, and galectin-3 as biomarkers for the assessment of CTEPH disease severity and effects of therapy. These biomarkers are associated with inflammation and fibrotic remodeling. Whereas galectin-3 did not show diagnostic value, sST2 and GDF-15 levels were significantly elevated in patients with a progressed disease state. This supports the hypothesis of an involvement of inflammatory and fibrotic remodeling processes in the pathophysiology of CTEPH.

Another biomarker that is known to be associated with inflammatory remodeling, particularly in vascular tissue, is PAPP-A. The results of publication 5 show for the first time the dynamics of PAPP-A expression in patients with CTEPH during a specific therapy. Due to an apparent lack of correlation with hemodynamic parameters, the diagnostic significance and benefit of PAPP-A measurement is not clear at present. However, these data are consistent with the involvement of inflammatory remodeling processes in CTEPH.

Publication 6 describes the continuous improvement in renal function, quantified by renal biomarkers, in CTEPH patients during BPA therapy. Concerns that repeated use of contrast media may lead to an increased risk of acute-on-chronic renal failure and permanent deterioration of renal function, especially in this vulnerable cohort, could not be confirmed.

Right heart function is the key diagnostic and therapeutic parameter in CTEPH. Publication 7 investigated the use of noninvasive biomarkers to identify CTEPH patients with progressive right heart failure and specifically those with a limited therapy response. NT-proBNP and MR-proANP in particular showed a very strong diagnostic performance in this context.

The publications in the last section of this thesis (publications 8 to 10) focus on the use of exercise testing (exercise right heart catheterization, eRHC) for the assessment of impaired pulmonary hemodynamics and its secondary effects. Publication 8 presents eRHC as a valuable diagnostic method for the evaluation of severe mitral regurgitation and the assessment of treatment response after interventional therapy. Publication 9 shows the first standardized use of eRHC to assess CTEPH patients prior to and after BPA therapy. The results illustrate that a normalization of resting hemodynamics should not be automatically interpreted as normalized hemodynamics in general. The finding that all of the patients in this study showed persistent exercise PH despite normalized resting hemodynamics motivated the routine use of eRHC for the assessment of true disease severity.

A completely new concept to illustrate hemodynamic changes during exercise is the measurement of cardiac biomarker levels during physical exercise. Publication 10 illustrates the dynamics of MR-proANP in association with right atrial pressure during physical exercise by simultaneous measurement of the two parameters. The dynamics

of MR-proANP were identified as a strong indicator of pathological values of right atrial pressure during exercise and thus as an indicator of exercise-dependent right heart failure.

In conclusion, CTEPH is presented as a model disease for reversible pulmonary hypertension and associated right heart failure in this habilitation thesis. Noninvasive biomarkers were identified as valuable diagnostic tools for the assessment of (mal-)adaptative and regenerative (cardiac) processes in CTEPH.

7 Abkürzungsverzeichnis

ANP	Atrial-Natriuretic-Peptide
AUC	Area under the Curve
BPA	Pulmonale Ballonangioplastie
BNP	Brain-Natriuretic-Peptide
CI	Kardialer Index
CKD	Chronische Niereninsuffizienz
CO	Kardialer Auswurf
CTED	Chronisch Thromboembolische Erkrankung
CTEPD	Chronisch Thromboembolische Pulmonale Erkrankung
CTEPH	Chronisch Thromboembolische Pulmonale Hypertonie
DPG	diastolischer pulmonaler Gradient
eGFR	Geschätzte glomeruläre Filtrationsrate
eRAP	Rechtsatrialer Druck unter Belastung
eRHK	Belastungs-Rechtsherzkatheter
GDF-15	Growth differentiation factor-15
HF	Herzfrequenz
HFpEF	Herzinsuffizienz mit erhaltener Ejektionsfraktion
Hs-cTnT	kardiales hochsensitives Troponin T
IQR	Interquartilsabstand
Kardio-MRT	Kardiale Magnetresonanztomographie
LAE	Lungenarterienembolie
LVEF	Linksventrikuläre Ejektionsfraktion

LVEDV	Linksventrikuläres enddiastolisches Volumen
LVESV	Linksventrikuläres endsystolisches Volumen
LVSV	Linksventrikuläres Schlagvolumen
mPAP	Mittlerer pulmonalarterieller Druck
MR-proANP	midregionales pro-atriales natriuretisches Peptid
NPV	Negativprädiktiver Wert
NT-proBNP	N-terminales pro-B-Typ natriuretisches Peptid
NYHA	New York Heart Association
OR	Odds ratio
PAC	Pulmonalarterielle Compliance
PAPs	systolischer pulmonalarterieller Druck
PAPd	diastolischer pulmonalarterieller Druck
PAPP-A	Pregnancy-associated plasma protein-A
PAWP	Pulmonalkapillärer Verschlussdruck
PEA	Pulmonale Endarteriektomie
PH	Pulmonale Hypertonie
PPV	Positivprädiktiver Wert
PVR	Pulmonalvaskulärer Widerstand
RAP	Rechtsatrialer Druck
ROC	Receiver-Operating-Characteristics
RV	Rechter Ventrikel
RVEF	Rechtsventrikuläre Ejektionsfraktion
RVEDV	Rechtsventrikuläres enddiastolisches Volumen
RVESV	Rechtsventrikuläres endsystolisches Volumen

RVSV	Rechtsventrikuläres Schlagvolumen
sST2	Soluble suppression of tumorigenicity 2
SV	Schlagvolumen
SvO2	Zentralvenöse Sauerstoffsättigung
TAPSE	Tricuspid anular plane systolic excursion
TPG	Totaler pulmonaler Druckgradient
TPR	Totaler pulmonaler Widerstand
WHO-FC	World-Health-Organisation-Funktionsklasse
WU	Wood Unit
6-MFU	6-Monatsnachsorge
6-MWD	Gehstrecke im 6-Minutengehtest

8 Abbildungsverzeichnis

9 Tabellenverzeichnis

10 Literaturverzeichnis

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10.2 Publikationen des Verfassers

Erstautorenschaften / Seniorautorenschaften

1. *Exercise MR-proANP unmasks latent right heart failure in CTEPH*. **Kriechbaum SD,** Birmes J, Wiedenroth CB; Adameit MSD; Gruen D., Vietheer J; Richter MJ; Guth S,; Roller FC; Rademann M; Fischer-Rasokat U; Rolf A.; Liebetrau C; Hamm CV; Keller T; Rieth AJ; J Heart Lung Transplant 2022 Aug 27;S1053-2498(22)02084-8
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3. *Cardiac biomarkers as indicators of right ventricular dysfunction and recovery in CTEPH patients after BPA therapy – a cardiac magnetic resonance imaging cohort study.* **Steffen D. Kriechbaum,** Julia M. Vietheer; Christoph B. Wiedenroth; Felix Rudolph; Marta Barde; Jan-Sebastian Wolter; Moritz Haas; Ulrich Fischer-Rasokat; Maren Weferling; Andreas Rolf; Christian W. Hamm; Eckhard Mayer; Stefan Guth; Till Keller; Fritz C. Roller; Christoph Liebetrau; Pulm Circ. 2021 Dec 10;11(4):20458940211056500.
4. *Exercise hemodynamic profiling is associated with outcome in patients undergoing percutaneous mitral valve repair.* Andreas J. Rieth, **Steffen D. Kriechbaum**; Manuel J. Richter, Elena Wenninger, Ulrich Fischer-Rasokat, , Khodr Tello, Henning Gall, Hossein A. Ghofrani, Stefan Guth, Christoph B. Wiedenroth, Veselin Mitrovic, Christian W. Hamm, Christoph Liebetrau, Claudia Walther; Circ Cardiovasc Interv. 2021 Sep;14(9):e010453 **(geteilte Erstautorenschaft)**
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6. *Mid-regional pro-atrial natriuretic peptide and copeptin as indicators of disease severity and therapy response in CTEPH.* **Kriechbaum SD**, Scherwitz L,

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12 Publikationen dieser Habilitationsschrift im Original

1. N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Wolter JS, Hütz R, Haas M, Breithecker A, Roller FC, Keller T, Guth S, Rolf A, Hamm CW, Mayer E, Liebetrau C. J Heart Lung Transplant. 2018 May;37(5):639-646. **(Erstautorenschaft)**

2. Dynamics of high-sensitivity cardiac troponin T during therapy with balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Keller T, Wolter JS, Ajnwojner R, Peters K, Haas MA, Roller FC, Breithecker A, Rieth AJ, Guth S, Rolf A, Bandorski D, Hamm CW, Mayer E, Liebetrau C. PLoS One. 2018 Sep 25;13(9):e0204683 **(Erstautorenschaft)**

3. Mid-regional pro-atrial natriuretic peptide and copeptin as indicators of disease severity and therapy response in CTEPH. **Kriechbaum SD**, Scherwitz L, Wiedenroth CB, Rudolph F, Wolter JS, Haas M, Fischer-Rasokat U, Rolf A, Hamm CW, Mayer E, Guth S, Keller T, Konstantinides SV, Lankeit M, Liebetrau C; ERJ Open Res. 2020 Nov 2;6(4):00356-2020. **(Erstautorenschaft)**

4. Galectin-3, GDF-15, and sST2 for the assessment of disease severity and therapy response in patients suffering from inoperable chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Peters K, Barde MA, Ajnwojner R, Wolter JS, Haas M, Roller FC, Guth S, Rieth AJ, Rolf A, Hamm CW, Mayer E, Keller T, Liebetrau C. Biomarkers. 2020 Nov;25(7):578-586. **(Erstautorenschaft)**

5. Pregnancy-associated plasma protein A - a new indicator of pulmonary vascular remodeling in chronic thromboembolic pulmonary hypertension? **Kriechbaum SD**, Rudolph F, Wiedenroth CB, Mielzarek L, Haas M, Guth S, Hamm CW, Mayer E, Liebetrau C, Keller T. Respir Res. 2020 Aug 3;21(1):204. **(Erstautorenschaft)**

6. Development of renal function during staged balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension. **Kriechbaum SD**, Wiedenroth CB, Hesse ML, Ajnwojner R, Keller T, Sebastian Wolter J, Haas M, Roller FC, Breithecker A, Rieth AJ, Guth S, Rolf A, Hamm CW, Mayer E, Liebetrau C. Scand J Clin Lab Invest. 2019 Jul;79(4):268-275. **(Erstautorenschaft)**

7. Cardiac biomarkers as indicators of right ventricular dysfunction and recovery in CTEPH – a cardiac magnetic resonance imaging cohort study; **Kriechbaum SD,** Julia M. Vietheer; Christoph B. Wiedenroth; Felix Rudolph; Marta Barde; Jan-Sebastian Wolter; Moritz Haas; Ulrich Fischer-Rasokat; Maren Weferling; Andreas Rolf; Christian W. Hamm; Eckhard Mayer; Stefan Guth; Till Keller; Fritz C. Roller; Christoph Liebetrau; Pulm Circ. 2021 Dec 10;11(4):20458940211056500. **(Erstautorenschaft)**

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

9. Exercise right heart catheterization before and after balloon pulmonary angioplasty in inoperable patients with chronic thromboembolic pulmonary hypertension. CB Wiedenroth, AJ Rieth, **SD Kriechbaum**, HA Ghofrani, A Breithecker, M Haas, F Roller, MJ Richter, M Lankeit, L Mielzarek, A Rolf, CW Hamm, E Mayer, S Guth, C Liebetrau; Pulm Circ 2020 Aug 18;10(3):2045894020917884 **(Koautorenschaft)**

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

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N-terminal pro–B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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KEYWORDS:
NT-proBNP;
BPA;
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non-invasive monitoring

BACKGROUND: Balloon pulmonary angioplasty (BPA) is an emerging interventional treatment option for chronic thromboembolic pulmonary hypertension (CTEPH). The non-invasive monitoring of CTEPH patients is a clinical challenge. In this study we examined changes in N-terminal pro–B-type natriuretic peptide (NT-proBNP) in patients undergoing BPA for inoperable CTEPH and related them to peri-procedural success.

METHODS: In this study we analyzed a total of 51 consecutive patients who underwent BPA treatment and completed a 6-month follow-up (6-MFU) between March 2014 and March 2017. Serum samples for NT-proBNP measurement were collected before every BPA and at 6-MFU.

RESULTS: The 51 patients underwent 265 interventions involving angioplasty of a total of 410 vessels. The 6-month survival rate was 96.1%. The baseline (BL) mean pulmonary artery pressure (PAP) was 39.5 ± 12.1 mm Hg, pulmonary vascular resistance (PVR) was 515.8 ± 219.2 dynes/s/cm^5 and the median NT-proBNP level was 820 (153 to 1,871.5) ng/liter. At BL, World Health Organization functional class (FC) was ≥III in 96.1% of the patients, whereas, at 6-MFU, 11.8% were in WHO FC ≥III. At 6-MFU, mean PAP (32.6 ± 12.6 mm Hg; $p < 0.001$), PVR (396.9 ± 182.6 dynes/s/cm^5; $p < 0.001$) and NT-proBNP (159.3 [84.4 to 464.3] ng/liter; $p < 0.001$) levels were reduced. The decrease in NT-proBNP levels correlated with the decrease in mean PAP ($r_{rs} = 0.43$, $p = 0.002$) and PVR ($r_{rs} = 0.50$, $p = 0.001$). A reduction in the NT-*pro*BNP level of 46% indicated a decrease in mean PAP of ≥25% (area under the curve [AUC] = 0.71) and a reduction of 61% indicated a decrease in PVR of ≥35% (AUC 0.77).

CONCLUSIONS: Our results demonstrate that NT-proBNP levels decrease after BPA, providing valuable evidence of procedural success. NT-proBNP measurement allows identification of patients who are BPA

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non-responders and may thus be a valuable adjunct in therapy monitoring.
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Chronic thromboembolic pulmonary hypertension (CTEPH) is diagnosed in about 0.1% to 9% of all patients surviving acute pulmonary embolism.[1] The persistence of thrombotic material leads to obstruction of the pulmonary arteries, which compounded by secondary inflammation, cell proliferation and vascular remodeling.[1–3] The result is an elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), resulting in long-term impairment of pulmonary hemodynamics and right heart function accompanied by a poor prognosis.[4] The currently established therapy is pulmonary endarterectomy (PEA), a potentially curative approach[1]; however, in up to one third of patients, PEA is not feasible and not indicated, mostly due to the presence of peripheral lesions.[5] For these patients, medical treatment with riociguat is recommended,[1] with balloon pulmonary angioplasty (BPA) considered an emerging interventional treatment option.[6–9]

In the context of CTEPH treatment, natriuretic peptides have predictive value for right ventricular recovery after PEA.[10,11] N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) has been established as a biomarker in various cardiovascular diseases.[12,13] Its release is related to ventricular wall stress and/or myocardial ischemia/hypoxia, and it is mainly used for diagnosis and predicting the prognosis of patients with acute and chronic heart failure.[12–14]

Elevated NT-proBNP concentrations in CTEPH patients undergoing PEA or BPA have proven to be mostly reversible, except in patients developing chronic right heart failure.[10,11,15] In this context, serial measurement of NT-proBNP in patients undergoing BPA can be used to identify patients at risk. Whereas natriuretic peptides have proven to be reliable markers in the diagnostics and monitoring of patients with systolic heart failure, data for CTEPH patients undergoing BPA are limited.[6,12,15–17] The best time-point to determine NT-proBNP remains unclear: BPA is a staged procedure, and early changes in NT-proBNP after BPA are not well described. The knowledge of NT-proBNP concentrations after BPA could aid the interpretation of postprocedural findings, in particular decreased PAP, improvement of right heart function. This might increase the accuracy of risk stratification in these patients.

The aim of our study was to characterize the time course of NT-proBNP concentrations in patients undergoing BPA as a staged procedure and to determine the value of NT-proBNP as a marker for dynamics of PAP and PVR in the peri-procedural episode and at 6-month follow-up.

Methods

Study population

The present study included 51 consecutive patients who were treated by BPA at the Kerckhoff Heart and Thorax Center and completed a 6-month follow-up (6-MFU) after the final BPA treatment between March 2014 and March 2017. Pre- and post-procedural management data of the patients were recently published.[6,18] In brief, clinical examination, echocardiography, 12-lead electrocardiography (ECG), laboratory tests, 6-minute walk tests, ventilation–perfusion scan, computed tomographic (CT) angiography, right–left heart catheterization and pulmonary angiography were assessed for all patients. The final diagnosis of CTEPH was made according to the current guidelines.[1,19] All patients were presented in an interdisciplinary CTEPH conference to define the therapeutic concept. In this course, it is crucial to assess the technical operability with regard to the localization of the target lesions and the operability in dependence to the patients' comorbidities. BPA was performed as a staged procedure according to standard clinical practice by a dedicated BPA team (interventional radiologist, cardiologist, thoracic surgeon). Between the BPA procedures follow-up examinations were performed that were adjusted to the individual requirements of each patient, always including re-evaluation of clinical status and laboratory findings. Finally, an in-house follow-up examination was performed 6 months after the last BPA procedure.

All patients enrolled in the study gave written informed consent, which included consent for biomarker analyses. The ethics board of the Justus Liebig University of Giessen approved the study (AZ 43/14).

Balloon pulmonary angioplasty

BPA was performed as staged procedure under smooth sedation using femoral or jugular access. A 6F sheath (Vista Brite Tip, Johnson & Johnson, Fremont, CA) was placed in the pulmonary artery, and a 6F guiding catheter (mostly MB1 Launcher, Medtronic, Minneapolis, MN, or JR 4, Dublin, Ireland) was inserted into the pulmonary artery to selectively intubate the obstructed segmental arteries. During the procedure, patients received heparin intravenously at 100 IE/kg to maintain an activated clotting time >250 seconds. The guide-wire (Run-through NS-PTCA, Terumo, Tokyo, Japan) was placed into the sub-segmental arterial branches, passing the obstructing endoluminal material. The sub-segmental branches were then dilated by multiple inflations of semi-compliant balloons (Emerge 2.0/20 mm, 3.0/20 mm and 4.0/20 mm, Boston Scientific, Marlborough, MA). A final fluoroscopy documented the post-procedural morphologic result.

Right heart catheterization

Right heart catheterization (RHC) was performed as a part of the diagnostic work-up.[1] In all BPA patients, RHC was repeated 6 months after the last BPA procedure. RHC was routinely performed via the right internal jugular vein using a 6F sheath and a standard Swan–Ganz catheter. Medication of the patients was not modified before or during RHC; in particular, no vasoactive agents were administered.

Laboratory assessment

Venous blood samples for determination of NT-proBNP were collected in plain tubes at baseline, before every BPA procedure, and at the 6-MFU. NT-proBNP was measured in serum with an electrochemiluminescence immunoassay using monoclonal antibodies (NT-proBNP assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The lower detection limit for the NT-proBNP assay is 5.0 ng/liter and concentrations above the measuring range are reported as >35,000 ng/liter. The lowest concentration measurable with a coefficient of variation (CV) of 20% for this assay is 50.0 ng/liter. At the cut-off value of 150 ng/liter, the CV is <3%. The upper limit of normal is 300.0 ng/liter.[14]

Statistical analysis

All data for continuous variables are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical variables are reported as number and percent. Parametric distribution was assessed using the Shapiro–Wilk test.

Sub-cohorts at BL and 6-MFU were compared using Student's *t*-test for normally distributed parameters and the Mann–Whitney *U*-test for all other continuous variables. Chi-square and Fisher–Yates tests were used for categorical variables.

Parameters that were obtained at baseline and at the 6-MFU were subjected to paired sample testing. We used Student's *t*-test for normally distributed parameters and the Wilcoxon signed-rank test for all other continuous variables. Bivariate correlations were analyzed for selected clinical and hemodynamic parameters as well as laboratory findings.

To detect a significant benefit of BPA, we defined a reduction in the mean PAP of ≥25% or a reduction in the PVR ≥35% as significant. These cut-off values were retrospectively chosen, as receiver operating characteristic (ROC) curve analysis suggested the highest area under the curve (AUC) for NT-proBNP movement at these values. Further, we defined reduction of the NT-proBNP level of ≥25% as being significant. For comparisons, we split the cohort using these cut-off-values.

The role of NT-proBNP as an indicator of changes in mean PAP and PVR was analyzed via ROC analysis combined with the Youden index (YI = sensitivity + specificity – 1). All statistical tests were performed with SPSS version 19.0 (IBM SPSS, Armonk, NY). Two-tailed $p < 0.05$ was considered statistically significant.

Results

Clinical and procedural characteristics of all 51 patients (28 women, 23 men; age [mean ± SD] 63.1 ± 11.5 years) enrolled in the study are presented in Table 1. The indication for the BPA therapy was a technically inoperable status due to peripheral lesions in 47 (92.2%) patients and a status after PEA with insufficient effects on hemodynamics and clinical parameters in 4 patients (7.8%) (Figure 1).

At baseline, 49 (96.1%) patients were in World Health Organization functional class (WHO FC) ≥III. All patients were on oral anti-coagulation therapy for at at least 3 months and 29 (56.9%) were undergoing specific medical treatment for pulmonary hypertension. A total of 265 (mean = 5/patient) BPA interventions treating a total of 410 (mean = 8/patient) vessels were performed. The most common complications were reperfusion injury in 3.4% and hemoptysis in 7.4% of all interventions. The 6-month survival rate was 96.1%. At 6-MFU, the WHO FC was improved ($p < 0.001$), with 6 (11.8%) patients in WHO FC ≥III (Figure 2 and Table 2). The median 6-minute-walk distance increased significantly (BL: 375.0 meters [interquartile range 281 to 445.5]; 6-MFU: 409 meters [IQR 332.3 to 445.8]; $p = 0.017$) (Table 2).

Table 1 Sociodemographic Data, Comorbidities and Medication Given at Baseline

Parameter	Number, mean ± SD or median (IQR)	%
Female gender	28	54.9
Age at first BPA (years)	63.1 ± 11.5	
Body mass index (kg/m²)	25.7 ± 3.8	
Diabetes mellitus	5	9.8
Arterial hypertension	31	60.8
Dyslipidemia	7	13.7
Current smoker	14	27.5
Chronic renal failure	10	19.6
GFR (ml/min)	79.2 ± 26.7	
Creatinine (µmol/liter)	0.94 (0.78 to 1.12)	
Coronary artery disease	9	17.9
Atrial fibrillation	3	5.9
History of stroke	5	9.8
Chronic obstructive pulmonary disease	4	7.8
History of cancer	9	17.6
History of deep vein thrombosis	6	11.8
History of acute pulmonary embolism	23	45.1
Pro-coagulant coagulopathy	2	3.9
OAC	51	100
PDE5 inhibitor	7	13.7
ERA	6	11.8
Riociguat	21	41.2
Riociguat alone	17	33.3
PDE5 inhibitor alone	5	9.8
ERA alone	2	3.9
Riociguat + PDE5 inhibitor	1	2.0
Riociguat + ERA	3	5.9
PDE5 inhibitor + ERA	1	2.0

BPA, balloon pulmonary angioplasty; ERA, endothelin-receptor antagonist; GFR, glomerular filtration rate; IQR, interquartile range; OAC, oral anti-coagulative therapy; PDE5, phosphodiesterase type 5.

The RHC and echocardiographic measurements at baseline and at 6-MFU are listed in Table 2. The mean PAP at baseline was 39.5 ± 12.1 mm Hg and decreased after BPA treatment to 32.6 ± 12.6 mm Hg ($p < 0.001$). In parallel, the PVR decreased from 516 ± 219 dynes/s/cm^5 to 397 ± 183 dynes/s/cm^5 ($p < 0.001$) (Table 2).

Comparison of serum NT-proBNP concentrations with BL values revealed a significant decrease at all pre-specified time-points after the first BPA, with the lowest value being measured at 6-MFU (821 ng/liter [IQR 153 to 1,871.5] vs 159 ng/liter [84.4 to 464.3]; $p < 0.001$) (Table 3 and Figure 3). Of the 51 patients, 37 showed a significant decrease (≥25%) of NT-proBNP at 6-MFU, with a mean percent reduction of 53.6% (IQR 22.4 to 85.5) (range of

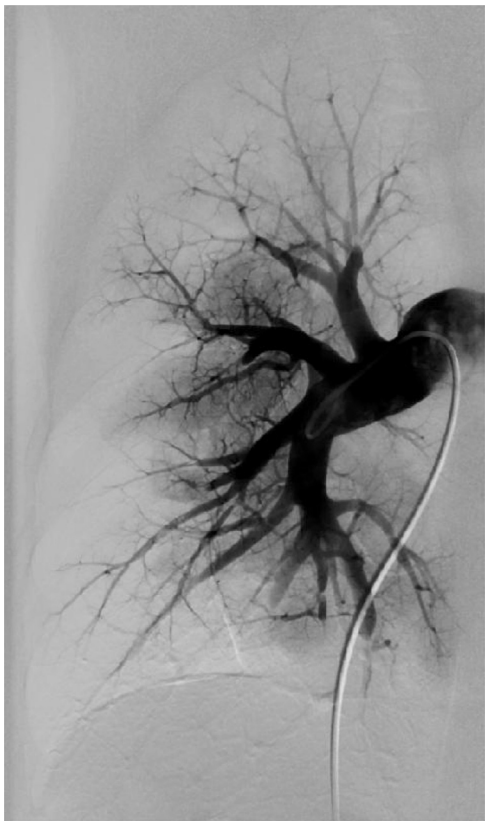

Figure 1 Illustration of multiple peripheral target lesions in a CTEPH patient.

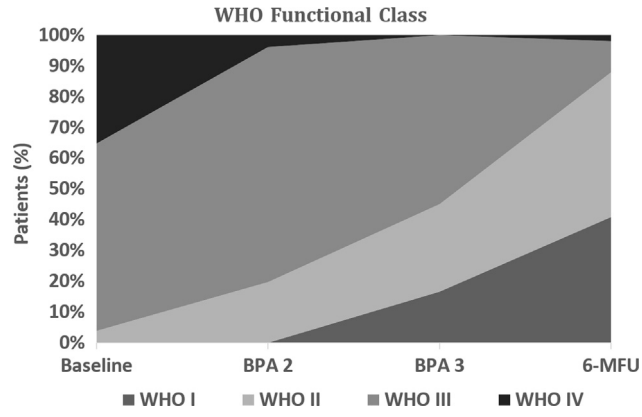

Figure 2 Development of WHO FC during staged BPA procedure (BPA = balloon pulmonary angioplasty; WHO = World Health Organization).

percent change [min–max]: +265 to –98%; range of absolute change [min–max]: +8,919 to –8,377 ng/liter) (Table 2).

When we compared patients with a significant reduction in NT-proBNP level at the 6-MFU to those without a reduction, a higher initial NT-proBNP level was the only significant ($p = 0.010$) difference at BL. The percent reduction of PVR ($p = 0.002$) and percent reduction of the mean PAP ($p = 0.007$) were significantly greater among patients with a significant decrease in NT-proBNP level of ≥25% (Table 4).

NT-proBNP concentrations correlated significantly with WHO FC at BL ($r_{rs} = 0.49$, $p < 0.001$) and at 6-MFU ($r_{rs} = 0.44$, $p = 0.001$) as well as with the mean PAP (BL: $r_{rs} = 0.65$, $p \leq 0.001$ 6-MFU: $r_{rs} = 0.49$, $p \leq 0.001$) and PVR (BL: $r_{rs} = 0.31$, $p = 0.032$; 6-MFU: $r_{rs} = 0.37$, $p = 0.016$). Furthermore, the percent decrease in NT-proBNP levels correlated significantly with percent decrease in mean PAP ($r_{rs} = 0.43$, $p = 0.002$) and percent decrease in PVR ($r_{rs} = 0.50$, $p = 0.001$) (Table 5).

ROC analysis employing the Youden index revealed a decrease of 46% in the BL NT-proBNP level as the best cut-off value (AUC = 0.71) for indicating a reduction of the

Table 2 Functional, Echocardiographic and Hemodynamic Data at BL and 6-MFU

Parameter	Baseline	6-MFU	*p*-value
WHO FC (I to IV)	I: 0; II: 2; III: 31; IV: 18	I: 20; II: 23; III: 5; IV: 1	<0.001
LVEF (%)	60 (60)	65 (60 to 65)	0.002
TAPSE (mm)	19 (13 to 20.5)	21.5 (17 to 24)	0.09
6-MWD (m)	375.0 (281 to 445.5)	408.5 (332.3 to 445.8)	0.017
NT-proBNP (ng/liter)	820.55 (153 to 1,871.5)	159.3 (84.4 to 464.3)	<0.001
NT-proBNP reduction (%)		53.6 (22.4 to 85.5)	
PCWP (mm Hg)	9.0 (8 to 12)	10.0 (8 to 11)	0.269
RA pressure (mm Hg)	7.5 ± 4.1	6.1 ± 2.7	0.008
Systolic PAP (mm Hg)	67.8 ± 21.6	55.8 ± 22.7	<0.001
Diastolic PAP (mm Hg)	22.1 ± 8.2	16.9 ± 7.7	<0.001
Mean PAP (mm Hg)	39.5 ± 12.1	32.6 ± 12.6	<0.001
Mean PAP reduction (%)		19.2 (4.3 to 28.7)	
PVR (dynes/s/cm^5)	515.8 ± 219.2	396.9 ± 182.6	<0.001
PVR reduction (%)		23.4 (4.4 to 34.7)	
CI (liters/min/m²)	2.5 ± 0.6	2.5 ± 0.5	0.326
SVO_2 (%)	66.4 (61.5 to 70)	70.4 (76.5 to 73)	0.003

Data expressed as number of patients (WHO), mean +/- SD or median with IQR. 6-MFU, 6-month follow-up; 6MWD, 6-minute walk test distance; BL, baseline; CI, cardiac index; FC, functional class; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; SVO_2, mixed venous saturation of oxygen; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

Table 3 Time Course of NT-proBNP Levels During the Staged BPA Procedure

	Baseline	Second BPA	Third BPA	After BPA	6-MFU
NT-proBNP (ng/liter)	821 (153 to 1,872)	384 (155 to 1,376)	310 (119 to 1,067)	257 (115 to 508)	159 (84 to 464)

6-MFU, 6-month follow-up; BPA, balloon pulmonary angioplasty; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

mean PAP of ≥25% and a decrease of 61% as the best cut-off value (AUC = 0.77) for indicating a reduction of PVR ≥35%.

Discussion

Practical experience with BPA, including both beneficial improvements and negative side effects, has accumulated over the last decade.[6,8,9,15,18,20,21] BPA is a safe procedure, with pulmonary reperfusion edema and vessel injuries being the leading complications.[7,21] Published data on the effect of BPA on pulmonary hemodynamics are quite heterogeneous, with a broad range of results concerning the reduction of PVR and mean PAP after BPA[21]; however, right ventricular function and reverse remodeling have been linked to outcome.[22–24] Natriuretic peptide levels mirror ventricular wall stress, and therefore right ventricular remodeling, and may be helpful in monitoring these patients. Accordingly, the aim of the present study was to characterize the time course of NT-proBNP concentrations in patients undergoing BPA as a staged procedure and to determine the value of NT-proBNP as an indicator for reductions in PAP and PVR.

The main findings of this study are: (1) staged BPA results in a substantial decrease in NT-proBNP concentrations in most of the patients that is already significant after the first BPA procedure; (2) this NT-proBNP decrease is associated with a significant reduction of mean PAP and PVR and indicates the procedural success of BPA; and (3) the 40% reduction of post-procedural NT-proBNP 6 months after BPA indicates a mean PAP decrease of ≥25%, and a reduction of 60% indicates a PVR decrease of ≥35%.

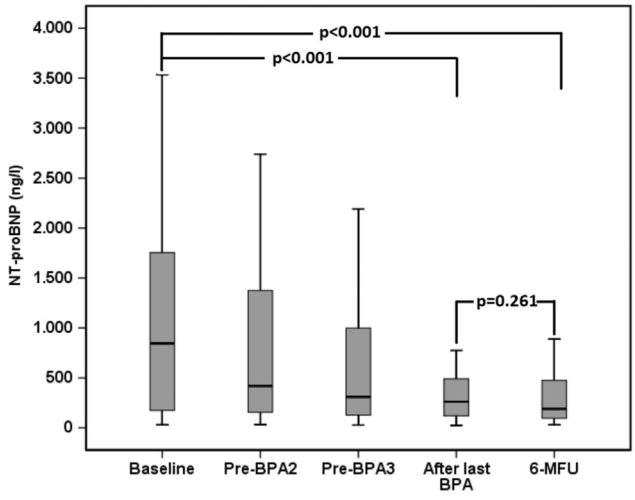

Figure 3 Analysis of the time course of NT-proBNP levels during staged BPA procedure (BPA = balloon pulmonary angioplasty; NT-proBNP = N-terminal pro–B-type natriuretic peptide).

Since Feinstein et al reported a significant reduction of mean PAP and an improvement of WHO FC with an improvement in 6-minute walk test results after BPA, several reports have confirmed these findings.[6,8,9,15,20] Recently reported BPA complication rates for severe reperfusion edema and vessel dissection range from 0% to 7%.[7,21] We observed a rate of 3.4% for reperfusion edema and 7.4% for parenchymal hemorrhage with hemoptysis, which is comparable to other observations. Our results show a mortality rate within 6 months after BPA of 3.9%, which is lower than previously reported.[15]

About 50% of the patients in our cohort were under specific medical treatment before BPA. This mainly resulted from the off-label character of therapy with phosphodiesterase-5 (PDE5) inhibitors or ERA, due to the lack of any approved medication for CTEPH before 2014. There are several drugs that were considered for the treatment of CTEPH patients because of their beneficial effects in other subgroups of pulmonary hypertension. In previous investigations, the use of endothelial receptor antagonists and inhibitors of PDE5 resulted in improved pulmonary hemodynamics, but failed to be beneficial with regard to physical capacity, and randomized, controlled trials did not meet their primary end-point.[25–27] Meanwhile, riociguat has been approved exclusively as drug therapy for CTEPH patients and is recommended in the current guidelines based on significant improvement of pulmonary hemodynamics and physical capacity in inoperable CTEPH patients.[1] Thus, over time, we adjusted our treatment approach and established a standardized therapeutic sequence at our center. Exclusively riociguat is administered for at least 3 months before possible BPA in inoperable CTEPH patients. Thereafter, a comprehensive reassessment of clinical and hemodynamic status is performed.

Long-term outcome among patients with pulmonary hypertension correlates with extent of mean PAP elevation.[28] Various studies have provided strong evidence that this impact on mortality is mainly mediated by the secondary impairment of right ventricular function.[22,23,29] In this context, right heart functional parameters have been shown to predict outcome in patients with pulmonary hypertension.[24,30] PEA and BPA treatments resulting in a reduction in PAP and PVR are also effective in promoting right ventricular remodeling, as documented by magnetic resonance tomography and echocardiography.[31–34] However, it is currently not possible to predict which patients will benefit from BPA as a staged procedure and which patients will not benefit. Moreover, there exists no distinct definition of a successful BPA treatment, neither by a fixed extent of hemodynamic changes nor any biomarkers. In our

Table 4 Comparison of Patients With or Without a Significant NT-proBNP Reduction (Cut-off = 25%)

Parameter	NT-proBNP decrease <25% ($n = 12$)	NT-proBNP decrease ≥25% ($n = 37$)	p-value
Female gender	8	20	0.517
Age at first BPA (years)	64.6 ± 12.3	62.7 ± 11.5	0.636
Body mass index (kg/m²)	27.6 ± 3.9	25.1 ± 3.7	0.145
Diabetes mellitus	1	3	0.999
Arterial hypertension	7	22	0.999
Dyslipidemia	0	5	0.315
Current smoker	2	12	0.466
eGFR (ml/min/1.73 m²)	81.3 ± 12.3	79.4 ± 27.3	0.834
Creatinine (μmol/liter)	0.86 (0.67 to 1.20)	0.94 (0.8 to 1.07)	0.771
Coronary artery disease	2	6	0.999
Atrial fibrillation	1	2	0.999
History of stroke	2	2	0.248
COPD	0	3	0.566
History of cancer	4	5	0.195
History of deep vein thrombosis	1	5	0.999
History of acute pulmonary embolism	4	18	0.507
LVEF (%)	60 (60-60)	60 (60-60)	0.316
TAPSE (mm)	19.5 (11.5 to 20)	18.5 (13.0 to 22.0)	0.592
6MWD (m)	367 (276.5 to 407.5)	380 (278.0 to 475.0)	0.453
NT-proBNP (ng/liter)	159.5 (41.3 to 498.8)	1,122.0 (200.2 to 2,137.0)	0.010
PCWP (mm Hg)	10.5 (8.3 to 14.3)	8.0 (9.0 to 12.0)	0.258
RA pressure (mm Hg)	6.9 ± 4.3	7.6 ± 4.1	0.629
Systolic PAP (mm Hg)	57.4 ± 22.8	70.2 ± 20.7	0.102
Diastolic PAP (mm Hg)	18.1 ± 9.0	23.4 ± 7.9	0.089
MeanPAP (mm Hg)	33.8 ± 13.0	41.0 ± 11.6	0.105
MeanPAP reduction (%)	2.1 (−8.5 to 20.3)	21.7 (8.1 to 29.9)	0.007
PVR (dynes/s/cm^5)	391.53 ± 258.7	551.8 ± 196.4	0.068
PVR reduction (%)	4.6 (−14.9 to 22.2)	28.9 16.6 to 40.5	0.002
CI (liters/min/m²)	2.8 ± 0.6	2.5 ± 0.6	0.172
SVO_2 (%)	65.1 (54.1 to 74.8)	66.7 (62.1 to 70.7)	0.584

Data expressed as number of patients (WHO), mean +/- SD or median with IQR. 6-MFU, 6-month follow-up; 6-MWD, 6-minute walk test distance; BPA, balloon pulmonary angioplasty; CI, cardiac index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; SVO_2, mixed venous saturation of oxygen; TAPSE, tricuspid annular plane systolic excursion.

study, NT-proBNP levels were measured at BL and immediately before each consecutive BPA session, which led to an interval of 4 to 8 weeks between BPA session and the subsequent NT-proBNP measurement. Thus, the NT-proBNP level is an indicator for the movement of cardiac wall stress since the previous treatment session, although it is not known how long it takes for a single angioplasty to reach its steady-state hemodynamic effect.

In our study NT-proBNP concentrations decreased toward normal values starting with the first BPA treatment. Moreover, NT-proBNP levels stabilized after the last BPA with a persistently low level in the 6-MFU. This overall decrease in NT-proBNP levels indicates the procedural success of BPA with regard to improvement of pulmonary hemodynamics, which was accompanied by a lowering of right ventricular wall stress and evidenced by the decrease in

Table 5 Analysis of Bivariate Correlation Between NT-proBNP Levels and WHO FC, Mean PAP Changes and PVR

	NT-proBNP at BL	NT-proBNP at 6-MFU	NT-proBNP reduction
WHO FC at baseline	$r_{rs} = 0.49$, $p < 0.001$		
WHO FC at 6-MFU		$r_{rs} = 0.44$, $p = 0.001$	
Mean PAP at baseline	$r_{rs} = 0.65$, $p \leq 0.001$		
Mean PAP at 6-MFU		$r_{rs} = 0.49$, $p \leq 0.001$	
meanPAP reduction			$r_{rs} = 0.43$, $p = 0.002$
PVR at baseline	$r_{rs} = 0.31$, $p = 0.032$		
PVR at 6-MFU		$r_{rs} = 0.37$; $p = 0.016$	
PVR reduction			$r_{rs} = 0.50$, $p = 0.001$

BL, baseline; CI, cardiac index; FC, functional class; NT-proBNP; N-terminal pro–B-type natriuretic peptide; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; WHO, World Health Organization; 6-MFU, 6-month follow-up.

PAP and PVR. Only 12 of the 51 patients showed no significant changes in NT-proBNP concentrations while under treatment. These patients were characterized by a significantly smaller decrease in mean PAP and PVR during follow-up.

Andreassen et al identified an elevated NT-proBNP level as an independent risk factor for reduced survival in patients with pre-capillary pulmonary hypertension.[15] Surie et al reported baseline BNP cut-off values to be predictive of worse post-operative survival in CTEPH patients undergoing PEA.[10] Natriuretic peptides are established diagnostic and prognostic biomarkers in patients with acute and chronic left heart failure.[12] Furthermore, natriuretic peptide–guided therapy has been shown to improve outcome in patients with left heart failure.[35] Nagaya et al showed that natriuretic peptides are elevated in patients with right heart stress,[36] and Reesink et al identified BNP as a marker of the degree of right ventricular dysfunction in CTEPH patients.[11] Our study indicates that consecutive NT-proBNP measurement under staged BPA therapy may help to assess the effects of BPA on hemodynamics and right ventricular function, which would lead to a better monitoring of BPA success. It should alse be mentioned that correlations between NT-proBNP and hemodynamic changes were of moderate strength. We hypothesize that the diagnostic power of NT-proBNP may be increased in patients with significant impairment of right ventricular function in progress.

In this study we have employed NT-proBNP measurement at every stage in CTEPH patients undergoing BPA as a staged procedure. Our results indicate that NT-proBNP is able to discriminate patients who profit from BPA regarding the improvement of pulmonary hemodynamics and therefore by improvements in right ventricular function. This assumption is strengthened by the fact that the BPA itself lowers the PVR and mean PAP, and therefore the ventricular wall stress, which leads to a decrease in natriuretic peptide levels.

There are limitations to this study that must be considered. The sample size was small. Nevertheless, our BPA program is one of the largest worldwide and our data clearly demonstrate the significant decrease in NT-proBNP concentrations from baseline at every stage of the procedure. BPA is effective, although the hemodynamic changes in patients undergoing BPA are not comparable to the hemodynamic outcome of PEA. The extent of the decrease in NT-proBNP levels allows for estimation of mean PAP reduction and therefore the procedural success. Due to a lack of approved cut-off values in the current literature, the identification of cut-off values was performed retrospectively from ROC curves, which limits their strength.

This study has covered the association between NT-proBNP levels and hemodynamic parameters under therapy and within the 6-MFU. Further investigation is needed to determine whether NT-proBNP levels may serve as a reliable marker for long-term procedural success.

Finally, our results demonstrate that serum NT-proBNP levels decrease after BPA, providing early evidence of procedural success. Measurement of NT-proBNP concentrations allows discrimination of patients who do not respond to the procedure with a lowering of PAP and PVR, which should be helpful in the identification of patients at risk.

Disclosure statement

C.B.W. received consultant honoraria and/or speaker fees from Actelion, Bayer AG, MSD, Pfizer and BTG; M.H. received lecture honoraria from Daiichi-Sankyo and Pfizer. T.K. received speaker fees from Abbott. S.G. received speaker fees from Actelion, Bayer, GSK and Pfizer; A.R. received lecture honoraria from Astra Zeneca, Boehringer Ingelheim and Pfizer-Bristol-Myers Squibb; C. W.H. received lecture or consulting honoraria from Astra Zeneca, Bayer, Boehringer Ingelheim, GSK, Daiichi-Sankyo and Pfizer-Bristol-Myers Squibb. E.M. received lecture or consulting honoraria from Actelion, Bayer, MSD, GSK, Pfizer and MSD. C.L. received lecture or consulting honoraria from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer-Bristol-Myers Squibb. The remaining authors have no conflicts of interest to disclose. We are grateful to the William G. Kerckhoff Stiftung, Bad Nauheim, Germany for research funding. We also thank Elizabeth Martinson, PhD, from the KHFI editorial office for editorial assistance.

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RESEARCH ARTICLE

Dynamics of high-sensitivity cardiac troponin T during therapy with balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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Abstract

Aims

Balloon pulmonary angioplasty (BPA) is an interventional treatment modality for inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Therapy monitoring, based on non-invasive biomarkers, is a clinical challenge. This post-hoc study aimed to assess dynamics of high-sensitivity cardiac troponin T (hs-cTnT) as a marker for myocardial damage and its relation to N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels as a marker for cardiac wall stress.

Methods and results

This study included 51 consecutive patients who underwent BPA treatment and completed a 6-month follow-up (6-MFU) between 3/2014 and 3/2017. Biomarker measurement was performed consecutively prior to each BPA and at 6-MFU.

In total, the 51 patients underwent an average of 5 BPA procedures. The 6-month survival rate was 96.1%. The baseline (BL) meanPAP (39.5±12.1mmHg) and PVR (515.8 ±219.2dyn×sec×cm^{-5}) decreased significantly within the 6-MFU (meanPAP: 32.6 ±12.6mmHg, P<0.001; PVR: 396.9±182.6dyn×sec×cm^{-5}, P<0.001). At BL, the median hs-cTnT level was 11 (IQR 6–16) ng/L and the median NT-proBNP level was 820 (IQR 153–1872) ng/L. The levels of both biomarkers decreased steadily after every BPA, showing the first significant difference after the first procedure. Within the 6-MFU, hs-cTnT levels (7 [IQR 5–12] ng/L; P<0.001) and NT-proBNP levels (159 [IQR 84–464] ng/l; P<0.001) continued to

Competing interests: CBW received consultant honoraria and/or speaker fees from Actelion, Bayer AG, MSD, Pfizer and BTG; MH received lecture honoraria from Daiichi-Sankyo and Pfizer; TK received speaker fees from Abbott; SG received speaker fees from Actelion, Bayer, GSK and Pfizer; AR received lecture honoraria from Astra Zeneca, Boehringer Ingelheim 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; EM received lecture or consulting honoraria from Actelion, Bayer, MSD, GSK, Pfizer and MSD; CL received lecture or consulting honoraria from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer-Bristol-Myers Squibb. AJR received speaker fees from Servier, St. Jude Medical and Actelion, honoraria from Novartis and traveling support by Orion Pharma and Actelion. SDK, JSW, RA, DB, KP, AB, and FCR have nothing to declare. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

decrease. The hs-cTnT levels correlated with the PVR (r_{rs} = 0.42; p = 0.005), the meanPAP (r_{rs} = 0.32; p = 0.029) and the NT-proBNP (r_{rs} = 0.51; p<0.001) levels at BL.

Conclusion

Non-invasive biomarker measurement provides valuable evidence for the decreasing impairment of myocardial function and structure during BPA therapy. Changes in hs-cTNT levels are suggestive for a reduction in ongoing myocardial damage.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) occurs in about 0.1 to 9% of all patients surviving acute pulmonary embolism [1]. Due to a distinct impairment of pulmonary hemodynamics and secondary right heart dysfunction, the prognosis of CTEPH is poor without therapy. [2] Pulmonary endarterectomy is the treatment of choice, offering a potential curative approach. [1] For patients deemed to be inoperable, targeted medication and a consecutive balloon pulmonary angioplasty (BPA) as an interventional treatment option is recommended. [1, 3–7]

Risk prediction is essential for patient-centric care but therapy monitoring with non-invasive biomarker measurement is debatable as these option is considered to be inferior to invasive hemodynamic assessment and cardiac imaging. [1] However, since secondary impairment of cardiac function determines the prognosis in the progression of CTEPH, non-invasive detection of cardiac damage might be a valuable diagnostic adjunct.

Natriuretic peptides are shown to have a predictive value regarding therapy response and right ventricular recovery after pulmonary endarterectomy and BPA. [8–11] We could recently provide data about decreasing N-terminal pro-B-type natriuretic peptide levels (NT-proBNP) after BPA with the possibility of therapy monitoring and identification of patients who are BPA non-responders. [8] Cardiac troponins have diagnostic and prognostic value in various cardiovascular diseases. Cardiac troponins are used as outstanding markers for risk stratification and therapy guiding in acute coronary syndrome patients. [12] They serve further to redefine myocardial infarction, and risk stratification in patients with pulmonary embolism and have finally also become a risk factor in apparently healthy subjects. In addition, first data indicate the possibility of cardiovascular risk reduction mirrored by a decrease of high-sensitive troponin I due to blood pressure lowering in patients with arterial hypertension. [13]

The role of troponin in CTEPH patients undergoing BPA and its relation to NT-proBNP levels is not well described. It can be speculated that a decrease of pulmonary hemodynamics after BPA is accompanied by a decrease of troponin level, which might represent a cardiovascular risk reduction. Therefore, the aim of the present study was to characterize the time course of high-sensitively measured troponin T in patients undergoing BPA as a staged procedure and to determine relation to pulmonary hemodynamics and NT-proBNP levels in the periprocedural episode and at six months follow-up.

Methods

The principles of the clinical and scientific work-up of patients who undergo treatment for CTEPH at our center have been recently published by our group. [8] The study population and the respective methods are described in brief as follows.

Study population

This study included fifty-one consecutive patients undergoing BPA treatment at the Kerckhoff Heart and Thorax Center and completed a 6-month follow-up (6-MFU) after the final BPA treatment between March 2014 and March 2017. The performed pre- and post-procedural diagnostic and therapeutic work up of patients suffering from CTEPH was published by our group. [3, 14, 15] The routinely performed diagnostic work up of all patients includes clinical examination, 12-lead ECG, laboratory tests, 6-minute walk tests (6-MWD), echocardiography, CT angiography, right-heart catheterization, and pulmonary angiography. [3, 8] The findings of all patients were assessed in an interdisciplinary CTEPH conference to proof the final diagnosis of CTEPH in accordance with the current guidelines and to define the individual therapeutic concept. [1, 7] Primarily, the patients were evaluated regarding their technical operability with regards to the localization of the target lesions and the operability in dependence to the patients' comorbidities. Consecutively the distinct staged BPA sequence was planned. In line with our standard clinical practice, the BPA procedures were performed by a dedicated BPA team (interventional radiologist, cardiologist, and thoracic surgeon). [3] The BPA sessions are performed with an interval of about 4 to 8 weeks. In preparation of each consecutive BPA procedure, the patients underwent follow-up examinations, adjusted to the individual requirements, but always including a re-evaluation of the clinical status and the laboratory findings. Six months after the completed BPA sequence, all patients underwent a comprehensive in-house follow-up examination, including a reassessment of clinical status, hemodynamics, cardiac function, laboratory findings, and functional capacity.

The investigation conforms with the principles outlined in the *Declaration of Helsinki*. All patients enrolled in the study gave written informed consent, which included consent for biomarker analyses. The study concept was approved by the ethics board of the Justus Liebig University of Giessen (AZ 43/14).

Balloon pulmonary angioplasty and right heart catherization

BPA was performed as staged procedure under conscious sedation using femoral or jugular access as previously described. [3] Right heart catheterization (RHC) was performed as a part of the preprocedural diagnostic work-up and within the 6-MFU after the completed BPA sequence. [1] Usually a 6F sheath in the right internal jugular vein and a standard Swan-Ganz catheter were used for the RHC. To allow a reliable assessment of hemodynamics, as close to the real-life conditions as possible, we performed no modification of the given medication prior or during the RHC. In particular, no vasoactive agents were administered. [8]

Laboratory assessment

At baseline (BL), prior to each BPA procedure and at the 6-MFU, venous blood samples for biomarker (hs-cTnT, NT-proBNP) were collected in plain tubes. The measurement of high-sensitivity cardiac troponin T (hs-cTnT) was performed with a high-sensitivity electro-chemiluminescence immunoassay (hs-cTnT assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The limit of detection (LOD) is 5ng/l. Due to this LOD, we used 5ng/l as the lowest level of hs-cTnT in the statistical analysis. The limit of quantification is 13ng/l. The lowest level, measurable with a coefficient of variation (CV) $<$10%, is 13ng/l. The recommended cut-off value for ACS decision making with this assay is 14 ng/l. The measurement of NT-proBNP in serum used an electrochemiluminescence immunoassay with monoclonal antibodies (NT-proBNP assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The LOD for this assay is 5.0 ng/l, whereas levels above the measuring range are reported as

>35,000 ng/l. The lowest level measurable with a CV of 20% is 50.0 ng/l and at the cut-off value of 150 ng/l the CV is <3%. The upper limit of normal is 300.0 ng/l. [16]

Statistical analysis

The results for continuous variables are displayed as mean ± standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical variables are expressed as the absolute number and the percentage of the whole cohort. Parametric distribution was assessed using the Shapiro-Wilk test. Subcohorts at BL and 6-MFU were compared with the Student t-test for normally distributed parameters and the Mann-Whitney-U test for all other continuous variables. Dynamics of parameters that were obtained at baseline and at the 6-MFU underwent paired sample testing with the Student's t-test for normally distributed parameters and the Wilcoxon signed-rank test for all other continuous variables. Bivariate parametric Pearson's correlations were analyzed for selected clinical and hemodynamic parameters as well as laboratory findings. All statistical tests were performed with SPSS software, version 19.0. A two-tailed *P* value <0.05 was considered to be statistically significant.

Results

Clinical characteristics and periprocedural data

Baseline characteristics of the evaluated 51 patients (28 women; mean age [±SD] 63.1±11.5 y) are summarized in Table 1. In all patients, the indication for BPA therapy was a technically inoperable status with peripheral target lesions in 47 (92.2%) patients and a status after PEA with recurrent pulmonary hypertension in 4 patients (7.8%). All patients in our cohort were on oral anticoagulation therapy for >3 months and in 29 (56.9%) patients a specific medical treatment for pulmonary hypertension was established. In total 265 (mean 5/patient) BPA interventions with a treatment of 410 (mean 8/patient) vessels were performed. The most frequent complications after BPA were hemoptysis in 7.4% and reperfusion injury in 3.4% of all interventions. The survival rate in the 6-MFU was 96.1%.

Impact of BPA therapy on physical capacity and pulmonary hemodynamics

At baseline, 49 (96.1%) patients were in WHO functional class ≥III which decreased to 6 (11.8%) patients at the 6-MFU (P<0.001) (Table 2). The median 6-minute-walk distance increased significantly (375.0 m [IQR 281–446] at BL vs. 409 m [IQR 332–446] at the 6-MFU; P = 0.017). Table 2 presents the data of the RHC and echocardiographic measurements at baseline and at 6-MFU. The meanPAP (BL: 39.5±12.1 mmHg vs. 6-MFU: 32.6±12.6 mmHg; P<0.001) and the PVR (BL: 516±219 dyn×sec×cm^{-5} vs. 6-MFU: 397±183 dyn×sec×cm^{-5}; P<0.001) decreased significantly.

Biomarkers at baseline and impact of BPA treatment on biomarker levels

At BL, the median hs-cTnT level was 11 (IQR 6–16) ng/L and the median NT-proBNP level was 820 (IQR 153–1872) ng/L. Among all patients, 16 (31.4%) showed a hs-cTnT above the 99th percentile at baseline.

NT-proBNP as marker reflecting hemodynamic changes showed a robust reduction after BPA treatment with 821 ng/l at BL to 159ng/l at the 6-MFU as published recently. [8]

Table 1. Sociodemographic characteristics, comorbidities, and medication at baseline.

Parameter	N or Mean (±SD) or Median (IQR)	%
Age at 1st BPA, y	63.1 (±11.5)	
Female gender	28	54.9
Body-mass index, kg/m^2	25.7 (±3.8)	
Current smoker	14	27.5
Diabetes mellitus	5	9.8
Dyslipidemia	7	13.7
Arterial hypertension	31	60.8
Chronic renal failure	10	19.6
GFR, ml/min	79.3 (62.2–93.9)	
Creatinine, μmol/l	0.94 (0.78–1.13)	
Atrial fibrillation	3	5.9
History of stroke	5	9.8
Coronary artery disease	9	17.9
History of cancer	9	17.6
Chronic obstructive pulmonary disease	4	7.8
History of acute pulmonary embolism	23	45.1
History of deep vein thrombosis VT	6	11.8
Procoagulant coagulopathy	2	3.9
OAC	51	100
ERA	6	11.8
PDE5 inhibitor	7	13.7
Riociguat	21	41.2
Riociguat alone	17	33.3
PDE5 inhibitor alone	5	9.8
ERA alone	2	3.9
Riociguat + PDE5 inhibitor	1	2.0
Riociguat + ERA	3	5.9
PDE5 inhibitor + ERA	1	2.0

Abbreviations: BPA = Balloon pulmonary angioplasty, ERA = endothelin receptor antagonist, GFR = glomerular filtration rate, OAC = oral anticoagulative therapy, PDE5 = phosphodiesterase type 5;

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Comparison of serum hs-cTnT levels with BL values revealed a significant decrease at all pre-specified time points following the first BPA, with the lowest value being measured at the 6-MFU (11 ng/l [IQR 6–16] vs. 7 ng/l [IQR 5–12]; P<0.001) (Fig 1).

The median percentage change in hs-cTnT at the 6-MFU was a reduction of 11% (IQR 0% change to a decrease of 43%; range of percent change [min-max]: increase of 39.0 to a decrease of 86.0%; range of absolute change [min-max]: increase of 10 to a decrease of 50 ng/l) (Table 2).

Out of 51 patients, 16 (31.4%) showed unchanged (n = 8; 15.7%) or even increased (n = 8; 15.7%) hs-cTnT level at the 6-MFU. In 9 (17.6%) patients, the hs-cTnT level remained above the 99th percentile at the 6-MFU. The 8 patients with unchanged hs-cTnT level were characterized by a static hs-cTnT level at the LOD (5ng/l) or below. Patients with an increase of the hs-cTnT level did not differ from the rest of the cohort regarding their functional baseline characteristics (age (p = 0.69), body mass index (p = 0.77), LV-EF (p = 0.43), TAPSE (p = 0.21),

Table 2. Functional, biomarker, echocardiographic, and hemodynamic data at BL and 6-MFU.

Parameter	Baseline	6-MFU	p-value
LVEF, %	60 (60–60)	65 (60–65)	0.002
TAPSE, mm	19 (13–20.5)	21.5 (17–24)	0.09
6-MWD, m	375.0 (281–445.5)	408.5 (332.3–445.8)	0.017
WHO FC (I-IV)	I:0; II:2; III:31; IV:18;	I:20; II:23; III:5; IV:1;	<0.001
Hs-cTnT, ng/l	11 (6–16)	7 (5–12)	<0.001
Hs-cTnT reduction, %	11 (0.0–43.0)		
NT-proBNP, ng/l	820.55 (153–1871.5)	159.3 (84.4–464.3)	<0.001
NT-proBNP reduction, %	53.6 (22.4–85.5)		
GFR, ml/min	79.3 (62.2–93.9)	79.6 (67.1–95.0)	0.22
Creatinine, μmol/l	0.94 (0.78–1.13)	0.88 (0.76–1.04)	0.09
RA pressure, mmHg	7.5 (±4.1)	6.1 (±2.7)	0.008
PCWP, mmHg	9.0 (8–12)	10.0 (8–11)	0.269
Diastolic PAP, mmHg	22.1(±8.2)	16.9 (±7.7)	<0.001
Systolic PAP, mmHg	67.8 (±21.6)	55.8 (±22.7)	<0.001
MeanPAP, mmHg	39.5(±12.1)	32.6 (±12.6)	<0.001
MeanPAP reduction, %	19.2 (4.3–28.7)		
PVR, dyn×sec×cm^{-5}	515.8 (±219.2)	396.9(±182.6)	<0.001
PVR, reduction %	23.4 (4.4–34.7)		
SVO2, %	66.4 (61.5–70)	70.4 (76.5–73)	0.003
CI, l/min/m^2	2.5 (±0.6)	2.5 (±0.5)	0.326

Abbreviations: CI = cardiac index, FC = functional class, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PAP = pulmonary artery pressure, PCWP = Pulmonary capillary wedge pressure, PVR = pulmonary vascular resistance, RA = right atrium, TAPSE = Tricuspid Annular Plane Systolic Excursion, WHO = World health organization, 6-MWD = 6-minute-walk-test-distance, 6-MFU = 6-month follow-up;

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meanPAP (p = 0.63), PVR (p = 0.38), WHO-FC (p = 0.40), 6-MWD (p = 0.14), GFR (p = 0.45), serum creatinine level (p = 0.41).

Association of hs-troponin T with the procedural extent, pulmonary hemodynamics, NT-proBNP levels and clinical outcome under BPA treatment

The hs-cTnT levels and the NT-proBNP levels correlated significantly (BL: $r_{rs} = 0.51$; $p \leq 0.001$; 6-MFU: $r_{rs} = 0.42$; p = 0.002). Correspondingly, patients with a persistent hs-cTnT level above the 99th percentile at the 6-MFU were characterized by significantly ($p<0.001$) higher NT-proBNP levels.

Invasively determined meanPAP and PVR significantly correlated with hs-cTnT with r_{rs} = 0.32 (p = 0.029) and $r_{rs} = 0.42$ (p = 0.005) at BL. There was no significant correlation with the meanPAP ($r_{rs} = 0.16$; p = 0.27) and the PVR ($r_{rs} = 0.26$; p = 0.10) at 6-MFU.

The hs-cTnT levels did not correlate with the WHO FC at BL ($r_{rs} = 0.24$; p = 0.10) but at the 6-MFU: $r_{rs} = 0.46$; p = 0.001). The relative change of the baseline hs-cTnT did not correlate significantly with the number of treated vessels ($r_{rs} = 0.11$; p = 0.53) or the number of BPA sessions ($r_{rs} = 0.25$; p = 0.10).

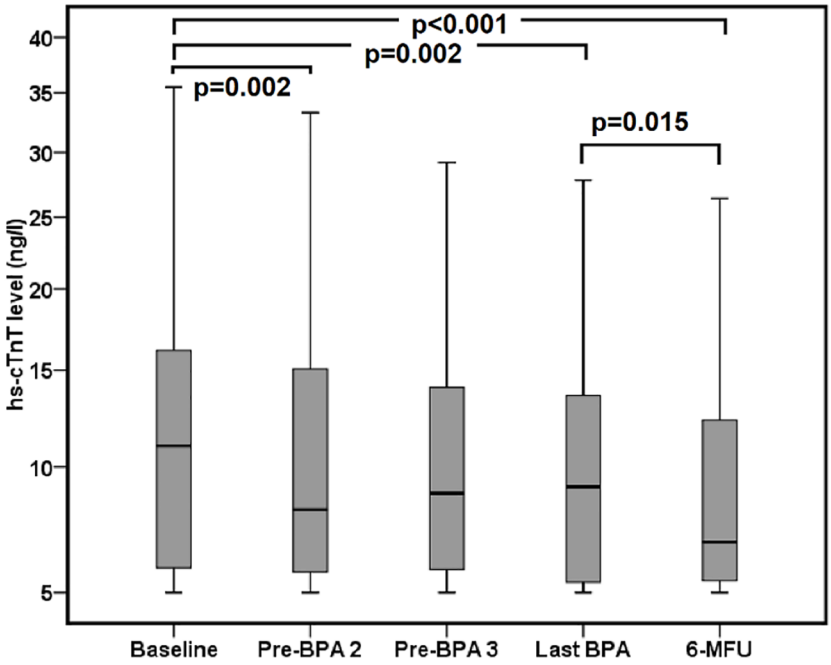

Fig 1. Analysis of the time course of hs-cTnT levels during staged BPA procedure (BPA = Balloon pulmonary angioplasty, hs-cTnT = high-sensitivity cardiac troponin T, 6-MFU = 6-month follow-up).

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Two patients died within the 6-MFU. In both deceased patients, an increase of the baseline hs-cTnT level was observed after the completion of the BPA sequence (patient 1: BL: 5.6 ng/l vs. last BPA: 8.4ng/l; patient 2: BL: 16.7ng/l vs. last BPA: 20.8ng/l).

Baseline hs-troponin T to stratify patients before BPA therapy

Among patients with a BL hs-cTnT above the 99th percentile (16 patients, 31.4%), 14 patients (87.5%) showed a decrease of hs-cTnT level at 6-MFU. In this subgroup, 12 patients (75.0%) showed concomitant a significant decrease of NT-proBNP levels >25%.

NT-proBNP levels were significantly higher among patients with a BL hs-cTnT level above the 99th percentile at BL (267.9ng/l [IQR 107.15–1212.5] vs. 1819.5ng/l [IQR 1112.0–4458.0]; p = 0.001) and within the 6-MFU (127.2ng/l [IQR 69.7–248.0] vs. 356.9ng/l [IQR 144–2010.0]; p = 0.005). Besides the NT-proBNP levels, the 16 patients with a BL hs-cTnT above the 99th percentile, showed a significantly higher PVR (522 dyn×sec×cm^{-5} [IQR 339–668] vs. 328 dyn×sec×cm^{-5} [IQR 208–491]; p = 0.021)) and borderline significant higher meanPAP (35mmHg [IQR 29–47 vs. 27mmHg [IQR 23–36]; p = 0.65), lower 6-MWD (275m [IQR 327–431] vs. 429m [IQR 371–447]; p = 0.077) at the 6-MFU. The differences regarding the TAPSE (17mm [IQR 13–23] vs. 24mm [IQR 18–26]; p = 0.171), LVEF (63% [IQR 58–65] vs. 65% [IQR 61–65]; p = 0.296) were not statistically significant.

Discussion

BPA is a promising treatment option for inoperable CTEPH patients. [1] Over the last decade, data about the beneficial effects accumulated and procedural improvements led to a high level of periprocedural safety. [3, 5, 6, 11, 14, 17, 18] In CTEPH, intravascular thrombotic obstruction compounded by vascular remodeling leads to an increased PVR and meanPAP. [1, 19, 20]

The pathological changes of pulmonary hemodynamics trigger an impairment of cardiac, particularly right ventricular, function. [21, 22] Right ventricular afterload elevation causes increased wall tension and leads to myofibrillar damage. [23] Natriuretic peptide levels correlate with myocardial wall stress and proved to indicate right ventricular remodeling and cardiac troponins are highly sensitive for the detection of myocardial injury. [9, 24–26] Accordingly, the aim of the present study was to characterize the time course of hs-cTnT mirroring myocardial damage in CTEPH patients undergoing BPA and to determine the relation to NT-proBNP levels as an indicator for cardiac wall stress.

The main findings of this study are: 1) Hs-cTnT levels decrease substantially after BPA showing significant difference already after the first procedure; 2) The hs-cTnT decrease is most distinct in patients with a hs-cTnT level above the 99th percentile at baseline. 3) The hs-cTnT levels correlate with NT-proBNP levels at baseline and in the follow-up indicating a relation to wall stretch induced hs-cTnT release.

Cardiac troponins I and T are the leading biomarkers for the detection of myocardial injury and are one corner stone in the diagnostic work up of suggested acute myocardial infarction. [12] However, cardiac troponins are not only released due to acute myocardial infarction. [23] Since the implementation of high-sensitive cardiac troponin assays with improved sensitivity, elevated cardiac troponin levels are regularly seen in patients with various cardiac diseases but no acute myocardial infarction. [23] Reversible conditions (cytosolic membrane leakage, transient ischemia, wall stretch) versus definite necrosis of cardiomyocytes are controversially discussed as underlying release mechanisms. [23, 27]

In our study, hs-cTnT levels were measured at BL and immediately in advance to each consecutive BPA session. Thus, the particular hs-cTnT level mirrors the degree of persistent myocardial stress followed by myocardial injury after an interval of 4 to 8 weeks to the previous BPA procedure.

Hs-cTnT levels decreased significantly starting with the first BPA treatment. It has to be mentioned, that NT-proBNP levels also decreased from BL to the last BPA but stabilized over time with no significant level changes after the last BPA compared to the 6-MFU. The hs-cTnT levels continuously decreased during all pre-specified time points including the 6-MFU. This observation indicates that the reverse cardiac remodeling process with decrease of right ventricular after load and therefore less ventricular wall stress starts already after the first BPA session. Interestingly, the reverse remodeling process seems to be ongoing beyond the last BPA procedure as indicated by further lowering hs-cTnT levels at the 6 months follow-up.

High-sensitivity cardiac troponin (hs-cTn) assays in daily clinical practice allow the assessment of low troponin levels with precise analytical accuracy. Cardiac troponin indicated disease severity and predicted worse outcome in mixed cohorts of patients with pulmonary hypertension. [28, 29] Völkers et al. observed elevated hs-cTnT levels in PH patients at rest and significant dynamics after the performance of cardiopulmonary exercise testing.

The hs-cTnT decrease was most pronounced in those patients who had hs-cTnT level above the 99th percentile at baseline. NT-proBNP levels were significantly higher at BL and within the 6-MFU among those patients with a hs-cTnT level above the 99th percentile at the 6-MFU.

NT-proBNP levels were significantly higher at the 6-MFU among those patients with a persistent hs-cTnT level above the 99th percentile. Patients with a BL hs-cTnT above the 99th percentile further showed higher PVR and meanPAP values and a lower 6-MWD at the 6-MFU. We hypothesize that hs-cTnT levels above the 99th percentile at BL or a lack of decrease under therapy accompanied by elevated NT-proBNP levels indicate the disease severity and probably ongoing cardiac damage.

In this context Kimura et al. reported that patients with higher meanPAP, PVR, and BNP levels at BL to be those with the highest decrease of hs-cTnT levels in the follow-up.

In facts, it is not known up to which degree of right ventricular remodeling, the RV-dysfunction is reversible under BPA therapy. [30] Although the right ventricular origin of this release is not proven, hs-cTnT dynamics correlated significantly with meanPAP and NT-proBNP. [27] In this context, Andreassen et al. reported low levels of NT-proBNP and troponin T to be a an indicator for reduced right ventricular strain in CTEPH patients. [11]

To the best of our knowledge, this is the first study employing hs-cTnT measurement at every stage in CTEPH patients undergoing BPA as a staged procedure. Our results show that hs-cTnT is decreasing stepwise under therapy, indicating a decrease of ongoing myocardial damage presumably due to reduced right ventricular afterload after BPA therapy. This assumption is strengthened by correlation of hs-cTnT-levels and NT-proBNP levels at baseline and in the 6-MFU.

Our study indicates that consecutive hs-cTnT and NT-proBNP measurement under staged BPA therapy might help to assess the effects of BPA on hemodynamics and impairment of right ventricular structure and function, which would lead to a better monitoring of BPA therapy.

Some limitations of this study need to be mentioned. The study included a relatively small number of patients. Nevertheless, our BPA program is among the largest worldwide and the observed results clearly demonstrate the significant decrease in hs-cTnT levels from baseline at every stage of the procedure. High-sensitive troponin assays enabled the detection of lower protein levels, but we can still not definitely define the exact pathophysiological meaning of low-level cardiac troponin. The prognostic value of elevated hs-cTnT levels, even below the 99th percentile has been investigated in in several non-CTEPH cohorts. The results of a large meta-analysis, including more than 65.000 individuals of a general population, associated elevated troponin concentrations, also below the 99th percentile, with a higher rate of mortality. [31] The assessment of the exact diagnostic value of low-level cardiac troponins in CTEPH patients undergoing BPA therapy requires prolonged follow-up periods. At present we can state, that in our cohort, even patients with troponin below the 99th percentile showed significant reduction of their baseline levels, which suggests to be response to reduced cardiac wall stress.

Cardiac troponin levels might also be influenced by other conditions like heart failure worsening or other adverse cardiac events. Within the follow-up we detected no progression of coronary artery disease or myocardial infarction within the 9 patients suffering from coronary artery disease at baseline. Left ventricular heart failure worsening seems to be unlikely in our cohort in face of a slight improvement of LVEF under BPA therapy.

In conclusion hs-cTnT is elevated in CTEPH patients and indicates ongoing subclinical myocardial damage presumably triggered by increased right ventricular afterload. The hs-cTnT level decreases significantly under BPA therapy and correlates with the reduction of right ventricular wall stress, indicated by NT-proBNP levels.

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ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASE

Mid-regional pro-atrial natriuretic peptide and copeptin as indicators of disease severity and therapy response in CTEPH

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ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) leads to right heart failure. Pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA) restore pulmonary haemodynamics and allow cardiac recovery. This study examined the relationship of copeptin and mid-regional pro-atrial natriuretic peptide (MR-proANP) levels to disease severity and therapy response.

Methods: This observational cohort study included 125 patients (55 PEA/70 BPA) who underwent treatment and completed a 6-/12-month follow-up. Biomarkers, measured at baseline, prior to every BPA and at follow-up, were compared to 1) severe disease at baseline (right atrial pressure (RAP) ⩾8 mmHg and cardiac index ⩽2.4 $L \cdot min^{-1} \cdot m^{-2}$) and 2) optimal therapy response (no persistent pulmonary hypertension combined with a normalised RAP (mean PAP ⩽25 mmHg, pulmonary vascular resistance (PVR) ⩽3 WU and RAP ⩽6 mmHg) or a reduction in mean PAP ⩾25%, PVR ⩾35% and RAP ⩾25%).

Results: Severely diseased patients had higher levels of MR-proANP (320 (246–527) $pmol \cdot L^{-1}$ *versus* 133 (82–215) $pmol \cdot L^{-1}$; p=0.001) and copeptin (12.7 (7.3–20.6) $pmol \cdot L^{-1}$ *versus* 6.8 (4.4–12.8) $pmol \cdot L^{-1}$; p=0.015) at baseline than the rest of the cohort. At baseline, MR-proANP (area under the curve (AUC) 0.91; cut-off value 227 $pmol \cdot L^{-1}$; OR 56, 95% CI 6.9–454.3) and copeptin (AUC 0.70; cut-off value 10.9 $pmol \cdot L^{-1}$; OR 1.5, 95% CI 1.2–1.9) identified severely diseased patients. After PEA/BPA, levels of MR-proANP (99 (58–145) $pmol \cdot L^{-1}$; p<0.001) and copeptin (6.3 (3.7–12.6) $pmol \cdot L^{-1}$; p=0.009) decreased and indicated optimal therapy response (MR-proANP <123 $pmol \cdot L^{-1}$ (AUC 0.70) and copeptin <10.1 $pmol \cdot L^{-1}$ (AUC 0.58)).

Conclusion: MR-proANP and copeptin levels are affected in CTEPH and decrease after therapy. MR-proANP identifies a severe disease status and optimal therapy response.

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The assessment of cardiac stress and impact of therapy is crucial in CTEPH. Serum levels of MR-proANP are associated with haemodynamic disease severity and therapy response, and might thus support individualised patient management. https://bit.ly/2QKwb7x

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Introduction

Up to 4% of the patients who survive an acute pulmonary embolism are later diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) [1]. The persistence of pulmonary artery obstructions, compounded by pulmonary vascular remodelling, progressively impairs pulmonary haemodynamics [1–4]. Under these conditions, elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) burden the right heart and cause compensatory right heart remodelling [1–4]. Without treatment, this sequence leads to right heart failure, which is the major determinant of outcome in CTEPH [5]. It should be noted that CTEPH is the only potentially curable subtype of pulmonary arterial hypertension [1], and surgical pulmonary endarterectomy (PEA) is the treatment of choice [1]. In patients in whom surgery is not feasible, a sequence of medical therapy with riociguat and balloon pulmonary angioplasty (BPA) should be considered [1, 6]. Both therapeutic approaches aim to restore pulmonary haemodynamics and thus allow right heart recovery to optimise patients' resilience and quality of life. A structured diagnostic work-up, including individualised risk stratification and assessment of therapy response, is challenging in daily clinical practice but crucial for an optimal outcome [1].

Noninvasive biomarkers of haemodynamic conditions and cardiac stress can provide valuable information in this context [7–10]. Atrial natriuretic peptide (ANP) is released upon cardiac (in particular, atrial) wall stress and has diuretic, vasodilatory and tissue-protective effects [11]. Further, an increase in circulating vasopressin is triggered by systemic stress, hypotension and an increase in plasma osmolality and impacts haemodynamics *via* peripheral vasoconstriction and renal reabsorption of sodium-free fluid [12]. Both biomarkers are characterised by low plasma protein stability, which limits the reproducibility of laboratory measurements and thus hampers their investigation in the context of cardiac diseases [12, 13]. Mid-regional pro-atrial natriuretic peptide (MR-proANP) and copeptin are by-products of ANP and vasopressin, respectively [12, 13]. Their higher plasma stability allows a valid equimolar measurement as surrogates for the mature proteins. ANP and MR-proANP levels correlate with disease severity and outcome in heart failure [13], acute pulmonary embolism [14] and pulmonary hypertension [15–17]. Copeptin gained importance in the diagnostic work-up of acute cardiovascular disease, particularly acute coronary syndrome [18]. In addition, copeptin was identified as a strong predictor of outcome in acute pulmonary embolism [19, 20]. Data on the relevance of MR-proANP and copeptin in patients with CTEPH are limited to animal models [21], small subcohorts and mixed pulmonary hypertension cohorts [15, 16, 22, 23]. There are no data on the time course of changes in these biomarkers after CTEPH therapy. The aim of the current study was to investigate the levels of MR-proANP and copeptin in CTEPH patients treated with PEA or BPA and assess their association with disease severity and therapy response.

Methods

Study population

The present observational cohort study included 125 patients with confirmed CTEPH who were treated by BPA (n=70) or PEA (n=55) at the Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany between 2014 and 2016 and who completed a 6-month follow-up (6-MFU) after the final BPA or a 12-month follow-up (12-MFU) after PEA. A total of 52 (74%) patients of the BPA cohort and 16 (29%) of the PEA cohort were also treated with riociguat. This was the result of the off-label character of other medication and the lack of any approved medication for CTEPH prior to 2014. Since then, riociguat has been approved for CTEPH treatment and recommended in the guidelines [1]. Thus, over time we adjusted our treatment approach and riociguat is administered for at least 3 months prior to possible BPA in inoperable CTEPH patients at our centre.

All patients were discussed in an interdisciplinary CTEPH conference to decide about the most appropriate individual treatment. The pre- and post-procedural management of the patients was recently published by our group [8, 24, 25]. All patients gave written informed consent. The ethics board of the Justus Liebig University of Giessen approved the study (AZ 43/14). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Pulmonary endarterectomy and balloon pulmonary angioplasty

PEA surgery and BPA interventional therapy were performed as standardised techniques. The detailed procedures have been published previously (PEA[25]/BPA[24]).

Right heart catheterisation

Right heart catheterisation was routinely performed *via* the right internal jugular vein using a 6F sheath and a standard Swan–Ganz catheter. The medication was not modified prior to or during the procedure.

Laboratory assessment

Venous blood samples for biomarker analysis were collected in plain tubes at baseline prior to the PEA or first BPA procedure, before every consecutive BPA procedure in BPA patients, and at 6-MFU or 12-MFU. All measurements were carried out batch-wise on thawed samples by experienced staff blinded to patient characteristics.

Copeptin was measured in serum/plasma (EDTA, heparin) by TRACE (time-resolved amplified cryptate emission) technology (BRAHMS Copeptin proAVP KRYPTOR assay, Kryptor Compact Plus; BRAHMS GmbH, Hennigsdorf, Germany): lower detection limit (LOD) 0.69 pmol·L^{-1}; standard curve range (SCR) 0.7–2000 pmol·L^{-1}; intra-assay coefficient of variation (CV)<15%; inter-assay CV<18%.

MR-proANP was measured in serum by TRACE technology (BRAHMS MR-proANP KRYPTOR assay, Kryptor Compact Plus; BRAHMS GmbH): LOD 2.1 pmol·L^{-1}; SCR 2.1 to 10 000 pmol·L^{-1}; intra-assay CV ⩽5%; inter-assay CV ⩽6.5%.

Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were measured using an electrochemiluminescence immunoassay (NT-proBNP assay, Elecsys Analyser 2010; Roche Diagnostics, Mannheim, Germany): LOD 5 ng·L^{-1}; SCR 5 to 35 000 ng·L^{-1}. The lowest concentration measurable with a CV of 20% is 50.0 ng·L^{-1}. At the cut-off value of 150 ng·L^{-1} the CV is <3%.

Statistical analysis

All continuous variables are expressed as mean±standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical variables are reported as number and percentage. Parametric distribution was assessed using the Shapiro–Wilk test. Subcohorts at baseline, prior to PEA/BPA therapy, or at the follow-up were compared using the t-test for normally distributed parameters and the Mann–Whitney U-test for all other continuous variables. The Chi-squared test and Fisher–Yates test were used for categorical variables. Parameters that were obtained at baseline and at the 6-/12-MFU were subjected to paired sample testing. We used *t*-test for normally distributed parameters and the Wilcoxon signed-rank test for other continuous variables.

Correlations were analysed using bivariate Spearman correlation (Pearson's ρ). For further assessment of an association between biomarkers and haemodynamics, the cohort was divided into tertiles according to the degree of impairment of each haemodynamic parameter and biomarker levels were analysed in each subgroup.

Two predefined study outcomes were assessed:

1. Severe disease: In accordance with the recommendations in the guidelines for diagnosis and treatment of pulmonary hypertension [1], this outcome was defined as a right atrial pressure (RAP) ⩾8 mmHg in combination with a cardiac index ⩽2.4 L·min^{-1}·m^{-2}.
2. Optimal therapy response: This was defined as pulmonary haemodynamics below the thresholds of pulmonary hypertension (mean PAP ⩽25 mmHg, PVR ⩽3 WU) [1] and a normalised RAP (⩽6 mmHg) [26] or at least a distinct reduction in all of the three haemodynamic parameters (mean PAP ⩾25%, PVR ⩾35% and RAP ⩾25%) after PEA or BPA. The rational for this parameter selection was to address pulmonary haemodynamics (PVR, mean PAP) as well as a recovery of right heart failure (RAP), which is one major determinant of outcome in CTEPH.

The diagnostic performance of noninvasive biomarkers and certain other diagnostic findings to indicate study outcomes was analysed using receiver operating characteristics (ROC). Results are presented as AUC with corresponding 95% confidence intervals. The optimal cut-off values with regard to study outcomes were calculated using Youden index quantification. AUCs were compared using DeLong test.

To assess the prognostic performance of optimal biomarker cut-off levels with regard to study outcomes, sensitivity, specificity, and negative (NPV) and positive (PPV) predictive values were calculated. Results are presented as odds ratios with corresponding 95% confidence intervals.

Statistics were performed with SPSS software (IBM Corp., Armonk, NY, USA), version 21.0. A two-tailed p-value <0.05 was considered to be statistically significant.

Results

Patient characteristics, biomarker levels, treatment and effects of therapy

The sociodemographic and clinical data of all 125 patients (51 women; mean age (±SD) 59±14 years) enrolled in the study are presented in table 1. The indications for an interventional treatment were peripheral lesions in 65 (93%) patients and persisting pulmonary artery obstructions after prior PEA in 5 (7%) patients. The 70 patients who were allocated for an interventional treatment underwent a total of 413 BPA sessions (median 6 (5–7) per patient). Table 2 shows the effects of therapy on haemodynamics and

TABLE 1 Sociodemographic characteristics and comorbidities at baseline of the entire cohort

Parameter	
Subjects n	125
Age years,	59±14
Female sex	51 (40.8)
Body mass index kg·m^{-2}	25.9±4.5
Chronic renal failure	26 (20.8)
Estimated glomerular filtration rate mL·min^{-1}	82.5±25.7
Creatinine µmol·L^{-1}	86±27
Coronary artery disease	20 (16.0)
History of cancer	18 (14.4)
Chronic obstructive pulmonary disease	8 (6.4)
History acute pulmonary embolism	110 (88.0)
History of isolated deep vein thrombosis	18 (14.4)
History of splenectomy	9 (7.2)
History of chronic inflammatory bowel disease	1 (<1)
Systemic inflammatory disease	2 (1.6)

Values are presented as n (%) or mean±SD, unless otherwise stated.

physical capacity. The beneficial effects on haemodynamics were more apparent 12 months after PEA compared with 6 months after BPA.

The measured serum biomarker levels of MR-proANP, copeptin and NT-proBNP at baseline are illustrated in table 3. No differences between PEA and BPA patients were observed: MR-proANP (p=0.66), copeptin (p=0.52), NT-proBNP (p=0.63). MR-proANP levels correlated with PVR (ρ=0.51; p<0.001), RAP (ρ=0.51; p<0.001) and mean pulmonary arterial pressure (mPAP) (ρ=0.44; p<0.001), whereas copeptin showed no relevant correlations with haemodynamics (table 4). Correlations with other diagnostic findings at baseline are also illustrated in table 4. The levels of MR-proANP and copeptin in subgroups divided according to the degree of haemodynamic impairment (divided into tertiles) are illustrated in figures 1a–d (MR-proANP) and figures 1e–h (copeptin).

TABLE 2 Comparison of diagnostic findings at baseline and 6-month (balloon pulmonary angioplasty (BPA)) or 12-month (pulmonary endarterectomy (PEA)) follow-up

Parameter	Baseline			6-MFU/12-MFU			p-value (total)
	Total	PEA	BPA	Total	PEA	BPA	
WHO-FC n							
I	0	0	0	69	30	39	
II	14	14	0	45	22	23	
III	78	31	47	9	3	6	
IV	33	10	23	2	0	2	
RAP mmHg	7 (5–9)	7 (5–9)	7 (5–9)	5 (4–7)	5 (4–7)	5 (4–7)	<0.001
PCWP mmHg	9 (8–12)	9(8–13)	9 (8–11)	9 (7–11)	9 (7–12)/	9 (8–11)	0.175
Mean PAP mmHg	42 (36–49)	44(36–50)	40 (36–49)	25 (20–33)	20 (17–24)	30 (25–35)	<0.001
Mean PAP reduction %				35 (21–53)	53 (36–63)	10 (6–16)	
PVR Wood units	6.8 (5.3–9.6)	7.1 (5.2–11.9)	6.8 (5.2–8.6)	3.4 (2.4–4.9)	2.5 (1.8–3.5)	3.9 (3.0–5.3)	<0.001
PVR reduction %				46 (25–63)	63 (40–81)	40 (23–54)	
CI L·min^{-1}·m^{-2}	2.4 (2.1–2.8)	2.3 (1.9–2.6)	2.6 (2.1–3.0)	2.6 (2.3–2.9)	2.4 (2.3–2.8)	2.7 (2.4–3.0)	0.009
6MWD m	405±99	409±145	410±101	445±113	438±129	449±106	<0.001
LVEF %	55 (55–60)	55 (55–60)	55 (55–60)	55 (55–60)	55 (55–58)	55 (55–60)	0.21
TAPSE mm	19±5	19±6	19±5	19±5	17±4	21±4	0.90

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. 6-/12-MFU: 6-/12-month follow-up; WHO: World Health Organization; FC: functional class; RAP: right atrial pressure; PCWP: pulmonary capillary wedge pressure; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; CI: cardiac index; 6MWD: 6-min walk distance; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion.

TABLE 3 Comparison of biomarker findings at baseline and 6-month (balloon pulmonary angioplasty (BPA)) or 12-month (pulmonary endarterectomy (PEA)) follow-up

Parameter	Baseline			6-MFU/12-MFU			p-value (total)
	Total	PEA	BPA	Total	PEA	BPA	
MR-proANP pmol·L^{-1}	156 (91–246)	170 (97–243)	145 (86–246)	99 (58–145)	98 (57–160)	101 (59–142)	<0.001
Copeptin pmol·L^{-1}	7.7 (4.6–14.2)	8.0 (4.4–14.7)	7.1 (4.6–13.5)	6.3 (3.7–12.6)	6.2 (3.8–13.7)	6.4 (3.7–12.2)	0.009
NT-proBNP ng·L^{-1}	845 (178–1875)	1094 (136–2163)	744 (195–1564)	142 (72–335)	192 (98–408)	121 (67–243)	<0.001
Creatinine µmol·L^{-1}	86±28	88±31	84±0.30	80±26	81±31	78±21	<0.001
eGFR mL·min^{-1}·m^{-2}	82.5±25.7	81.1±24.7	83.6±26.6	91.7±37.7	92.0±27.1	91.5±44.5	<0.001
eGFR ⩽60 mL·min^{-1}·m^{-2}		21 (16.8)			12 (9.6)		

Data are presented as median (interquartile range), mean ±SD or n (%), unless otherwise stated. 6-/12-MFU: 6-/12-month follow-up; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; eGFR: estimated glomerular filtration rate.

Identification of patients with more severe disease (primary outcome)

Haemodynamically compromised patients with severe disease (n=17) had higher baseline levels of MR-proANP (320 (246–527) pmol·L^{-1} *versus* 133 (82–215) pmol·L^{-1}; p=0.001), copeptin([12.7 (7.3–20.6) pmol·L^{-1} *versus* 6.8 (4.4–12.8) pmol·L^{-1}; p=0.015) and NT-proBNP (2986 (1474–5255) ng·L^{-1} *versus* 544 (110–1393) ng·L^{-1}; p=0.001). The strongest association between biomarker concentration and severe disease was found for MR-proANP levels ⩾227 pmol·L^{-1} (AUC 0.91; OR 56 (95% CI 6.9–454.3)) and NT-proBNP ⩾1050 ng·L^{-1} (AUC 0.89; OR 4.9 (95% CI 1.5–15.8)) (AUCs: p=0.31). Table 5 shows the diagnostic performance of other diagnostic findings to identify patients with severe disease.

Biomarker dynamics after PEA/BPA

Table 3 illustrates the comparison of serum biomarker levels at baseline and at follow-up. In the PEA cohort, MR-proANP (p=0.001), copeptin (p=0.017) and NT-proBNP (p<0.001) levels decreased from baseline to 12-MFU. In the BPA cohort, MR-proANP (p<0.001) and NT-proBNP (p<0.001) decreased significantly from baseline to 6-MFU, but copeptin did not change (p=0.18). The analysis of biomarker level dynamics during the staged BPA procedures showed a continuous decrease in MR-proANP levels at all pre-specified time points following the first BPA, with the lowest value being measured at the 6-MFU (figure 2), but no dynamics of copeptin levels (supplementary figure).

Identification of patients with optimal therapy response (secondary outcome)

The strongest association between biomarker concentration and therapy response was observed for MR-proANP levels ⩽123 pmol·L^{-1} (AUC 0.70; OR 5.2, 95% CI 2.0–13.5) and NT-proBNP ⩽369 ng·L^{-1}

TABLE 4 Bivariate Spearman correlation of biomarker levels and other diagnostic findings at baseline

Parameter	MR-proANP pmol·L^{-1}	Copeptin pmol·L^{-1}
Age years	ρ=0.20; p=0.03	ρ=0.28; p=0.002
Body mass index kg·m^{-2}	ρ=−0.29; p=0.001	ρ=−0.06; p=0.53
GFR mL·min^{-1}	ρ=−0.31; p<0.001	ρ=−0.27; p=0.003
Serum creatinine µmol·L^{-1}	ρ=0.31; p<0.001	ρ=0.35; p<0.001
mPAP mmHg	ρ=0.44; p<0.001	ρ=0.07; p=0.47
PVR WU	ρ=0.51; p<0.001	ρ=0.07; p=0.46
RAP mmHg	ρ=0.51; p<0.001	ρ=0.26; p=0.008
CI·min^{-1}·m^{-2}	ρ=−0.36; p<0.001	ρ=−0.13; p=0.15
6MWD m	ρ=−0.26; p=0.03	ρ=−0.27; p=0.02
LVEF %	ρ=−0.30; p=0.002	ρ=−0.03; p=0.74
TAPSE mm	ρ=−0.28; p=0.004	ρ=−0.20; p=0.04

MR-proANP: mid-regional pro-atrial natriuretic peptide; GFR: glomerular filtration rate; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; CI: cardiac index; 6MWD: 6-min walk distance; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion.

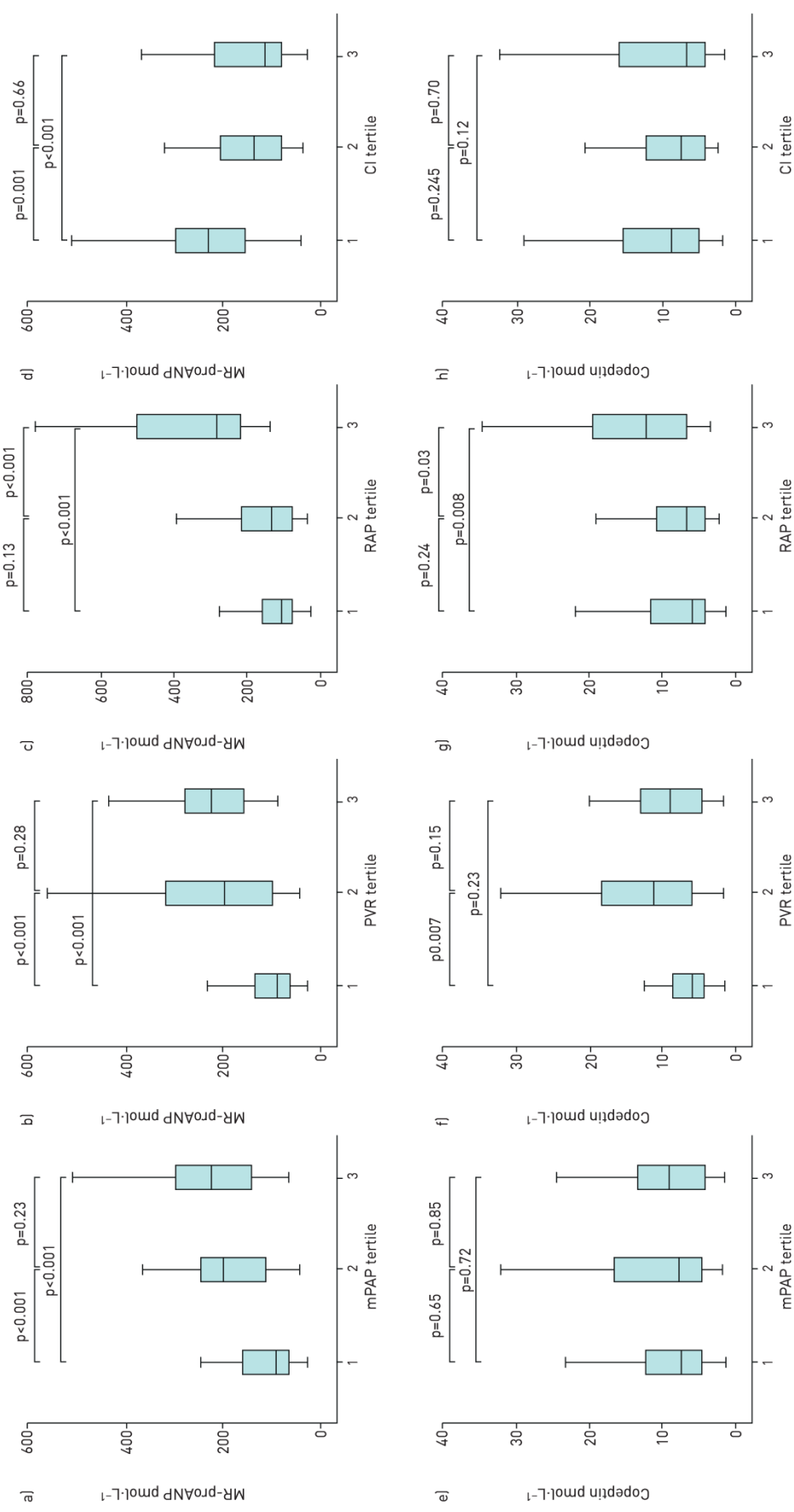

FIGURE 1 Biomarker levels (a–d: mid-regional pro-atrial natriuretic peptide (MR-proANP); e–h: copeptin) as a function of haemodynamic parameter. The cohort of n=125 chronic thromboembolic pulmonary hypertension patients was divided into tertiles for each haemodynamic parameter according to the following cut-off values: a, e) mean pulmonary arterial pressure (mPAP; ⩽38/⩽47 mmHg); b, f) pulmonary vascular resistance (PVR; ⩽5.7/⩽8.3 WU); c, g) right atrial pressure (RAP; ⩽5/⩽8 mmHg); and d, h) cardiac index (CI; ⩽2.1/⩽2.7 L·min^{-1}·m^{-2}).

TABLE 5 Prognostic performance of different parameters for the identification of patients with severe disease (primary outcome) and optimal therapy response (secondary outcome)

	Cut-off value	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	NPV (%, 95% CI)	PPV (%, 95% CI)	OR (95% CI)
Identification of patients at a severe disease state (primary outcome); n=17							
MR-proANP pmol·L^{-1}	227	0.91 (0.86–0.97)	93 (68–100)	80 (70–88)	99 (92–100)	43 (33–54)	56 (6.9–454.3)
Copeptin pmol·L^{-1}	10.9	0.70 (0.57–0.83)	67 (38–88)	71 (61–80)	93 (86–96)	27 (19–38)	1.5 (1.2–1.9)
NT-proBNP ng·L^{-1}	1050	0.89 (0.82–0.96)	100 (79–100)	65 (54–75)	100 (100)	31 (26–38)	4.9 (1.5–15.8)
eGFR mL·min^{-1}·m^{-2}	66	0.68 (0.52–0.83)	53 (28–77)	82 (73–90)	91 (87–95)	33 (21–48)	5.3 (1.8–15.8)
6-min walk distance m	355	0.72 (0.52–0.92)	67 (30–93)	78 (66–88)	94 (85–97)	33 (20–49)	7.2 (1.5–32.9)
WHO functional class	III	0.67 (0.53–0.81)	100 (80–100)	11 (5–19)	100 (100)	15 (5–19)	1.2 (1.1–1.3)
TAPSE mm	18	0.70 (0.54–0.85)	67 (86–96)	69 (57–79)	93 (86–96)	26 (18–36)	4.4 (1.4–14.3)
Identification of optimal therapy responders (secondary outcome); n=53							
MR-proANP pmol·L^{-1}	123	0.70 (0.60–0.79)	87 (74–94)	45 (31–59)	82 (68–91)	53 (47–59)	5.2 (2.0–13.5)
Copeptin pmol·L^{-1}	10.1	0.58 (0.47–0.69)	81 (68–91)	39 (27–53)	74 (60–85)	49 (43–55)	2.8 (1.2–6.7)
NT-proBNP ng·L^{-1}	369	0.64 (0.53–0.75)	96 (85–100)	28 (16–43)	90 (68–97)	49 (44–54)	8.4 (1.8–39.2)
eGFR mL·min^{-1}·m^{-2}	89	0.66 (0.56–0.77)	68 (54–80)	66 (52–78)	74 (65–81)	59 (49–69)	4.1 (1.9–9.2)
6-min walk distance m	494	0.72 (0.61–0.84)	63 (45–79)	77 (61–88)	74 (64–82)	66 (52–78)	5.6 (2.1–15.0)
WHO functional class	III	0.65 (0.55–0.76)	96 (87–100)	14 (6–26)	84 (54–96)	45 (42–48)	4.3 (0.86–21.0)
TAPSE mm	18	0.58 (0.45–0.70)	60 (43–75)	24 (12–45)	45 (30–61)	36 (30–44)	0.47 (0.18–1.2)

AUC: area under the curve; CI: confidence interval; NPV: negative predictive values; PPV: positive predictive values; OR: odds ratio; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; WHO: World Health Organization; TAPSE: tricuspid annular plan systolic excursion.

(AUC 0.64; OR 8.4, 95% CI 1.8–39.2) (AUC: p=0.83). Table 5 illustrates the diagnostic performance of biomarker levels measured at 6-/12-MFU and other diagnostic findings to identify patients with optimal therapy response after PEA or BPA (n=53). In total, 34 (27.2%) of the patients showed an mPAP ⩽20 mmHg at the follow-up.

Discussion

In the course of CTEPH disease progression, cardiac compensatory adaption mechanisms gradually fail, which leads to right heart failure [2, 4]. This eventually affects the systemic circulation, which leads to a deteriorating clinical status and strongly correlates with adverse outcome [2–5]. Therefore, noninvasive measurement of biomarkers that mirror haemodynamic conditions and right heart stress is a valuable adjunct for individual assessment of disease severity, risk stratification and therapy monitoring [1, 7–9, 27].

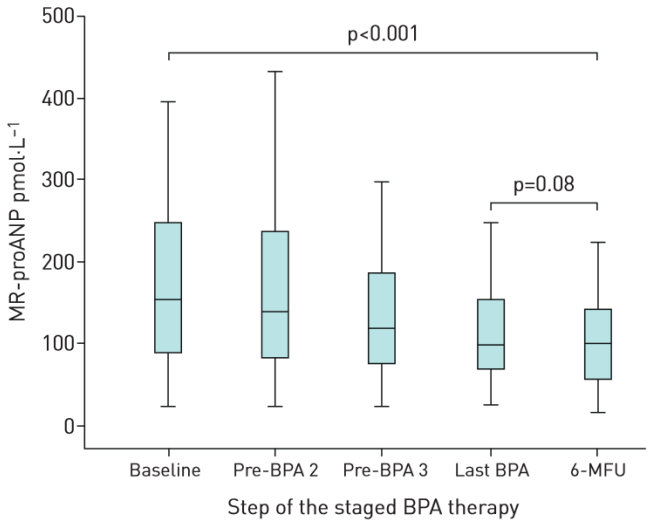

FIGURE 2 Dynamics of mid-regional pro-atrial natriuretic peptide (MR-proANP) levels during staged balloon pulmonary angioplasty (BPA) procedures. Biomarker measure-ment was carried out at the specified stage in BPA therapy of 55 chronic thromboembolic pulmonary hypertension patients. 6-MFU: 6-month follow-up.

Key findings

We determined that baseline MR-proANP levels are associated with disease severity defined by haemodynamic parameters in CTEPH and decrease after PEA/BPA. Copeptin levels are lower in CTEPH than in acute cardiovascular disease and do not substantially change after therapy. MR-proANP was associated with an AUC of 0.91 in ROC analysis for the identification of patients with impaired haemodynamics and thus severe disease (primary outcome) at baseline. MR-proANP identified patients with optimal therapy response (secondary outcome) with an AUC of 0.70 at the 6-MFU after BPA and at the 12-MFU after PEA.

MR-proANP and copeptin in patients with CTEPH

Natriuretic peptides are released from the myocardium in response to an increased wall tension due to volume or pressure overload [11, 15]. Circulating levels of NT-proBNP strongly correlate with haemodynamic disease severity in pulmonary hypertension and CTEPH [1, 8, 9, 15, 16, 23]. However, it should be noted that subtypes of natriuretic peptides show different expression characteristics [11]. In contrast to NT-proBNP, ANP mainly derives from the atria [11] and thus predominantly reflects right atrial stress. Right atrial dilatation, a consequence of chronic right ventricular dysfunction in pulmonary hypertension, is usually detected by imaging and has been shown to be a strong predictor of outcome [28]. Measurement of ANP/MR-proANP levels provides a simple and noninvasive way of obtaining this information. An MR-proANP level of 120 pmol·L^{-1} was shown to rule out acute heart failure with a sensitivity >90% [29]. In acute pulmonary embolism [17] and different forms of pulmonary hypertension [15, 16, 23], the reported median MR-proANP level ranges from 105 to 201 pmol·L^{-1} and was 130 pmol·L^{-1} in a small subcohort of seven CTEPH patients [15]. The median MR-proANP level of 156 (91–246) pmol·L^{-1} in our cohort is comparable to these data and reflects chronic cardiac stress in the majority of CTEPH patients. The hypothesis that MR-proANP can be used as a noninvasive surrogate of atrial stress is supported by the correlation of MR-proANP levels and RAP in our cohort.

Besides expression characteristics, the independence of MR-proANP levels from obesity and anaemia might also be a useful feature in selected patients [30].

Vasopressin and copeptin are released from the hypothalamus in response to hypotension, systemic stress and changes in plasma osmolality [12]. Vasopressin acts as a fast regulator of fluid homeostasis through the promotion of renal salt-free fluid reabsorption and peripheral vasoconstriction [12]. Whereas cardiac wall stress [8, 10] and subacute myocardial ischaemia [7, 10] are reflected by elevated natriuretic peptides and cardiac troponins in CTEPH, vasopressin or its derivative copeptin might serve as a surrogate for the impairment of systemic circulation as a result of progressive right heart failure. In acute pulmonary embolism, median copeptin levels ranging between minimum values of 10 and 14 pmol·L^{-1} up to values of 705 pmol·L^{-1} were observed [19, 20]. In studies including mixed cohorts of patients with pulmonary hypertension and only a very small number of CTEPH patients, the median copeptin level ranged from 8 to 20 pmol·L^{-1}, which is comparable to our observations [16, 22, 23]. In acute pulmonary embolism a copeptin level of 24 pmol·L^{-1} was identified as the optimal cut-off value to predict adverse outcome [19], and a level of 10 pmol·L^{-1} is used to rule out acute myocardial infarction [31]. In the present study, median copeptin levels at baseline (8 pmol·L^{-1}) and follow-up (6 pmol·L^{-1}) were low. This might be explained by the function of vasopressin as an acute, fast-acting regulator of haemodynamic imbalance and the fact that the majority of CTEPH patients were not in an acute, life-threatening situation with acute haemodynamic impairment at the time of admission (and study enrolment) for elective BPA or PEA.

If noninvasive biomarker measurement is used as a diagnostic tool, potential confounders need to be considered. Chronic renal failure frequently occurs as one negative side effect of pulmonary hypertension and right heart failure [32, 33]. In this context, the decrease of renal clearance and the cardiac stress impacts biomarker levels [34]. This diagnostic limitation is moderate in patients with preserved renal function (estimated glomerular filtration rate (eGFR) >60 mL·min^{-1}·m^{-2}) whereas adapted cut-off values have to be used in patients with chronic renal failure [34]. In our cohort, the majority of patients had preserved renal function or slightly reduced eGFR at baseline. PEA and BPA lead to an improvement of renal function, which lowered the number of patients with an eGFR ⩽60 mL·min^{-1}·m^{-2} from 21 (16.8%) at baseline to 12 (9.6%) at follow-up. Our data are not representative to demonstrate an impact of renal function on MR-proANP and copeptin levels. Both biomarkers correlated moderately with serum creatinine and eGFR at baseline in our cohort. Thus, the individual renal function should be considered when serum levels of both biomarkers are assessed.

Biomarker-based identification of patients with severe disease

Published data demonstrate the superiority of MR-proANP compared with established biomarkers for predicting an adverse outcome in chronic heart failure [13], pulmonary embolism [17] and pulmonary

hypertension [16]. In heart failure, the additive measurement of MR-proANP improved disease detection and risk stratification compared to a sole measurement of brain natriuretic peptides [35, 36]. In a cohort of 710 patients who were admitted due to dyspnoea, no other natriuretic peptide performed better than MR-proANP as a predictor of 5-year survival.

In our study, CTEPH patients with higher mPAP, PVR, RAP and lower cardiac index had higher levels of MR-proANP, which conforms with the data from a mixed pulmonary hypertension cohort of KAISER *et al.* [15]. Consistent with this, the 17 patients of our cohort with severe disease (primary outcome) had higher MR-pro-ANP levels than the rest of the cohort. Patients with a calculated optimal MR-proANP cut-off value $\geqslant$227 pmol·L^{-1} had a 56-fold increased risk of impaired haemodynamics and thus severe disease (95% CI 6.9–454.3). In this context, MR-proANP performance was at least comparable to NT-proBNP and superior to that of copeptin and other diagnostic findings, including 6-min walking distance, World Health Organization functional class (WHO-FC) and tricuspid annular plane systolic excursion (TAPSE) (table 5). MR-proANP measurement addresses not only right heart stress in general but also right atrial stress and the associated retrograde right heart failure, which might be the strength of this parameter.

Certain studies have revealed an association of copeptin levels and outcome in pulmonary hypertension; however, this was predominantly with an inferior predictive value compared with natriuretic peptides [16, 23]. While copeptin levels correlated with functional capacity and clinical symptoms in cohorts of patients with different types of pulmonary hypertension [16, 22, 23], the studies report inconsistent data concerning the correlation with pulmonary and systemic haemodynamics [16, 22]. In our cohort, there was no relevant correlation of copeptin levels with haemodynamic parameters. The only association we observed was that patients with the highest RAP tertile had distinctly elevated copeptin levels at baseline. Accordingly, RAP was the main driver for the observed higher copeptin levels in patients with severe disease compared with the rest of the cohort. Elevation of copeptin above the calculated optimal cut-off level of 10.9 pmol·L^{-1} was associated with an OR of only 1.5 (95% CI 1.2–1.9) to identify patients with severe disease, which is inferior compared with MR-proANP, NT-proBNP and other diagnostic parameters.

Identification of patients with optimal therapy response

Data on MR-proANP levels after established therapy for pulmonary hypertension (secondary outcome), particularly after surgical or interventional CTEPH treatment, are not available. In the current study, PEA and BPA led to a decrease in mPAP and PVR that was comparable to previously published data from our group and other cohorts [8, 25, 37]. The consequently reduced right heart stress was mirrored by a decrease in MR-proANP levels in the current study, irrespective of the therapeutic approach. The time course of MR-proANP levels during BPA therapy with a stepwise decrease after each session and an ongoing decrease at the follow-up illustrates progressive recovery of retrograde right heart failure. An MR-proANP concentration of 123 pmol·L^{-1} at follow-up was identified as the best threshold to identify patients with an optimal therapy response.

Less is known about the impact of pulmonary hypertension therapies on copeptin levels. A study by NICKEL *et al.* [22] is the only one that reported decreasing levels of copeptin in patients with pulmonary artery hypertension who received targeted medication. In our study, a slight decrease in copeptin levels (from 8 to 6 pmol·L^{-1}) was observed after PEA, but not after BPA. Copeptin levels above the calculated optimal cut-off value of 10.1 pmol·L^{-1} predicted an optimal haemodynamic therapy response; however, the overall prognostic performance was poor, as indicated by an AUC of only 0.58. As discussed above, this further indicates that vasopressin/copeptin is a better marker of acute haemodynamic compromising diseases rather than of chronic processes.

Study limitations

First, the absolute number of patients included in this study was relatively small with heterogeneous treatment groups. Second, the follow-up assessment after PEA and BPA is performed in different intervals after treatment, which might limit the comparability between the treatment groups. Third, follow-up in this study is limited to 12 months after PEA and 6 months after BPA. However, the results of the biomarker analysis are consistent between CTEPH patients treated with PEA and those treated with BPA.

Conclusion

Serum levels of MR-proANP are associated with haemodynamic disease severity in CTEPH patients, providing evidence in favour of using this biomarker for individual risk stratification and assessment of therapy response. Further, the continuous decrease in MR-proANP levels after each BPA session parallel the immediate and beneficial short-term effects of this therapy. However, the clinical applicability is limited at the current state. Further studies are needed to confirm the association of MR-proANP levels to

progressive right heart failure, and long-term data are required to assess the performance as a predictor of outcome.

Copeptin showed a weak diagnostic performance in CTEPH and thus appears to be a marker of acute rather than chronic haemodynamic impairment.

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ORIGINAL ARTICLE

Galectin-3, GDF-15, and sST2 for the assessment of disease severity and therapy response in patients suffering from inoperable chronic thromboembolic pulmonary hypertension

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ABSTRACT

Purpose: This study examined sST2, GDF-15, and galectin-3 as indicators of disease severity and therapy response in chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: This study included 57 inoperable CTEPH patients who underwent balloon pulmonary angioplasty and 25 controls without cardiovascular disease. Biomarker levels were examined in relation to advanced hemodynamic impairment [tertile with worst right atrial pressure (RAP) and cardiac index], hemodynamic therapy response [normalized hemodynamics (meanPAP $\leq$25 mmHg, PVR $\leq$3 WU and RAP $\leq$6 mmHg) or a reduction of meanPAP $\geq$25%; PVR $\geq$ 35%, RAP $\geq$25%].

Results: GDF-15 [820 (556–1315) pg/ml vs. 370 (314–516) pg/ml; $p < 0.001$] and sST2 [53.7 (45.3–74.1) ng/ml vs. 48.7 (35.5–57.0) ng/ml; $p = 0.02$] were higher in CTEPH patients than in controls. At baseline, a GDF-15 level $\geq$1443 pg/ml (AUC 0.88; OR 31.4) and a sST2 level $\geq$65 ng/ml (AUC 0.80; OR 10.9) were associated with advanced hemodynamic impairment. At follow-up GDF-15 $\leq$ 958 pg/ml (AUC = 0.74, OR 18) identified patients with optimal hemodynamic therapy response and $\leq$760 pg/ml (AUC = 0.79, OR 14).

Conclusion: GDF-15 and sST2 levels are higher in CTEPH and identified patients with advanced hemodynamic impairment. Further, decreased GDF-15 levels at follow-up were associated with hemodynamic therapy response. The diagnostic strength was not superior to NT-proBNP.

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Galectin-3; GDF-15; ST2; BPA; CTEPH; biomarker; remodelling

1. Introduction

In chronic thromboembolic pulmonary hypertension (CTEPH), right ventricular afterload increases as a result of persisting pulmonary artery obstructions, leading to impaired pulmonary hemodynamics (Muller and Liebetrau 2016, Simonneau *et al.* 2017, Olsson *et al.* 2017). During disease progression, initial compensatory right heart adaptation gradually fails and right heart failure impacts the systemic circulation (Ogo 2015, Tatebe *et al.* 2016, Simonneau *et al.* 2017). The progression through this sequence parallels progression of disease severity and is associated with worse outcome. Pulmonary endarterectomy is the treatment of choice in CTEPH, but for inoperable patients, balloon pulmonary angioplasty (BPA) may be considered as an interventional treatment option (Kataoka *et al.* 2012, Mizoguchi *et al.* 2012, Galiè *et al.* 2016, Muller and Liebetrau 2016, Wilkens *et al.* 2016, Wiedenroth 2018). This specific therapy can improve pulmonary hemodynamics and interrupt progressive right heart failure (Galiè *et al.* 2016, Wilkens *et al.* 2016).

Individual assessment of disease severity is crucial for therapeutic decision making and risk stratification. A major focus lies on the detection and quantification of right heart maladaptation and remodelling, which is often challenging, even with modern cardiac imaging techniques. Non-invasive biomarker measurement might be a valuable diagnostic adjunct in this context (Mueller *et al.* 2015, Passino 2015). Natriuretic peptides are well established indicators of myocardial wall stress. However, the effects of chronic pulmonary hemodynamic impairment are merely limited to increased myocardial wall stress, but also cause chronic maladaptive right heart remodelling, failure and systemic stress. Chronic tissue damage, inflammation and fibrosis are decisive mechanisms in this context, which could also be addressed by non-invasive biomarker measurement.

Soluble suppression of tumorigenicity 2 (sST2) acts as a mediator of tissue-protective interleukin (IL)-33 effects and is mainly linked to inflammatory tissue damage (Mueller and Dieplinger 2013, Pascual-Figal and Januzzi 2015, Luk *et al.* 2017). Growth differentiation factor-15 (GDF-15), is expressed

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from numerous cell types in response to different kinds of tissue injury resulting from inflammation, shear stress, or ischaemia (Nickel *et al.* 2011, Mueller *et al.* 2015) and was suggested as a non-disease-specific indicator of systemic stress in cardiac diseases (Wollert *et al.* 2017). Galectin-3, a β-galactoside-binding lectin, moderates fibrotic remodelling processes in response to tissue damage through the interaction with other components of the intercellular matrix (Passino 2015, Maron 2016). These remodelling biomarkers are thought to mirror disease severity, and outcome in heart failure and other diseases (Mueller *et al.* 2015, Passino 2015, AbouEzzeddine 2017). A limited number of studies have investigated the pathophysiological role and diagnostic value of these biomarkers in pulmonary hypertension (Klok *et al.* 2011, Carlomagno *et al.* 2013, Zelniker 2015, Fenster *et al.* 2016, Luk *et al.* 2017, Geenen 2020, Mirna *et al.* 2020), but their association with disease severity and dynamics after therapy has not been investigated in CTEPH patients.

The hypothesis underlying this study is that biomarkers indicating different facets of tissue remodelling may facilitate individual assessment of disease severity and potential recovery after treatment of CTEPH. Here we characterize the circulating levels of sST2, galectin-3, and GDF-15 in patients with inoperable CTEPH at baseline, assess how well they correlate with hemodynamic disease severity, and examine any changes 6 months after BPA therapy.

Clinical significance

- Maladaptive right heart remodeling and failure are the major determinants of outcome in CTEPH.
- Non-invasive biomarkers adress different facets of CTEPH.
- Whereas natriuretic peptides mirror hemodynamic stress, sST2 and GDF-15 adress chronic tissue damage and (inflammatory) remodeling.
- GDF-15 and sST2 levels are higher in CTEPH patients than in healthy controls and are associated to advanced hemodynamic impairment.
- GDF-15 levels provide information for the assessment of individual therapy response after BPA therapy.

2. Materials and methods

2.1. Study population

This observational cohort study included 57 consecutive patients who underwent BPA therapy for inoperable CTEPH at the Kerckhoff Heart and Thorax Centre between 2014 and 2016 and who had completed a 6-month follow-up (6-MFU) after the final BPA treatment. Pre- and post-procedural management as well as the detailed descriptions of the BPA procedure have recently been published (Olsson *et al.* 2017, Kriechbaum *et al.* 2018). Diagnostics, determination of the therapeutic concept, and BPA therapy were performed according to current guidelines by a dedicated CTEPH/BPA team (Galiè *et al.* 2016, Wilkens *et al.* 2016, Wiedenroth 2018).

There is very limited knowledge about reference values for serum levels of sST2, galectin-3, and GDF-15 in pulmonary hypertension, particularly CTEPH. Therefore, in the current study, CTEPH patients were compared with a control group that consisted of 25 healthy volunteers. Inclusion criteria for this group were no diabetes mellitus, no chronic pulmonary disease, and no malignant or systemic inflammatory disease, high-sensitivity cardiac troponin levels below the 99th percentile [21 of 25 (84%) individuals showed a level below the limit of detection], normal N-terminal pro-hormone B-type natriuretic peptide levels, and normal findings in transthoracic echocardiography.

All patients gave written informed consent prior to inclusion. The ethics board of the Justus Liebig University of Giessen approved the study (AZ 43/14). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

2.2. Balloon pulmonary angioplasty and right heart catheterization

Detailed descriptions of the BPA procedure and right heart catheterization at our centre were recently published (Guth *et al.* 2016, Kriechbaum *et al.* 2018, Wiedenroth 2018). In brief, right heart catheterization was performed routinely via the right internal jugular vein using a 6 F sheath and a standard Swan-Ganz catheter. There was no modification of the medication prior to or during the procedure, in particular, no vasoactive agents were administered. BPA therapy was performed as staged procedure via femoral or jugular access. A 6 F sheath (Johnson&Johnson Vista britetip, Fremont, CA, USA) was placed in the pulmonary artery, and a 6 F guiding catheter (mostly Medtronic Launcher MB-1 or JR 4, Dublin, Ireland) was inserted into the pulmonary artery for selective intubation of the obstructed segmental arteries. An activated clotting time >250 s was maintained by intravenous heparin administration at 100 IE/kg during the procedure. A guidewire (mostly Runthrough NS-PTCA Guide Wire, Terumo, Tokyo, Japan) was placed into the subsegmental artery, passing the obstructing endoluminal material. Subsequently, multiple inflations of semi-compliant balloons (Emerge™ 2.0/20 mm, 3.0/20 mm and 4.0/20 mm, Boston Scientific, Marlborough, MA, USA) were performed for a dilatation of the subsegmental artery branches. The post-procedural results were documented by a final angiogram.

2.3. Laboratory assessment

Biomarker analysis was performed in the CTEPH cohort and the control group at baseline (BL) and once more in the CTEPH cohort at the 6-month follow-up (6-MFU). Venous blood samples (sST2, galectin-3, GDF-15) were collected in plain tubes, and all measurements were carried out batch-wise on thawed serum samples by enzyme-linked immunosorbent assay conducted by experienced staff blinded to patient characteristics. The limit of detection for the sST2 assay is 1.8 ng/ml (Presage ST2 assay, Critical Diagnostics, San Diego, CA, USA). The manufacturer of the galectin-3

assay cites a mean minimum detectable level of 0.016 ng/ml (Human Galectin-3, Quantikine ELISA, R&D Systems, Abingdon, UK). The mean minimum detectable level for the GDF-15 assay is 2.0 pg/ml (GDF-15 assay, Quantikine ELISA, R&D Systems, Abingdon, UK).

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical variables are reported as number and percentage. Parametric distribution was assessed using the Shapiro–Wilk test. Independent subcohorts were compared using Student's *t*-test for normally distributed parameters and the Mann–Whitney *U* test for all other continuous variables. The Chi-squared test and Fisher–Yates test were used for categorical variables. Paired sample testing was carried out using Student's *t*-test for normally distributed parameters and the Wilcoxon signed-rank test for all other continuous variables. Among CTEPH patients, the correlation between biomarker levels and hemodynamic findings was analysed using bivariate Spearman correlation (Spearman's Rho). For further assessment of the association between biomarkers and hemodynamic findings, the cohort was divided into tertiles according to the degree of hemodynamic impairment. Biomarker levels were analysed separately in each subgroup.

Three predefined study outcomes were assessed:

1. Advanced hemodynamic impairment: right atrial pressure (RAP) and cardiac index are established hemodynamic parameters for the assessment of disease severity in pulmonary hypertension (Galiè *et al.* 2016). Patients with findings for both parameters in the worst tertile of the entire cohort were classified as advanced hemodynamically impaired.
2. Optimal hemodynamic therapy response: This was defined as a normalization of pulmonary hemodynamics (meanPAP ≤25 mmHg, PVR ≤3 WU and RAP ≤6 mmHg) or at least a reduction in all of the three hemodynamic parameters (meanPAP ≥25%, PVR ≥35%, and RAP ≥25%) 6 months after BPA therapy.

The diagnostic performance of non-invasive biomarkers that showed a different expression in CTEPH patients compared to the control group, to indicate study outcomes was analysed using receiver operating characteristics (ROC). Models, combining the different biomarkers, were also assessed. Results are presented as area under the curve [AUC; 95% confidence interval (95% CI)]. The optimal cut-off values with regard to study outcomes were calculated using the Youden index. AUCs were compared using DeLong test. To assess the prognostic performance of optimal biomarker cut-off levels with regard to study outcomes, sensitivity, specificity, negative predictive values (NPV), and positive predictive values (PPV) were calculated. Binary logistic regression was used to analyse the strength of association between biomarkers and study outcomes and the results are presented as odds ratios (OR; 95% CI).

In all statistical analyses, differences with a two-tailed *p* value ≤0.05 were considered to be significant. All statistical tests were performed with SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Clinical characteristics and baseline biomarker levels

The clinical and sociodemographic characteristics of the 57 CTEPH patients and the 25 controls are presented in Table 1. At baseline, the median levels of GDF-15 [CTEPH: 820 (556–1315) pg/ml vs. control: 370 (314–516) pg/ml; $p < 0.001$] and sST2 [CTEPH: 53.7 (45.3–74.1) ng/ml vs. control: 48.7 (35.5–57.0) ng/ml; $p = 0.02$] were higher in CTEPH patients than in healthy controls. No differences were observed for galectin-3 levels [CTEPH: 13.2 (10.4–16.8) ng/ml; control: 13.6 (10.8–16.0) ng/ml; $p = 0.912$].

3.2. Biomarker-based identification of advanced hemodynamic impairment

Figure 1 illustrates the biomarker levels in subgroups of patients with a different degree of hemodynamic impairment. The tertile of patients with the highest RAP and the lowest cardiac index had higher GDF-15 and sST2 levels than the rest of the cohort. The results of the correlation analysis of biomarkers and hemodynamics are presented in Table 2. Patients with advanced hemodynamic impairment ($N = 6$; primary outcome) had significantly higher levels of GDF-15 [1964 (1344–3693) vs. 780 (533–1138) pg/ml; $p = 0.001$], sST2 [81.7 (62.5–109.1) vs. 53.3 (44.6–71.7) ng/ml; $p = 0.013$] and NT-proBNP [3445 (2186–4657) vs. 554 (147–1273) ng/L; $p < 0.001$]. There was no difference between the two groups regarding age [$p = 0.52$] and gender [$p = 0.22$].

A GDF-15 level of 1443 pg/ml (AUC 0.88), a sST2 level of 65 ng/ml (AUC 0.80) and a NT-proBNP level of 1449 ng/L (AUC 0.92) were revealed to be the optimal cut-off values to identify patients with advanced hemodynamic impairment at baseline prior to therapy (Table 3(a)). The comparison of AUCs revealed no difference for GDF-15 vs. sST2 ($p = 0.36$) and NT-proBNP ($p = 0.67$) and for sST2 vs. NT-proBNP ($p = 0.15$).

A model combining NT-proBNP with GDF-15 (AUC = 0.89) and a model combining NT-proBNP, GDF-15 and sST2 (AUC = 0.89) provided no additive diagnostic strength to identify patients with advanced hemodynamic impairment at baseline in comparison to a use of NT-proBNP alone [NT-proBNP vs. NT-proBNP + GDF-15 + sST2 ($p = 0.48$); NT-proBNP vs. NT-proBNP + GDF-15 ($p = 0.48$)].

Table 1. Sociodemographic characteristics, comorbidities, and medication of the CTEPH cohort and the control group at baseline.

Parameter	CTEPH (N = 57)	Control group (N = 25)	*p* Value
Age, years, mean ± SD	61.9 ± 13.4	56.3 ± 10.5	0.07
Female sex, n, (%)	25 (43.9)	15 (60.0)	0.18
Body mass index, kg/m^2, mean ± SD	24.7 ± 3.4	29.2 ± 4.2	<0.001
Current smoker, n, (%)	25 (43.9)	8 (32.0)	0.31
Diabetes mellitus, n, (%)	3 (5.3)	0 (0)	0.55
Dyslipidemia, n, (%)	14 (24.6)	14 (56.0)	0.006
Arterial hypertension, n, (%)	33 (57.9)	14 (56.0)	0.87
Chronic renal failure, n, (%)	8 (14.0)	0 (0)	0.05
Glomerular filtration rate, ml/min, mean ± SD	82.9 ± 26.9	115.5 ± 14.2	<0.001
Creatinine, µmol/l, mean ± SD	0.83 ± 0.3	0.65 ± 0.1	<0.001
NT-proBNP, ng/l, median (IQR)	802 (186–1611)	52 (48–68)	<0.001
Hs-cTnT, ng/l, median (IQR)	10.4 (5.8–16.0)	2.9 (2.9–2.9)	<0.001
Atrial fibrillation, n, (%)	4 (7.0)	0 (0)	0.31
History of stroke, n, (%)	3 (5.3)	0 (0)	0.55
Coronary artery disease, n, (%)	13 (22.8)	0 (0)	0.01
History of cancer, n, (%)	11 (19.3)	0 (0)	0.02
Chronic obstructive pulmonary disease, n, (%)	3 (5.3)	0 (0)	0.55
History of acute pulmonary embolism, n, (%)	45 (78.9)	0 (0)	<0.001
Procoagulant coagulopathy, n, (%)	6 (10.5)	0 (0)	0.17
Systemic inflammatory disease, n, (%)	0 (0)	0 (0)	n.a.

Values represent N (%) or mean ± SD or median (IQR). CTEPH: chronic thromboembolic pulmonary hypertension; hs-cTnT: high-sensitivity cardiac troponin T, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

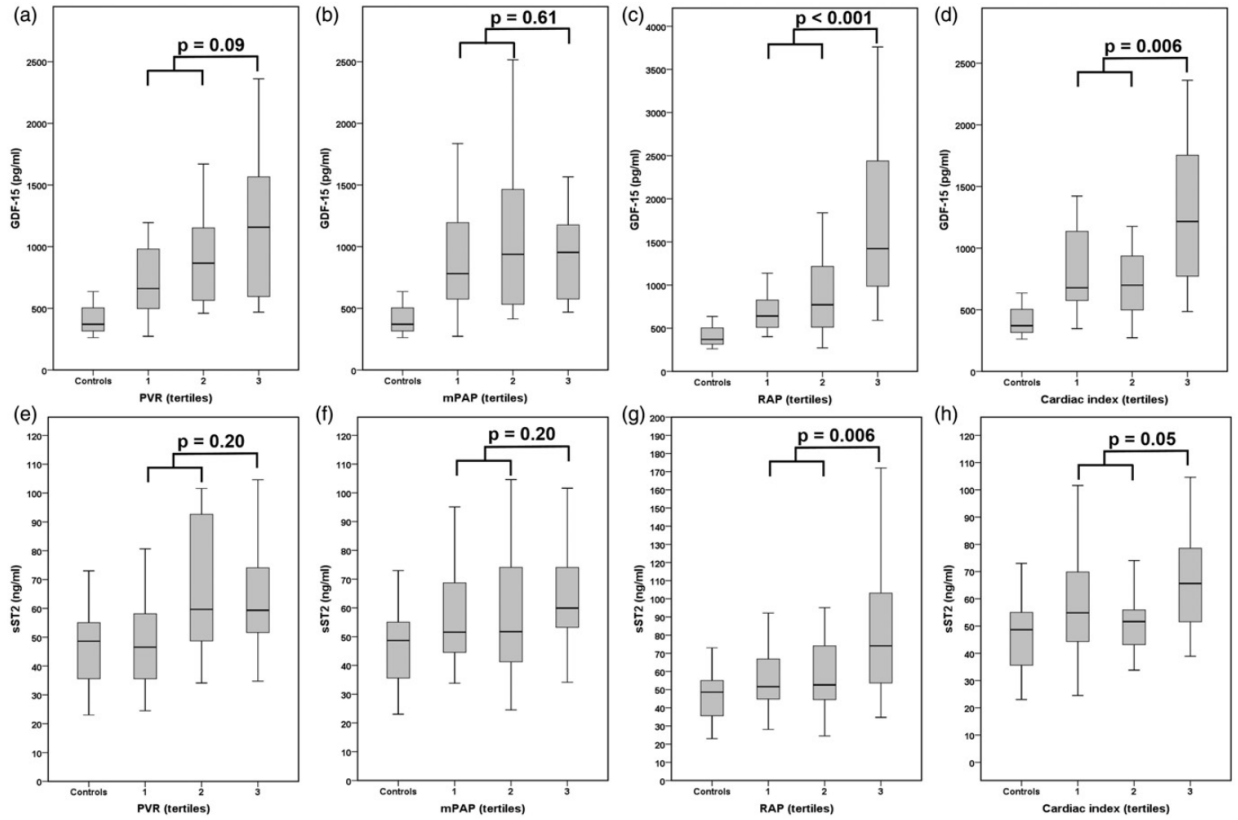

Figure 1. (a–h) Biomarker levels as a function of hemodynamic parameter. The cohort of n = 57 CTEPH patients was divided into tertiles for each hemodynamic parameter according to the following cut-off values: mPAP (≤38/≤47 mmHg), PVR (≤5.8/≤8.3 WU), RAP (≤5/≤8 mmHg), cardiac index (≤2.4/≤2.8 L/min/m^2). CI: cardiac index; mPAP: mean pulmonary artery pressure; GDF-15: growth differentiation factor-15; sST2: soluble suppression of tumorigenicity 2; PVR: pulmonary vascular resistance; RAP: right atrial pressure.

3.3. Therapy effects and biomarker-based identification of optimal therapy response

In all CTEPH patients, the indication for interventional BPA therapy was the presence of peripheral lesions. A total of 342 BPA sessions [median 6 (5–7) per patient] were performed in the study cohort. The effects of BPA therapy on hemodynamics and physical capacity are provided in Table 4.

Analysis of biomarker levels in the whole cohort revealed a decrease in sST2 levels [53.7 (45.3–74.1) to 48.1 (39.0–58.4) ng/ml; $p \leq 0.001$], but no change in GDF-15 levels [820 (556–1315) to 893 (640–1293) pg/ml; $p = 0.73$] or galectin-3 levels [6.6 (5.2–8.4) to 6.6 (5.0–48.6) ng/ml; $p = 0.41$]. Patients

who fulfilled the criteria for optimal hemodynamic therapy response ($n = 17$) were characterized by lower levels of GDF-15 [responder: 646 (498–884) pg/ml vs. rest: 968 (732–1474); $p = 0.005$] and of NT-proBNP [responder: 75 (31–186) ng/L vs. rest: 140 (73–347) ng/L; $p = 0.013$] than the rest of the CTEPH cohort at the follow-up. No difference between the two groups was observed for sST2 levels [responder 47.5 (37.8–58.2) ng/ml vs. rest: 48.2 (39.7–58.5) ng/ml; $p = 0.86$].

A GDF-15 level of ≤958 pg/ml [AUC = 0.74] and a NT-proBNP level of ≤75ng/L [AUC 0.74] were identified as the best cut-off value to identify patients with optimal hemodynamic therapy response at the follow-up (Table 3(b)). The comparison of AUCs revealed no difference between GDF-15 and NT-proBNP ($p = 0.75$). However, GDF-15 was superior ($p = 0.03$) and NT-proBNP superior by trend ($p = 0.07$) compared to sST2.

A model combining NT-proBNP with GDF-15 (AUC = 0.77) failed to provide an additive diagnostic strength to identify patients with advanced hemodynamic impairment at baseline in comparison to a use of NT-proBNP alone [NT-proBNP vs. NT-proBNP + GDF-15 ($p = 0.22$)]. Figure 2 provides a flowchart that illustrates the different study cohorts and study outcomes.

4. Discussion

4.1. Main study findings

This study investigated sST2, GDF-15, and galectin-3 as biomarkers of disease severity and therapy response in CTEPH. We determined that: i) serum levels of GDF-15 and sST2 are elevated in CTEPH patients compared with healthy individuals from a control group; ii) a GDF-15 level ≥1443 pg/ml (AUC 0.88; OR 31.4) and a sST2 level ≥65 ng/ml (AUC 0.80; OR 10.9) were strongly associated with advanced hemodynamic impairment at baseline prior to BPA therapy; iii) a GDF-15 level ≤958 pg/ml (AUC = 0.74, OR 18) at follow-up identified patients with optimal hemodynamic therapy response.

4.2. Biomarkers in CTEPH compared with controls and as indicators of hemodynamic disease severity in CTEPH

ST2 exists as transmembrane and soluble isoforms that are both receptors for interleukin (IL)-33. Whereas transmembrane ST2 promotes tissue-protective, antihypertrophic, antifibrotic, and antiapoptotic effects of IL-33, sST2 acts as an opposing decoy receptor (Pascual-Figal and Januzzi 2015). sST2 is expressed in various cell types (e.g. cardiomyocytes, smooth muscle cells, endothelial cells) and is linked to inflammation, tissue injury, and remodelling (Mueller and Dieplinger 2013, Luk *et al.* 2017). An upregulation of the IL-33-(s)ST2 pathway was detected in response to cardiac stress and remodelling (Sanada *et al.* 2007, Weir *et al.* 2010, Sanchez-Mas 2014, Pascual-Figal and Januzzi 2015). Several studies found elevated sST2 levels in cardiac, pulmonary, and inflammatory diseases, with the highest levels associated with inflammatory diseases (Dieplinger 2009, Daniels *et al.*

Table 2. Bivariate Spearman correlation between baseline biomarkers and hemodynamics.

Baseline	GDF-15, pg/ml	sST2, ng/ml
RAP, mmHg	ρ = 0.53; $p < 0.001$	ρ = 0.31; $p = 0.02$
PVR, WU	ρ = 0.24; $p = 0.08$	ρ = 0.31; $p = 0.02$
mPAP, mmHg	ρ = 0.10; $p = 0.45$	ρ = 0.16; $p = 0.23$
CI, L/min/m^2	ρ = −0.24; $p = 0.07$	ρ = −0.18; $p = 0.18$
Follow-up		
RAP, mmHg	ρ = 0.12; $p = 0.36$	ρ = −0.12; $p = 0.39$
PVR, WU	ρ = 0.40; $p = 0.002$	ρ = 0.20; $p = 0.13$
mPAP, mmHg	ρ = −0.27; $p = 0.04$	ρ = −0.05; $p = 0.70$
CI, L/min/m^2	ρ = −0.23; $p = 0.09$	ρ = −0.25; $p = 0.06$
Change	GDF-15, %	sST2, %
RAP, %	ρ = 0.42; $p = 0.001$	ρ = 0.14; $p = 0.30$
PVR, %	ρ = 0.15; $p = 0.27$	ρ = 0.07; $p = 0.59$
mPAP, %	ρ = 0.13; $p = 0.35$	ρ = −0.20; $p = 0.14$
CI, %	ρ = −0.26; $p = 0.05$	ρ = −0.37; $p = 0.005$

CI: Cardiac index; GDF-15: growth differentiation factor-15; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; sST2: soluble suppression of tumorigenicity 2.

Table 4. Diagnostic findings at baseline and the 6-month-follow-up in study cohort of 57 CTEPH patients.

Parameter	Baseline	6-month follow-up	*p* Value
mPAP, mmHg	42.9 ± 9.4	32.2 ± 10.0	<0.001
mPAP, % reduction		26.9 (16.6–35.0)	
PVR, wood units	7.3 ± 2.7	4.6 ± 1.8	<0.001
PVR, % reduction		38.9 (23.0–52.4)	
CI, l/min/m^2	2.6 ± 0.7	2.8 (±0.6)	0.06
RAP, mmHg	7.4 ± 4.1	5.3 ± 2.1	<0.001
PCWP, mmHg	9.3 ± 2.4	9.1 ± 2.4	0.64
LVEF, %	56.9 ± 7.4	58.2 ± 4.8	0.66
TAPSE, mm	19 ± 5	22 ± 4	0.01
6-MWD, m	405 ± 93	450 ± 107	<0.001
WHO FC (I–IV)	I:0; II:9; III:41; IV:7;	I:22; II:31; III:3; IV:1;	

Values represent mean ± SD or median (IQR). CI: cardiac index; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TAPSE: tricuspid annular plane systolic excursion; WHO FC: World Health Organisation functional class; 6-MWD: 6-minute walk test distance.

Table 3. Prognostic performance of biomarkers for the identification of patients with advanced hemodynamic impairment (primary outcome), optimal therapy response (secondary outcome).

Biomarker	Cut-off value	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	NPV (%, 95% CI)	PPV (%, 95% CI)	OR (95% CI)
a) Identification of patients with an advanced hemodynamic impairment (primary outcome); N = 6							
GDF-15, pg/ml	1443	0.88 (0.77–0.99)	83 (36–100)	86 (74–94)	98 (87–100)	43 (26–62)	31 (3–310)
sST2, ng/ml	65	0.80 (0.66–0.95)	83 (36–100)	69 (54–81)	97 (85–100)	25 (16–36)	11 (1–101)
NT-proBNP, ng/L	1449	0.92 (0.85–0.92)	100 (54–100)	82 (69–91)	100	41 (28–55)	∞
b) Identification of optimal therapy responders (secondary outcome); N = 17							
GDF-15, pg/ml	958	0.74 (0.61–0.89)	94 (71–100)	52 (36–68)	95 (75–99)	46 (38–55)	18 (2–146)
sST2, ng/ml	65	0.51 (0.35–0.68)	not calculated	not calculated	not calculated	not calculated	not calculated
NT-proBNP, ng/L	77	0.71 (0.56–0.85)	59 (33–82)	75 (59–87)	81 (71–89)	50 (34–66)	4 (1–14)

AUC: area under the curve; CI: confidence interval; GFR: glomerular filtration rate; GDF-15: growth differentiation factor-15; sST2: soluble suppression of tumorigenicity 2; OR: odds ratio; NPV: negative predictive value; PPV: positive predictive value.

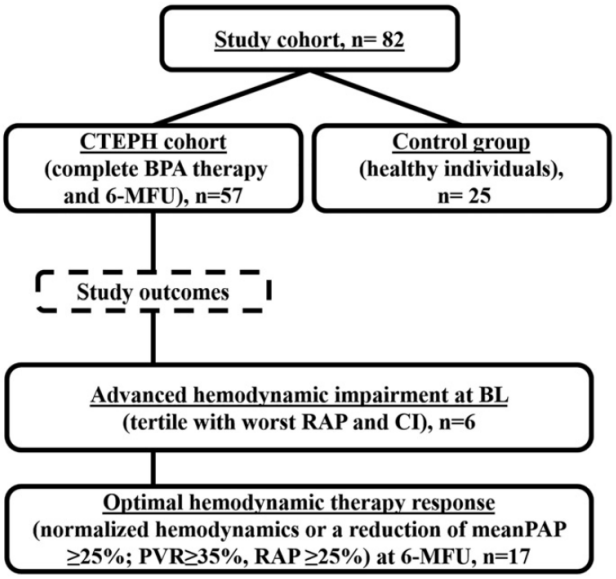

Figure 2. Patient flow chart. BL: baseline; BPA: balloon pulmonary angioplasty; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; meanPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WU: wood units; 6-MFU: 6-month-follow-up.

2012, Carlomagno *et al.* 2013, Hur *et al.* 2015, Mueller *et al.* 2015). However, serum levels showed a wide range and a notable overlap between diseased and healthy individuals (Dieplinger 2009, Bayes-Genis 2013, Carlomagno *et al.* 2013, Chida 2014, Hur *et al.* 2015, Mueller *et al.* 2015). One study reported elevated sST2 levels in 12 CTEPH patients compared with a healthy control group (Mirna *et al.* 2020). The median sST2 level in our CTEPH cohort was also slightly higher than in the control group and comparable to reported findings in pulmonary hypertension (PH) (Carlomagno *et al.* 2013, Plácido *et al.* 2017). Cardiac or vascular tissue remodelling and inflammation, processes that contribute significantly to disease progression in CTEPH, could be the drivers for the elevated levels of sST2 in CTEPH (Matthews and Hemnes 2016).

sST2 has been investigated as a marker of disease severity and prognosis in several diseases (Mueller and Dieplinger 2013). In myocardial infarction and heart failure, elevated sST2 levels indicated cardiac remodelling and adverse outcome (Shimpo *et al.* 2004, Mueller *et al.* 2008, Daniels *et al.* 2010, Bayes-Genis 2013) and provided additive value to natriuretic peptides with regards to individual risk stratification (de Boer *et al.* 2015). Further, elevated sST2 levels were associated with right ventricular dilatation and dysfunction (Carlomagno *et al.* 2013, Chida 2014) and increased mortality in PH (Luk *et al.* 2017). In a PH cohort, sST2 levels correlated with the severity of hemodynamic impairment. In our study the patients with the highest RAP and the lowest cardiac index showed significantly higher sST2 levels at baseline (Figure 1). Patients with advanced hemodynamic impairment had consistently higher sST2 levels at baseline compared with the rest of the cohort. A calculated optimal sST2 cut-off level of 65 ng/ml was associated with an 11-fold increased risk for an advanced hemodynamic impairment. This is supported by the data from a study on PH patients, which reported a 7.8-fold increased risk of mortality for patients who have a sST2 level >68.6 ng/ml (Plácido *et al.* 2017).

GDF-15, a member of the transforming growth factor-β superfamily, is expressed at a low level in almost all types of tissue (Mueller *et al.* 2015) and is upregulated in response to different kinds of tissue injury resulting from inflammation, shear stress, or ischaemia that occur in various diseases (Nickel *et al.* 2011, Mueller *et al.* 2015). A wide range of GDF-15 levels have been reported in healthy and diseased individuals (Wollert *et al.* 2017). Median values between 600 and 1500 pg/ml, with an upper limit of normal of 1200 ng/L (patients >50 years), were reported in population studies (Wollert *et al.* 2017) , and for patients with stable coronary artery disease, acute myocardial ischaemia, or heart failure levels ranging from 1200 to 3600 pg/ml have been cited (Wollert *et al.* 2017). In a mixed PH cohort the values ranged from 400 to 1495 pg/ml, with the few CTEPH patients included mostly showing values in the lower tertile (Geenen 2020). Two further studies reported median GDF-15 levels of 1580 pg/ml ($n = 82$) (Klok *et al.* 2011) and 1306 pg/ml ($n = 12$) (Mirna *et al.* 2020) in CTEPH patients. In our study, CTEPH patients had higher GDF-15 levels (median of 820 [556–1315] pg/ml) than healthy controls.

Thus far, no data about the origin of the higher GDF-15 levels in CTEPH are available. One review characterized the role of GDF-15 as a biomarker in cardiovascular diseases and concluded that GDF-15 is a non-disease-specific indicator of systemic stress (Wollert *et al.* 2017). It is known that cardiomyocytes (Xu *et al.* 2006, Heger *et al.* 2010) and vascular endothelial cells (Nickel *et al.* 2011) overexpress GDF-15 in response to hemodynamic and shear stress. Under these conditions, GDF-15 acts as a preventive regulator of maladaptive myocardial (Xu *et al.* 2006, Heger *et al.* 2010) and vascular (Nickel *et al.* 2011) remodelling, which are significant determinants of disease progression in CTEPH. The interpretation that GDF-15 levels mirror these processes might thus also be applicable in CTEPH. However, comorbidities also seem to impact serum GDF-15 levels (Wollert *et al.* 2017).

GDF-15 has been associated with disease severity and adverse outcome in various diseases, particularly in acute and chronic heart failure (Mueller *et al.* 2015, Wollert *et al.* 2017). In cohorts of patients with mixed types of PH (Geenen 2020) and idiopathic PH (Nickel *et al.* 2008, Rhodes *et al.* 2011), GDF-15 levels correlated with RAP and cardiac index. Accordingly, in our cohort, patients with high RAP and low cardiac index had higher GDF-15 levels than the rest of our cohort (Figure 1), and GDF-15 levels correlated with RAP at baseline. In one study, increased mortality rates for patients with PH and GDF-15 levels ≥920 pg/ml (age <50 y) or ≥1330 pg/ml (age >50 y) were reported (Geenen 2020). In our cohort, a baseline GDF-15 level ≥1443 pg/ml was associated with a 31-fold increased risk for advanced hemodynamic impairment. In this context, GDF-15 performed better than sST2 as a biomarker of this condition.

Although, sST2 and GDF-15 levels identified patients with an advanced hemodynamic impairment at baseline, they provided no additive diagnostic value to the established

biomarker NT-proBNP neither alone nor in combination with NT-proBNP.

Galectin-3, a β-galactoside-binding lectin, is expressed by monocytes, endothelial cells, and other cells in response to tissue damage and is a mediator of inflammation and fibrosis. It promotes tissue remodelling through the interaction with fibroblasts and profibrotic proteins of the intercellular matrix (Passino 2015, Maron 2016). Elevated galectin-3 levels were reported in a very small cohort of patients with PH and showed a correlation with right heart function in this cohort (Fenster *et al.* 2016). No data on galectin-3 levels in association with disease severity of CTEPH are available. Our study was the first investigation of galectin-3 in relation to disease severity and therapy response in CTEPH and revealed no diagnostic benefit.

4.3. Therapy effects and biomarker-based identification of optimal therapy response

BPA therapy improved hemodynamics, as published before by our group and others (Kriechbaum *et al.* 2018, Wiedenroth 2018), with an optimal treatment response in 17 patients. Several studies reported decreasing sST2 levels during heart failure therapy and suggested using sST2 for therapy guidance in this context (de Boer *et al.* 2015). No data on the impact of therapy on sST2 levels in pulmonary hypertension, particularly CTEPH, are currently available. In our study, the median sST2 concentration decreased to the range of the control group after BPA therapy but was not associated with the individual degree of therapy response, which raises questions about the underlying mechanism of sST2 dynamics. In cardiac as well as non-cardiac diseases, the inflammatory disease component seems to be the main driver of changes in sST2 levels (Mueller and Dieplinger 2013, Hur *et al.* 2015, de Boer *et al.* 2018). BPA therapy improves hemodynamics, which might attenuate systemic tissue injury and consecutive inflammation. However, the inflammatory response and recovery seem to vary significantly among individuals and do not strictly correlate with hemodynamic recovery. Notably, increased sST2 levels have also been reported after iatrogenic vascular damage, e.g. peripheral endarterectomy (Willems *et al.* 2013); thus, the BPA procedure itself might even impact the expression of sST2.

Data on the dynamics of GDF-15 levels during CTEPH therapy are not available. Exclusively one study investigated GDF-15 in idiopathic PH ($n = 22$) prior to administration of a specific medication and at a 3- or 6-month follow-up (Nickel *et al.* 2008). Here, the changes in GDF-15 levels correlated with the changes in the mixed venous oxygen saturation and NT-proBNP concentration, although the median GDF-15 levels remained unaffected (Nickel *et al.* 2008). Consistent with these results, GDF-15 levels did not generally change after therapy in our cohort, but the delta change in the biomarker levels correlated with the change in RAP and cardiac index. Moreover, low levels of GDF-15 identified therapy responders [GDF-15 $\leq$ 958 pg/ml (AUC = 0.74, OR 18)] at the follow-up.

However, the diagnostic strength of GDF-15 was not superior to NT-proBNP alone and provided no additive diagnostic value in a model combining both biomarkers.

Our results provide limited data about the origins of GDF-15 changes after therapy. To determine whether low GDF-15 levels reflect decreased hemodynamic stress in patients with therapy response or specific myocardial and vascular recovery responses needs further assessment.

4.4. Limitations

Some limitations of this study must be considered. First, the sample size and consequently the number of patients who reached predefined study outcomes is relatively small. This needs to be taken into account when the diagnostic strength of different biomarkers is assessed and compared. Second, although biomarker levels are associated with disease severity, the results provide limited information about the origin of the observed biomarker changes in CTEPH. Third, the investigation of biomarkers as diagnostic tools to assess therapy response is limited by a lack of established definitions of therapeutic success after BPA.

5. Conclusion

GDF-15 and sST2 levels are higher in CTEPH patients than in healthy controls and are associated with advanced hemodynamic impairment in CTEPH. Moreover, GDF-15 levels provide information for the assessment of individual therapy response after BPA therapy.

However, as biomarkers with a focus on remodelling processes, GDF-15 and sST2 did not provide any additional diagnostic value to indicate hemodynamic study outcomes in comparison to a NT-proBNP measurement alone.

Galectin-3 proved to have no diagnostic utility in the context of risk stratification and assessment of therapy response in CTEPH.

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Disclosure statement

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Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. Sharing the underlying data is not in line with the written informed consent of the patients in this study. The data will be shared on reasonable request to the corresponding author.

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Respiratory Research

LETTER TO THE EDITOR Open Access

Pregnancy-associated plasma protein A – a new indicator of pulmonary vascular remodeling in chronic thromboembolic pulmonary hypertension?

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Abstract

Background: In chronic thromboembolic pulmonary hypertension (CTEPH) impaired pulmonary hemodynamics lead to right heart failure. Natriuretic peptides reflect hemodynamic disease severity. Pregnancy-associated plasma protein-A (PAPP-A) might address another aspect of CTEPH - chronic tissue injury and inflammation. This study assessed dynamics of PAPP-A in CTEPH patients who undergo therapy with pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA).

Methods: The study included a total of 125 CTEPH patients scheduled for treatment (55 PEA/ 70 BPA) and a control group of 58 patients with pulmonary hypertension other than CTEPH. Biomarker measurement was performed at baseline and follow-up in the CTEPH cohort, prior to each BPA in the BPA cohort and once in the control group.

Results: The median PAPP-A level was slightly higher ($p = 0.05$) in CTEPH patients [13.8 (11.0–18.6) mU/L], than in the control group [12.6 (8.6–16.5) mU/L], without a difference between the BPA and PEA group ($p = 0.437$) and without a correlation to mean pulmonary artery pressure ($p = 0.188$), pulmonary vascular resistance ($p = 0.893$), cardiac index ($p = 0.821$) and right atrial pressure ($p = 0.596$). PEA and BPA therapy decreased the mean pulmonary artery pressure ($p < 0.001$) and pulmonary vascular resistance ($p < 0.001$) and improved the WHO-functional-class (baseline: I:0/II:25/III:80/IV:20 vs. follow-up: I:55/II:58/III:10/IV:2). PAPP-A levels decreased after PEA [13.5 (9.5–17.5) vs. 11.3 (9.8–13.6) mU/L; $p = 0.003$) and BPA treatment [14.3 (11.2–18.9) vs. 11.1 (9.7–13.3) mU/L; $p < 0.001$). The decrease of PAPP-A levels is delayed in comparison to N-terminal pro-B-type natriuretic peptide.

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(Continued from previous page)
Conclusion: PAPP-A is overexpressed in CTEPH and decrease significantly after surgical or interventional therapy, however without association to hemodynamics. Further investigation is needed to define the underlying mechanism of PAPP-A expression and changes after therapy in CTEPH.

Keywords: PAPP-A, Pregnancy-associated plasma protein A, Pappalysin-1, BPA, PEA, CTEPH, Vascular remodeling

Introduction

In chronic thromboembolic pulmonary hypertension (CTEPH) insufficient thrombus resolution and vascular remodeling lead to chronic obstructions of the pulmonary arteries [1]. The corresponding impaired pulmonary hemodynamics burden the right heart, cause right heart remodeling and ultimately failure [1]. Pulmonary endarterectomy (PEA), medical treatment targeting pulmonary hypertension (PH) and balloon pulmonary angioplasty (BPA) are specific treatment modalities [1]. Impaired pulmonary hemodynamics in CTEPH correlate with non-invasively measured blood biomarkers such as natriuretic peptides and render such markers as indicators for disease severity and therapy response [2]. Considering the multifaceted pathophysiology of CTEPH, biomarkers not primarily reflecting hemodynamics might further provide information about individual disease mechanisms facilitating treatment decisions. Pregnancy-associated plasma protein-A (PAPP-A), clinically established in the pregnancy first-trimester-screening, was identified as key regulator of insulin-like growth factor (IGF)/IGF-binding-protein pathways via cleaving of IGF-binding-protein [3]. This pathway has been reported in the context of atherosclerosis, coronary artery disease, heart failure and non-cardiac conditions [4]. Its role in PH, especially CTEPH, has not been investigated so far.

The current study aimed to evaluate PAPP-A levels in CTEPH and to explore the potential modification of PAPP-A levels by PEA or BPA treatment.

Methods

We analyzed 125 consecutive patients with CTEPH and 58 controls (Patients with PH and suspected CTEPH that was excluded after diagnostic workup). Standardized diagnostic and therapeutic work-up of CTEPH patients has been published earlier [2]. The CTEPH group of the study included 55 patients that underwent PEA and 70 in whom BPA was performed. In PEA patients, biospecimen were obtained at baseline and 12 months after surgery (12-MFU), in BPA at baseline, before each staged procedure and 6 months after the final procedure (6-MFU). In control patients, biomaterial was obtained at enrollment. The biomaterial included venous blood samples that were aliquoted and frozen at − 80 °C. The study was approved by the respective local ethics committee and each patient gave written informed consent. PAPP-A was measured in frozen serum samples using an automated immunofluorescence assay on the Kryptor compact plus instrument (PAPP-A Thermo Scientific, BRAHMS GmbH, Henningsdorf, Germany).

Variables are expressed as median (IQR), mean ± SD or number (%) as appropriate. Comparative analyses used the Student t-test, Mann-Whitney-U-test, Wilcoxon signed-rank test, X^2-test and Fisher-Yates test. Bivariate Pearson correlation assessed associations of PAPP-A with pulmonary hemodynamics and other biomarkers. All *p*-values are seen as descriptive. Statistical analyses were performed with R3.5.1 software package (R Foundation for Statistical Computing, Vienna, Austria).

Results

The comparative analysis of hemodynamic findings revealed a higher pulmonary artery pressure (meanPAP; 43.1 ± 9.7 vs. 39.9 ± 10.9 mmHg; $p = 0.041$) and pulmonary vascular resistance (PVR; 6.76(5.27–9.61) vs. 4.63(3.15–10.3) WU; $p = 0.006$) in CTEPH patients compared to the PH control group at baseline. A comprehensive illustration of baseline characteristics of the CTEPH cohort and the control group is provided in Table 1.

PAPP-A levels at baseline were comparable in CTEPH patients [13.8(IQR 11.0–18.6) mU/L] and PH controls [12.6(IQR 8.6–16.5) mU/L] ($p = 0.051$). No relevant correlation between PAPP-A and hemodynamic parameters such as meanPAP ($r = 0.120$; $p = 0.188$), pulmonary vascular resistance (PVR) ($r = 0.013$; $p = 0.893$) or NT-proBNP ($r = 0.128$; $p = 0.169$) was observed in CTEPH patients. Nevertheless, PAPP-A correlated with C-reactive protein ($r = 0.259$; $p = 0.004$).

Surgical and interventional treatment led to an improvement of pulmonary hemodynamics and a decrease of natriuretic peptides, which is illustrated in Table 2.

The PAPP-A levels did not differ between the PEA and BPA treatment group (13.7 (10.4–17.6) vs. 14.5 (11.2–18.9) mU/L; $p = 0.437$) at baseline (Fig. 1, *left panel*). PAPP-A levels decreased significantly after treatment from 13.7 (10.4–17.6) to 11.4 (9.9–14.6) mU/L ($p = 0.003$) after PEA and 14.5 (11.2–18.9) to 11.1 (9.8–12.9) mU/L ($p < 0.001$) after BPA therapy (Fig. 1, *left panel*).

Table 1 Baseline characteristics of the CTEPH cohort and the control group

		CTEPH (total)	CTEPH (BPA)	CTEPH (PEA)	Pulmonary Hypertension other than CTEPH (Controls)	PEA vs. BPA	CTEPH vs. Controls
		n = 125	***n*** = 70	***n*** = 55	***n*** = 58	(***p***-value)	(***p***-value)
	Data availability						
Demographics							
Age, y; mean ± SD	183/183	59.3 ± 14.3	60.83 ± 13.5	57.35 ± 15.2	62.28 ± 14.6	0.277	0.14
Female sex; n (%)	183/183	52 (41.6%)	30 (42.86%)	22 (40%)	35 (60.34%)	0.89	0.028
Body mass index, kg/m^2; mean ± SD	183/183	25.94 ± 4.5	25.09 ± 3.7	27.02 ± 5.1	30.89 ± 7.9	0.046	< 0.001
History and risk factors							
Smoker; n (%)	181/183	55 (44.72%)	31 (45.59%)	24 (43.64%)	31 (53.45%)	0.973	0.348
Diabetes mellitus; n (%)	183/183	6 (4.8%)	4 (5.71%)	2 (3.64%)	16 (27.59%)	0.694	< 0.001
Dyslipidemia; n (%)	182/183	23 (18.55%)	17 (24.29%)	6 (11.11%)	14 (24.14%)	0.101	0.499
Arterial hypertension; n (%)	182/183	59 (47.58%)	36 (51.43%)	23 (42.59%)	36 (62.07%)	0.426	0.096
Chronic renal failure; n (%)	183/183	26 (20.8%)	13 (18.57%)	13 (23.64%)	15 (25.86%)	0.638	0.566
Coronary artery disease; n (%)	182/183	20 (16.13%)	14 (20.29%)	6 (10.91%)	12 (20.69%)	0.244	0.586
History of cancer; n (%)	183/183	18 (14.4%)	13 (18.57%)	5 (9.09%)	16 (27.59%)	0.214	0.054
History of acute pulmonary embolism; n (%)	182/183	110 (88.71%)	56 (81.16%)	54 (98.18%)	45 (77.59%)	0.003	0.081
Chronic obstructive pulmonary disease; n (%)	175/183	8 (6.84%)	4 (6.35%)	4 (7.41%)	12 (20.69%)	1	0.014
History of splenectomy; n (%)	183/183	9 (7.2%)	6 (8.57%)	3 (5.45%)	3 (5.17%)	0.73	0.755
Chronic inflammatory disease; n (%)	183/183	3 (2.4%)	1 (1.43%)	2 (3.64%)	6 (10.34%)	0.582	0.030
Laboratory parameters							
Ceatinine, μmol/l; mean ± SD	183/183	0.97 ± 0.3	0.95 ± 0.3	1 ± 0.3	0.93 ± 0.4	0.298	0.058
eGFR, ml/min; mean ± SD	183/183	82.5 ± 25.7	83.62 ± 26.6	81.08 ± 24.7	86.63 ± 34.5	0.603	0.558
NT-proBNP, ng/l; median (IQR)	176/183	845 (184.2–1860)	743.7 (197.2–1470)	1094 (149.775–2078.25)	412 (181.8–1454.5)	0.296	0.282
PAPP-A, mU/L	183/183	13.8 (11.0–18.6)	14.5 (11.2–18.9)	13.7 (10.4–17.6)	12.6 (8.6–16.5)	0.437	0.051
Symptoms and medication							
Guanylate cyclase stimulator; n (%)	183/183	65 (52%)	49 (70%)	16 (29.09%)	8 (13.79%)	< 0.001	< 0.001
WHO-functional class (I-IV)	183/183	I:0;II:25;III:80;IV:20	I:0;II:11;III:49;IV:10	I:0;II:14;III:31;IV:10	I:0;II:7;III:40;IV:11		
Examination results							
LVEF, %; median (IQR)	158/183	55 (55–60)	55 (55–59.25)	55 (55–60)	55 (55–55)	0.416	< 0.001
TAPSE, mm; mean ± SD	153/183	19.08 ± 5.3	18.68 ± 4.8	19.54 ± 5.8	19.5 ± 5.3	0.449	0.788
6-min-walk distance, m; mean ± SD	85/183	405.18 ± 99.1	404.52 ± 91.8	409.44 ± 144.7	329.56 ± 122.3	0.312	0.01
Hemodynamics							
RAP, mmHg; median (IQR)	108/183	7 (5–9)	7 (5–9)	7 (5–8)	7.5 (4.5–11.75)	0.977	0.764
MeanPAP, mmHg; mean ± SD	181/183	43.09 ± 9.7	42.44 ± 9.1	43.93 ± 10.6	39.86 ± 10.9	0.384	0.041
PVR, WU (IQR)	172/183	6.76 (5.27–9.61)	6.76 (5.27–8.56)	7.065 (5.3075–11.8075)	4.63 (3.15–10.265)	0.184	0.006

Table 1 Baseline characteristics of the CTEPH cohort and the control group *(Continued)*

		CTEPH (total)	CTEPH (BPA)	CTEPH (PEA)	Pulmonary Hypertension other than CTEPH (Controls)	PEA vs. BPA	CTEPH vs. Controls
		n = 125	***n*** = 70	***n*** = 55	***n*** = 58	(***p***-value)	(***p***-value)
CI, L/min/m^2; mean ± SD	169/183	2.5 ± 0.6	2.61 ± 0.7	2.33 ± 0.6	2.58 ± 0.8	0.015	0.705
PCWP, mmHg; median (IQR)	179/183	9 (8–12)	9 (8–11)	9 (8–13)	11 (9–13)	0.332	0.004

Values represent N (%) or mean ± SD or median (IQR)
Abbreviations: *BPA* Balloon pulmonary angioplasty, *CI* cardiac index, *GFR* glomerular filtration rate, *hs-cTnT* high-sensitivity cardiac troponin T, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *PAP* pulmonary artery pressure, *PCWP* Pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *TAPSE* Tricuspid Annular Plane Systolic Excursion

BPA is a staged procedure (median 6 procedures/patient) with only a limited number of pulmonary segments treated per session. PAPP-A levels decreased continuously reaching a significant change after 4 procedures in contrast to the hemodynamic marker NT-proBNP as a comparator that was significantly lowered already after the first procedure (Fig. 1, *right panel*).

Discussion

Key findings of this study are: (1) PAPP-A levels might be associated with CTEPH and decrease after interventional or surgical treatment. (2) The PAPP-A treatment response shows a slow and continuous lowering in marker levels in contrast to the rapid improvement in hemodynamics reflected by biomarkers such as NT-proBNP.

The PAPP-A levels in CTEPH patients, which are modifiable by treatment. Seem not to be mediated by hemodynamics and their improvement after treatment raising the question about the origin and role of PAPP-A in CTEPH.

Acute pulmonary embolism impairs pulmonary vascular homeostasis. The mechanisms leading to development of CTEPH in a subset of PE patients are not fully understood. Endothelial damage, dysfunction and inflammation are known to be involved in vascular remodeling. The IGF-I/IGF-receptor signaling promotes inflammation, anti-apoptosis and proliferation in various cell types such as endothelial and smooth muscle cells [5, 6]. Yang et al. reported a key role of the IGF-I/IGF-receptor signaling in neonatal PH, revealing an upregulation of IGF-I expression in pulmonary endothelial and smooth muscle cells under experimental hypoxia [7, 8]. Further, Harrington et al. identified PAPP-A as a promotor of atherosclerotic plaque progression and plaque vulnerability. This processes seemed to be driven by PAPP-A-mediated proinflammatory effects of macrophage cytokines and a consecutive upregulation of the IGF-I/IGF-receptor axis [9].

One might hypothesize, that an overexpression of PAPP-A might thus reflect chronic vascular remodeling in CTEPH. The potential use as a biomarker indicating disease mechanisms other than hemodynamics is further supported by the availability of robust automated measurement technology due to the routine use in the context of pregnancy. Further, as the IGF pathway plays a relevant role in certain cancer entities, PAPP-A has already been discussed as treatment target that led to e.g. development of monoclonal PAPP-A antibodies [10].

The present clinical study is based on relatively small cohort and therefore the results only allow to

Table 2 Comparison of hemodynamic findings and NT-proBNP levels between baseline and follow-up in CTEPH patients

	Baseline mean ± SD or median (IQR)	Follow-up mean ± SD or median (IQR)	***p***-value
PEA			
MeanPAP; mmHg	43.9 ± 10.6	22.3 ± 7.5	p < 0.001
PVR; WU	7.1 (5.3–11.8)	2.5 (1.8–3.5)	p < 0.001
NT-proBNP; ng/L	1094 (150–2078)	192 (102–382)	p < 0.001
BPA			
MeanPAP; mmHg	42.4 ± 9.1	31.7 ± 9.6	p < 0.001
PVR; WU	7.1 (5.3–11.8)	3.9 (3.1–5.3)	p < 0.001
NT-proBNP; ng/L	744 (197–1470)	121 (70–238)	p < 0.001

Values represent as mean ± SD or median (IQR)
Abbreviations: *BPA* Balloon pulmonary angioplasty, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *meanPAP* mean pulmonary artery pressure, *PEA* pulmonary endarterectomy, *PVR* pulmonary vascular resistance

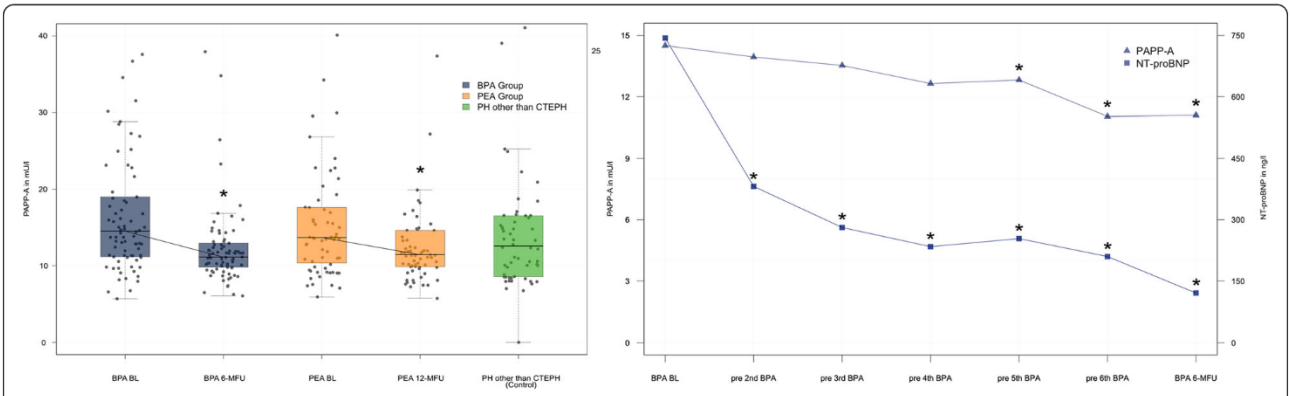

Fig. 1 Impact of treatment on pregnancy-associated plasma protein A (PAPP-A) levels in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The left panel shows PAPPA-A levels in CTEPH patients before undergoing treatment with pulmonary endarterectomy (PEA BL) or balloon pulmonary angioplasty (BPA BL) and 12 months after PEA (PEA 12-MFU) respectively 6 months after the final BPA (BPA 6-MFU) procedure compared to controls of patients with pulmonary hypertension in whom CTEPH was excluded (PH Controls). The right panel shows the time dependent effect of the staged BPA procedure on PAPP-A levels. For comparison, data on NT-proBNP as a biomarker reflecting hemodynamics is provided. * Indicates *p*-value < 0.05 comparing difference in PAPP-A level at procedure compared to the baseline level

hypothesize about the potential role of PAPP-A. However, it is the first analysis showing an association of PAPP-A with CTEPH. Especially the modification of PAPP-A levels by treatment not primary mediated via hemodynamic improvement should stimulate further investigations to confirm the present results from a small cohort and further analyze the specific role of PAPP-A in the pathophysiology of CTEPH and a potential clinical use as biomarker or even treatment target.

Abbreviations

12-MFU: Follow-Up twelve month after PEA; 6-MFU: Follow-Up six month after last BPA; BPA: Balloon pulmonary angioplasty; CTEPH: Chronic thromboembolic pulmonary hypertension; eGFR: estimated glomerular filtration rate; IGF(−I): Insulin-like growth factor (− 1); IQR: Interquartile range; meanPAP: Mean pulmonary artery pressure; NT-proBNP: N-terminal pro brain natriuretic peptide; PAPP-A: Pregnancy-associated plasma protein A or Pappalysin-1; PCWP: Pulmonary capillary wedge pressure; PEA: Pulmonary endarterectomy; PH: Pulmonary hypertension; PVR: Pulmonary vascular resistance; SD: Standard deviation; WU: Wood units

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Authors' contributions

SDK: data management, statistical analysis and interpretation, first draft of the manuscript. FR: data management, statistical analysis and interpretation, first draft of the manuscript. CBW treatment and follow-up of patients, data interpretation, proofreading of the manuscript. SG treatment and follow-up of patients, data interpretation, proofreading of the manuscript. MH treatment and follow-up of patients, data interpretation, proofreading of the manuscript. EM treatment and follow-up of patients, data interpretation, proofreading of the manuscript. LM data management, proofreading of the manuscript. CWH conceptualization of the study, acquisition of funding, proofreading of the manuscript. CL conceptualization of the study data interpretation, proofreading of the manuscript. TK conceptualization of the study data interpretation, proofreading of the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. Sharing the underlying data is not in line with the written informed consent of the patients in this study. The data will be shared on reasonable request to the corresponding author.

Ethics approval and consent to participate

The study was approved by the local ethics committee of the Facility of Medicine of the Justus-Liebig-University in Giessen, Germany in July of 2014 (referral numbers 43/14 and 44/14). All participating patients were comprehensively informed by a physician and gave written informed consent.

Consent for publication

All participants gave written informed consent to be included in the study. This manuscript does not include any individual person's data in any form, including individual details, images or videos. Therefore, no dedicated consent for publication is needed.

Competing interests

CBW received consultant honoraria and/or speaker fees from Actelion, Bayer AG, MSD, Pfizer and BTG; CWH received lecture or consulting honoraria from BRAHMS/ Thermo Fisher; EM received lecture or consulting honoraria from Actelion, Bayer, MSD, GSK, Pfizer and MSD; CL received lecture or consulting honoraria from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer-Bristol-Myers Squibb. TK received speaker fees from Abbott and Brahms; SDK, FR and LM have nothing to declare.

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Development of renal function during staged balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension

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ORIGINAL ARTICLE

Development of renal function during staged balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension

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ABSTRACT

Balloon pulmonary angioplasty (BPA), for chronic thromboembolic pulmonary hypertension, improves pulmonary and systemic hemodynamics. The kidney might benefit from this effect. However, staged BPA therapy comes along with repetitive administration of contrast agent. This study examined the overall effect of BPA therapy on renal function. This study included consecutive patients who underwent BPA treatment and completed a 6-month follow-up between March 2014 and March 2017. Biomarker-based evaluation of renal function was performed at baseline, consecutively prior to and after each BPA and at 6-month follow-up. The 51 patients underwent an average of 5 (±2) BPA sessions. In this course, patients received 133 (±48; 21–300) mL of contrast agent per session and 691 (±24; 240–1410) mL during the whole sequence. Acute kidney injury occurred after 6 (2.3%) procedures. The creatinine [80.1 (IQR 67.8–96.8) µmol/L vs. 77.4 (IQR 66.9–91.5) µmol/L, $p = .02$] and urea level [13.7 (IQR10.7–16.6) mmol/L vs. 12.5 (IQR 10.0–15.5) mmol/L, $p = .02$] decreased from baseline to the 6-month follow-up. The estimated glomerular filtration rate (eGFR) [79 (IQR 59–94) mL/min/m^2 vs. 79.6 (IQR 67.1–95.0) mL/min/m^2, $p = .11$] did not change. The Chronic kidney disease (CKD) stages at baseline were: G1:15; G2:23; G3a:10; G3b:2; G4:1; G5:0. Among patients with a CKD-stage $\geq$2, analysis revealed an increase of eGFR, decrease of creatinine and urea from baseline to 6-month follow-up. Among those patients, the baseline-CKD-stage improved in 14 (41.2%) patients. BPA therapy improves pulmonary and systemic hemodynamics, with positive effects on renal function. Repetitive administration of contrast agent seems not to be harmful regarding renal function.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), leads to impairment of pulmonary hemodynamics and triggers secondary right heart dysfunction, regularly accompanied by systemic malperfusion [1]. CTEPH has a poor prognosis without therapy, but in contrast to other subclasses of pulmonary hypertension, pulmonary endarterectomy offers a potentially curative therapy [1]. For patients in whom surgical therapy is not feasible as first line treatment, a sequence of targeted medication and consecutive balloon pulmonary angioplasty (BPA) as an interventional therapy option is recommended [2–5].

Chronic kidney disease (CKD) is a frequent comorbidity in patients suffering from right heart dysfunction due to pulmonary arterial hypertension [6–8]. In this context, cardiorenal syndrome terms the complex bilateral interaction of renal and cardiac function and is suggested to be the underlying mechanism of renal failure in pulmonary arterial hypertension [7]. Several studies identified CKD to be an indicator for disease severity and an independent predictor for outcome in pulmonary arterial hypertension [6,8].

BPA improves pulmonary hemodynamics and facilitates right ventricular (RV) recovery, which is beneficial for systemic circulation and venous congestion and might therefore enhance systemic organ perfusion [9,10]. Renal function might serve as an indicator for systemic circulation and might mirror the effects of BPA on systemic circulation. However, procedural aspects need to be considered as the BPA is done as staged procedure to avoid severe complications like reperfusion edema. The staged character comes along with repetitive administration of contrast agent, which might increase the risk of acute kidney injury (AKI) [11].

This periprocedural AKI due to nephrotoxic effects of iodine contrast agent or hemodynamic changes is frequently described [12–14].

It can be speculated that both, the improvement of systemic hemodynamics and the repetitive administration of

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contrast agent might influence renal function in CTEPH patients undergoing BPA. Therefore, the aim of the present study was to characterize the incidence of AKI during BPA and its impact on CKD during follow-up.

Methods

The principles of the clinical and scientific work-up of patients who undergo treatment for CTEPH at our center have been recently published by our group [3,5,10]. The study population and the respective methods are described in brief as follows.

Study population

The present study included 51 consecutive patients undergoing BPA at the Kerckhoff Heart and Thorax Center and completed a 6-month follow-up after the final BPA treatment between March 2014 and March 2017. During the study period, two patients retracted their written consent and were thus excluded from analysis.

Suggested pre- and post-procedural management of the patients was recently published [3,5,15,16]. In brief, clinical examination, echocardiography, 12-lead electrocardiogram, laboratory tests, 6-minute walk tests, computed tomography angiography, right-heart catheterization and pulmonary angiography were assessed for all patients. The final diagnosis of CTEPH was made according to the current guidelines [2,4]. All patients were presented in an interdisciplinary CTEPH conference to define the therapeutic concept. In this course, it is crucial to assess the technical operability with regards to the localization of the target lesions and the operability in dependence to the patients' comorbidities. BPA was performed as a staged procedure according to standard clinical practice by a dedicated BPA team (interventional radiologist, cardiologist and thoracic surgeon). The interval between each BPA sessions is about 4–8 weeks. Prior to the next BPA procedure, follow-up examinations were performed that were adjusted to the individual requirements of each patient, always including re-evaluation of clinical status and laboratory findings. Finally, an in-house follow-up examination was performed 6 months after the last BPA procedure.

The investigation conforms to the principles outlined in the *Declaration of Helsinki*.

All patients enrolled in the study gave written informed consent, which included consent for biomarker analyses. The ethics board of the Justus Liebig University of Giessen approved the study (reference number: AZ 43/14) [10].

Periprocedural preventive renal protection

All patients who undergo BPA intervention receive 500 mL saline, 300 mg acetylcystein, 10 mg furosemide and 10 mmol potassium chloride once one day prior to a BPA session, once immediately after BPA and once on the day after the BPA, individually adapted to serum electrolytes if necessary.

BPA and right heart catheterization

BPA was performed as staged procedure under smooth sedation using femoral or jugular access as previously described [3]. As contrast agent, we used Iohexol 350 mg/ml (ACCUPAQUE^{TM} 350, GE Healthcare Buchler GmbH & Co. KG, Braunschweig, Germany). Adapted to individual conditions, the contrast agent got diluted at a ratio of 1:1 with saline.

Right heart catheterization was performed as a part of the diagnostic work-up at baseline [2]. In all BPA patients, right heart catheterization was repeated 6 months after the last BPA procedure. Right heart catheterization was routinely performed via the right internal jugular vein using a 6F sheath and a standard Swan–Ganz catheter [10].

Laboratory assessment of renal function

Venous blood samples for determination of serum creatinine and serum urea were collected in plain tubes at baseline, prior to and after each BPA procedure, and at the 6-month follow-up. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated modification of diet in renal disease formula and was used as the main parameter for the assessment of chronic renal function [17]. In accordance with the recommendations of the Acute Kidney Injury Network, acute renal failure was defined as an increase of the serum creatinine of $\geq$0.3 mg/dL ($\geq$26.4 µmol/L) or to $\geq$150% from baseline [18]. Contrast-induced renal failure usually occurs within 72 h after exposure [19]. Thus, renal biomarkers were measured prior to, 24, 48 and 72 h after the BPA in this study. Patients were divided into subgroups according to their CKD stage, based on the KDIGO guidelines on the Evaluation and Management of Chronic Kidney Disease [20].

Statistical analysis

All data for continuous variables are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Categorical variables are reported as number and percentage. Parametric distribution was assessed using the Shapiro–Wilk test.

Parameters that were obtained at baseline and at the 6-month follow-up were subjected to paired sample testing. We used Student's *t*-test for normally distributed parameters and the Wilcoxon signed-rank test for all other continuous variables. Bivariate correlations (Pearson) were analyzed for selected clinical and hemodynamic parameters as well as laboratory findings.

A subgroup analysis was performed for all patients with a CKD-stage of $\geq$2.

All statistical tests were performed with SPSS software, version 19.0 (IBM, Armonk, NY, USA). A two-tailed p value $<$.05 was considered to be statistically significant.

Table 1. Baseline characteristics and dynamics of pulmonary hemodynamics and biomarkers during therapy.

Parameter	N (%) or mean (±SD) or median (IQR) at baseline	Mean (±SD) or median (IQR) at the 6-month follow-up	*p*-value
Age at 1st BPA, years	63.1 (±11.5)		
Female gender	28 (54.9)		
Body-mass index, kg/m^2	25.7 (±3.8)		
Current smoker	14 (27.5)		
Diabetes mellitus	5 (9.8)		
Dyslipidemia	7 (13.7)		
Arterial hypertension	31 (60.8)		
Atrial fibrillation	3 (5.9)		
History of stroke	5 (9.8)		
Coronary artery disease	9 (17.9)		
History of cancer	9 (17.6)		
Chronic obstructive pulmonary disease	4 (7.8)		
History of acute pulmonary embolism	23 (45.1)		
History of deep vein thrombosis VT	6 (11.8)		
Procoagulant coagulopathy	2 (3.9)		
PVR, dyn × sec × cm^{-5}	516 ± 219	397 ± 183	<.001
MeanPAP, kPa	5.2 ± 1.6	4.3 ± 1.7	<.001
RAP, kPa	7.1 ± 0.6	0.8 ± 0.4	.008
Cardiac index, mL/min/m^2	2530 ± 600	2530 ± 5l0	.33

BPA: balloon pulmonary angioplasty; meanPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure.

Results

Clinical characteristics

Baseline characteristics of the evaluated 51 patients [28 women; mean age (±SD) 63.1 ± 11.5 years] are summarized in Table 1. In all patients, the indication for BPA was a technically inoperable status with peripheral target lesions in 47 (92.2%) patients and a status after pulmonary endarterectomy with recurrent pulmonary hypertension in 4 patients (7.8%). All patients in our cohort were on oral anticoagulation therapy for >3 months and in 29 (56.9%) patients a targeted medical treatment was established.

(Peri-)procedural data

In total 265 (mean 5/patient, range 3–9) BPA interventions with a treatment of 410 (mean 8/patient) vessels were performed. The most frequent complications after BPA were hemoptysis in 7.4% and reperfusion injury in 3.4% of all interventions. The survival rate in the 6-month follow-up was 96.1%. The median time interval between the first BPA and the 6-month follow-up was 443 (IQR 367–500) days with a range from 275 to 723 days.

The median dose area product after the completed BPA therapy was 247.3 (IQR 159.8–386.8) Gy × cm^2. The mean amount of iodine contrast agent per BPA session was 133 (±48) mL with a range from 21 to 300 mL. Patients with a CKD-stage ≥3a at baseline received significantly less contrast agent compared to the rest of the cohort (CKD-stage ≥3a 119 ± 27 mL; CKD-stage ≤2 137 ± 22 mL; $p = .022$).

In 265 BPA interventions, an AKI occurred after 6 (2.3%) procedures in 5 (9.8%) different patients. All of these events were classified as an AKI stage I. There was no significant difference between the patients with AKI and the rest of the cohort, regarding their baseline hemodynamics [meanPAP (AKI: 5.4 ± 1.3 kPa; no AKI: 5.3 ± 1.7 kPa; $p = .75$); pulmonary vascular resistance (PVR; AKI: 573.5 ± 200.5 dyn × sec × cm^{-5}; no AKI: 509.3 ± 222.4 dyn × sec × cm^{-5}; $p = .47$)] and baseline renal function [serum creatinine (AKI: 123.2 (IQR 79.2–140.8) µmol/L; no AKI: 79.2 (IQR 70.4–96.8) µmol/L; $p = .06$); eGFR (AKI: 54 (IQR 41–82) mL/min/m^2; no AKI: 79 (IQR 64–95) mL/min/m^2; $p = .09$); serum urea (AKI: 11.5 (IQR 5.3–13.9) mmol/L; no AKI: 6.3 (IQR 4.8–7.5) mmol/L; $p = .13$].

During the BPA sequence, no patient required transient or long-term renal dialysis.

The all-over amount of contrast agent correlated significantly with the total number of BPA sessions (r_{rs}=0.84; $p < .001$). The mean amount of iodine contrast agent overall BPA sessions per patient was 691 (±241) mL with a range from 240 to 1410 mL. The total amount of contrast agent and the amount per session did not significantly differ between patients with a decrease of renal function during the sequence and the rest of the cohort. There was no significant correlation of the absolute change of eGFR and the amount of contrast agent (r_{rs}=0.08; $p = .60$). In the whole cohort, 27 CT-scans were performed for different indications between the first BPA and the 6-month follow-up. Only one of these scans used contrast agent and no AKI is reported afterwards. CT scans for the diagnostic workup of pulmonary hemorrhage were native scans in all cases.

Impact of BPA therapy on physical capacity, pulmonary hemodynamics and NT-proBNP levels

The data on the impact of BPA therapy on physical capacity, pulmonary hemodynamics and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a marker for cardiac stress were recently published by our group [10]. The mean pulmonary artery pressure (meanPAP) (baseline: 5.2 ± 1.6 kPa vs. 6-month follow-up: 4.3 ± 1.7 kPa; $p < .001$), the PVR (baseline: 516 ± 219 dyn × sec × cm^{-5} vs. 6-month follow-up: 397 ± 183 dyn × sec × cm^{-5}; $p < .001$) and the right atrial pressure (RAP) (baseline: 1.1 ± 0.6 kPa vs. 6-month follow-up: 0.8 ± 0.4 kPa; $p = .008$) decreased

Table 2. Dynamics of renal functional parameters during BPA therapy (laboratory analysis prior to the BPA procedure).

	Prior to 1.BPA	Prior to 2.BPA	Prior to 3.BPA	Prior to last BPA	6-month follow-up
Creatinine (µmol/L)	80.1 (67.8–96.8)	80.1 (69.5–102.1)	81.8 (71.3–98.6)	80.1 (67.9–98.6)	77.4 (66.9–91.5)
eGFR (mL/min/m^2)	79.3 (59.0–93.9)	75.7 (63.3–91.3)	74.7 (62.9–85.4)	79.1 (60.5–87.8)	79.6 (67.1–95.0)
Urea (mmol/L)	13.7 (10.7–16.6)	14.3 (11.8–18.2)	13.2 (10.7–17.5)	12.9 (10.7–15.4)	12.5 (10.0–15.5)

BPA: balloon pulmonary angioplasty; eGFR: estimated glomerular filtration rate.

significantly. The cardiac index (CI) did not significantly change (baseline: 2530 ± 600 mL/min/m^2 vs. 6-month follow-up: 2530 ± 5l0 mL/min/m^2; $p = .33$). The median NT-proBNP level decreased from 97.0 (IQR 18.1–221.4) pmol/L at baseline to 18.8 (IQR 9.9–54.9) pmol/L ($p < .001$) within the 6-month follow-up.

Renal function at baseline and dynamics of renal functional biomarkers during BPA treatment

At baseline, the median eGFR was 79.3 (IQR 59.0–93.9) mL/min/m^2, the median serum creatinine level was 80.1 (IQR 67.8–96.8) µmol/L and the median serum urea level was 13.7 (IQR10.7–16.6) mmol/L. Comparison of baseline and 6-month follow-up values in the whole cohort revealed no significant difference for eGFR but for serum creatinine and serum urea. Based on the stages of CKD, the patients were subclassified at baseline: G1:15, G2:23, G3a:10, G3b:2, G4:1, G5:0. Comparing the CKD-stage at baseline and after the last BPA, the stage improved in 11 (21.6%) patients, worsened in 14 (27.5%) patients and stayed unchanged in 26 (51.0%) patients. Comparing the CKD-stage at baseline and at the 6-month follow-up, the stage improved in 14 (28.6%) patients, worsened in 4 (8.2%) patients and stayed unchanged in 31 (63.3%) patients. The maximum worsening was one CKD stage. The improvement was one CKD stage in 13 (26.5%) patients and two CKD stages in one (2.0%) patient. The overall change of the median CKD-stage in the whole cohort was not significant from baseline to last BPA and to the 6-month follow-up. There was no change of the CKD-stage among the five patients, who suffered from AKI during the BPA sequence. Table 2 illustrates the dynamics of eGFR, serum creatinine and urea during the BPA sequence and at the 6-month follow-up. Figure 1 shows the change of CKD-stages during the BPA sequence.

Subgroup analysis of patients with an impaired renal function at baseline (CKD stage ≥2, n = 36)

Among patients with a CKD-stage ≥2, the comparison of baseline and 6-month follow-up values revealed an increase of eGFR [baseline: 69 (IQR 54–80) mL/min/m^2 vs. 6-month follow-up: 74 (IQR 63–90) mL/min/m^2; $p = .004$] and a decrease of serum creatinine [baseline: 88.4 (IQR 79.2–105.6) µmol/L; 6-month follow-up: 79.2 (IQR 70.4–96.8) µmol/L; $p = .002$] and serum urea [baseline: 15.7 (IQR 12.3–18.4) mmol/L; 6-month follow-up: 13.9 (IQR 11.8–17.1) mmol/L; $p = .043$]. Accordingly, among the survivors, the CKD-stage at baseline improved in 14 (41.2%), stayed unchanged in 19 (55.9%) patients and worsened in one (2.9%) patient. Table 3 presents the comparison of baseline characteristics between patients with a CKD-stage ≥2 and the rest of the cohort. Patients with a CKD-stage ≥2 were significantly older had higher NT-proBNP concentrations and tended to have worse pulmonary hemodynamics.

Association of renal function with hemodynamic parameters and NT-proBNP under BPA treatment

The eGFR did not correlate with the meanPAP ($r_{rs} = -0.17$; $p = .23$), the PVR ($r_{rs} = -0.18$; $p = .21$) and the CI ($r_{rs} = 0.26$; $p = .06$) at baseline. There was a moderate, inverse correlation with the RAP ($r_{rs} = -0.44$; $p = .002$) and the NT-proBNP level ($r_{rs} = -0.50$; $p < .001$) at baseline.

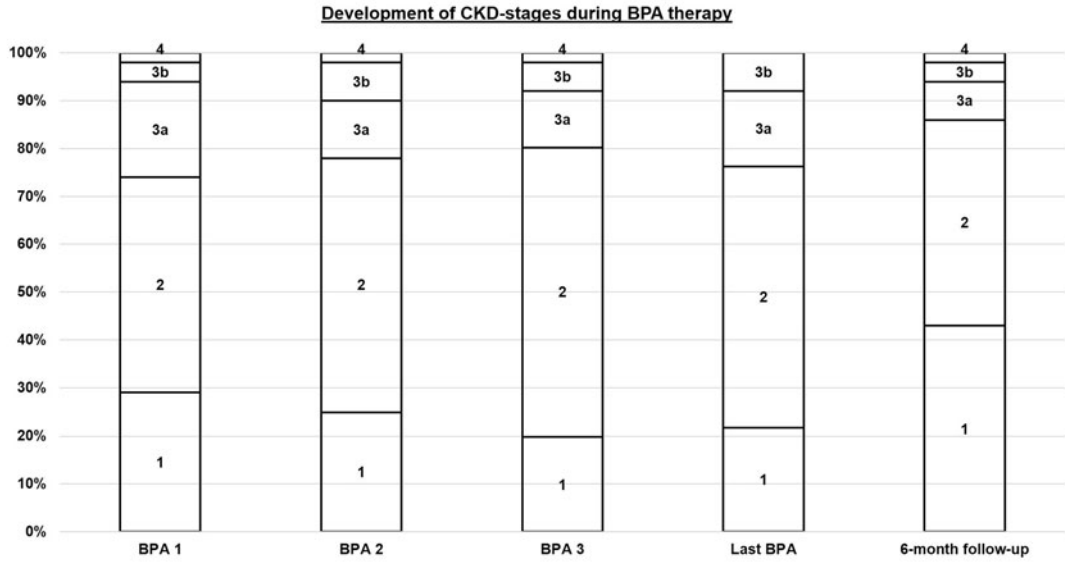
In contrast, the eGFR at 6-month follow-up did not correlate significantly with the meanPAP ($r_{rs} = 0.13$; $p = .38$), PVR ($r_{rs} = 0.05$; $p = .75$), RAP ($r_{rs} = 0.10$; $p = .50$), and the NT-proBNP level ($r_{rs} = -0.13$; $p = .38$) except the CI ($r_{rs} = 0.33$; $p = .03$).

Comparison of patients with a worsening of the CKD-stage ≥1 versus the rest of the cohort revealed no significant differences regarding the baseline characteristics: meanPAP (CKD-worsening: 4.7 ± 2.4 kPa; no CKD-worsening: 5.2 ± 1.6 kPa; $p = .53$), PVR (480 ± 329.5 dyn × sec × cm^{-5}; no CKD-worsening: 503.8 ± 210.4 dyn × sec × cm^{-5}; $p = .75$), RAP (CKD-worsening: 0.9 ± 0.5 kPa; no CKD-worsening: 1.0 ± 0.6 kPa; $p = .84$), CI (CKD-worsening: 2337 ± 462 mL/min/m^2; no CKD-worsening: 2570 ± 415 mL/min/m^2; $p = .51$), NT-proBNP [CKD-worsening: 79.1 (IQR 15.8–237.6) pmol/L; no CKD-worsening: 64.2 (IQR 16.0–197.5) pmol/L; $p = .96$], eGFR [CKD-worsening: 91.7 (IQR 66.2–99.6) mL/min/m^2; no CKD-worsening: 79.5 (IQR 59.7–94.7) mL/min/m^2; $p = .40$].

Discussion

The main findings of this study are: 1) BPA therapy is a safe approach regarding the periprocedural effects on renal function. 2) Among patients suffering from CKD at baseline, renal function improved after BPA, which might be related to the improvement of systemic circulation.

In the context of renal function assessment in CTEPH patients undergoing BPA, procedural aspects need to be further elucidated. Since the first BPA series, performed by Feinstein et al. prior to 2001, BPA developed to a staged procedure, which includes a sequence of sessions with an interval of 4–8 weeks [11,21]. This distinctly reduced the rate of reperfusion injury, but increased the number of interventions, the use of radiation and iodine contrast agent [11]. Periinterventional AKI in the course of cardiac interventions is a well described and frequent complication [14].



CDK-stage (N)	BPA 1	BPA 2	BPA 3	Last BPA	6-month follow-up
All over	51	51	51	51	49
Stage 1	15	13	10	11	21
Stage 2	23	27	31	28	21
Stage 3a	10	6	6	8	4
Stage 3b	2	4	3	4	2
Stage 4	1	1	1	0	1
Stage 5	0	0	0	0	0

Figure 1. Dynamics of the CKD-stages during staged BPA procedure (BPA: balloon pulmonary angioplasty; CKD: chronic kidney disease).

Table 3. Comparison of patients with impaired renal function (CKD-stage ≥2) and other patients (CKD-stage <2) regarding their baseline characteristics.

Parameter	CKD-stage <2 mean (±SD) or median (IQR)	CKD-stage ≥2 mean (±SD) or median (IQR)	*p*-value
Age at 1st BPA, years	56.9 ± 11.4	65.7 ± 10.6	.01
eGFR, mL/min/m^2	101.8 (95.0–114.2)	68.6 (54.2–80.0)	<.001
NT-proBNP, pmol/l	12.5 (7.1–132.7)	138.2 (26.3–309.7)	.002
PVR, dyn × sec × cm^{-5}	453.4 ± 249.5	543.4 ± 202.3	.188
MeanPAP, kPa	4.6 ± 1.9	5.6 ± 1.4	.048
RAP, kPa	0.8 ± 0.5	1.1 ± 0.6	.14
Cardiac index, mL/min/m^2	2530 ± 440	2528 ± 655	.99

BPA: balloon pulmonary angioplasty; eGFR: estimated glomerular filtration rate; meanPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PVR: pulmonary vascular resistance; RAP: right atrial pressure.

To the best of our knowledge, the effects of repetitive contrast agent administration within BPA, have not been systematically analyzed yet.

Focusing on the periprocedural short-term dynamics of renal function, AKI was a rare phenomenon in our cohort. It is to be mentioned, that, due to the small absolute number of patients, with an advanced CKD at baseline, the results provide limited information about the effects of BPA in this subcohort. However, the current data suggest a safe performance of BPA regarding the short-term effects on renal function. All of the AKI events in our study were classified as a stage I and no transient or long-term renal dialysis was needed. The patients with an AKI did not significantly differ from the others regarding their baseline renal function and hemodynamics. Even though, the current data allow no final assessment of BPA therapy in patients with severe CKD, the results do not suggest advanced renal dysfunction as a contraindication for BPA therapy. In this context it is a relevant observation, that there was no worsening of the CKD-stage at the 6-month follow-up among patients with a baseline CKD-stage G3b or G4.

The low rate of AKI in this study might be interpreted as a combination of both, improvement of hemodynamics with reduced venous filling pressure and the stringent periprocedural renal protection.

Strategies to prevent contrast-induced acute renal failure were subject to intensive investigations during the last decades. However, no definite recommendation exists, particularly for the special field of BPA therapy. The renal protection strategy in the current study is based on the pathophysiological hypothesis that an elevated intravascular volume, promoted diuresis and balanced serum electrolytes might reduce the nephrotoxic effects of contrast agent. Periprocedural, intravenous hydration proofed to be effective for the prevention of contrast-induced renal failure in several studies [19,22]. Although, the evidence for the

benefit of additional administration of loop diuretics is weaker, the standardized combination of matched hydration and loop diuretics was associated with a lower incidence of acute renal failure in several studies [19,22]. The use of antioxidants, mainly acetylcysteine, is discussed controversially, since the initially published benefit regarding the prevention of contrast-induced renal failure could not be confirmed in large randomized trials [19,23]. Given the limited negative side effects and the inhomogeneous recommendations in the literature, the use of acetylcysteine is maintained at our center.

Besides the acute aspect, the chronic impairment of renal function needs to be taken into account as a relevant comorbidity in the context of pulmonary hypertension. Among patients suffering from pulmonary arterial hypertension, due to inconsistent definitions and inclusion criteria, reported rates of a CKD stage $\geq$3 range from 4% to 36% [7]. But even a mild renal dysfunction with an eGFR between 60 and 80 mL/min/1.73m^2 is an independent risk factor for cardiovascular disease [24,25]. There is broad evidence of correlation of renal function and outcome in pulmonary arterial hypertension patients [26,27]. In several cohorts, CKD was associated with all-cause mortality [26,27]. The absolute number of two deceased patients in our cohort does not allow a reasonable assessment of the correlation between renal function and survival. However, it has to be mentioned, that the deceased patients suffered from CKD stage 2 and 3a at baseline.

The frequent coincidence of cardiac diseases and renal dysfunction has been subject to intensive investigations. Malperfusion due to low cardiac output, the retrograde venous congestion and secondary neuro-humoral feedback are discussed as the leading mechanisms [7]. In patients suffering from left-heart disease, renal function rather correlates with diastolic ventricular function and elevated RAP than with LVEF and CI [7,28,29]. Venous congestion has been reported to be the main underlying cause for renal dysfunction [30]. In a cohort of patients suffering from pulmonary arterial hypertension, Bietker et al. [6] reported a correlation of eGFR with CI at baseline and with RAP within the longitudinal follow-up. In contrast, Kaiser et al. [27] showed a correlation of eGFR only with CI within a mixed cohort suffering from pulmonary hypertension. In further series, renal function was linked to CI, RAP or both parameters [8,26,31]. These controversies triggered a discussion about the leading underlying mechanism of renal failure in patients with pulmonary hypertension – venous congestions versus impaired antegrade perfusion. Bietker et al. [6] describe the predominant mechanism of an increasing RV afterload and chronic RV failure leading to decreased cardiac output with renal malperfusion. Finally progressive right heart dysfunction leads to backward failure and triggers venous congestion which further promotes renal failure [6,30]. In our cohort, the eGFR correlated moderately with RAP and NT-proBNP at baseline but not with CI, which we interpret as a predominant role of venous congestions in the context of renal function.

After the BPA therapy, improved pulmonary hemodynamics lead to reduced right heart stress, mirrored by decreased NT-proBNP concentrations, even without a significant change of the CI. We rather observed a significant reduction of RAP, which comes along with a relevant decrease of venous congestion and an improvement of renal function. Our results suggest that this benefit is particularly apparent among patients with an impaired renal function at baseline and cannot be generally expected in all CTEPH patients. Recently published data indicate a comprehensive improvement of metabolic impairments, also renal function, in CTEPH patients after BPA [32]. Kimura et al. [33] reported no significant change of renal function after BPA for their whole cohort, but for those patients with an eGFR $<$57 mL/min/1.73m^2 at baseline. This basically supports our findings, that a significant improvement of renal function might only be observed among patients with an impaired renal function at baseline.

Overall, these observations support the hypothesis that renal failure in CTEPH is an expression of failing compensatory right heart adaption. Beneficial therapeutic effects on renal function might thus be more distinct in patients suffering from progressive disease.

In addition to impaired hemodynamics and neurohormonal activation, disease progression of CTEPH is contributed by inflammatory and fibrotic effects [7]. Renal malperfusion impairs renal function which leads to decreased clearance of uremic toxins and inflammatory cytokines [7]. This promotes systemic inflammation and thus contributes again the progression of CTEPH with cardiac remodeling and secondary vasculopathy as a circulus vitiosus. Therefore, the improvement of renal function mirrors improvement of pulmonary hemodynamics and RV function.

Some limitations of this study need to be mentioned. The study included a small number of patients. Nevertheless, our BPA program is among the largest worldwide. With only two deceased patients within the 6-month follow-up, a correlation of renal functional parameters and long-term survival seemed not reasonable and was therefore not performed. Overall only a few patients with severe renal dysfunction at baseline were included which might be the result of improved screening mechanisms for CTEPH over the years, coming along with a reduced rate of severe disease stages.

Conclusion

BPA as a staged procedure in CTEPH patients is safe with regard to renal function. Patients with CKD $\geq$2 showed a slight improvementin renal function. However further investigation is needed to understand the underlying mechanisms.

Disclosure statement

The study BioCTEPH is part of the Kerckhoff Biomarker Registry (Bioreg) of the Kerckhoff Heart Research Institute (KHFI). BioReg is financially supported by the KHFI and the German Center for Cardiovascular Research (DZHK). The sponsor had no influence on

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Data availability statement

The raw data set, underlying this work is part of the Kerckhoff Biomarker Register and is locally available at the study site. Researchers and research groups from other institutions may access the data as partner within scientific research projects after proving legitimate scientific interest.

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Original Research Article

Pulmonary Circulation

Cardiac biomarkers as indicators of right ventricular dysfunction and recovery in chronic thromboembolic pulmonary hypertension patients after balloon pulmonary angioplasty therapy – a cardiac magnetic resonance imaging cohort study

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Abstract

Background: In chronic thromboembolic pulmonary hypertension, right heart failure determines outcome. Balloon pulmonary angioplasty therapy allows right heart recovery, which can be monitored by cardiac magnetic resonance imaging. This study evaluates whether cardiac biomarkers (NT-proBNP, MR-proANP, sST2, and PAPP-A) are associated with cardiac magnetic resonance imaging findings prior to and after balloon pulmonary angioplasty therapy.

Methods: This observational cohort study enrolled 22 chronic thromboembolic pulmonary hypertension patients who underwent balloon pulmonary angioplasty therapy and completed a six-month follow-up including cardiac magnetic resonance imaging. Biomarker levels were compared with findings for right heart morphology and function derived from cardiac magnetic resonance imaging.

Results: Pulmonary hemodynamics improved after balloon pulmonary angioplasty therapy [pulmonary vascular resistance: 7.7 (6.0–9.0) vs. 4.7 (3.5–5.5) wood units, $p < 0.001$; mean pulmonary artery pressure 41 (38–47) vs. 32 (28–37) mmHg, $p < 0.001$]. Cardiac magnetic resonance imaging findings indicated right heart maladaptation at baseline and recovery after therapy [right ventricular end-diastolic volume 192 (141–229) ml vs. 143 (128–172) ml, $p = 0.002$; right ventricular end-systolic volume 131 (73–157) ml vs. 77 (61–99) ml ($p < 0.001$); right ventricular ejection fraction (RVEF) 34 (28–41) % vs. 52 (41–54) %; $p < 0.001$]. Biomarker level cut-offs [NT-proBNP 347 ng/L (area under the curve (AUC) 0.91), MR-proANP 230 pg/L (AUC 0.78), PAPP-A 14.5 mU/L (AUC 0.81), and sST2 48.0 ng/ml (AUC 0.88)] indicated a RVEF $\leq$ 35% at baseline. The dynamics of NT-proBNP ($rs = -0.79$; $p < 0.001$), MR-proANP ($rs = -0.80$; $p < 0.001$), and sST2 ($rs = -0.49$; $p = 0.02$) correlated inversely with the improvement in RVEF after therapy. A relative decrease of NT-proBNP $< 53\%$ (AUC 0.86) and MR-proANP $< 24\%$ (AUC 0.82) indicated a limited RVEF response.

Conclusions: In chronic thromboembolic pulmonary hypertension patients, cardiac magnetic resonance imaging findings illustrate right heart failure and recovery after balloon pulmonary angioplasty therapy. Cardiac biomarker levels correlate with right heart parameters at baseline and their dynamics after therapy.

Keywords

Pulmonary hypertension, balloon pulmonary angioplasty, right ventricle function and dysfunction, risk stratification and biomarkers

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Chronic thromboembolic pulmonary hypertension (CTEPH) is diagnosed in about 3% of patients who survive an acute pulmonary embolism.[1] Progressive impairment of pulmonary hemodynamics burdens the right heart and causes maladaptive morphological and functional right heart remodeling.[2] The ensuing right heart failure is the major determinant of outcome in CTEPH.[2,3]

Surgical pulmonary endarterectomy is the first-line therapy for CTEPH.[1,4] In inoperable patients, a sequence of medical therapy with riociguat and balloon pulmonary angioplasty (BPA) is the recommended therapeutic concept.[1,4] Both therapeutic approaches improve pulmonary hemodynamics and thus allow right heart recovery.[5,6] Notably, it has been suggested that changes in right heart function under specific therapy for pulmonary hypertension (PH) outperform pulmonary hemodynamics as a predictor of outcome.[7] A structured diagnostic work-up focused on the individual severity of right heart disease is therefore crucial for optimal patient management.

Cardiac magnetic resonance imaging (CMR) is the reference imaging modality for the right heart, facing particularly its complex anatomy with 3D-based measurement of dimensions and function.[8] In PH, CMR provides detailed information about the severity of morphological and functional right heart maladaptation.[9,10] However, availability, costs, and the necessity of specific expertise limit the use of CMR as a standard approach.

Several noninvasive biomarkers were found to be associated with different aspects of right heart maladaptation and failure. Hemodynamic right heart stress can be estimated by measurement of circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) and mid-regional pro-atrial natriuretic peptide (MR-proANP).[11,12] The conversion from hemodynamic stress to cardiac tissue remodeling as a secondary maladaptive response to chronic pressure overload is more difficult to address. Biomarkers as soluble suppression of tumorigenicity 2 (sST2)[13] and pregnancy-associated plasma protein-A (PAPP-A)[14] which are expressed in response to mechanic myocardial stress but also contribute to inflammatory and fibrotic tissue remodeling pathways might be of use in this context. The current study investigates the potential of these biomarkers as indicators of right ventricular function and dimensions by using CMR as a reference method in a cohort of patients with inoperable CTEPH treated by BPA.

Methods

Study population

The present observational cohort study consecutively included 22 patients with confirmed inoperable CTEPH who were treated by BPA, completed a six-month follow-up (6-MFU) after therapy, and underwent CMR at both baseline and follow-up at the study center. The patients were deemed to be inoperable because of peripheral obstructive lesions of the pulmonary arteries. All patients were discussed in a multidisciplinary CTEPH conference to confirm the diagnosis and decide about the individual treatment. The diagnostic and therapeutic management of CTEPH patients at our center was recently published.[6,15] CMR, which is not routinely performed in all CTEPH patients, was used as supplementary imaging in these 22 patients for extended right heart assessment. The individual decision to perform a CMR was made by the multidisciplinary CTEPH conference.

Only a subset of 15 (68%) patients was treated with riociguat prior to BPA therapy, as prior to 2014 there was no approved medication for CTEPH. Meanwhile, riociguat is recommended in the guidelines.[4] Thus, we adjusted our treatment approach over time, and riociguat is administered at least for three months prior to BPA in inoperable CTEPH patients. There were no changes of medication between the baseline diagnostic assessment prior to interventional BPA therapy and the follow-up.

All patients gave written informed consent. The ethics board of our University approved the study (AZ 43/14). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Right heart catheterization

Right heart catheterization was performed routinely via the right internal jugular vein using a 6F sheath and a standard Swan-Ganz catheter. The medication was not modified prior to or during the procedure.

Balloon pulmonary angioplasty

BPA interventional therapy was performed as a standardized technique as previously published in detail.[5,15]

Cardiac magnetic resonance imaging

Imaging was performed with a 1.5-T scanner system (Avanto; Siemens Healthineers, Erlangen, Germany; gradient strength and slew rate: SQ-Engine [45 mT/m at 200 T/m/s]) using a six-element phased array cardiac coil and a dedicated CMR protocol containing axial, coronal, and sagittal thoracic survey images, steady-state-free precession sequences (SSFP), CINE in two-chamber view, three-chamber view, four-chamber view, and stacked transaxial and short-axis views from base to apex.

SSFP imaging parameters were slice thickness 8 mm; field of view: 300 × 400 mm; matrix 256 × 154; TR 59.62; and TE 1.15. The SSFP images were obtained during breath-hold, and the LV and RV systolic and diastolic volumes (absolute values) were calculated from short-axis and transaxial CINE images. Measurements were performed on end-diastolic images (first phase after the R-wave trigger) and end-systolic images (CINE with the visually smallest cavity area). Endocardial contours of the left and right ventricle were obtained by manual tracing with exclusion of papillary

muscles and trabeculae from the cavity. Ventricular volumes were estimated using the Simpson rule. The left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) was calculated as [end-diastolic volume – end-systolic volume]/end-diastolic volume. The post-processing was performed with the ARGUS software package (Siemens Syngo MMWP Version VE40A; Siemens Healthineers).

The radiologists who performed the imaging diagnostics were blinded to results from biomarker analysis.

Laboratory assessment

Venous blood samples for biomarker analysis were collected as serum samples in serum tubes (S-Monovette®, Sarstedt, Nümbrecht, Germany) at baseline prior to BPA therapy and at the 6-MFU, each at the same time as CMR and were processed for storage immediately. All serum samples were transferred to plain uncoated tubes for storage at a temperature of –80°. The median storage time was 43 (41–46) months. All measurements were carried out batch-wise on once thawed samples by experienced staff blinded to patient characteristics.

NT-proBNP levels were measured using an electrochemiluminescence immunoassay (NT-proBNP assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The limit of detection (LOD) for this assay is 5 ng/L; concentrations above the measuring range are reported as >35,000 ng/L. The lowest concentration measurable with a coefficient variation (CV) of 20% is 50.0 ng/L. At the cut-off value of 150 ng/L the CV is <3%.

MR-proANP levels were measured by TRACE (time-resolved amplified cryptate emission) technology (BRAHMS MR-proANP KRYPTOR assay, Kryptor Compact Plus, BRAHMS GmbH, Hennigsdorf, Germany). The LOD is 2.1 pmol/L; concentrations above the measuring range are reported as >10,000 pmol/L. The intra-assay is CV ≤ 5%; inter-assay CV ≤ 6.5%.

sST2 levels were measured using an electrochemiluminescence immunoassay (Presage ST2 assay, Critical Diagnostics, San Diego, CA, USA). The LOD is 1.8 ng/ml; concentrations above the measuring range are reported as >200 ng/ml. At a concentration between 33 and 159 ng/ml, the CV ranges from 5.5 to 4.8%.

PAPP-A was measured by time-resolved amplified cryptate emission (BRAHMS PAPP-A KRYPTOR Assay, Thermo Scientific, BRAHMS GmbH, Henningsdorf, Germany). The LOD is 0.004 U/L; concentrations above the measuring range are reported as >90 U/L. The mean CV is 3.1%.

Statistical analysis

In consideration of the small study cohort, all continuous variables are expressed as median and interquartile range (IQR). Categorical variables are reported as number and percentage. Subcohorts at baseline, prior to BPA therapy, or at the follow-up were compared using the Mann-Whitney U test for all other continuous variables. The χ^2 test and Fisher-Yates test were used for categorical variables. Parameters that were obtained at baseline and at the 6-MFU were subjected to paired sample testing using the Wilcoxon signed-rank test. Correlations were analyzed using bivariate Spearman correlation (r_s).

The study assessed the diagnostic performance of non-invasive biomarkers to indicate severe right heart dysfunction at baseline and the change of right heart function after BPA therapy, using receiver operating characteristics (ROC). In the literature, inconsistent data about optimal RVEF cut-off values to predict outcome in cardiac diseases are reported[16]; however, a RVEF ≤ 35% derived from CMR was strongly associated to worse outcome in patients with pulmonary artery hypertension.[7] Accordingly, we predefined severe right heart dysfunction as a RVEF ≤ 35%, quantified by CMR.

We further defined a limited change of right heart function after therapy as a relative change of RVEF ≤ 25% compared to the baseline RVEF. Biomarkers with a correlation ($r_s \geq |0.5|$) to RVEF change after therapy were analyzed in this context.

Results are presented as area under the curve (AUC) with corresponding 95% confidence intervals (CIs). The optimal cut-off values with regard to study outcomes were calculated using Youden index quantification.

To assess the prognostic performance of optimal biomarker cut-off levels with regard to study outcomes, sensitivity, specificity, and negative (NPV) and positive (PPV) predictive values were calculated. Results are presented as odds ratios (OR) with corresponding 95% CIs.

Statistics were performed with SPSS software (IBM Corp., Armonk, NY, USA), version 21.0. A two-tailed p value <0.05 was considered to be statistically significant.

Results

Characteristics of the study cohort and treatment effects

The sociodemographic data and comorbidities of all 22 patients (12 women; median age [IQR] 70 [63–77] y) enrolled in the study are presented in Table 1. In all patients, the BPA therapy was indicated due to obstructive lesions of the pulmonary arteries, which were too peripheral for a surgical pulmonary endarterectomy. The interventional treatment included 122 BPA sessions, a median of 6 (5–7) per patient, with a median number of 10 (9–12) treated vessels. Table 1 shows the effects of therapy on physical capacity and hemodynamic findings.

Biomarker measurement and CMR findings at baseline

The detailed findings from CMR and biomarker measurements at baseline are given in Table 1. The majority (n = 19;

86%) of patients showed normal left ventricular dimensions and function at baseline. In three patients, the LVEF was mildly (n = 1) or moderately (n = 2) impaired. The levels of all four biomarkers measured, particularly the natriuretic peptides, correlated with right ventricular dimensions and RVEF at baseline (Table 2).

A total of 14 (64%) patients showed severely impaired RVEF of ≤35% at baseline. These patients were characterized by higher baseline levels of NT-proBNP [RVEF ≤ 35%: 1427 (931–3377) ng/L vs. RVEF > 35%: 214 (45–779) ng/L; p = 0.001], sST2 [RVEF ≤ 35%: 65.3 (51.7–96.8) ng/mL vs. RVEF > 35%: 42.9 (39.0–50.7) ng/mL; p = 0.003], PAPP-A [RVEF ≤ 35%: 20.6 (14.9–29.5) mU/L vs. RVEF > 35%: 13.0 (8.7–17.3) mU/L; p = 0.02], and MR-proANP [RVEF ≤ 35%: 261 (105–422) pmol/L vs. RVEF > 35%: 122 (58–149) pmol/L; p = 0.04].

An NT-proBNP level of 347 ng/L (AUC 0.91), an MR-proANP level of 230 pg/L (AUC 0.78), a PAPP-A level of 14.5 mU/L (AUC 0.81), and an sST2 level of 48.0 ng/ml (AUC 0.88) were revealed to be the optimal cut-off values for identifying patients with severely impaired RVEF (Table 3).

None of the patients (n = 4) with all biomarker levels below the listed cut-off values at baseline showed an RVEF ≤ 35% at baseline.

Changes in biomarker and CMR findings during therapy

After BPA, morphological and functional right heart parameters improved (Table 1). The absolute levels of all four biomarkers decreased after therapy (Table 1). The relative change in the RVEF correlated with the relative change in the levels of NT-proBNP (Fig. 1a), MR-proANP (Fig. 1b), and sST2 (Fig. 1c) after therapy, but not with changes in PAPP-A (Table 2). A total of 13 (59%) patients had an RVEF of ≥50% after BPA. A group of eight (36%) patients showed no significant (<25%) change of their RVEF after therapy. A relative change of the NT-proBNP level less than 53% (AUC 0.86) and a change of the MR-proANP level less than 24% (AUC 0.82) respectively was indicative for an unchanged RVEF (Table 3).

Discussion

The key findings of the current study were (I) CMR findings indicate a morphological and functional right heart impairment in CTEPH patients at baseline that improves after BPA therapy; (II) NT-proBNP, MR-proANP, sST2, and PAPP-A levels correlate with right ventricular dimensions and function at baseline; and (III) the relative change of biomarker levels, particularly NT-proBNP and MR-proANP, after therapy correlates with the relative improvement in right ventricular dimensions and function after BPA therapy.

CMR and biomarker findings at baseline

In CTEPH, impaired pulmonary hemodynamics burden the right heart, which leads to compensatory right heart remodeling and finally chronic right heart failure.[2] Considering this sequence, there is no doubt that the extent of pulmonary hemodynamic impairment is a determinant of disease severity in PH. However, the extent of maladaptive right heart remodeling as a fatal consequence can vary[9,17] and was suggested to be an even more consistent determinant of disease severity and outcome in PH than altered hemodynamics.[7]

CMR provides morphological and functional parameters of right heart maladaptation in pulmonary hypertension.[10,17–19] In comparison to reference values, gathered from CMR in healthy individuals,[20,21] the CTEPH patients in our cohort were characterized by distinct right ventricular dilatation and reduced RVEF, which is comparable to other CTEPH cohorts.[18,19,22]

Although CMR is the primary method for right heart assessment, it is unsuitable for a regular follow-up. Non-invasive biomarkers address different aspects of cardiac remodeling and might thus be a feasible tool for the assessment of structural and functional right heart impairment in PH.[11,12,23–27] Circulating levels of natriuretic peptides mirror myocardial stress due to pressure and volume overload and are established diagnostic and prognostic markers in heart failure.[28] In PH, natriuretic peptides are associated with secondary right heart failure and assessment of these biomarkers is recommended for screening, individual risk stratification, and therapy monitoring.[29] The current study found a strong correlation of NT-proBNP with right ventricular dimensions and function prior to BPA therapy, which is in line with the findings from other series.[25,30] The current guidelines on PH suggest an NT-proBNP level >300 ng/L as a cut-off to distinguish low-risk and elevated-risk patients.[29] Consistent with this, patients in our cohort with a severely impaired RVEF were identified by an NT-proBNP level ≥347 ng/L and showed a median level of 1427 ng/L at baseline, whereas patients with an RVEF > 35% had a median level of 214 ng/L. The correlation of MR-proANP levels with right heart CMR parameters was inferior to that of NT-proBNP, which might be explained by its mechanism of expression.[31] MR-proANP is produced in response to atrial stretch due to hemodynamic stress, and MR-proANP levels are related to right atrial pressure in CTEPH.[12] Considering that right atrial stress follows right ventricular deterioration in PH, right atrial failure is a strong indicator of right ventricular failure, but not vice versa.

In its role as a receptor for interleukin (IL)-33, ST2 regulates the tissue-protective effects of this cytokine and exists in both transmembrane (promoting) and soluble (opposing) isoforms.[13] An upregulation of the IL-33-(s)ST2 pathway was detected in relation to inflammation, tissue injury, and remodeling[32,33] and in the context of cardiac stress

Table 1. Patient characteristics and diagnostic findings (N = 22).

Sociodemographic characteristics and comorbidities			
Age, years, median (IQR)	70 (63–77)		
Female sex, n (%)	12 (55)		
Body mass index, kg/m^2, median (IQR)	24.3 (22.4–27.0)		
Diabetes mellitus, n (%)	None		
Arterial hypertension, n (%)	13 (59)		
Smoking, n (%)	8 (36)		
Coronary artery disease, n (%)	4 (18)		
Atrial fibrillation, n (%)	2 (9)		
Glomerular filtration rate, mL/min, median (IQR)	81 (68–93)		
Creatinine, μmol/L, median (IQR)	0.92 (0.75–0.99)		
History of cancer, n (%)	5 (23)		
Chronic obstructive pulmonary disease, n (%)	1 (5)		
History acute pulmonary embolism, n (%)	18 (82)		
History of splenectomy, n (%)	1 (5)		
History of chronic inflammatory disease, n (%)	none		
	Baseline	Follow-up	
Medication			
Novel oral anticoagulants (%)	16 (73)	21 (95)	
Vitamin K antagonist (%)	6 (27)	1 (5)	
Guanylate cyclase stimulator (%); Riociguat 1–7.5 mg/d	14 (64)	15 (68)	
Endothelin receptor antagonist; Bosentan 250 mg, Macitentan 10 mg	3 (14)	3 (14)	
Inhibitor of Phosphodiesterase 5; Tadalafil 40 mg	1 (5)	1 (5)	
	Baseline	Follow-up	p-value
Clinical status			
WHO FC I/II/III/IV	0/0/13/9	14/6/2/0	<0.001
6-MWD, m (IQR)	387 (333–472)	427 (357–451)	0.03
Echocardiography			
LVEF, % (IQR)	55 (55–58)	55 (55–58)	1.0
TAPSE, mm (IQR)	20 (17–22)	24 (22–26)	0.03
Right heart catheterization			
meanPAP, mmHg (IQR)	41 (38–47)	32 (28–37)	<0.001
Relative change in meanPAP, %	Decrease of 22 (12–29)		
PVR, wood units (IQR)	7.7 (6.0–9.0)	4.7 (3.5–5.5)	<0.001
Relative change in PVR, %	Decrease of 34 (21–49)		
Cardiac index, L/min/m^2 (IQR)	2.4 (2.1–2.8)	2.7 (2.4–3.1)	0.06
RAP, mmHg (IQR)	6 (5–9)	5 (4–8)	0.05
PCWP, mmHg (IQR)	9 (8–11)	9 (8–11)	0.85
Cardiac magnetic resonance imaging			
LVEDV, ml (IQR)	87 (81–99)	108 (95–130)	0.001
LVESV, ml (IQR)	33 (22–45)	37 (26–54)	0.08
LVEF, % (IQR)	65 (56–72)	65 (62–70)	0.12
RVEDV, ml (IQR)	192 (141–229)	143 (128–172)	0.002
RVEDV index, ml/m^2 (IQR)	100 (74–129)	84 (71–97)	0.001
RVESV, ml (IQR)	131 (73–157)	77 (61–99)	0.001
RVESV index, ml/m^2 (IQR)	76 (44–87)	46 (34–52)	<0.001
RVSV, ml (IQR)	66 (51–74)	73 (67–86)	0.003
RVSV index, ml/m^2 (IQR)	37 (28–43)	39 (35–51)	0.003
RVEF, % (IQR)	34 (28–41)	52 (41–54)	<0.001
Biomarkers			
NT-proBNP, ng/L	1122 (295–2365)	149 (71–341)	<0.001
sST2, ng/mL	52.6 (43.7–76.1)	44.7 (37.6–58.4)	0.002
PAPP-A, mU/L	17.2 (13.1–28.6)	11.7 (10.3– 13.5)	0.006
MR-proANP, pmol/L	145 (102–285)	125 (58–155)	0.002

Values are presented as n (%) or median (IQR). Abbreviations: LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; meanPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RVEDV: right ventricular end-diastolic volume; RVEF: right ventricular ejection fraction; RVESV: right ventricular end-systolic volume; TAPSE: tricuspid annular plane systolic excursion; WHO FC =World Health Organization functional class; 6-MWD: 6-minute walk test distance; 6-MFU: 6-month follow-up.

Table 2. Bivariate Spearman correlation of biomarker levels and right heart parameters derived from CMR findings and other diagnostic findings.

Parameter	NT-proBNP (ng/L)	MR-proANP (pmol/L)	sST2 (ng/ml)	PAPP-A (mU/L)
Baseline				
RVEDV, ml	$r_s = 0.68$; $p = 0.001$	$r_s = 0.34$; $p = 0.12$	$r_s = 0.36$; $p = 0.11$	$r_s = 0.46$; $p = 0.03$
RVEDV index, ml/m^2	$r_s = 0.73$; $p < 0.001$	$r_s = 0.49$; $p = 0.02$	$r_s = 0.45$; $p = 0.04$	$r_s = 0.47$; $p = 0.03$
RVESV, ml	$r_s = 0.80$; $p < 0.001$	$r_s = 0.46$; $p = 0.03$	$r_s = 0.47$; $p = 0.03$	$r_s = 0.48$; $p = 0.02$
RVESV index, ml/m^2	$r_s = 0.81$; $p < 0.001$	$r_s = 0.56$; $p = 0.007$	$r_s = 0.58$; $p = 0.004$	$r_s = 0.42$; $p = 0.05$
RVEF, %	$r_s = -0.80$; $p < 0.001$	$r_s = -0.59$; $p = 0.004$	$r_s = -0.63$; $p = 0.002$	$r_s = -0.48$; $p = 0.02$
meanPAP, mmHg	$r_s = 0.27$; $p = 0.24$	$r_s = -0.01$; $p = 0.98$	$r_s = 0.19$; $p = 0.39$	$r_s = 0.22$; $p = 0.34$
PVR, wood units	$r_s = 0.61$; $p = 0.004$	$r_s = 0.50$; $p = 0.02$	$r_s = 0.67$; $p = 0.001$	$r_s = 0.18$; $p = 0.44$
Cardiac index, L/min/m^2	$r_s = -0.73$; $p < 0.001$	$r_s = -0.67$; $p = 0.001$	$r_s = -0.61$; $p = 0.003$	$r_s = -0.13$; $p = 0.57$
RAP, mmHg	$r_s = 0.57$; $p = 0.03$	$r_s = 0.44$; $p = 0.04$	$r_s = 0.48$; $p = 0.03$	$r_s = 0.1$; $p = 0.66$
Relative change from baseline to 6-month follow-up				
RVEDV, %	$r_s = 0.56$; $p = 0.01$	$r_s = 0.67$; $p = 0.001$	$r_s = 0.09$; $p = 0.68$	$r_s = 0.30$; $p = 0.17$
RVEDV index, %	$r_s = 0.56$; $p = 0.01$	$r_s = 0.67$; $p = 0.001$	$r_s = 0.09$; $p = 0.68$	$r_s = 0.30$; $p = 0.17$
RVESV, %	$r_s = 0.83$; $p < 0.001$	$r_s = 0.89$; $p < 0.001$	$r_s = 0.47$; $p = 0.03$	$r_s = 0.42$; $p = 0.05$
RVESV index, %	$r_s = 0.83$; $p < 0.001$	$r_s = 0.89$; $p < 0.001$	$r_s = 0.47$; $p = 0.03$	$r_s = 0.42$; $p = 0.05$
RVEF, %	$r_s = -0.79$; $p < 0.001$	$r_s = -0.80$; $p < 0.001$	$r_s = -0.49$; $p = 0.02$	$r_s = -0.28$; $p=0.21$
meanPAP, %	$r_s = 0.13$; $p = 0.57$	$r_s = 0.02$; $p = 0.92$	$r_s = 0.08$; $p = 0.70$	$r_s = 0.005$; $p = 0.98$
PVR, %	$r_s = 0.34$; $p = 0.15$	$r_s = 0.27$; $p = 0.25$	$r_s = 0.57$; $p = 0.007$	$r_s = 0.006$; $p = 0.98$
Cardiac index, %	$r_s = 0.61$; $p = 0.003$	$r_s = 0.58$; $p = 0.005$	$r_s = 0.61$; $p = 0.003$	$r_s = 0.25$; $p = 0.27$
RAP, %	$r_s = 0.44$; $p = 0.05$	$r_s = 0.49$; $p = 0.02$	$r_s = 0.23$; $p = 0.3$	$r_s = 0.25$; $p = 0.27$

Abbreviations: LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; meanPAP: mean pulmonary artery pressure; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAPP-A: pregnancy-associated plasma protein-A; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RVEDV: right ventricular end-diastolic volume; RVEF: right ventricular ejection fraction; RVESV: right ventricular end-systolic volume; sST2: soluble suppression of tumorigenicity 2.

Table 3. Prognostic performance of biomarkers.

Biomarker level at baseline for the identification of patients (N = 14/22) with severely impaired right ventricular ejection fraction

	Cut-off value	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	NPV (%, 95% CI)	PPV (%, 95% CI)	OR (95% CI)
NT-proBNP, ng/L	347	0.91 (0.79–1)	92 (64–100)	75 (35–97)	85 (44–97)	87 (66–96)	36 (2.7–481)
sST2, ng/mL	48.0	0.88 (0.72–1)	93 (66–100)	75 (35–97)	86 (46–98)	87 (66–96)	39 (2.9–519)
PAPP-A, mU/L	14.5	0.81 (0.60–1)	86 (57–98)	75 (35–97)	75 (44–92)	86 (64–95)	18 (2–161)
MR-proANP, pmol/L	230	0.78 (0.58–0.99)	57 (29–82)	100 (63–100)	57 (42–71)	100 (100)	not calculated[a]

Relative change of biomarker level after therapy for the identification of patients (N = 8/22) without a change of right ventricular ejection fraction

	Cut-off value (%)	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	NPV (%, 95% CI)	PPV (%, 95% CI)	OR (95% CI)
NT-proBNP change, %	<53	0.86 (0.66–1)	88 (47–100)	92 (66–100)	93 (68–99)	87 (51–98)	91 (4.9–1687)
MR-proANP change, %	<24	0.82 (0.63–1)	88 (47–100)	79 (49–95)	92 (64–99)	07 (45–87)	26 (2.3–298)

Abbreviations: AUC: area under the curve; CI: confidence interval; MR-proANP: mid-regional pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OR: odds ratio; PAPP-A: pregnancy-associated plasma protein-A; sST2: soluble suppression of tumorigenicity 2; NPV: negative predictive value; PPV: positive predictive value.

[a]No patient with a severely impaired RVEF showed a MR-proANP level below the cut-off.

and remodeling.[13,34–36] Moreover, there is evidence for an association of elevated sST2 levels with right ventricular dilatation and dysfunction[26,37] and increased mortality in PH.[33] Recent studies reported elevated sST2 levels in PH and CTEPH patients compared with healthy controls.[23,38] Thus, serum levels >65 ng/ml were associated with severe hemodynamic impairment and mortality.[23,39] Consistent with these finding, sST2 levels correlated with right heart parameters from CMR: they were significantly elevated in patients with an RVEF < 35%, and a level >48.0 ng/ml was associated with a severe impairment of RVEF in our study.

Pregnancy-associated plasma protein-A (PAPP-A) is a regulator of insulin-like growth factor (IGF)/IGF-binding protein pathways,[40] which promote inflammation,

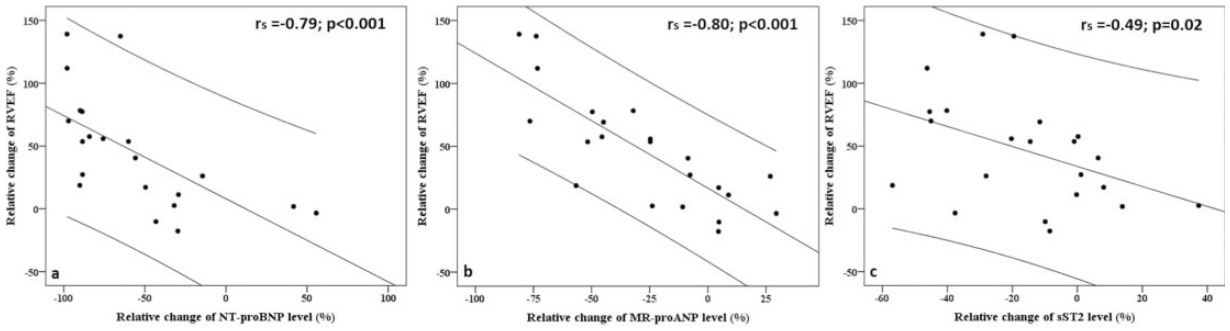

Fig. 1. Correlation between the relative change in biomarker levels and right ventricular ejection fraction (RVEF). NT-proBNP: N-terminal pro-B-type natriuretic peptide; MR-proANP: mid-regional pro-atrial natriuretic peptide; RVEF: right ventricular ejection fraction; sST2: soluble suppression of tumorigenicity 2.

anti-apoptosis, and proliferation in various cell types such as endothelial and smooth muscle cells.[41,42] There is some evidence for an involvement of PAPP-A and IGF-I/IGF-receptor signaling in PH.[24,43,44] Recently, our group found elevated PAPP-A levels in patients with CTEPH and non-CTEPH PH compared with healthy controls that were not associated with pulmonary hemodynamics.[24] In the present study, PAPP-A levels moderately correlated with right heart parameters from CMR: patients with an RVEF $< 35\%$ had elevated PAPP-A levels, and a level >14.5 mU/L was associated with an RVEF $\leq 35\%$.

Dynamics of CMR and biomarker findings after BPA therapy

BPA therapy improves pulmonary hemodynamics and thus allows right heart recovery with consequent positive effects on clinical symptoms and physical capacity.[1,11] Right heart reverse remodeling, manifested by a normalization of right heart dimensions and improved RVEF, was illustrated by imaging studies.[17,19,45,46] In pulmonary artery hypertension, the RVEF and the indexed right ventricular end-systolic volume (RVESVi), gathered from CMR at baseline, distinguished patients with a low, intermediate, or high risk of one-year mortality. Remarkably, the outcome of patients who moved to the low-risk RVEF or RVESVi group after specific PH therapy, documented by a follow-up CMR, was comparable to those patients with low-risk characteristics at baseline.[47]

This again confirms right heart recovery as the major therapy goal in CTEPH. In line with other series, right ventricular dimensions and RVEF improved after BPA therapy in the vast majority of patients in our study, which was documented by CMR findings.[17,19,45,46] As a consequence of right heart dilatation, interventricular septum shift, and septum dyssynchrony, concomitant left heart impairment, with a reduced left ventricular filling, is regularly observed in PH.[48] Concomitant to right heart recovery, CMR findings documented a reexpansion of the left ventricle after BPA therapy in our cohort, which might allow improved left ventricular filling.

Although an optimal assessment of right heart conditions should be a major focus of CTEPH follow-up regimes, routine assessment by CMR would not seem to be applicable due to the limitations mentioned. A few studies reported a correlation of NT-proBNP[49,50] and sST2[26] with right heart dimensions and function and their response to therapy in PH. In our cohort, there was a significant decrease in the levels of all four biomarkers measured after BPA therapy. Particularly the changes in NT-proBNP (RVESVi: $r_s = 0.83$; $p < 0.001$; RVEF: $r_s = -0.79$; $p < 0.001$) and MR-proANP (RVESVi: $r_s = 0.89$; $p < 0.001$; RVEF: $r_s = -0.80$; $p < 0.001$) strongly correlated with the dynamics of right heart dimensions and function after therapy.

A limited decrease of the baseline NT-proBNP level (<53%) or MR-proANP level (<24%) was indicative for an unchanged RVEF after therapy. Including NT-pro-BNP and MR-proANP measurement in the follow-up examinations of CTEPH patients might be an easily applied tool for noninvasive right heart "imaging."

Certain limitations of the study need to be mentioned. This study included a relatively small number of patients. Furthermore, CMR is not included in the routine diagnostic work-up of CTEPH patients. The decision to perform a CMR was made by the interdisciplinary CTEPH conference. Thus, the study consecutively included patients with a CMR, but not those CTEPH patients in between without a CMR. The results, particularly those concerning the diagnostic strength of biomarkers to predict CMR findings, should be interpreted as hypothesis-generating findings.

In conclusion, CMR findings illustrate significant right heart remodeling and failure in CTEPH patients. BPA therapy allows right heart recovery, particularly an improvement of right ventricular function. In consideration of the mentioned limitations, our study suggests that cardiac biomarkers can identify patients with a severely reduced RVEF at baseline, CMR documents changes in RV reverse remodeling, and changes in biomarker levels correlate with RV functional improvement after therapy.

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Conflict of interest

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Ethical approval

The ethics board of the Justus Liebig University of Giessen approved the study (AZ 43/14).

Guarantor

SDK and CBL.

Authors' contribution

SDK: study conception, interpretation of data, data management, first draft of the manuscript; JMV: interpretation of data, proofreading of the manuscript; CBW: treatment of patients, interpretation of data, proofreading of the manuscript; FR and MB: follow-up of patients, data management, proofreading of the manuscript; JSW: statistics, interpretation of data, proofreading of the manuscript; MH: treatment of patients, interpretation of data, proofreading of the manuscript; UFR, MW, AR, CWH, EM, SG, and TK: interpretation of data, proofreading of the manuscript; FCR: CMR diagnostics, interpretation of data, proofreading of the manuscript; CL: study conception, treatment of patients, interpretation of data, proofreading of the manuscript.

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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

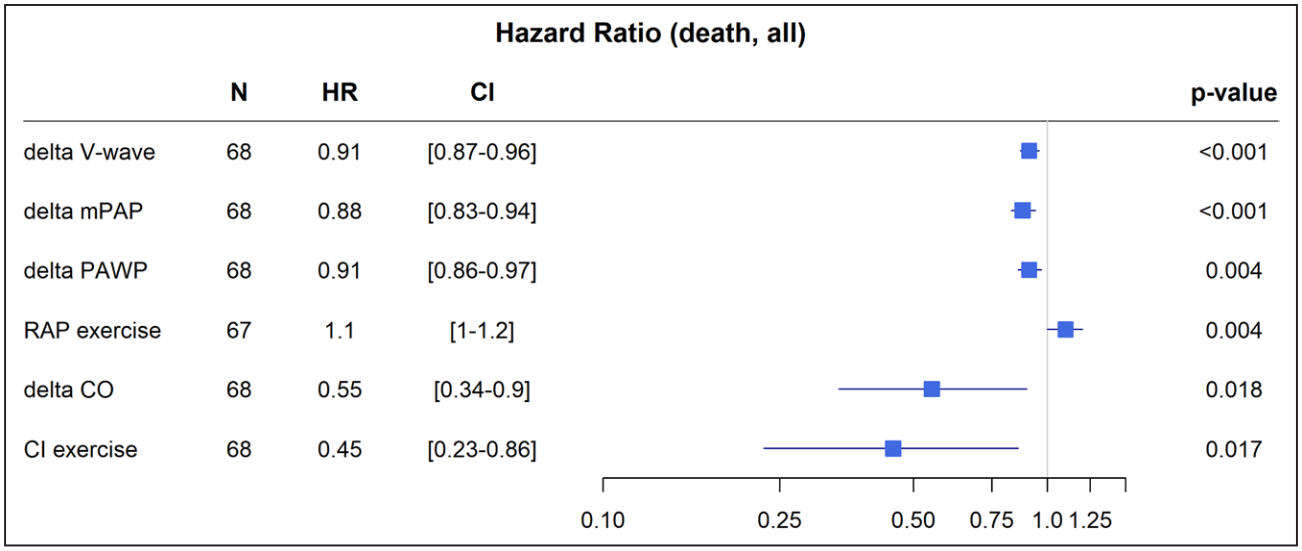

Figure 1. Comparison of univariate hazard ratios (HR) for all-cause mortality of significant invasive hemodynamic parameters during exercise in all patients (Cox regression).
CI indicates cardiac index (L/min/m²); CO, cardiac output (L/min); delta, difference between rest and exercise; mPAP, mean pulmonary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

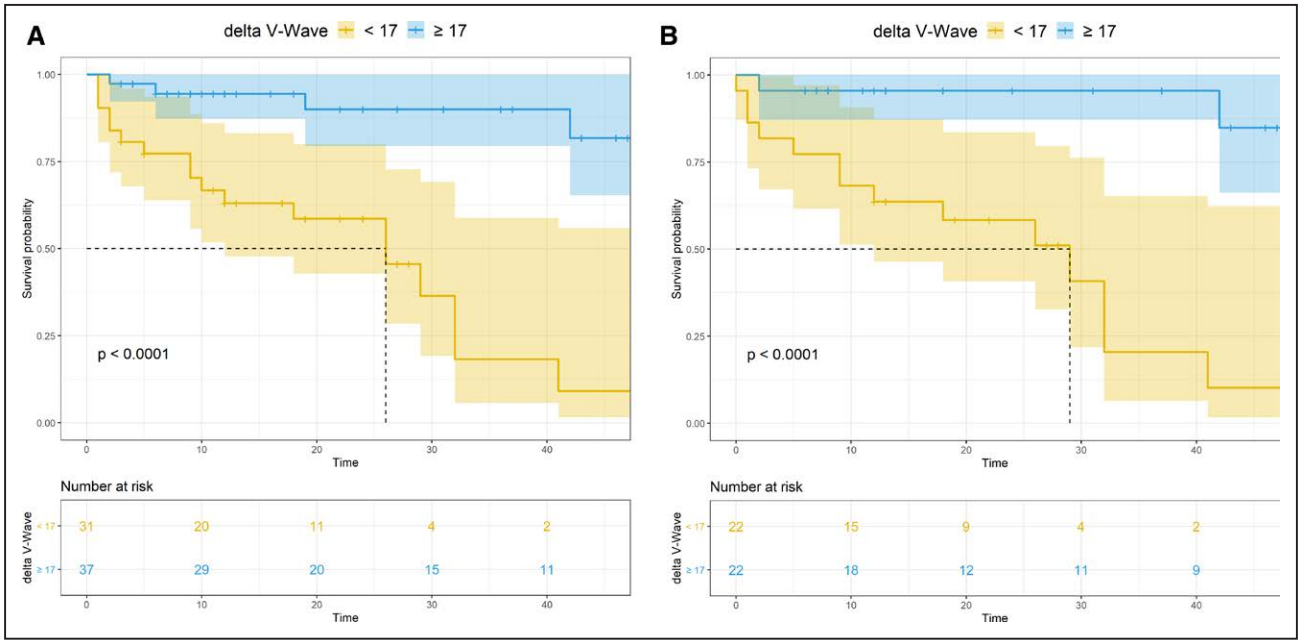

Figure 2. Kaplan-Meier survival curves as a function of hemodynamic profile based on ΔV-wave dichotomized at a cutoff derived from receiver operating characteristic analysis (time axis truncated at 48 mo).
A, All patients and (**B**) only secondary mitral regurgitation.

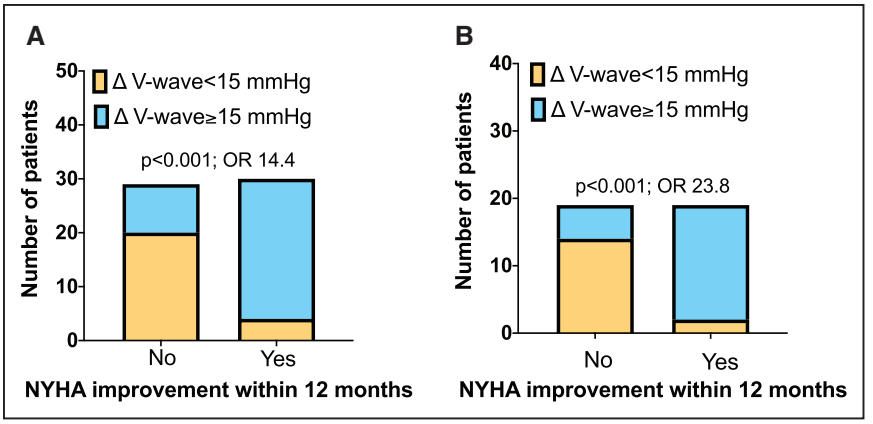

Figure 3. Patients with or without New York Heart Association (NYHA) class improvement within 12 mo (death within 12 mo = failure to improve) dichotomized based on ΔV-wave at a cutoff derived from receiver operating characteristic analysis.
A, All patients and (**B**) only secondary mitral regurgitation.

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

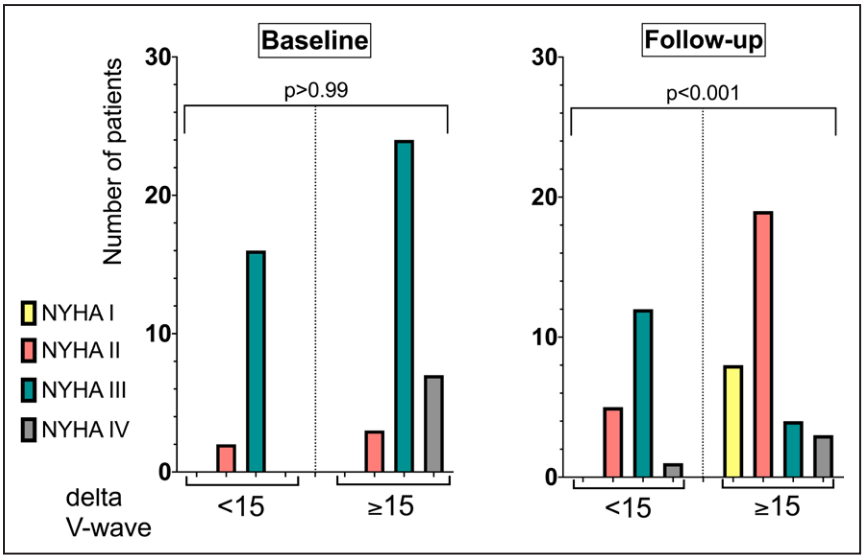

Figure 4. New York Heart Association (NYHA) class distributions (n=52) at baseline and follow-up, dichotomized based on ΔV-wave at a cutoff derived from receiver operating characteristic analysis.

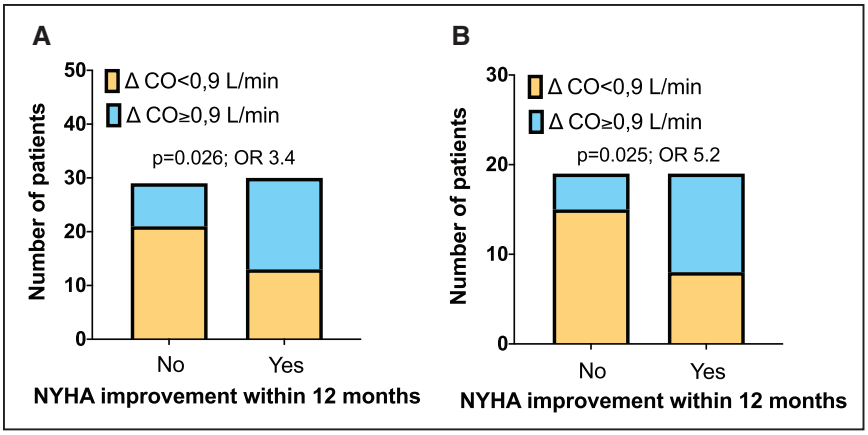

Figure 5. Patients with or without New York Heart Association (NYHA) class improvement within 12 mo (death within 12 mo = failure to improve) dichotomized based on Δ cardiac output (CO) at a cutoff derived from receiver operating characteristic analysis.
A, All patients and (**B**) only secondary mitral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

Pulmonary Circulation

Exercise right heart catheterization before and after balloon pulmonary angioplasty in inoperable patients with chronic thromboembolic pulmonary hypertension

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Abstract

Background: Balloon pulmonary angioplasty is an evolving, interventional treatment option for inoperable patients with chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary hypertension at rest as well as exercise capacity is considered to be relevant outcome parameters. The aim of the present study was to determine whether measurement of pulmonary hemodynamics during exercise before and six months after balloon pulmonary angioplasty have an added value.

Methods: From March 2014 to July 2018, 172 consecutive patients underwent balloon pulmonary angioplasty. Of these, 64 consecutive patients with inoperable CTEPH underwent a comprehensive diagnostic workup that included right heart catheterization at rest and during exercise before balloon pulmonary angioplasty treatments and six months after the last intervention.

Results: Improvements in pulmonary hemodynamics at rest and during exercise, in quality of life, and in exercise capacity were observed six months after balloon pulmonary angioplasty: WHO functional class improved in 78% of patients. The mean pulmonary arterial pressure (mPAP) at rest was reduced from 41 ± 9 to 31 ± 9 mmHg ($p < 0.0001$). The mPAP/cardiac output slope decreased after balloon pulmonary angioplasty (11.2 ± 25.6 WU to 7.7 ± 4.1 WU; $p < 0.0001$), and correlated with N-terminal fragment of pro-brain natriuretic peptide ($p = 0.035$) and 6-minute walking distance ($p = 0.01$).

Conclusions: Exercise right heart catheterization provides valuable information on the changes of pulmonary hemodynamics after balloon pulmonary angioplasty in inoperable CTEPH patients that are not obtainable by measuring resting hemodynamics.

Keywords

Chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, right heart catheter, exercise

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Introduction

An increasing number of inoperable patients with chronic thromboembolic pulmonary hypertension (CTEPH) are being treated with balloon pulmonary angioplasty (BPA) with or without targeted medication.[1–7] As the level of evidence for BPA remains limited, with a lack of controlled clinical trials and very few long-term studies, this interventional therapy is not strongly recommended by current guidelines.[8,9]

Improvements in pulmonary hemodynamics are often used as the main outcome variable of BPA; the actual concept of the intervention, which is meanwhile used worldwide, has been reinvented and developed mainly in Japanese centers with reported normalization or near-normalization of pulmonary hemodynamics at rest in up to 50% of the patients.[2–4,10] In European centers, outcomes of BPA have also been promising, with auspicious changes in physical capacity,[5,7,11] although the improvements in pulmonary hemodynamics at rest were less pronounced than in the Japanese cohorts. These differences have been discussed,[7,12,13] but it seems obvious that there is a need for a more thorough evaluation of hemodynamics. The assessment of pulmonary hemodynamics during exercise may provide additional information[14] and has not yet been demonstrated in inoperable CTEPH patients after BPA.

The aim of the present study was to evaluate the changes in pulmonary hemodynamics at rest and during exercise due to BPA in patients with inoperable CTEPH.

Methods

Patient selection for BPA

Our hospital serves as an international reference center for CTEPH, with more than 150 pulmonary endarterectomies (PEA) and more than 200 BPA interventions per year. Patients are routinely evaluated in a multidisciplinary CTEPH conference. Between March 2014 and July 2018, technically inoperable patients were included in the present prospective, observational cohort study. CTEPH was diagnosed in symptomatic patients after three months of anticoagulation who presented in at least WHO functional class (WHO FC) II, with a mean pulmonary arterial pressure (mPAP) of at least 25 mmHg at rest and with persistent pulmonary vascular lesions on computed tomography and/or conventional biplanar pulmonary artery angiography. Patients were deemed technically inoperable by experienced PEA surgeons based on a comprehensive assessment of imaging findings; they were included in the study if target lesions for BPA (i.e. subsegmentally located short-term stenosis or a long-segment network forming organized thrombi) were found in pulmonary angiography. Patients were usually treated with targeted medication, and BPA was planned to be performed after a period of at least three months of drug therapy if WHO FC was still $\geq$II. Targeted medication was left unchanged until the six-month follow-up.

All patients were informed in detail about the investigational nature of the study, including potential risks and benefits, and gave written informed consent to participate. The local ethics committee approved this prospective observational study (AZ 43/14, Giessen University Ethics Committee). All CTEPH patients included were also enrolled in the New International CTEPH Database of the International CTEPH Association (NCT02656238).

Clinical assessment

All patients underwent standardized assessment contemporary prior to the first BPA, and six months after the last intervention. Assessment included WHO FC, Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR),[15] 6-minute walking distance (6MWD), serum levels of the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), and right heart catheterization (RHC) at rest and during exercise.

Exercise right heart catheterization

RHC was performed using a Swan-Ganz catheter via brachial or jugular access under local anesthesia. The mid-thoracic level was used as zero reference in all supine measurements. Pressures (right atrial pressure (RAP); systolic pulmonary arterial pressure (PAPs); diastolic pulmonary arterial pressure (PAPd); mean pulmonary arterial pressure (mPAP); pulmonary arterial wedge pressure (PAWP)) were measured directly, and cardiac output (CO) was measured by the thermodilution technique, averaging three of five output determinations. Baseline parameters were assessed 30 min after insertion of the catheter.[16] PAWP measurement at rest was performed by digitized mean at end-expiratory breathhold and during exercise without breathhold. Exercise was performed using a cycle ergometer in the supine position. Exercise was prolonged in a steady-state manner for at least 8 min, depending on the clinical condition of the patient, usually corresponding to a workload between 1 and 50 W.[17,18] If the patient was able to continue cycling, the workload was increased to an adjusted higher level to reach at least submaximal exercise. $SvO_2 < 30\%$ at the end of exercise was regarded as valid maximal effort. During a constant workload, hemodynamic parameters were measured for a duration of 5–7 min beginning 3 min after the initiation of exercise.[19,20] Pulmonary pressures were averaged over several respiratory cycles.[18,20] Mixed venous oxygen saturation (SvO_2) was obtained via blood gas analysis at rest and at the end of exercise. The following hemodynamic parameters were calculated: pulmonary vascular resistance (PVR) = (mPAP – PAWP)/CO; cardiac index (CI) = CO/body surface area; total pulmonary resistance (TPR) = mPAP/CO; pulmonary arterial compliance (PAC) = (CO/heart rate)/(PAPs – PAPd);

transpulmonary gradient (TPG) = mPAP – PAWP; diastolic pulmonary gradient (DPG) = PAPd – PAWP; slope of the mPAP/CO relationship; and the stroke volume = CO/heart rate.[21]

Balloon pulmonary angioplasty

BPA was performed as a staged procedure, with a limited number of pulmonary segments being treated during each session. All procedures were performed in conscious patients under local anesthesia. The standard procedure has been described previously in detail.[7,22,23] Briefly, using femoral or jugular access, a sheath was placed in the pulmonary artery and a guiding catheter was inserted into the targeted segmental arteries. The guidewire was then advanced into the target subsegmental branches, which were subsequently dilated by multiple balloon inflations. Pulmonary angiography documented the final post-procedural morphological result. Antegrade flow with improved parenchymal perfusion and quick venous return was interpreted as successful treatment.

Statistical analysis

All data for continuous variables are expressed as mean ± SD or as median and interquartile range (IQR), as appropriate. Categorical variables are reported as number and percentage. Continuous variables were compared using the Wilcoxon signed-rank test. The cohort data were distributed parametrically, as determined by the Kolmogorov-Smirnov test. All statistical tests were performed with SPSS software, version 22.0. A two-tailed p value <0.05 was considered to indicate statistical significance. The reported p values are to be interpreted in the exploratory sense.

Results

Cohort selection and baseline characteristics

A total of 172 consecutive patients underwent BPA between March 2014 and July 2018. Of these, 64 patients with CTEPH had completed a full series of BPA interventions and underwent exercise RHC before the first intervention and six months after the last BPA procedure. Another 41 patients were still undergoing BPA treatments, 23 patients were waiting for the six-month follow-up, in four patients exercise RHC was contraindicated due to orthopedic disease or paraplegia, 15 patients were examined using very different exercise levels at baseline and at follow-up, 16 patients underwent their follow-up at another center (without exercise RHC), and 2 patients died in the early postinterventional phase. Seven patients were diagnosed with chronic thromboembolic disease (CTED; no PH at rest). Data from six of these CTED patients were already presented in a previous publication.[11] The demographics and baseline characteristics of the present study cohort are given in Table 1.

Table 1. Baseline characteristics and medication.

Number of patients, n	64
Age, years	61 ± 13
Female, n (%)	30 (47)
Body mass index, kg/m^2	25 ± 3.7
History of PEA, n (%)	5 (7.8)
Anticoagulation with vitamin K antagonists, n (%)	9 (14)
PDE 5 inhibitor, n (%)	8 (12.5)
ERA, n (%)	10 (15.6)
sGC, n (%)	40 (62.5)
Inhaled analogue of prostacyclin, n (%)	2 (3.1)
No medication, n (%)	14 (21.9)
Monotherapy, n (%)	41 (64.1)
Combination therapy, n (%)	9 (14.1)

Note: Values are given as mean ± SD unless otherwise indicated.
CTEPH: chronic thromboembolic pulmonary hypertensions; VTE: venous thromboembolism; PEA: pulmonary endarterectomy; PDE: phosphodiesterase; ERA: endothelin receptor antagonist; sGC: stimulator of soluble guanylate cyclase.

BPA procedures and effects on physical capacity and quality of life

The mean number of BPA sessions per patient was 5.6 ± 1.3. There were 11 ± 3 pulmonary segments targeted in all interventions. The mean time from diagnosis (=presentation in CTEPH conference) to first BPA was 3.5 (IQR 3.0–6.0) months. The effects of BPA on quality of life based on the CAMPHOR questionnaire (Table 2) showed improvement of scores for symptoms (10.1 ± 5.2 at baseline vs. 5.9 ± 3.8 after treatment, $p < 0.0001$), activity limitations (8.5 ± 4.6 vs. 5.3 ± 3.6, $p < 0.0001$), and quality of life (6.1 ± 4.5 vs. 3.4 ± 2.9, $p < 0.0001$). The WHO FC improved in 50 (78%) patients and was unchanged in 14 (22%). The 6MWD improved after BPA by an average of 47 m (10%).

Hemodynamic responses before and six months after BPA

In CTEPH patients, mPAP at rest was reduced from 41 ± 9 to 31 ± 9 mmHg ($p < 0.0001$) (Table 2 and Figure 1), with 14 (22%) patients having an mPAP < 25 mmHg six months after BPA. Of these patients, 10 had a PVR < 3.0 WU at rest. All patients with mPAP < 25 mmHg at rest six months after BPA had a substantial decrease of NT-proBNP values (baseline: median 298 ng/L (IQR 79–1048 ng/L) vs. six months after BPA: median 53 ng/L (IQR 31–189 ng/L); $p < 0.001$) and increase of 6MWD (baseline: mean 433.9 m ± SD 69.8 m vs. 6 months after BPA: mean 480.9 m ± SD 68.2 m; $p = 0.003$). At exercise, SvO_2 was 44 ± 10 %, in seven patients SvO_2 was below 30%.

Before BPA, the slope of the mPAP/CO relationship was above 3 WU in all patients (range: 4.0–24.5 WU), and the TPR was also above 3 WU. After BPA, the mPAP/CO slope

Table 2. Results of BPA.

	N	Prior to BPA	N	After BPA	p-value (exploratory)
Exercise capacity					
WHO functional class, n (%)	64		64		
I		0 (0)		38 (59.4)	
II		2 (3.2)		23 (35.9)	
III		49 (76.6)		3 (4.7)	
IV		13 (20.3)		0 (0)	
6MWD, m	53	416 ± 94	60	463 ± 96	<0.0001
Hemodynamics at rest					
Right atrial pressure, mmHg	64	7 ± 4	64	5 ± 2	<0.0001
mPAP, mmHg	64	41 ± 9	64	31 ± 9	<0.0001
PAPsyst, mmHg	64	70 ± 16	64	52 ± 16	<0.0001
PAPdiast, mmHg	63	23 ± 6	64	16 ± 6	<0.0001
PAWP, mmHg	63	10 ± 2	64	9 ± 3	0.335
DPG, mmHg	62	13.6 ± 6.2	57	6.6 ± 5.8	<0.0001
TPG, mmHg	63	31.8 ± 8.9	64	21.3 ± 8.4	<0.0001
CO, L/min	63	4.9 ± 1.2	64	5.1 ± 1.0	0.068
CI, L/min/m^2	64	2.6 ± 0.6	64	2.7 ± 0.5	0.138
PVR, WU	63	6.8 ± 2.3	64	4.3 ± 1.9	<0.0001
TPR, WU	63	8.9 ± 2.5	64	6.2 ± 2.1	<0.0001
PAC, ml/mmHg	63	1.5 ± 0.6	64	2.3 ± 0.9	<0.0001
HR, bpm	63	77 ± 13	64	71 ± 12	<0.0001
stroke volume, ml	63	66 ± 19	64	73 ± 15	<0.0001
Hemodynamics during exercise					
Work load, W	64	27 ± 14	64	28 ± 15	0.187
Right atrial pressure, mmHg	64	15 ± 7	64	11 ± 5	<0.0001
mPAP, mmHg	64	62 ± 11	64	52 ± 11	<0.0001
PAPsyst, mmHg	64	102 ± 22	64	86 ± 20	<0.0001
PAPdiast, mmHg	63	33 ± 8	64	26 ± 4	<0.0001
PAWP, mmHg	58	14 ± 7	63	15 ± 4	0.164
DPG, mmHg	57	18.5 ± 10.7	63	11.5 ± 7.0	<0.0001
TPG, mmHg	58	48.1 ± 13.7	63	37.3 ± 11.3	<0.0001
CO, L/min	62	7.0 ± 2.0	63	8.3 ± 2.0	<0.0001
CI, L/min/m^2	62	3.8 ± 1.1	63	4.4 ± 1.1	<0.0001
PVR, WU	56	8.0 ± 4.4	63	5 ± 2.4	<0.0001
TPR, WU	62	9.6 ± 3.0	63	6.7 ± 2.5	<0.0001
PAC, ml/mmHg	62	0.9 ± 0.8	63	1.5 ± 0.6	<0.0001
HR, bpm	63	104 ± 15	64	101 ± 15	0.022
mPAP/CO slope, WU	62	11.2 ± 25.6	63	7.7 ± 4.1	<0.0001
stroke volume, ml	62	69 ± 22	64	83 ± 21	<0.0001
Laboratory findings					
NT-proBNP, ng/L, median (IQR)	63	741 (192–1425)	64	139 (60–266)	<0.0001
CAMPHOR scores					
Symptoms	47	10.1 ± 5.2	34	5.9 ± 3.8	<0.0001
Activity	46	8.5 ± 4.6	38	5.3 ± 3.6	<0.0001
Quality of life	39	6.1 ± 4.5	34	3.4 ± 2.9	<0.0001

Note: Values are given as mean ± SD unless otherwise indicated.

WHO: World Health Organization; 6MWD: 6-min walking distance; mPAP: mean pulmonary arterial pressure; PAPsyst: systolic pulmonary arterial pressure; PAPdiast: diastolic pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary gradient; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; PAC: pulmonary arterial compliance; HR: heart rate; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; BPA: balloon pulmonary angioplasty.

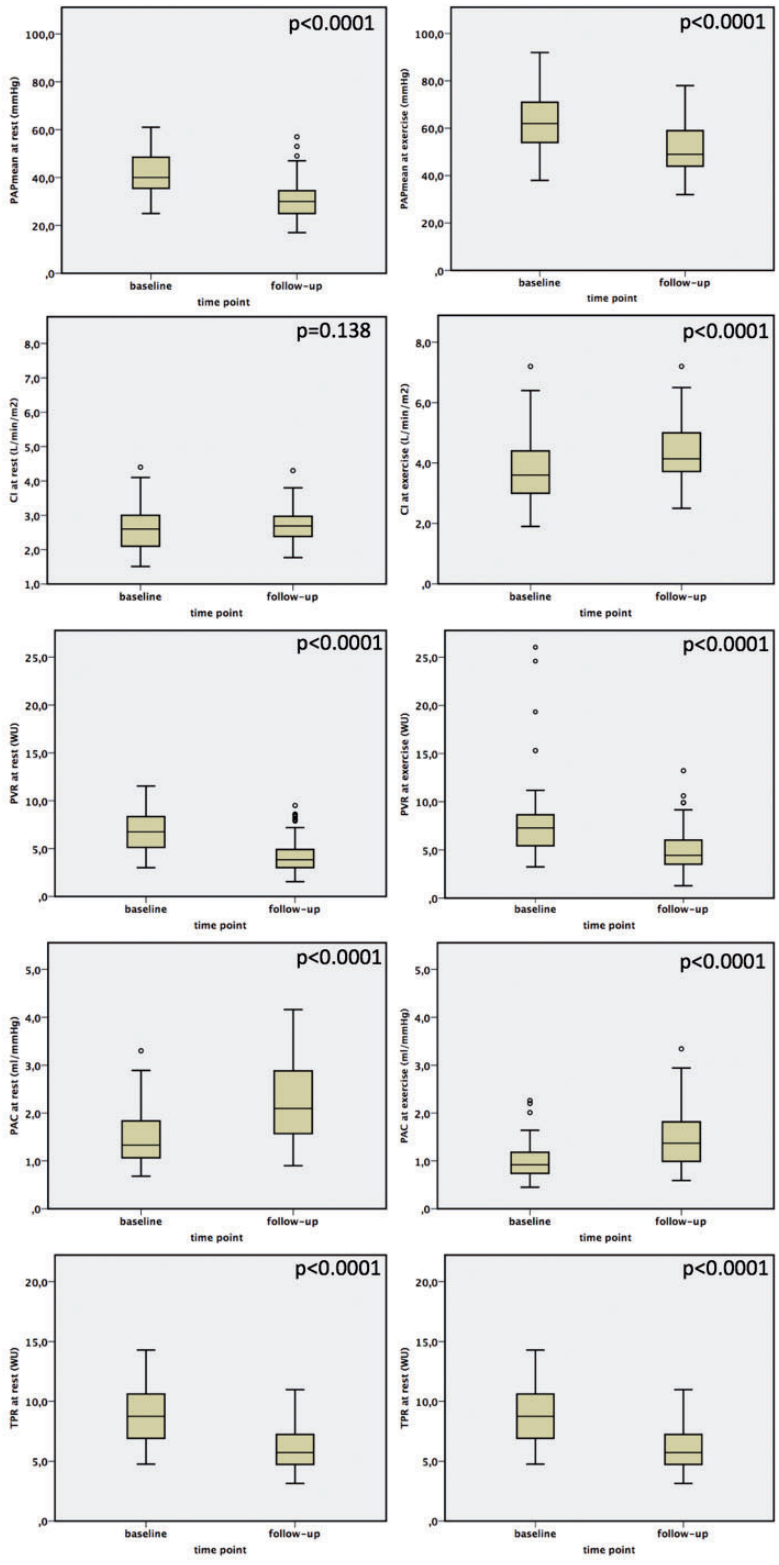

Figure 1. The effects of BPA on pulmonary hemodynamics.

decreased in all patients (range: 2.5–26.7 WU), although it was still above 3 WU in all but one patient. In the subgroup of patients having an mPAP < 25 mmHg after BPA (n = 14), the mPAP/CO slope decreased from median 8.6 WU (IQR 6.3–11.3 WU) to median 5.7 WU (IQR 4.8–8.1 WU). With that, after BPA all patients still fulfilled the proposed criteria of exercise PH, with mPAP > 30 mmHg and TPR > 3 WU at the six-month follow-up.[14] Both the TPR

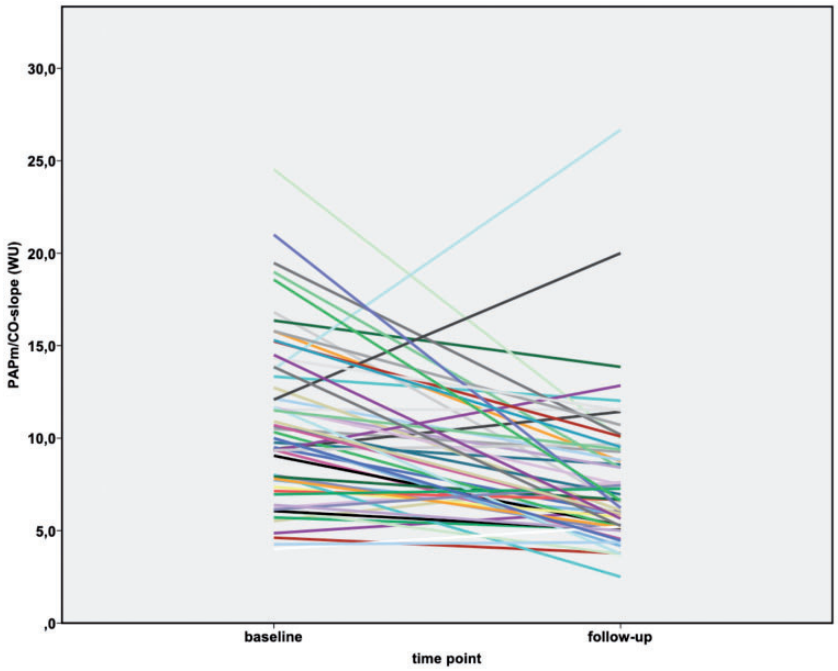

Figure 2. Changes in mPAP/CO slope before and after BPA in inoperable CTEPH patients.
mPAP: mean pulmonary arterial pressure; CO: cardiac output.

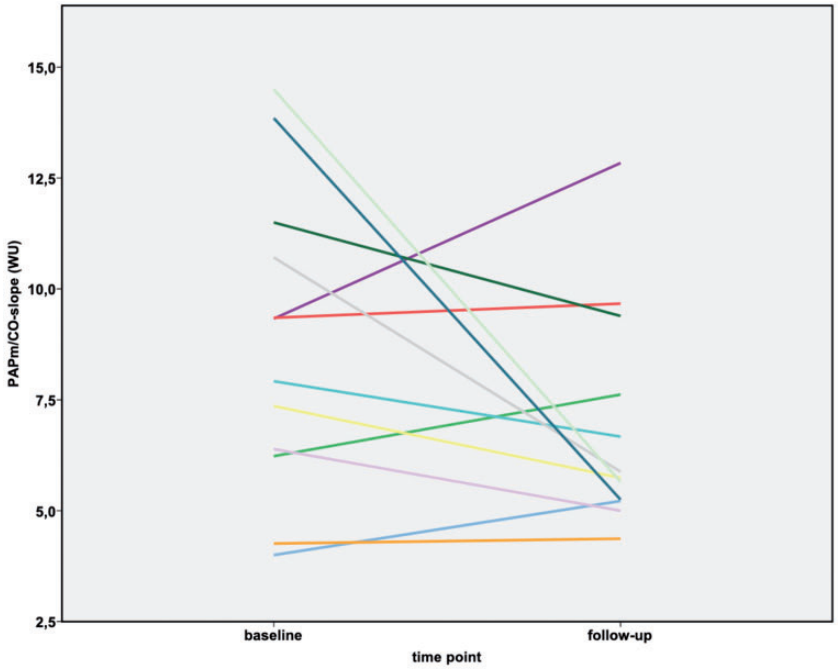

Figure 3. Changes in mPAP/CO slope before and after BPA in patients with mPAP < 25 mmHg at rest six months after BPA.
mPAP: mean pulmonary arterial pressure; CO: cardiac output.

and the mPAP/CO slope decreased after BPA ($p < 0.0001$) (Table 2; Figures 1 to 3) and correlated significantly with NT-proBNP (TPR 0.462 ($p < 0.0001$); mPAP/CO slope 0.252 ($p = 0.035$)) and 6MWD (TPR −0,450 ($p < 0.0001$); mPAP/CO slope −0.313 ($p = 0.01$)). Pulmonary artery compliance at rest and during exercise increased after BPA ($p < 0.0001$) and also did the stroke volume at rest and at exercise ($p < 0.0001$).

In the subgroup of patients, that did not receive targeted medication ($n = 14$), mPAP at rest was reduced from 38 ± 8

to 31 ± 8 mmHg ($p = 0.007$), mPAP at exercise improved from 60 ± 10 to 55 ± 10 mmHg ($p = 0.007$). CI at rest remained stable after BPA (mean $2.6 \pm$ SD 0.5 l/min/m^2 vs. mean $2.4 \pm$ SD 0.4 l/min/m^2; $p = 0.27$), while there was non-significant improvement at exercise (mean $3.9 \pm$ SD 1.4 l/min/m^2 vs. mean $4.2 \pm$ SD 1.2 l/min/m^2; $p = 0.23$). PVR at rest (mean $6.6 \pm$ SD 2.2 WU vs. mean $5.2 \pm$ SD 1.8 WU; $p = 0.013$) and at exercise (mean $8.6 \pm$ SD 5.6 WU vs. mean $6.0 \pm$ SD 2.2 WU; $p = 0.15$) improved non-significantly. These patients further had a substantial decrease of NT-proBNP values (baseline: median 264 ng/L (IQR 82–1121 ng/L) vs. six months after BPA: median 148 ng/L (IQR 48–371 ng/L); $p < 0.0001$) and non-significant increase of 6MWD (baseline: mean 398 m $\pm$ SD 84 m vs. six months after BPA: mean 412 m $\pm$ SD 101 m; $p = 0.49$).

Complications of BPA and exercise RHC

Twenty-five procedure-related complications occurred during the 363 interventions (6.9% of all interventions). These adverse events were mostly caused by wire perforation of the pulmonary vasculature, resulting in parenchymal bleeding with mild hemoptysis in some cases. Four patients developed reperfusion edema with clinical symptoms (coughing of frothy secretion, desaturation) and consolidations in chest X-rays during the post-procedural period of 6 to 24 h. Non-invasive ventilation was frequently performed after interventions for complications (mostly as a routinely performed procedure to avoid dystelectasis following parenchymal hemorrhage); invasive ventilation was not necessary. These complications are in line with our experience in the whole group of in our center interventionally treated inoperable CTEPH patients.[7,11,13,22,23] There were no complications due to exercise RHC, and there were no deaths in the study cohort.

Discussion

In the present study, we examined the effects of BPA on pulmonary hemodynamics at rest and during exercise six months after completion of the interventions in patients with inoperable CTEPH. The main findings of this study are: (1) BPA with or without targeted medication leads to significant improvements in pulmonary hemodynamics at rest and during exercise in CTEPH patients; (2) even when patients no longer presented with PH at rest after BPA, they still had signs of PH during exercise; (3) BPA leads to significant improvements in exercise capacity (WHO FC, 6MWD) and quality of life. To the best of our knowledge, this is the first study to compare the results of exercise RHC before and after BPA in CTEPH patients.

There is some evidence from smaller and mid-sized case series that BPA exerts beneficial effects on pulmonary hemodynamics and physical capacity in inoperable CTEPH patients, but the results differ from center to center with reported normalization or near-normalization of pulmonary hemodynamics in up to 50% of the patients[2–4,10] and less pronounced hemodynamic improvements in European centers.[5,7] The main reason for variations in the data may be differing indications for PEA and for BPA in different centers. In our study, patients selected for BPA comprised only those with clearly inoperable disease. However, pulmonary hemodynamics have thus far only been examined at rest.[2–5,7,10]

Exercise pulmonary hemodynamics can reveal pathophysiological details in patients with PH that are not apparent from measurements made at rest.[14] Our observations illustrate in particular the influence of BPA on exercise pulmonary hemodynamics in inoperable patients with CTEPH. Defining exercise PH is still a matter of debate, but an mPAP >30 mmHg with a TPR or mPAP/CO slope >3.0 WU is a reasonable definition among experts in the field.[17,21,24,25] In our cohort, there were 14 patients (22% of all patients) with an mPAP <25 mmHg at rest after BPA, but all still fulfilled the criteria of exercise PH. The relevance of these findings for the previously published outcomes of BPA treatment may be important, as they suggest that BPA does not necessarily lead to a normalization of pulmonary hemodynamics. Aside from secondary vasculopathy, an explanation for residual PH during exercise might be that obstructing material is left behind after BPA, which is, in fact, one of the major differences between BPA and surgical treatment by PEA. These findings underline the clinical relevance of exercise RHC for CTEPH patients, as advanced targeted medical therapy may be evaluated as an additional option.

Recently, the results of the World Symposium on Pulmonary Hypertension from 2018 in Nice were published[26] that suggest a change in the definition of PH: precapillary PH may be diagnosed in patients with a mPAP of >20 mmHg, a PAWP $\leq$15 mmHg, and a PVR of $\geq$3 WU. These novel ideas are currently still being critically discussed, however, and have not yet been transferred to a guideline recommendation. It is complex to interpret this shift in the threshold in mPAP, but it seems obvious that an mPAP in the range between 20 and 25 mmHg indicates a pathological change in pulmonary hemodynamics. In our CTEPH patients with a resting mPAP <25 mmHg after BPA, we were nevertheless able to demonstrate pathological pulmonary hemodynamics during exercise (Figure 3).

Another aspect of the evaluation of a PH patient is the description of their physical capacity and quality of life. For BPA, several groups have already shown improvements of exercise capacity,[27,28] but there are no data with regard to the CAMPHOR questionnaire. This offers much more discriminating information than WHO functional class.[15] In inoperable CTEPH patients, we observed significant improvements in activity, symptoms, and quality of life after BPA. Furthermore, NT-proBNP is often used as a biomarker in the clinical assessment of CTEPH patients,[23] which also showed significant improvement in the presented

cohort and correlated strongly with the changes in exercise hemodynamics. According to these beneficial changes, also PAC improved significantly, which is believed to be an important marker of prognosis in PH patients[29]; these findings underline the beneficial effects of BPA for inoperable CTEPH, but a normalization of all parameters has not been observed in the study cohort. The meaning of these findings with regard to the long-term management of this particular group of patients cannot be answered by the presented data. But against this background, a continuation of targeted medical treatment may be reasonable. On the other hand, Cannon et al. presented data on residual PH after PEA, showing a worse prognosis of patients with an mPAP > 38 mmHg and a PVR of >5.3 WU at rest.[30] But with actually only rare long-term data for inoperable CTEPH patients treated with BPA,[10] it can only be speculated, whether these data can be extrapolated on this group.

Our study must be evaluated with caution due to several potential limitations. There was no control group of patients with no specific treatment or with only targeted medication. But it is well known, that CTEPH is a progressive disease with a poor prognosis if left untreated.[31] Another important limitation is that the majority of patients did not undergo cardiopulmonary exercise testing as a standard examination.

In conclusion, patients with inoperable CTEPH benefit from BPA treatment as evidenced by measurement of pulmonary hemodynamics during exercise and assessment of functional capacity and quality of life. The complication rate of BPA was low and exercise RHC was without complications. Exercise RHC offers a differentiated insight into the hemodynamic changes after BPA. It is not easy to outline the clinical benefit of exercise hemodynamics, and the evaluation of a CTEPH patient is based on multiple findings. But our results indicate that improving exercise hemodynamics explain much better the improvement of physical capacity than mPAP at rest. On the other hand, our findings demonstrate that inoperable CTEPH is not cured by BPA. In particular, even in patients without PH at rest after BPA, signs of exercise PH were detectable.

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Conflict of interest

CB Wiedenroth has received speaker fees and/or consultant honoraria from Actelion, Bayer AG, BTG, MSD, and Pfizer.

AJ Rieth received speaker fees and/or consultant honoraria from Servier, St. Jude Medical/Abbott, Novartis and Actelion, and traveling support by Orion Pharma.

S Kriechbaum has nothing to disclose.

HA Ghofrani has reported receiving fees for serving as a board member for Bellerophon Pulse Technologies, Medscape, OMT, UCB Celltech, and Web MD Global; receiving consultancy fees and fees for serving on a steering committee for Actelion Pharmaceuticals, Bayer, Gilead Sciences, GlaxoSmithKline, Merck, Novartis, and Pfizer; receiving lecture fees from Actelion Pharmaceuticals, Bayer, GlaxoSmithKline, Merck, Novartis, and Pfizer; and receiving grant support from Actelion Pharmaceuticals, Bayer, Novartis, and Pfizer.

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A Rolf has nothing to disclose.

C Hamm has nothing to disclose.

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ORIGINAL CLINICAL SCIENCE

Exercise MR-proANP unmasks latent right heart failure in CTEPH

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

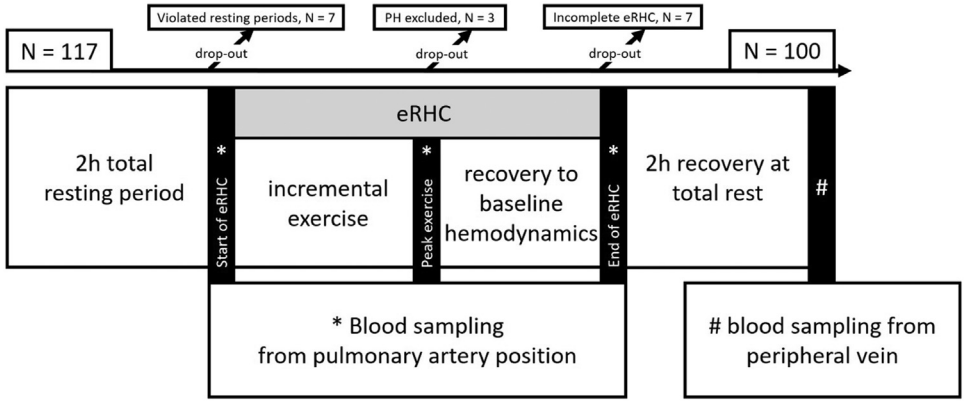

Figure 1 Workflow of the study. Seventeen patients were excluded to give a final cohort of N=100 patients. Abbreviations: eRHC = exercise right heart catheterization, PH = pulmonary hypertension.

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

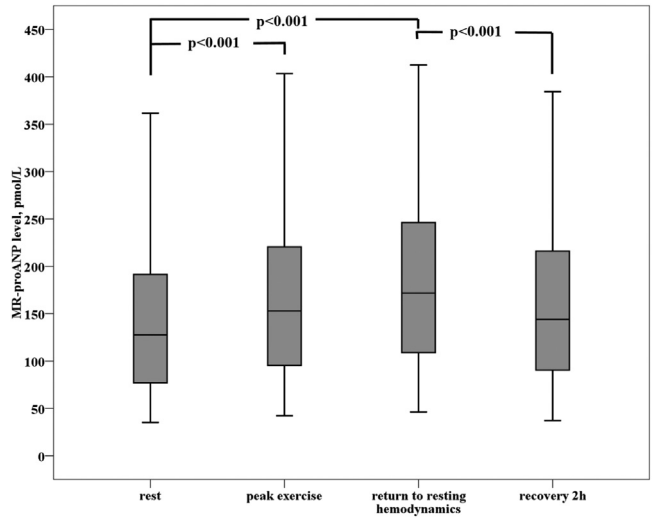

Figure 2 Development of MR-proANP levels during exercise right heart catheterization. Box-and-whiskers plot showing significant changes in median biomarker levels. Abbreviations: MR-proANP = mid-regional pro-atrial natriuretic peptide.

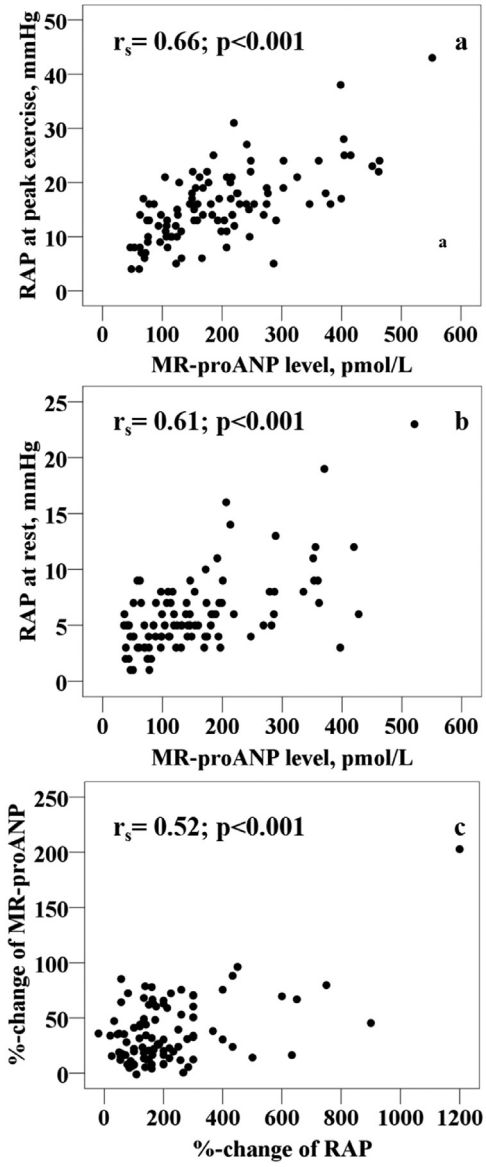

Figure 3 a-c Correlation of MR-proANP levels and right atrial pressure. Parameters compared at rest (a) and at peak exercise (b) with bivariate Pearson correlation of relative changes (c). Abbreviation: MR-proANP = mid-regional pro-atrial natriuretic peptide.

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^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

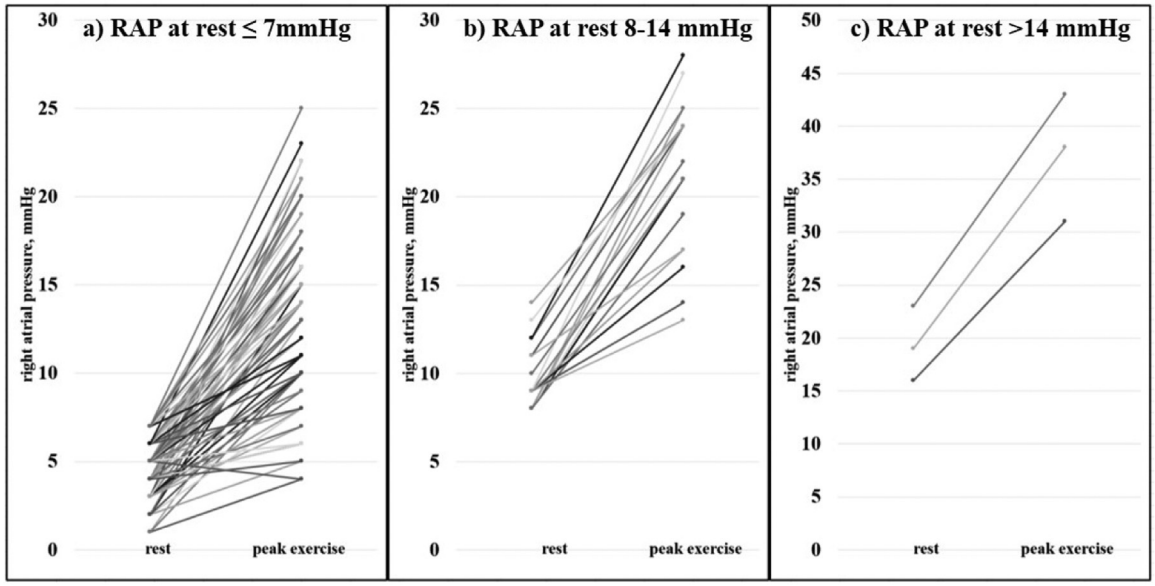

Figure 4 a-c: Dynamics of right atrial pressure during exercise right heart catheterization. Data for individual patients stratified according to right atrial pressure at rest: normal ≤7 mmHg (a); moderately elevated 8-14 mmHg (b); severely elevated >14 mmHg (c).

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

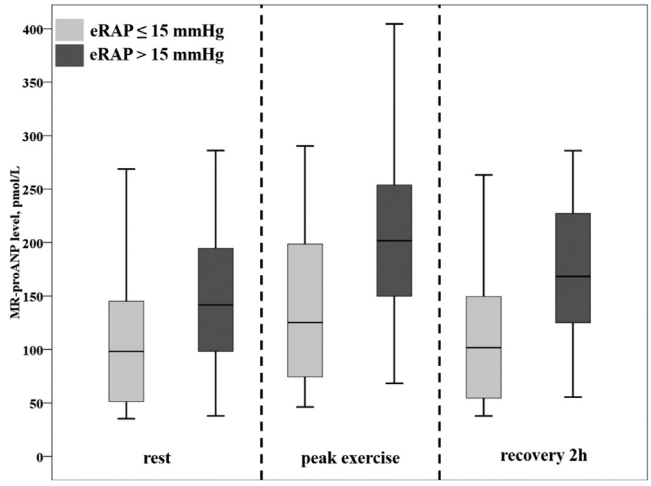

Figure 5 Comparison of MR-proANP dynamics between patients with a physiological or pathophysiological increase in right atrial pressure during exercise in subgroup 1. Box-and-whiskers plot showing the median levels of biomarker stratified according to eRAP at various stages of testing. Abbreviations: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

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.08.017.

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