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Multimodale Therapie der chronisch thromboembolischen pulmonalen Hypertonie (CTEPH)

Habilitationsschrift
zur Erlangung der Venia legendi
des Fachbereichs Medizin
der Justus-Liebig-Universität Gießen

für das Fach
„Thoraxchirurgie“

vorgelegt von

Dr. med. Christoph Bernhard Wiedenroth

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Inhaltsverzeichnis

Diese kumulative Habilitationsschrift basiert auf den folgenden Publikationen:

1. Lankeit M, Krieg V, Hobohm L, Kölmel S, Liebetrau C, Konstantinides S, Hamm CW, Mayer E, **Wiedenroth CB***, Guth S*. Pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2017 Jul 1. pii: S1053-2498(17)31877-6. * equal contribution

2. Olsson KM*, **Wiedenroth CB***, Kamp JC, Breithecker A, Fuge J, Krombach GA, Haas M, Hamm C, Kramm T, Guth S, Ghofrani HA, Hinrichs JB, Cebotari S, Meyer K, Hoeper MM, Mayer E, Liebetrau C, Meyer BC. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J. 2017 Jun 8;49(6). pii: 1602409. * equal contribution

3. 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. N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2018 May;37(5):639-46. * equal contribution

4. Roller FC, Kriechbaum S, Breithecker A, Liebetrau C, Haas M, Schneider C, Rolf A, Guth S, Mayer E, Hamm C, Krombach GA, **Wiedenroth CB**. Correlation of native T1 mapping with right ventricular function and pulmonary haemodynamics in patients with chronic thromboembolic pulmonary hypertension before and after balloon pulmonary angioplasty. Eur Radiol. 2019 Mar;29(3):1565-73.

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6. **Wiedenroth CB**, Ghofrani HA, Adameit MSD, Breithecker A, Haas M, Kriechbaum S, Rieth A, Hamm CW, Mayer E, Guth S, Liebetrau C. Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension. Pulm Circ. 2018 Jul-Sep;8(3):2045894018783996.

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1. Einführung

Die chronisch thromboembolische pulmonale Hypertonie (CTEPH) ist eine selten diagnostizierte Erkrankung mit unterschiedlichen Angaben zur Inzidenz: zwischen 0,5 und 4 % aller Patienten, die eine akute Lungenembolie überleben, entwickeln im weiteren Verlauf eine CTEPH (1-3). Dabei kommt es nicht zu einer vollständigen Resolution, sondern zu einem fibrotischen Umbau des thrombotischen Materials. Diese Veränderungen werden wahrscheinlich begünstigt durch begleitende Pathologien wie Entzündung, Infektion, Hemmung der Gefäßneubildung, abnormes Fibrinogen oder abnorme zirkulierende Phospholipide (4-8). Die fortbestehende Verlegung von Pulmonalarterien führt ab einer Beteiligung von etwa 40 – 60 % der pulmonalarteriellen Strombahn zur Ausbildung einer pulmonalen Hypertonie (PH) mit konsekutiver Rechtsherzbelastung (1). Zudem kommt erschwerend die mögliche Entwicklung einer Mikrovaskulopathie hinzu, derzeit verstanden als Folge von Hyperperfusion und shear-stress in den noch perfundierten Lungenarealen. Unbehandelt führt die Erkrankung zu Rechtsherzversagen, sekundärem Multiorganversagen und sie hat insgesamt eine schlechte Prognose (9, 10).

Entsprechend den Empfehlungen des „6th World Symposium on Pulmonary Hypertension“ wird die CTEPH anhand der Nizza-Klassifikation in die Gruppe 4 der verschiedenen Formen der PH eingeordnet (11). Für den europäischen Raum liegt eine zuletzt 2015 publizierte Leitlinie vor (12), für Deutschland haben die Empfehlungen der letzten Kölner Konsenus Konferenz von 2016 Leitliniencharakter (13, 14). Hier wurde die CTEPH anhand drei geforderter Komponenten definiert: (1) Vorliegen einer symptomatischen präkapillären PH (mittlerer pulmonalarterieller Druck (PAPm) ≥ 25 mmHg und pulmonalarterieller Verschlußdruck (PAWP) ≤ 15 mmHg in Ruhe) mit (2) mindestens einem größeren Perfusionsdefekt in einem Segment oder zwei Subsegmenten als mismatch-Befund in der Ventilations-/Perfusions-Szintigraphie, oder mit pulmonal-vaskulären Läsionen in der Computertomographie (CT), Magnetresonanztomographie (MRT) oder Pulmonalis-Angiographie (3) nach mindestens dreimonatiger effektiver Antikoagulation. Ohne Vorliegen einer PH in Ruhe, jedoch bei Erfüllen der anderen Kriterien liegt eine chronisch thromboembolische Erkrankung (CTED) vor (13).

Klinisch zeichnet sich die CTEPH häufig durch unspezifische Symptome, vor allem eine im Verlauf zunehmende Belastungsdyspnoe aus. Das macht die Diagnosestellung oft schwierig und erklärt die lange Latenz von 14,1 Monaten zwischen ersten Beschwerden und dem Stellen der Diagnose (15). **Abbildung 1** zeigt den Diagnostikalgorithmus der Kölner Konsensus Empfehlung. Insbesondere eine stattgehabte Lungenembolie in der Anamnese und eine seither fortbestehende Belastungseinschränkung sollten Anlass geben, eine weitere Abklärung des Patienten einzuleiten. Die Echokardiographie wird empfohlen, um Zeichen einer PH nachzuweisen. Zusätzlich kann bei Verdacht, aber unauffälliger Echokardiographie eine Spiroergometrie durchgeführt werden (16). Bei fortbestehendem Verdacht auf Vorliegen einer CTEPH wird die Anfertigung einer Lungenszintigraphie, bevorzugt als ventilation/perfusion single photon emission computed tomography (V/P SPECT), empfohlen (17, 18). Bei Nachweis eines typischen Missverhältnisses zwischen normaler Ventilation und keilförmigen Perfusionsdefekten sollte die Überweisung an ein CTEPH-Expertenzentrum erfolgen. Die weitere Abklärung basiert auf invasiven Untersuchungen wie Rechtsherzkatheter (RHK) und Pulmonalis-Angiographie, zudem auch auf CT (und MRT).

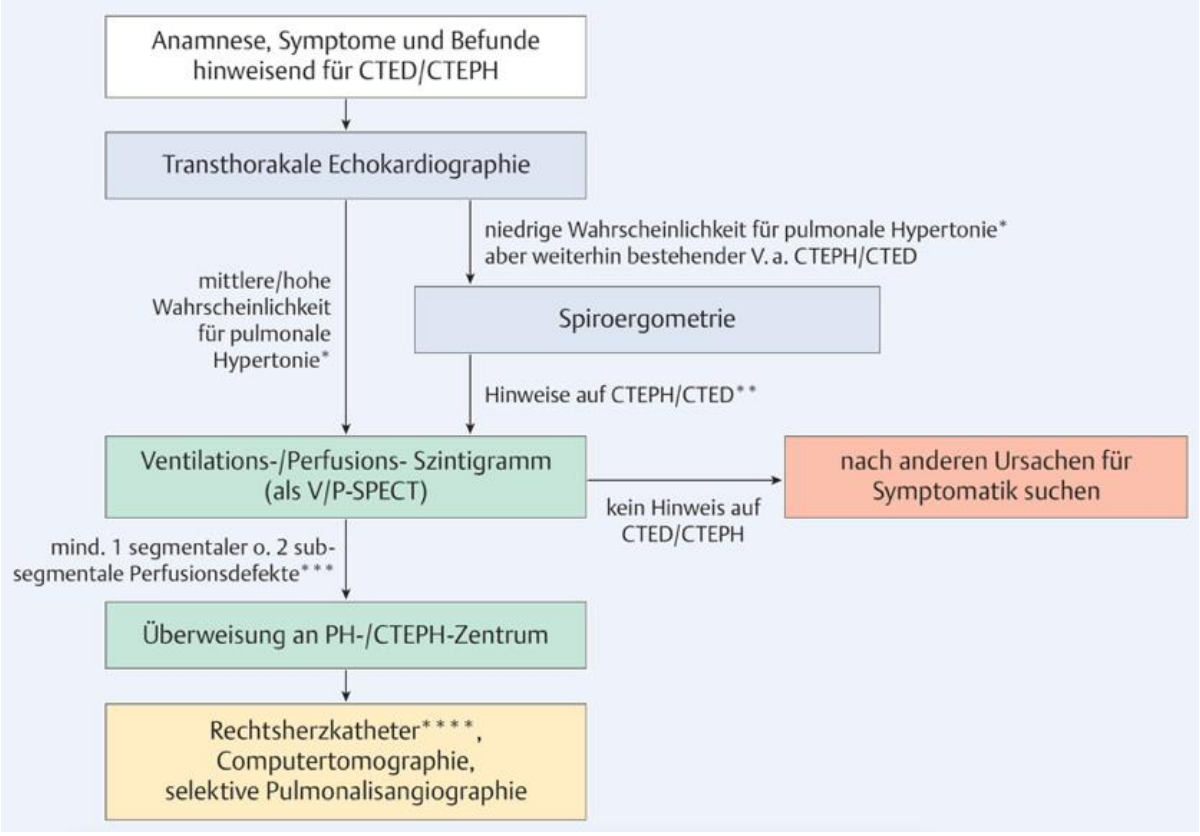

Abbildung 1: Diagnostikalgorithmus entsprechend den Empfehlungen der Kölner Konsensus Konferenz von 2016 (13)

Letztlich wird die Diagnose in einer multidisziplinären CTEPH-Konferenz bestätigt

und die weitere Therapie festgelegt. **Abbildung 2** zeigt den Therapiealgorithmus der Kölner Konsensus Empfehlung von 2016.

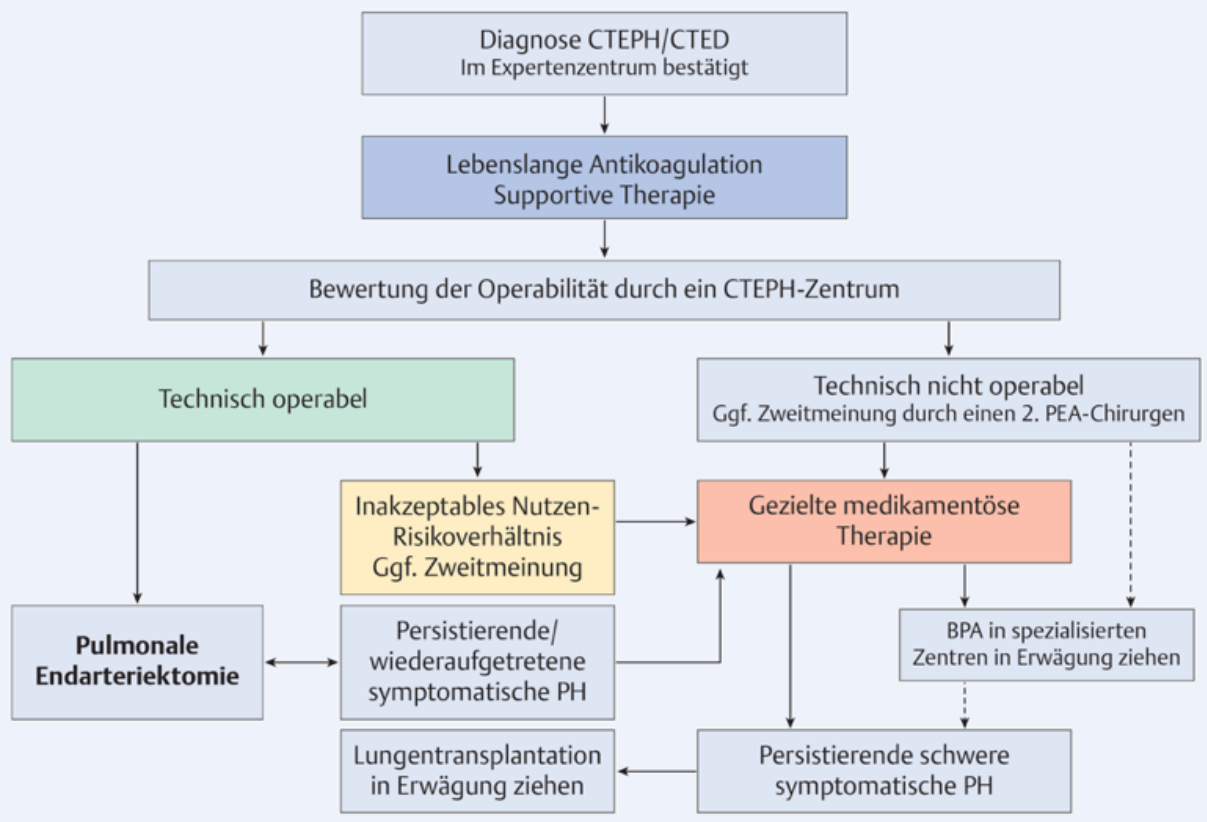

Abbildung 2: Therapiealgorithmus entsprechend den Empfehlungen der Kölner Konsensus Konferenz von 2016 (13)

Grundsätzlich werden alle Patienten mit CTEPH zeitlebens antikoaguliert. Daneben stehen an supportiven Therapien die Gabe von Diuretika wie auch eine Sauerstofflangzeittherapie bei Hypoxämie zur Verfügung.

Die spezifische Behandlung der CTEPH besteht derzeit aus drei Therapiemodalitäten: der chirurgischen pulmonalen Endarteriektomie (PEA), der gezielten medikamentösen Therapie und der interventionellen pulmonalen Ballonangioplastie (BPA). Interessant ist hierbei die fortwährende Weiterentwicklung des Therapiekonzeptes in den vergangenen 10 Jahren: so wurde in der europäischen Leitlinie für die Behandlung von pulmonaler Hypertonie von 2009 als Standardtherapie die PEA empfohlen (IC), für inoperable Patienten könne eine gezielte medikamentöse Therapie in Frage kommen (IIb/C), während die BPA zum damaligen Zeitpunkt keine Erwähnung fand (19). Die Empfehlung des letzten World Symposium on Pulmonary Hypertension von 2018 (**Abbildung 3**) zeigt wiederum eine Weiterentwicklung und letztlich auch Vereinfachung der oben dargestellten Kölner Konsensus Empfehlung mit der PEA als „treatment of choice“ und gezielter medikamentöser Therapie mit oder ohne BPA bei inoperablen Patienten (20).

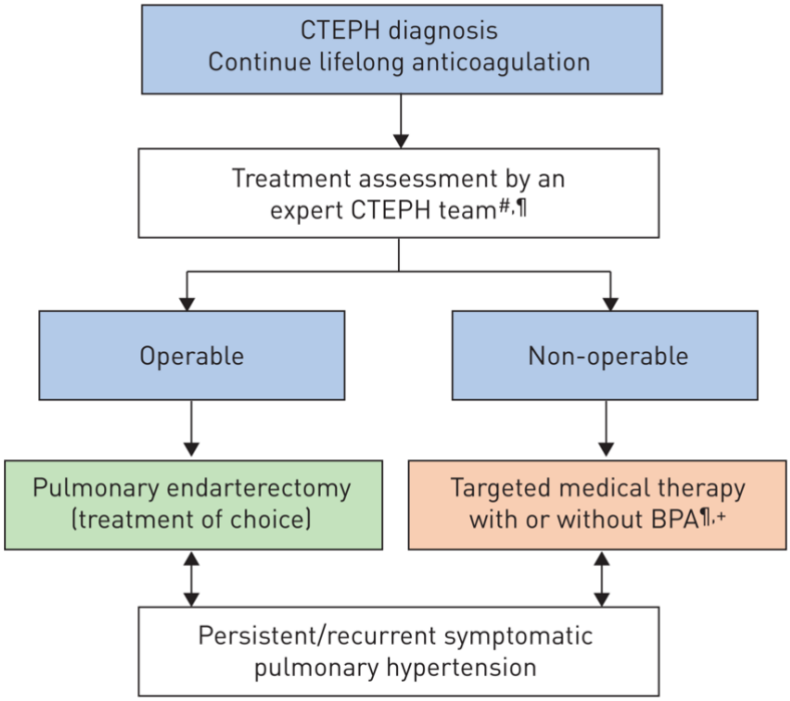

Abbildung 3: Therapiealgorithmus entsprechend den Empfehlungen des World Symposium on Pulmonary Hypertension von 2018 (20)

Da einzig die PEA einen kurativen Ansatz bietet, ist diese die Standardtherapie der operablen CTEPH. Es wurden deutliche Verbesserungen der pulmonalen Hämodynamik bis hin zur Normalisierung (pulmonal vaskulärer Widerstand (PVR) 700-800 dyn*sec/cm$_5$ auf 250 dyn*sec/cm$_5$) in einem Großteil der Patienten beschrieben und in internationalen Registerdaten bestätigt (21, 22). Darüber hinaus besteht eine gute Langzeitprognose mit deutlichem Überlebensvorteil mit 89 % (operiert) versus 70 % (nicht-operiert) 3 Jahres-Überleben (23) und > 80 % 5-Jahres-Überleben sowie > 70 % 6-10 Jahres-Überleben bei operierten Patienten (24-26), was eine relative Risikoreduktion für Sterblichkeit von 63 % bedeutet (23). Maßgeblich für die Entscheidung zur PEA sind neben der pulmonalen Hämodynamik und den bestehenden Komorbiditäten vor allem die Befunde der Bildgebung (insbesondere CT und Pulmonalis-Angiographie). In erfahrenen chirurgischen Zentren werden auch Patienten mit ausschließlich segmental/subsegmentalem Befallsmuster operiert (22, 27). Finden sich die pulmonalarteriellen Läsionen nur in der Peripherie der Lungenstrombahn, ist eine Operation nicht möglich. Im Zweifel, bzw. bei mangelnder chirurgischer Expertise sollte eine Zweitmeinung in einem erfahrenen Zentrum eingeholt werden (12, 14).

Insgesamt kommt eine operative Therapie für etwa 1/3 aller CTEPH Patienten nicht in Frage, meistens aufgrund zu peripher gelegener Läsionen (15). Die Leitlinien empfehlen für diese Patienten eine gezielte medikamentöse Therapie, wobei die sekundäre Mikrovaskulopathie als Ansatzpunkt und Rationale einer solchen

Behandlung gilt (15). Mittlerweile steht mit Riociguat eine zugelassene Substanz zur Verfügung (28). Hierbei handelt es sich um einen Stimulator der löslichen Guanylatzyklase, die auf den Stickstoffmonoxid-Signalweg einwirkt. Weitere Substanzklassen wie Phosphodiesterase-5-Inhibitoren, Prostanoid-Analoga und auch Endothelinrezeptor-Antagonisten wurden in klinischen Studien angewendet, jedoch konnte erstmals mit Riociguat neben einer Besserung der pulmonalen Hämodynamik (PVR -31%) auch eine Besserung der körperlichen Belastbarkeit nachgewiesen werden (6-Minuten-Gehstrecke (6MWD) +46m). Einzig Macitentan, ein Endothelinrezeptor-Antagonist der neueren Generation konnte hier ähnliche Ergebnisse erzielen (PVR -16%, 6MWD +34m), jedoch steht eine Zulassung bislang aus (29). Neben primärer Inoperabilität ist auch eine residuelle oder rezidivierende PH nach erfolgter PEA eine Indikation zur gezielten medikamentösen Therapie. Ein Einsatz vor PEA wird derzeit nicht empfohlen.

Als letzte Säule der Therapie der CTEPH wurde mit der BPA eine interventionelle Möglichkeit entwickelt, Patienten mit weit peripher gelegenen Läsionen zu behandeln. Dieses Verfahren wurde erstmals 1988 erwähnt (30), in 2001 wurde die erste Serie von 18 in den USA behandelten Patienten beschrieben (31), kurze Zeit später auch eine kleine Fallserie aus Deutschland präsentiert (32). Letztlich wurden alle diese Programme aufgrund hoher Komplikations- und Sterblichkeitsraten nicht weitergeführt. Nach etwa 10 Jahren wurde das Verfahren wieder erwähnt, nun fast ausschließlich in Japan angewendet und technisch „verfeinert“ (33): die BPA wurde als staged procedure auf mehrere Sitzungen aufgeteilt, so dass nur noch einzelne Segmente in einer Intervention behandelt wurden. So konnte die Komplikations- und Sterblichkeitsrate deutlich gesenkt werden. In mehreren Fallserien verschiedener japanischer Zentren wurde dabei eine Normalisierung oder Fast-Normalisierung in einem Großteil der behandelten Patienten mit Verbesserungen des PVR um bis zu 65 % gezeigt (33-35). In nicht-japanischen Zentren wurden dagegen etwas weniger effektive Verbesserungen (PVR etwa -30%) nachgewiesen (36). Diese Diskrepanz wurde auf unterschiedliche Indikationsstellungen und Zielsetzungen bei sehr unterschiedlicher, insbesondere chirurgischer Expertise in den CTEPH-Zentren zurückgeführt. Letztlich stehen kontrollierte, randomisierte Studien aus. Es liegen daneben kaum multizentrische Daten vor und es wurden nur zwei (japanische) Fallserien mit 4-Jahres-(Langzeit-)Daten mit niedrigen follow-up Quoten veröffentlicht (37, 38). Damit wird die BPA bis zuletzt nicht klar empfohlen, sondern sollte ausgewählten, inoperablen Patienten angeboten werden (12, 14, 20).

Zielsetzung dieser Habilitation ist die Etablierung und Entwicklung der einzelnen Therapiemodalitäten und insbesondere deren Verknüpfung im Rahmen multimodaler Therapieansätze.

2. Chirurgische Behandlung der CTEPH

2.1 Behandlung und Ergebnisse von Patienten mit operabler CTEPH

Inhalt der ersten Publikation war einerseits die Erfassung der chirurgischen Behandlung von CTEPH Patienten in Deutschland sowie die Darstellung der Behandlungszahlen von CTEPH in der Kerckhoff-Klinik und die Ergebnisse nach dort erfolgter PEA in den Jahren 2014 und 2015.

Zur Erfassung aller in Deutschland durchgeführten PEA Operationen erfolgte eine Abfrage beim statistischen Bundesamt (Fragestellung OPS-Code 5-381.42 sowie Letalität). **Abbildung 4** fasst die Anzahl der insgesamt durchgeführten Operationen wie auch die Anzahl der im selben Krankenhausaufenthalt verstorbenen Patienten zusammen: in 2014 wurden 194, in 2015 200 Eingriffe vorgenommen mit einer Mortalität von 6,2 % respektive 5,5 %. Von diesen Eingriffen wurden 64,2 % in der Kerckhoff-Klinik durchgeführt.

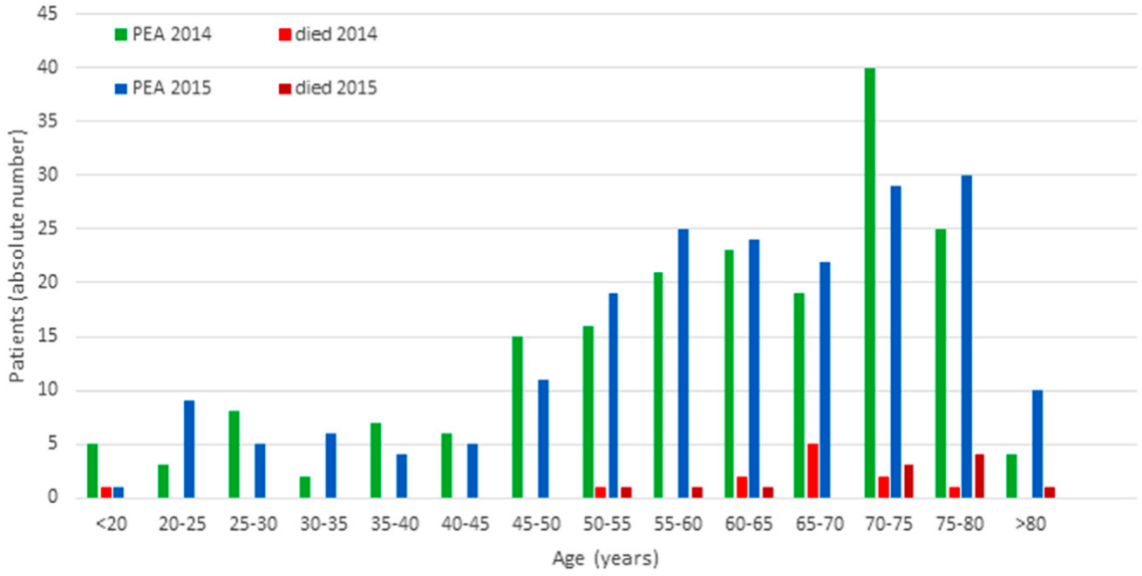

Abbildung 4: In Deutschland in 2014 (grün) und 2015 (blau) durchgeführte PEA-Operationen (OPS 5-381.42) und die Mortalität (rot 2014; dunkelrot 2015). 64,2 % dieser Eingriffe wurden in der Kerckhoff-Klinik durchgeführt.

Abbildung 5 gibt einen Überblick über die im Studienzeitraum in der Kerckhoff-Klinik mit Verdacht auf CTEPH behandelten Patienten, die alle in einer wöchentlich

stattfindenden multidisziplinären CTEPH-Konferenz besprochen wurden. Von den 253 in Bad Nauheim operierten Patienten wurden letztlich 237 (93,7 %) in die Studie eingeschlossen.

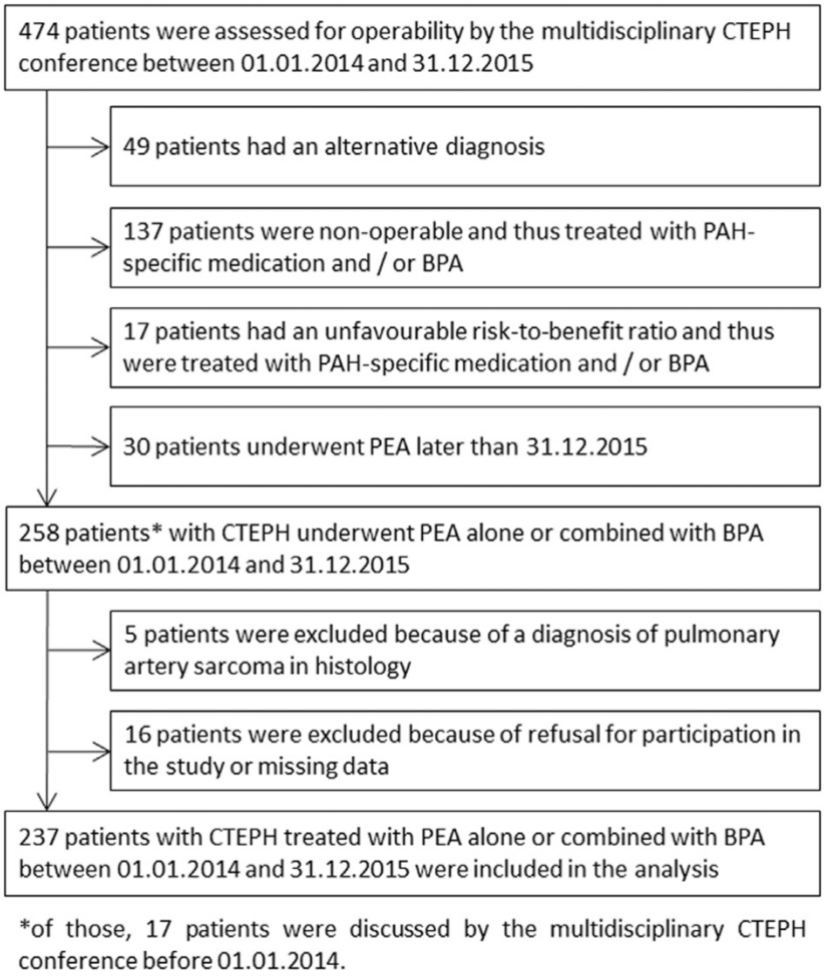

Abbildung 5: Das Studienprotokoll mit Ein- und Ausschlusskriterien zeigt alle in der multidisziplinären CTEPH-Konferenz der Kerckhoff-Klinik vorgestellten Patienten in 2014 und 2015.

Abbildung 6 fasst die Charakteristika der eingeschlossenen Patienten zusammen: das mediane Alter lag bei 62 Jahren, die meisten Patienten befanden sich in WHO-Funktionsklasse III (67,5 %) und hatten eine schwere PH (PAPm 43 mmHg; PVR 7,2 WU).

	All study patients; $n = 237$
Age, years	62 (52–72); range, 18–84
Female sex	109 (46.0%)
BMI, kg/m^2	26.3 (23.8–30.4); range, 16.0–55.0; $n = 235$
Comorbidities and risk factors for CTEPH	
Active cancer[a]	6 (2.5%)
Chronic left heart failure	10 (4.2%); $n = 236$
Coronary artery disease	44 (18.6%)
Atrial fibrillation	25 (10.6%); $n = 236$
Diabetes mellitus	23 (9.7%)
Previous stroke	12 (5.1%)
Renal insufficiency[b]	63 (26.8%); $n = 235$
Anemia[c]	28 (11.9%); $n = 235$
Systemic inflammatory disease[d]	24 (10.1%)
Pulmonary disease	66 (27.9%)
Previous pulmonary embolism	203 (85.7%)
Thrombophilia[e]	46 (19.4%)
Previous splenectomy	10 (4.2%)
Hypothyroidism	43 (18.1%)
Symptoms at admission	
Symptom onset >1 year	169 (72.2%); $n = 234$
WHO function class I/II/III/IV	1 (0.4%)/51 (21.5%)/160 (67.5%)/25 (10.5%)
Dyspnea NYHA I/II/III/IV	1 (0.4%)/50 (21.1%)/160 (67.5%)/26 (11.0%)
Cough	50 (23.5%); $n = 213$
Hemoptysis	10 (4.7%); $n = 212$
Cyanosis/LTOT	34 (16.0%); $n = 212$/71 (35.1%); $n = 202$
Fatigue	40 (18.6%); $n = 215$
Chest pain	26 (12.1%); $n = 214$
Syncope at exercise/at rest	20 (9.4%); $n = 213$/10 (4.7%); $n = 214$
Peripheral edema	82 (38.7%); $n = 212$
TTE; $n = 216$	
Peak tricuspid regurgitation velocity, m/sec	4.2 (3.8–4.5); $n = 133$
>2.8 m/sec	126 (94.7%)
Estimated systolic PA pressure, mm Hg	82 (68–96); $n = 132$
RV dilatation	160 (76.2%); $n = 210$
D-sign	130 (62.8%); $n = 207$
TAPSE, mm	18 (14–22); $n = 183$
<16 mm	52 (28.4%)
RA area, cm^2	22.9 (16.6–31.2); $n = 160$
>18 cm^2	114 (94.7%)
LVEF <60%	10 (5.8%); $n = 171$
Pericardial effusion	18 (8.6%); $n = 210$
RHC; $n = 206$	
Systolic PA pressure, mm Hg	74 (60–87); range, 21–125; $n = 168$
Mean PA pressure, mm Hg	43 (34–50); range, 13–73
PAWP, mm Hg	10 (8–13); range, 1–40; $n = 195$
PVR, Wood units	7.2 (5.0–10.3); range, 0.5–22.8; $n = 197$
Cardiac output, liters/min	4.5 (3.6–5.5); range, 2.0–9.2; $n = 197$
Cardiac index, liters/min/m^2	2.3 (1.9–2.7); range, 1.0–5.0; $n = 196$
Laboratory biomarkers	
NT-proBNP, ng/liter	792 (195–2,271); range, 13–27,617; $n = 200$
≥750 ng/liter	102 (51.0%)

Abbildung 6: Patientencharakteristika vor PEA mit Darstellung der Komorbiditäten, Risikofaktoren für CTEPH, Symptomen, funktionellem Status und echokardiographischen Befunden sowie der pulmonalen Hämodynamik.

Die Antikoagulation und eine etwaige gezielte medikamentöse Therapie bei Zuweisung bzw. bei Entlassung nach PEA zeigt **Abbildung 7**. Hierbei fällt die hohe Rate an bereits mit gezielter Medikation vorbehandelten Patienten auf (22 %), obwohl dies bei operabler CTEPH nicht indiziert ist. Andererseits wird auch das strikte Konzept in Bad Nauheim deutlich: postoperativ sinkt die Rate an Patienten mit gezielter medikamentöser Therapie auf 0,9 %. (Eine invasive Verlaufskontrolle insbesondere auch zur Entscheidung, ob eine gezielte medikamentöse Therapie indiziert ist, erfolgt leitliniengerecht 6-12 Monate nach PEA.)

	At admission: all study patients; $n = 237$	At discharge: survivors; $n = 231$
Therapeutic anticoagulation	235 (100%); $n = 235$	231 (100%)
Vitamin K antagonist	128 (54.5%)	119 (51.5%)
Rivaroxaban	90 (38.3%)	100 (43.3%)
Apixaban	2 (0.9%)	2 (0.9%)
Edoxaban	0	0
Dabigatran	3 (1.3%)	1 (0.4%)
Low-molecular-weight heparin	12 (5.1%)	9 (3.9%)
PAH-specific drugs	52 (22.0%); $n = 236$	2 (0.9%)
Riociguat	19 (8.1%)	1 (0.4%)
Sildenafil	23 (9.8%)	1 (0.4%)
Tadalafil	5 (2.1%)	0
Bosentan	10 (4.2%)	0
Macitentan	4 (1.7%)	0
Ambrisentan	3 (1.3%)	0
Prostacyclin	4 (1.7%)	0

Abbildung 7: Antikoagulation und gezielte medikamentöse Therapie vor und nach PEA.

Im Median dauerte der gesamte Eingriff 397 Minuten, wobei 267 Minuten extrakorporaler Zirkulation notwendig waren. Für die PEA waren im Median insgesamt 34 Minuten Kreislaufstillstand notwendig. **Abbildung 8** fasst die intra- und postoperativen Komplikationen zusammen. Bei 36 % der operierten Patienten traten intra- und/oder postoperative Komplikationen auf, wobei die Sterblichkeitsrate (im selben Krankenhausaufenthalt) bei 2,5 % lag. Dies stellt einen deutlichen Unterschied zu der Gesamtsterblichkeit nach PEA in Deutschland im gleichen Zeitraum von etwa 6 % dar.

	All study patients; $n = 237$
Intraoperative complications	
Major bleeding[a]	27 (11.4%)
Endobronchial/pulmonary bleeding	9 (3.8%)
Surgical bleeding	18 (7.6%)
Venoarterial/venovenous ECMO	10 (4.2%)/ 2 (0.8%)
Intraoperative death	0
Postoperative complications	
Reperfusion lung edema	23 (9.7%)
Requiring diuretics	10 (4.2%)
Requiring non-invasive/invasive mechanical ventilation	11 (4.6%)
Requiring venovenous ECMO	2 (0.8%)
Venoarterial/venovenous ECMO	4 (1.7%)/4 (1.7%)
Major bleeding[b]	13 (5.5%)
Surgical site bleeding	4 (1.7%)
Endobronchial/pulmonary bleeding	3 (1.3%)
Intracranial bleeding	3 (1.3%)
Other extrasurgical site bleeding	3 (1.3%)
Resternotomy <48 hours	7 (3.0%)
Pericardial tamponade requiring drainage or resternotomy	12 (5.1%)
Pneumothorax requiring drainage	10 (4.2%)
Acute/surgical abdomen	3 (1.3%)
Prolonged mechanical ventilation with tracheotomy	10 (4.2%)
CVVH or hemodialysis	13 (5.5%)
Sepsis	7 (3.0%)
Ischemic stroke	3 (1.3%)
Cardiopulmonary resuscitation	9 (3.8%)
In-hospital death	6 (2.5%)

Abbildung 8: Komplikationsrate intra- und postoperativ bei PEA in der Kerckhoff-Klinik im Zeitraum 2014 und 2015.

Es fanden sich keine Korrelationen zwischen Mortalität und präoperativen Parametern. Die Sterblichkeit korrelierte ausschließlich mit dem Auftreten intraoperativer Komplikationen bzw. der Operationsdauer. Wie **Abbildung 9** zeigt, erreicht die Kerckhoff-Klinik mit der PEA einen Spitzenwert in Bezug auf die Mortalität im Vergleich zu anderen chirurgischen Zentren.

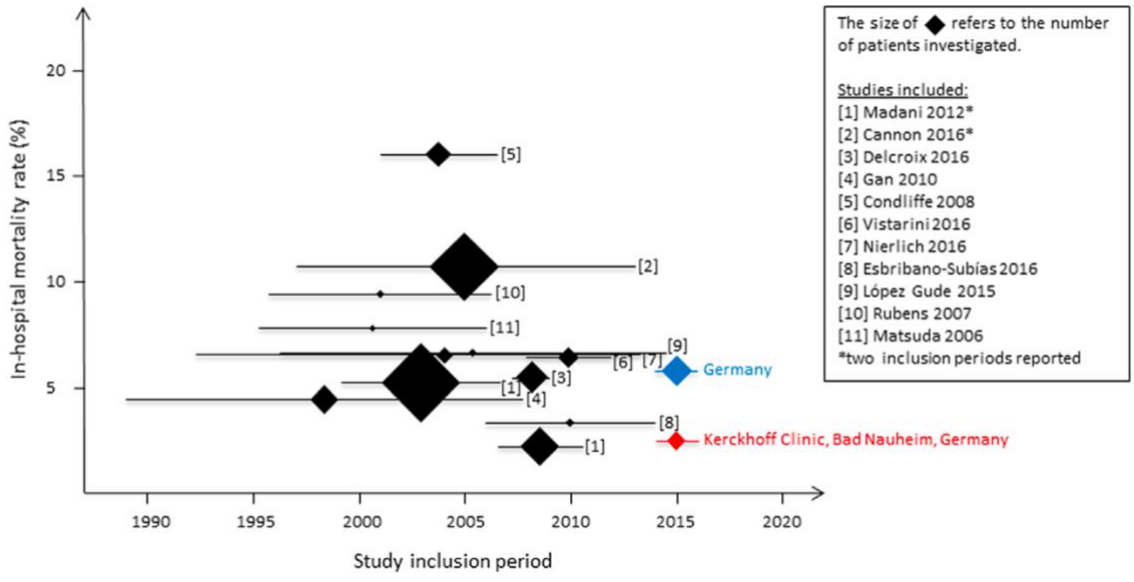

Abbildung 9: In-hospital Mortalität nach PEA in Relation zur Observationszeit. Es werden nur Studien mit mehr als 100 Patienten dargestellt. Die Größe der Raute ist abhängig von der Zahl der jeweils eingeschlossenen Patienten.

2.1.1 Schlussfolgerung

Die pulmonale Endarteriektomie (PEA) ist in einem erfahrenen Zentrum sicher und mit niedriger Mortalität durchführbar. In Deutschland werden die meisten dieser Eingriffe in der Kerckhoff-Klinik durchgeführt.

Erwähnenswert ist darüber hinaus das Verhältnis von operablen zu nicht-operablen Patienten: von den 425 Patienten mit der Diagnose CTEPH wurden 288 zur PEA geplant. Damit waren 36 % der Patienten nicht-operabel. Dies deckt sich mit den Daten des internationalen CTEPH Registers (15).

3. Interventionelle Behandlung der inoperablen CTEPH

3.1 Frühergebnisse der BPA bei inoperabler CTEPH

Über viele Jahre war die Behandlung der CTEPH ein rein chirurgisches Konzept. Noch in 2008 postulierte das weltweit führende chirurgische Zentrum (UCSD) mit der größten Expertise in PEA-Chirurgie, dass „wir nicht annehmen, dass es Patienten mit nicht-erreichbarer Erkrankung gibt – solange die Ursache der pulmonalen Hypertonie in Embolien liegt, dann nehmen wir per Definition eine chirurgische Erreichbarkeit bzw. Operabilität an“ (39). Dies war sicherlich auch geprägt durch die frustrierenden Erfahrungen mit der BPA in den USA und in Deutschland Anfang des einundzwanzigsten Jahrhunderts. Etwa zur selben Zeit wurde in einzelnen japanischen Zentren intensiv an einer Behandlungsmöglichkeit für CTEPH gearbeitet. Insbesondere aufgrund einer sehr limitierten chirurgischen Expertise wurde dort das Verfahren der BPA aufgegriffen, jedoch in seinem Ablauf verfeinert (33). Dies brachte den dortigen Zentren eine Vorreiterrolle in der interventionellen Behandlung der CTEPH, andererseits auch Kritik ein, operablen Patienten eine kurative Therapieoption vorzuenthalten. Bis zuletzt bleibt festzustellen, dass sich die Indikationsstellung, die Zielsetzung, auch die Benennung der Komplikationen, die technische Durchführung, der Umgang mit gezielter medikamentöser Therapie und das Nachsorgekonzept in den mittlerweile zahlreichen Zentren weltweit unterscheidet. Ein Versuch, diesbezüglich Vergleichbarkeit herzustellen ist das erste internationale BPA Register, das derzeit noch Patienten rekrutiert (NCT03245268).

Mit zunehmender Wahrnehmung der Erkrankung und letztlich auch Verbesserung der Bildgebung wurden aber auch Patienten mit weiter distal gelegenen Veränderungen detektiert. Spätestens mit den Registerdaten aus 2011 wurde offenbar, dass für etwa 1/3 der CTEPH-Patienten eine PEA nicht in Frage kommt (15). Zum damaligen Zeitpunkt stand keine zugelassene gezielte medikamentöse Therapie zur Verfügung und somit war eine Behandlung dieser Patientengruppe schwierig. Mit den vielversprechenden, wenn auch kritisch gesehenen Ergebnissen aus Japan (33, 34) führte dies zu der Entscheidung, auch in Deutschland wieder ein Programm zur interventionellen Behandlung dieser Patienten zu etablieren, was letztlich an zwei Standorten umgesetzt wurde.

Im Abstand von etwa einem halben Jahr wurden an der Medizinischen Hochschule Hannover und an der Kerckhoff-Klinik Bad Nauheim sehr ähnliche Konzepte eingeführt, um Patienten, die aufgrund zu peripher gelegener Veränderungen als nicht-operabel beurteilt wurden, interventionell zu behandeln. Dabei erfolgte stets eine Evaluation der Patienten im interdisziplinären Team bestehend aus interventionellen Kardiologen und Radiologen, PEA-Chirurgen, Pneumologen und Anaesthesisten. Die Diagnostik umfasste neben Erfassung der WHO-Funktionsklasse, Laboruntersuchung, Echokardiographie, Bodyplethysmographie mit Blutgasanalyse, 6MWD, Spiroergometrie auch Rechts- und Linksherzkatheter, Pulmonalis-Angiographie sowie CT des Thorax. Anschließend erfolgte nach intensiver Aufklärung der Patienten die BPA in mehreren Einzelsitzungen, üblicherweise über einen femoral-venösen Zugang. Durch eine 6 french Schleuse wurde ein 6 french Führungskatheter bis in die Zielsegmentarterie eingebracht, um eine superselektive Darstellung zu ermöglichen. Abschließend wurden die narbigen Stenosierungen mit einem Draht überwunden und hierüber ein Ballon eingebracht. Die Größe wurde mittels Angiographie abgeschätzt, wobei tendenziell ein kleinerer Diameter ausgewählt wurde. Das Ergebnis wurde anschließend mittels Angiographie morphologisch erfasst, wobei wie in **Abbildung 10** dargestellt eine Besserung der antegraden Perfusion mit Besserung oder Wiederherstellung der parenchymatösen Perfusion und raschem venösen Rückfluss als gutes Ergebnis gewertet wurden.

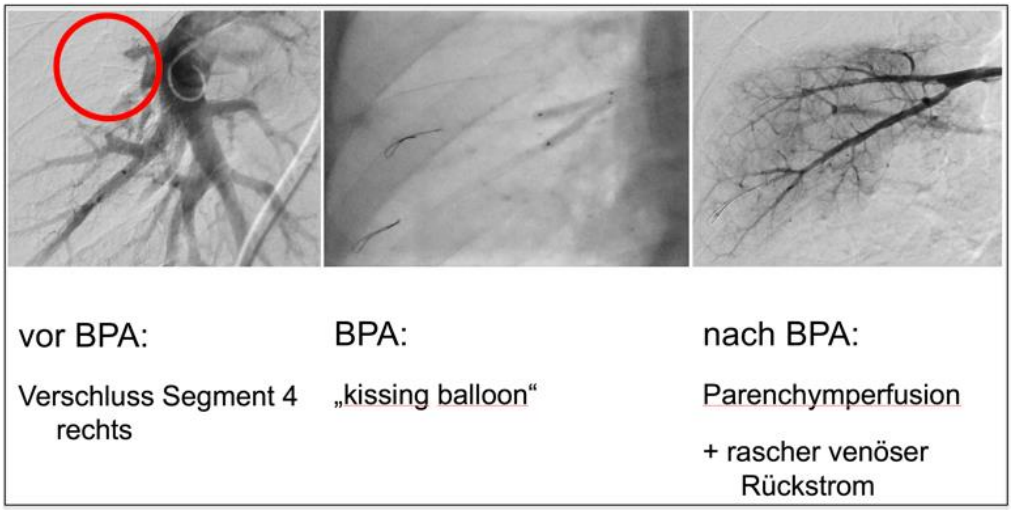

Abbildung 10: BPA in einem 79-jährigen Patienten mit einem PAPm von 39 mmHg und einem PVR von 6,7 WE: in 30° kontralateraler Projektion zeigt sich ein Verschluss des Segmentes 4 in der 1. Subsegmentgabel. 2 Drähte werden in die beiden Hauptsubsegmente eingebracht und die Bifurkation wird mit 2 Ballons gleichzeitig („kissing balloon“ Technik) aufgedehnt. Anschließend zeigt sich eine deutlich gebesserte Parenchymperfusion mit raschem venösem Rückstrom.

6 Monate nach der letzten Intervention erfolgte eine Verlaufskontrolle, die neben Erfassung der WHO-Funktionsklasse, Laboruntersuchung, Echokardiographie, Bodyplethysmographie mit Blutgasanalyse, 6MWD, Spiroergometrie auch RHK

sowie CT des Thorax umfasste.

Inhalt der zweiten Publikation waren die Ergebnisse der ersten 56 konsekutiven Patienten, die zwischen August 2013 und Januar 2016 an der Medizinischen Hochschule Hannover und der Kerckhoff-Klinik behandelt wurden. Im Median vergingen 14 Monate zwischen der Diagnosestellung CTEPH und der ersten Intervention. Die meisten Patienten wurden gezielt-medikamentös vorbehandelt, wobei dies mindestens 3 Monate vor Studienbeginn unverändert bestand. Insgesamt wurden 266 Interventionen durchgeführt, wobei im Median 5 (range 3-8) Interventionen pro Patient vorgenommen wurden. Wie **Abbildung 11** zeigt, besserte sich die WHO-Funktionsklasse in 59 % der Patienten und blieb in 41 % unverändert.

	Baseline		Week 24		p-value
	Subjects n	Value	Subjects n	Value	
Exercise capacity					
WHO functional class	56		55		<0.001
I		0 (0)		6 (13)	
II		9 (15)		33 (60)	
III		40 (70)		16 (25)	
IV		7 (15)		0 (0)	
6 min walking distance m	55	358±108	53	391±108	0.001
Borg dyspnoea scale (1–10)	55	4.7±2.0	53	3.1±2.0	<0.001
Haemodynamics and NT-proBNP					
Right atrial pressure mmHg	55	8±5	55	6±4	0.001
PAPm mmHg	56	40±12	55	33±11	<0.001
PAPsyst mmHg	56	66±20	55	55±19	<0.001
PAPdiast mmHg	56	23±9	55	19±8	<0.001
PAWP mmHg	56	10±3	55	9±3	0.738
DPG mmHg	55	14±8	55	10±8	<0.001
TPG mmHg	56	30±11	55	23±10	<0.001
CO $L \cdot min^{-1}$	56	4.4±1.1	55	4.6±1.2	0.071
CI $L \cdot min^{-1} \cdot m^{-2}$	56	2.4±0.6	55	2.5±0.6	0.259
PVR $dyn \cdot s \cdot cm^{-5}$	56	591±286	55	440±279	<0.001
S_{vO_2} %	55	64±8	55	69±6	<0.001
HR bpm	56	72±12	55	69±11	0.123
NT-proBNP	56	504 (233–1676)	55	242 (109–555)	0.002
Echocardiographic findings					
RVED diameter mm	51	38±9	49	34±8	0.002
RV free wall diameter mm	31	6.6±1.2	31	6.5±1.0	0.917
TAPSE mm	51	19±5	44	21±5	<0.001
RA dilation	50	38 (76)	49	19 (39)	<0.001
Blood gas analysis and pulmonary function					
P_{aO_2} mmHg	53	62±9	53	66±10	0.001
S_{aO_2} %	53	93±3	53	94±3	0.004
P_{aCO_2} mmHg	53	34±3	53	34±6	0.801
D_{LCO} % pred	53	57±16	53	58±19	0.261
Laboratory findings					
Creatinine $\mu mol \cdot L^{-1}$	55	87±36	55	87±26	0.746
eGFR $mL \cdot min^{-1}$	56	62±15	55	64±17	0.343

Abbildung 11: Entwicklung von WHO-Funktionsklasse, pulmonaler Hämodynamik, Echokardiographie, Blutgasanalyse und Laboruntersuchungen vor und 6 Monate nach BPA.

Die 6MWD besserte sich um 33 m (etwa + 9% des Ausgangswertes). Die pulmonale Hämodynamik besserte sich hinsichtlich PAPm und PVR signifikant.

Die Prozedur verlief in 25 Sitzungen komplikativ (entsprechend 9,4 % der Interventionen bzw. 32 % der Patienten), wobei ein Patient aufgrund einer zweizeitigen massiven Blutung 14 Tage nach der Intervention verstarb. Insbesondere die hämodynamischen Effekte waren im Vergleich zu den japanischen Vorarbeiten etwas weniger ausgeprägt (33-35), im Vergleich zu anderen europäischen Erfahrungen aber ähnlich (36). Dies wurde vor allem auf die bereits erwähnten Unterschiede in der Indikationsstellung zurückgeführt.

3.1.1 Schlussfolgerung

Zusammenfassend zeigen die Ergebnisse, dass die BPA zu Verbesserungen der pulmonalen Hämodynamik und der körperlichen Belastbarkeit bei Patienten mit inoperabler CTEPH führt. Die in Deutschland in den ersten 56 Patienten erreichten Ergebnisse sind denen der japanischen Arbeitsgruppen bezüglich der Verbesserungen der pulmonalen Hämodynamik unterlegen. Allerdings erscheint eine Übertragung japanischer Kohorten auf das westeuropäische Patientengut schwierig. Der sehr hohe Anteil weiblicher Patienten sei hier nur beispielsweise erwähnt. Nicht zuletzt liegen zudem erhebliche Unterschiede in der Expertise der behandelnden Zentren, insbesondere was die chirurgische Therapie angeht, vor.

Die Intervention ist teils mit bedrohlichen Komplikationen assoziiert, im Vergleich zu früheren Erfahrungen erscheint eine sichere Durchführung aber möglich.

3.2 Kinetik des N-terminalen pro-BNPs bei BPA bei inoperabler CTEPH

Die langfristige Kontrolle und damit auch Therapieentscheidungen im Verlauf bei Patienten mit PH haben sich über die Jahre fortwährend entwickelt. Dabei wurden verschiedene Parameter unterschiedlich gewichtet. Die Europäische Leitlinie für die Behandlung der PH von 2015 fasst die wichtigsten Parameter für die Risikobewertung zusammen (**Abbildung 12**): klinische Zeichen des Rechtsherzversagens, Symptomprogress, Synkopen, WHO Funktionsklasse, 6MWD, Spiroergometrie, Bildgebung, pulmonale Hämodynamik und N-terminales pro-BNP

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ⩾45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 pericardial effusion
Haemodynamics	RAP <8 mmHg CI ⩾2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Abbildung 12: Risikobewertung bei pulmonalarterieller Hypertonie (12).

(NT-pro-BNP) (12). Das letztgenannte erscheint als im Blut bestimmbarer, in den meisten Laboren verfügbarer Parameter gut geeignet, um Patienten mit PH im Verlauf zu kontrollieren. Da es vermehrt bei Ventrikeldehnung und myokardialer Hypoxie ausgeschüttet wird, wird es auch bei Patienten mit akuter oder chronischer Herzinsuffizienz zur Diagnostik und Prognosebestimmung genutzt (40-42). Sein prädiktiver Nutzen wurde darüber hinaus bereits für operable CTEPH Patienten nach PEA nachgewiesen (43, 44). Da bislang nur wenige Daten bezüglich des NT-pro-BNP-Verlaufes unter interventioneller Therapie inoperabler CTEPH Patienten vorlagen, bestand die Zielsetzung den Verlauf auch zwischen den einzelnen Sitzungen darzustellen und mit den Änderungen der pulmonalen Hämodynamik zu korrelieren.

Die Studienkohorte bestand aus 51 konsekutiven Patienten mit inoperabler CTEPH, die zwischen März 2014 und März 2017 alle Interventionen und auch die 6-Monats-Verlaufskontrolle abgeschlossen hatten. Alle Patienten wurden nach Evaluation im

Rahmen einer multidisziplinären CTEPH-Konferenz als inoperabel eingestuft und es wurden Zielgebiete für die BPA identifiziert. Unmittelbar vor der ersten Intervention sowie 6 Monate nach der letzten Intervention erfolgte eine umfangreiche Abklärung, wie bereits unter 2.1 beschrieben. Vor jeder Intervention wurde die WHO Funktionsklasse erfasst und das NT-pro-BNP bestimmt (**Abbildungen 13 und 14**).

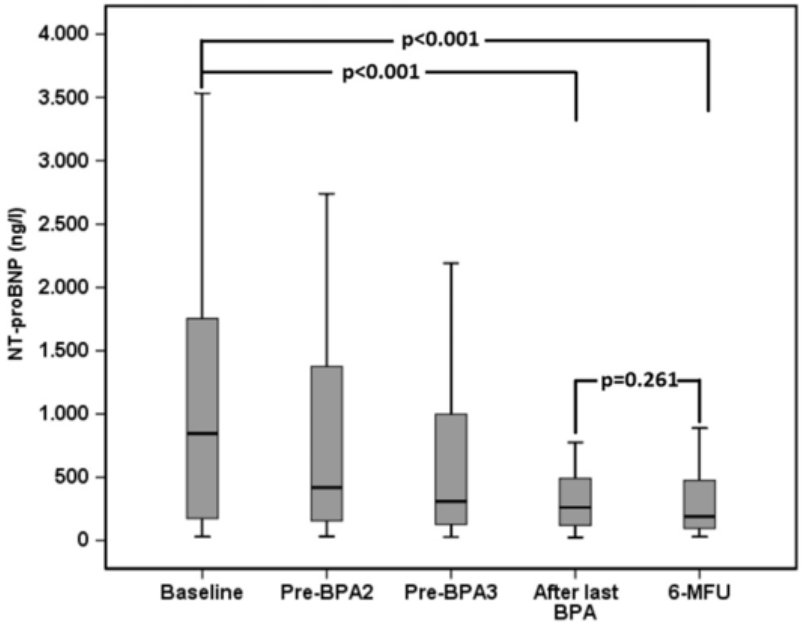

Abbildung 13: NT-pro-BNP im Verlauf der einzelnen BPA Interventionen und 6 Monate nach der letzten Sitzung.

Dabei konnte ein deutlicher Abfall der NT-pro-BNP-Konzentrationen in fast allen behandelten Patienten nachgewiesen werden, wobei bereits nach der ersten Sitzung ein fast signifikanter Abfall deutlich wurde. Der Abfall des NT-pro-BNP korreliert mit einer signifikanten Reduktion des PAPm und des PVR. Dabei bedeutet ein NT-pro-BNP Abfall um 40 % 6 Monate nach der letzten Intervention eine Besserung des PAPm um mehr als 25 %, eine Reduktion des NT-pro-BNP um 60 % sogar eine Besserung des PVR um mehr als 35 %.

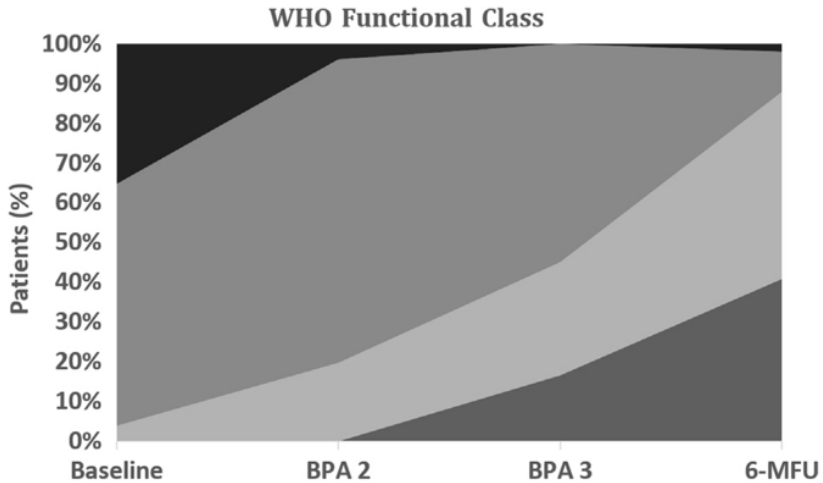

Abbildung14: WHO Funktionsklasse im Verlauf der einzelnen BPA Interventionen und 6 Monate nach der letzten Sitzung.

3.2.1 Schlussfolgerung

Bereits nach der ersten Intervention konnte ein Abfall des NT-pro-BNP auf fast normale Werte gezeigt werden. Dabei korrelierte die Reduktion mit den Veränderungen der pulmonalen Hämodynamik bei der 6-Monats-Kontrolle und lässt damit eine Erfolgsbeurteilung der interventionellen Therapie inoperabler CTEPH Patienten ableiten.

3.3 MRT zur nicht-invasiven Verlaufsbeurteilung nach BPA bei inoperabler CTEPH

Eine weitere Möglichkeit zur nicht-invasiven Beurteilung der rechtsventrikulären Struktur, Funktion und Morphologie stellt die kardiale MRT dar. So wurden bereits positive Effekte der PEA bei operablen CTEPH Patienten mittels MRT nachgewiesen (45, 46). Eine weitere Studie befasste sich mit den Effekten der medikamentösen Therapie idiopathischer PH auf die links- und rechtsventrikuläre Funktion (47). Mittlerweile wurde zudem eine Besserung der biventrikulären Funktion, des pulmonalen Flusses und der interventrikulären Dyssynchronie nach BPA bei inoperablen CTEPH Patienten nachgewiesen (48, 49). Weitere diagnostische Informationen in verschiedenen Herzerkrankungen liefert das native T1-mapping: hiermit kann das untersuchte Gewebe parametrisch charakterisiert werden, ohne Kontrastmittel zu benötigen (50-52). Erste Ergebnisse in Patienten mit verschiedenen Formen von PH waren vielversprechend und zeigten Korrelationen mit der rechtsventrikulären Funktion und der pulmonalen Hämodynamik (53-55). Darüber hinaus wurden im Tiermodell ein Anstieg der T1 Zeit mit dem Grad der septalen Fibrose nachgewiesen (56). Mit der Zielsetzung, einen weiteren Biomarker zur nicht-invasiven Verlaufsbeurteilung inoperabler CTEPH Patienten nach BPA zu etablieren, sollten die nativen T1 Werte vor und 6 Monate nach der letzten BPA untersucht und mit der rechtsventrikulären Funktion und der pulmonalen Hämodynamik korreliert werden.

Zwischen Januar 2014 und Februar 2015 wurden 21 konsekutive Patienten, die entsprechend dem bereits beschriebenen Vorgehen in das BPA-Programm eingeschlossen wurden, untersucht. Als Ausschlußkriterien wurden eine schwere Niereninsuffizienz (glomeruläre Filtrationsrate < 30 ml/min/1,73 m_2),

Vorhandensein MRT-inkompatibler Implantate, bekannte Gadolinium-Intoleranz, Klaustrophobie sowie Unmöglichkeit, für die Dauer der Untersuchung in liegender Position zu verweilen, festgelegt.

Es konnte eine Besserung der rechtsventrikulären Funktion wie auch ein Abfall des PAPm und des PVR nachgewiesen werden. Damit ging ein signifikanter Rückgang der T1 Zeiten im Bereich des Septums einher. **Abbildung 15** zeigt die Korrelation der rechtsventrikulären Funktion und der pulmonalen Hämodynamik mit der T1 Zeit. **Abbildung 16** zeigt die morphologischen Veränderungen nach BPA.

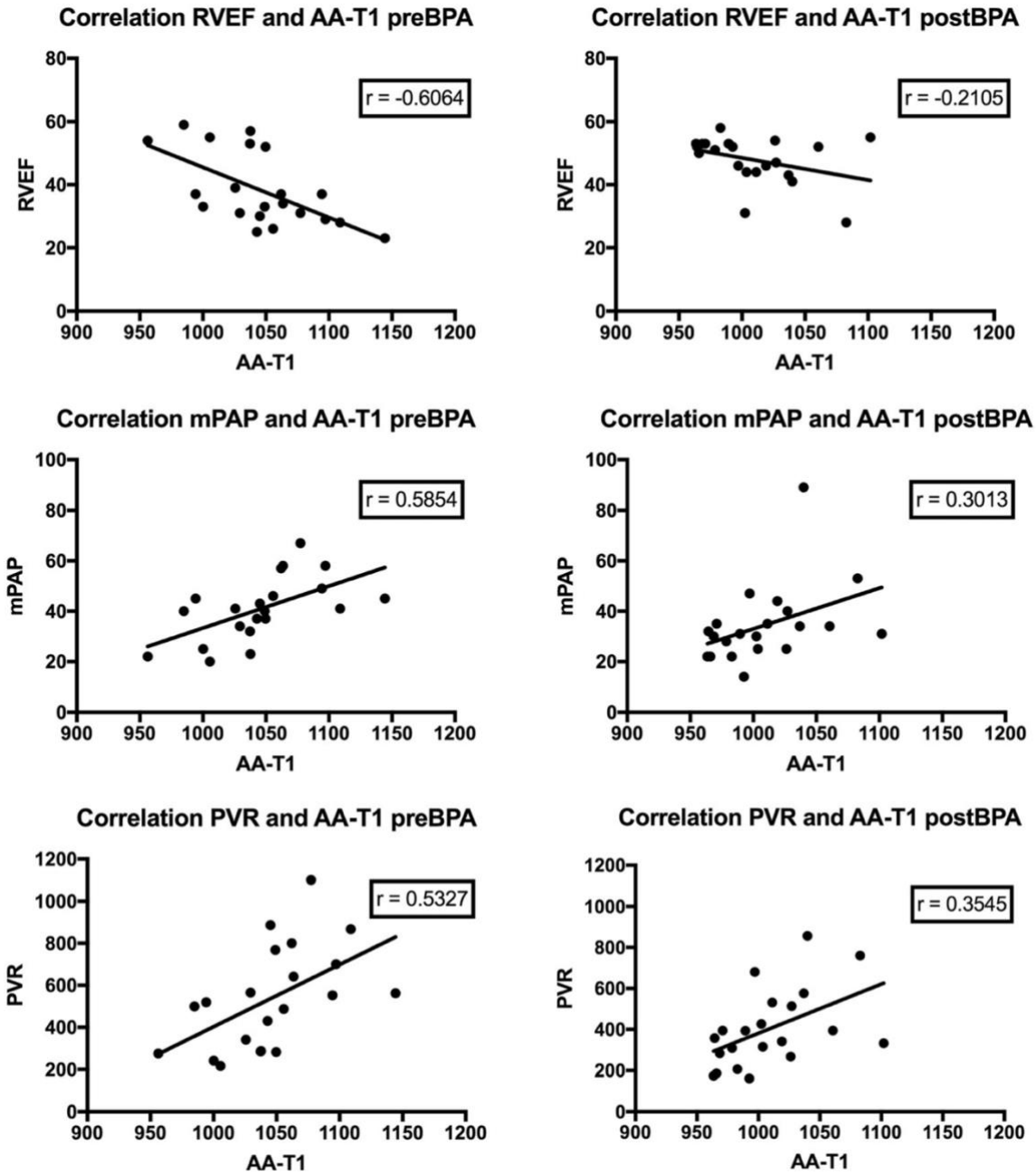

Abbildung 15: Korrelationen der T1 Zeiten (AA-T1) mit der pulmonalen Hämodynamik.

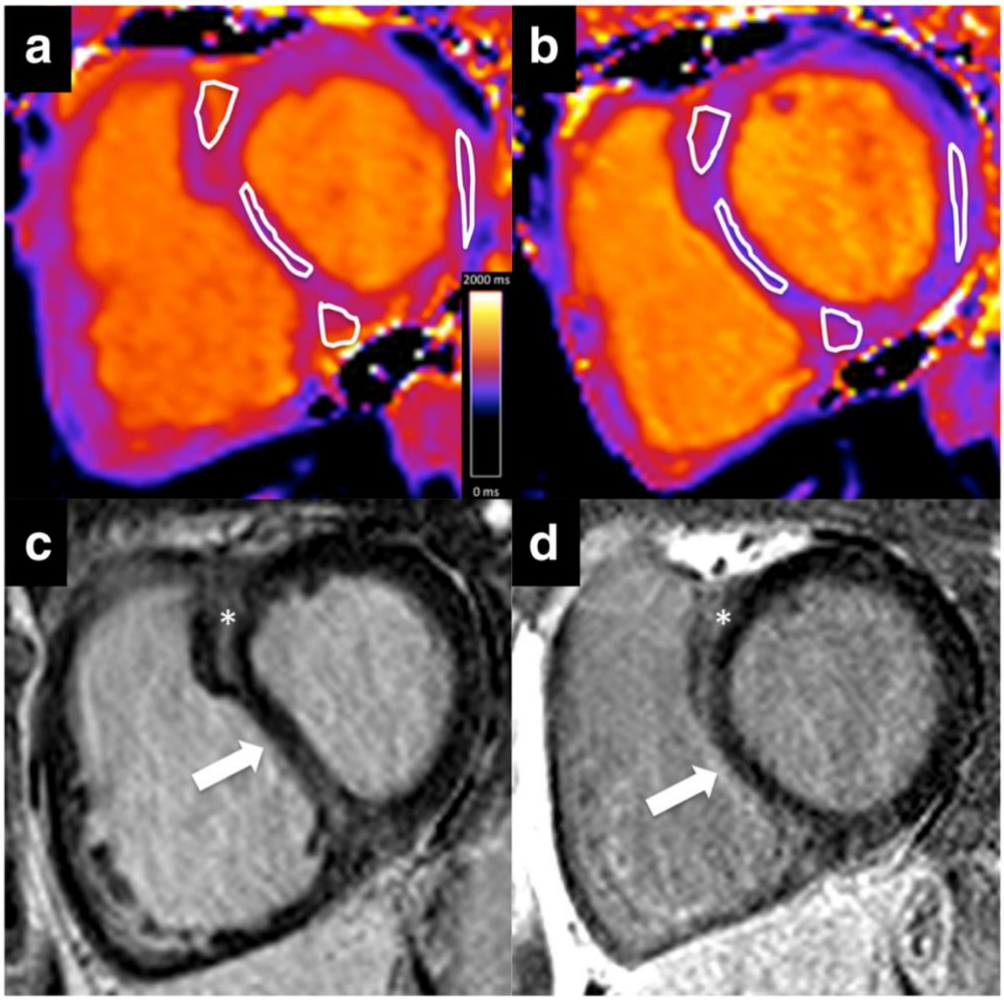

*Abbildung 16: Native T1 Karten vor (a) und nach BPA (b) mit den entsprechenden späten Kontrastmittelserien (c und d) in einem 55-jährigen Patienten mit schwerer PH vor der Intervention (PAPm 51 mmHg) und deutlicher Besserung nach der BPA (PAPm 35 mmHg). *-markiert die PH-typischen Veränderungen im oberen (und unteren) interventrikulären Septum, allerdings pfleilmarkiert die Veränderung der Septumposition nach der BPA und entsprechend die deutliche Verbesserung der Größe des linken und rechten Ventrikels.*

3.3.1 Schlussfolgerung

Zusammengenommen lässt sich aus den Ergebnissen ablesen, dass die BPA nicht nur zu einer deutlichen Besserung der pulmonalen Hämodynamik führt, sondern auch zu einem reverse Remodelling des rechtsventrikulären Myokards und damit zur Besserung der rechtsventrikulären Funktion.

3.4 BPA bei inoperabler CTED

Inhalt der fünften Publikation ist die Erweiterung der Indikation der BPA auf Patienten mit inoperabler CTED. Wie bereits beschrieben wird bei CTEPH neben den pulmonalarteriellen Läsionen eine präkapilläre PH vorausgesetzt. Allerdings gibt es auch symptomatische Patienten mit endoluminalen Obstruktionen, aber noch keiner PH in Ruhe. Wird die Einschränkung der körperlichen Belastbarkeit hierauf zurückgeführt, spricht man von einer CTED (13). Diese Erkrankung wird, wie die CTEPH auch, üblicherweise chirurgisch mittels PEA behandelt (21, 57, 58). Nimmt man entsprechend den Daten bei CTEPH eine Verteilung von 2/3 operabler versus 1/3 nicht-operabler Patienten an (15), drängt sich die Frage auf, ob für die Gruppe der inoperablen CTED Patienten eine BPA sinnvoll ist.

Da einerseits die Anzahl an zugewiesenen CTED Patienten gering ist, aber auch um die Aussagekraft zu erhöhen, wurden wiederum multizentrisch (Kerckhoff Klinik, Bad Nauheim und Medizinische Hochschule, Hannover) 10 konsekutive Patienten mit inoperabler CTED eingeschlossen. Die Evaluation erfolgte wie bereits beschrieben, wobei in der Zeit der Studie (August 2013 bis Juni 2017) PH ab einem PAPm von 25 mmHg diagnostiziert wurde.

Abbildungen 17 und 18 fassen die wesentlichen Ergebnisse zusammen. Dabei zeigt sich keine wesentliche Änderung der pulmonalarteriellen Druckwerte, jedoch eine Besserung des PVR. Zudem konnte eine Besserung der WHO Funktionsklasse als Ausdruck der gebesserten körperlichen Belastbarkeit nachgewiesen werden.

Diese Ergebnisse sind vergleichbar mit denen der Ergebnisse der PEA bei operabler CTED. Zudem konnte mit der Besserung der pulmonalarteriellen Compliance die positive Beeinflussung eines wichtigen prognostischen Markers bei P(A)H - Patienten (59) gezeigt werden.

	n	Baseline	n	Week 24	*P* value
Exercise capacity					
WHO functional class (n (%))	10		10		
I		0 (0)		4 (40)	**0.004**
II		1 (10)		5 (50)	
III		9 (90)		1 (10)	
IV		0 (0)		0 (0)	
6MWD (m)	10	365 ± 139	10	396 ± 142	0.11
Borg dyspnea scale (1–10)	6	4.0 ± 1.0	6	1.8 ± 0.9	0.13
Hemodynamics and NT-proBNP					
Right atrial pressure (mmHg)	10	4 ± 2	10	6 ± 3	0.12
mPAP (mmHg)	10	21 ± 2	10	20 ± 3	0.74
systPAP (mmHg)	10	35 ± 6	10	31 ± 7	0.31
diastPAP (mmHg)	10	10 ± 4	10	11 ± 2	0.38
PAWP (mmHg)	10	8 ± 3	10	10 ± 2	**0.02**
DPG (mmHg)	10	3 ± 3	10	1 ± 1	0.20
TPG (mmHg)	10	12 ± 3	10	9 ± 3	**0.02**
CO (L/min)	10	4.3 ± 0.5	10	4.5 ± 0.7	0.32
CI (L/min/m^2)	10	2.4 ± 0.3	10	2.5 ± 0.4	0.38
PVR (dyn·s·cm^{-5})	10	234 ± 68	10	167 ± 40	**0.004**
PAC (mL/mmHg)	10	3.2 ± 2.1	10	4.1 ± 1.7	**0.027**
SvO_2 (%)	10	65 ± 9	10	69 ± 4	0.22
HR (bpm)	10	65 ± 9	10	64 ± 8	0.66
NT-proBNP, ng/L (median (IQR))	10	144 (60–227)	10	109 (87–194)	0.56
Blood gas analysis and pulmonary function					
PaO_2 (mmHg)	7	68 ± 13	7	71 ± 7	0.69
SaO_2 (%)	7	95 ± 3	7	96 ± 1	0.94
$PaCO_2$ (mmHg)	7	34 ± 3	7	35 ± 3	0.38
DLCO (% predicted)	7	60 ± 11	7	69 ± 18	0.19
MRI findings					
LV-EF (%)	6	68 ± 9	6	69 ± 5	0.88
LV-SV (mL)	6	76 ± 3	6	76 ± 8	0.81
LV-EDV (mL)	6	114 ± 18	6	112 ± 15	0.63
LV-ESV (mL)	6	39 ± 15	6	36 ± 10	0.44
RV-EF (%)	6	55 ± 1	6	55 ± 4	0.99
RV-SV (mL)	6	75 ± 16	6	68 ± 10	0.31
RV-EDV (mL)	6	135 ± 26	6	125 ± 22	0.19
RV-ESV (mL)	6	60 ± 10	6	57 ± 14	0.38
Laboratory findings					
Creatinine (μmol/L)	10	76 ± 25	8	82 ± 23	0.99
eGFR (mL/min)	8	81 ± 28	8	67 ± 19	0.56

Abbildung 17: Veränderung der wesentlichen klinischen Parameter vor und 6 Monate nach BPA bei inoperabler CTED.

3.4.1 Schlussfolgerung

Zusammenfassend führt die interventionelle Behandlung inoperabler CTED Patienten zu einer Besserung der körperlichen Belastbarkeit und auch der pulmonalen Hämodynamik. Zudem war die BPA mit einer milden Blutungskomplikation (ohne Notwendigwerden weiterer Maßnahmen) bei insgesamt 35 Eingriffen sicher durchführbar. Aufgrund der geringen Patientenzahl kann keine klare Empfehlung abgeleitet werden, jedoch scheint die BPA bei selektionierten

Patienten eine therapeutische Option zu sein.

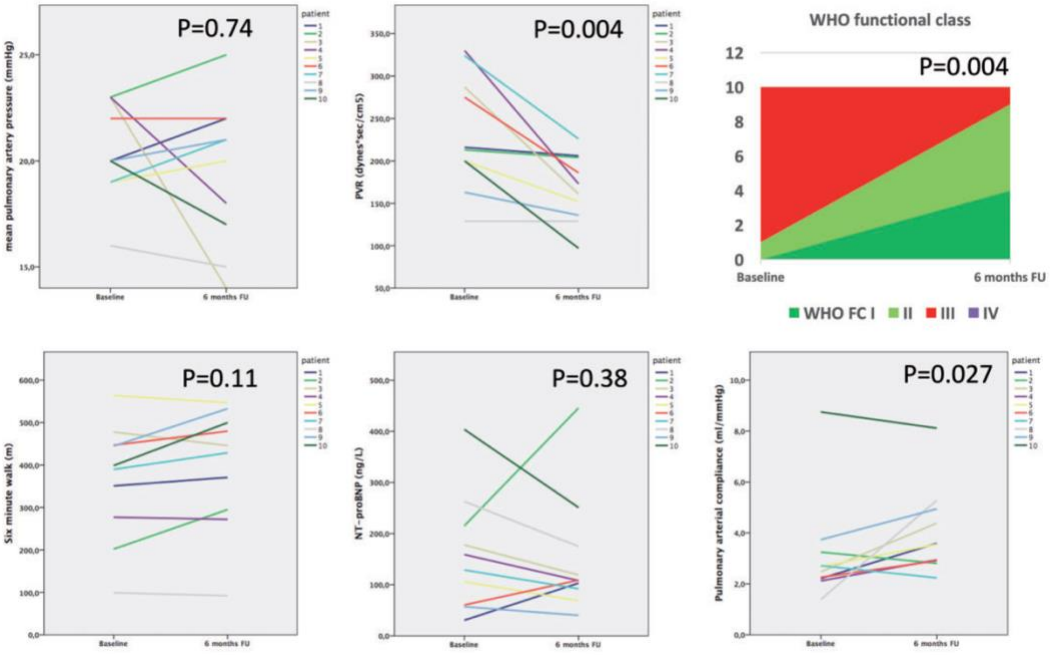

Abbildung 18: Verlauf von PAPm, PVR, 6MWD, NT-pro-BNP und pulmonalarterieller Compliance sowie der WHO-Funktionsklasse vor und 6 Monate nach BPA bei inoperabler CTED.

4. Multimodale Therapie der CTEPH

4.1 Multimodale Therapie der inoperablen CTEPH

Folgt man den aktuellen Leitlinien für CTEPH, so wird bei Feststellung der Inoperabilität die Einleitung einer gezielten medikamentösen Therapie empfohlen (12-14). In dieser Indikation steht bislang nur Riociguat als einzig zugelassene Substanz zur Verfügung, da der Stimulator der löslichen Guanylatzyklase nicht nur eine Besserung der pulmonalen Hämodynamik bewirkt, sondern auch der körperlichen Belastbarkeit (28, 60, 61). Zudem kann eine interventionelle Therapie erwogen werden (12-14). Für die Sequenz mit initial Riociguat und anschließend zusätzlicher BPA gab es bislang jedoch keine explizite Studie. Der Umgang mit der gezielten medikamentösen Therapie periinterventionell wird sehr unterschiedlich gehandhabt. So werden teils keine und teils verschiedene Medikamente eingesetzt, während mit Riociguat vorbehandelte Patienten oft nur einen kleinen Teil der Studienpopulationen ausmachen (31, 33-36, 62). In einem zu dieser Zeit aktuellen Review (63) wurde lediglich eine Arbeit erwähnt, bei deren Kohorte 40 % der Patienten mit Riociguat behandelt wurden (49).

Ziel der sechsten Publikation war daher, die Leitlinienempfehlung nachzuzeichnen: hierfür wurden Therapie-naive CTEPH Patienten nach Feststellung der Inoperabilität nach intensiver Evaluation für mindestens 3 Monate mit Riociguat behandelt. Anschließend folgte ein erneuter RHK und dann die interventionelle Behandlung. 6 Monate nach der letzten BPA erfolgte eine Reevaluation. Die medikamentöse Therapie blieb über den gesamten Zeitraum unverändert. **Abbildung 19** zeigt das Studienprotokoll.

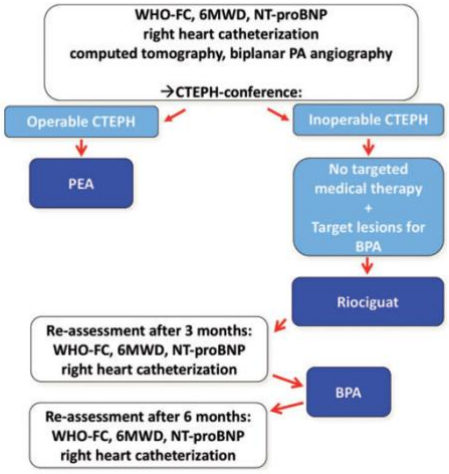

Abbildung 19: Studienprotokoll mit Darstellung der ersten Evaluation, nach Feststellung der Inoperabilität Initiierung der Riociguat-Therapie und nach 3 Monaten Re-Evaluation vor Beginn der BPA, 6 Monate nach der letzten Intervention wiederum Reevaluation.

Abbildung 20 zeigt die wesentlichen Befunde vor Einleitung der medikamentösen Therapie.

	n	Last measurement before riociguat treatment
Exercise capacity		
WHO FC (n (%))	36	
I		0 (0)
II		0 (0)
III		19 (52.8)
IV		17 (47.2)
6MWD (m)	26	389 ± 108
Hemodynamics and NT-proBNP		
mPAP (mmHg)	36	49 ± 12
PAWP (mmHg)	36	9 ± 4
CO (L/min)	36	4.3 ± 1.3
CI (L/min/m^2)	36	2.2 ± 0.6
PVR (dyn·s·cm^{-5})	36	956 ± 501
NT-proBNP (ng/L) (median (IQR))	31	1137 (283–2142)

Abbildung 20: Zusammenfassung der Befunde vor Beginn der medikamentösen Therapie.

Abbildungen 21 und 22 fassen die Änderungen unter medikamentöser Therapie und nach BPA zusammen.

	n	Under riociguat	n	6 months after BPA	*P* value
Exercise capacity					
WHO FC (n (%))	36		36		0.0001
I		0 (0)		18 (50.0)	
II		7 (19.4)		16 (44.4)	
III		18 (50.0)		2 (5.6)	
IV		11 (30.6)		0 (0)	
6MWD (m)	32	409 ± 102	30	467 ± 95	0.0001
Hemodynamics					
Right atrial pressure (mmHg)	36	7 ± 4	36	6 ± 3	0.02
mPAP (mmHg)	36	43 ± 12	36	34 ± 14	0.0001
sPAP (mmHg)	36	74 ± 21	36	59 ± 25	0.0001
dPAP (mmHg)	36	25 ± 7	36	18 ± 8	0.0001
PAWP (mmHg)	36	10 ± 3	36	10 ± 3	0.92
DPG (mmHg)	36	15 ± 7	36	8 ± 8	0.0001
TPG (mmHg)	36	33 ± 11	36	24 ± 13	0.0001
CO (L/min)	36	5.0 ± 1.5	36	5.5 ± 1.3	0.0001
CI (L/min/m^2)	36	2.6 ± 0.7	36	2.9 ± 0.6	0.02
PVR (dyn·s·cm^{-5})	36	517 ± 279	36	360 ± 175	0.0001
PAC (mL/mmHg)	36	1.4 ± 0.6	36	2.3 ± 1.0	0.0001
HR (bpm)	36	78 ± 12	36	70 ± 11	0.001
Laboratory findings					
NT-proBNP (ng/L) (median (IQR))	29	1,010 (128–1,887)	35	150 (75–385)	0.0001
Creatinine* (mg/dL)	28	0.98 ± 0.31	36	0.91 ± 0.28	0.02
eGFR (mL/min)	28	82 ± 28	36	94 ± 59	0.05

Abbildung 21: Zusammenfassende Darstellung der Veränderungen unter medikamentöser Therapie (linke Spalte) und zusätzlicher BPA (rechte Spalte). Die p-Werte beziehen sich auf die Veränderungen durch die zusätzliche BPA.

Mit der Studie konnten die bekannten Effekte der Riociguat-Therapie bei inoperabler CTEPH bestätigt werden. Darüber hinaus bewirkte die BPA eine weitere Verbesserung sowohl der pulmonalen Hämodynamik als auch der körperlichen Belastbarkeit. Die Kombination der beiden Therapiemodalitäten war bei niedriger Komplikationsrate und insgesamt guter Verträglichkeit der medikamentösen Therapie sicher durchführbar.

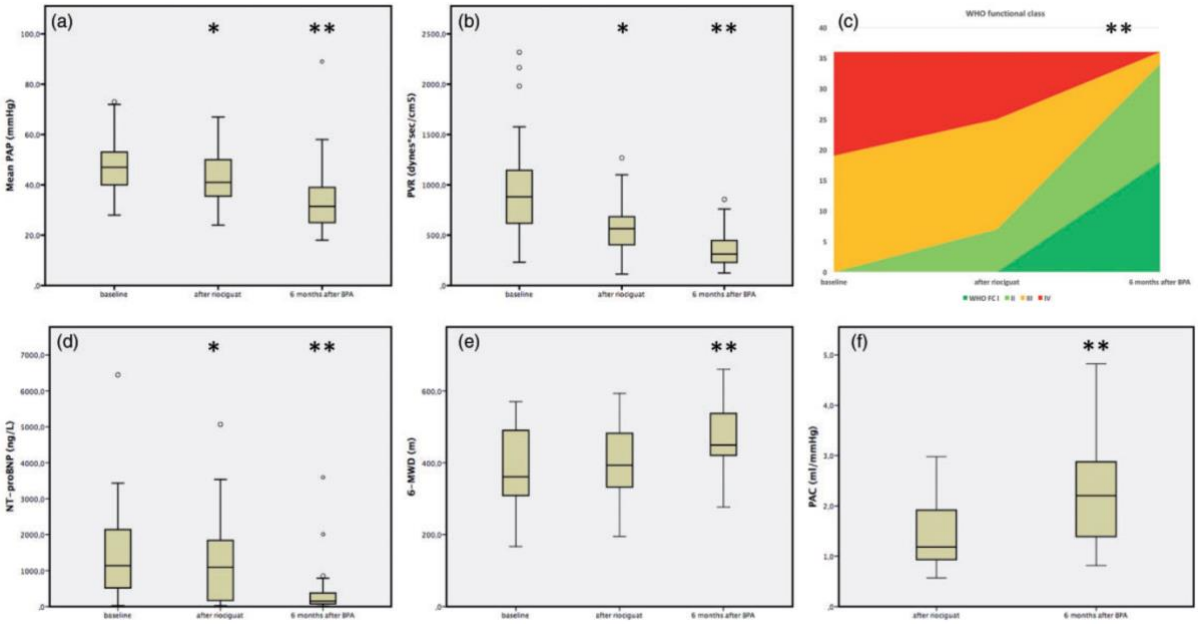

Abbildung 22: Vergleichende Darstellung der Effekte der gezielten medikamentösen und der interventionellen Therapie bei inoperabler CTEPH.

4.1.1 Schlussfolgerung

Insgesamt konnte erstmalig die Leitlinienempfehlung nachgezeichnet und in ihrer Evidenz gestärkt werden. Eine multimodale Therapie inoperabler CTEPH Patienten erscheint sicher durchführbar und mit einem guten mittelfristigen Ergebnis assoziiert. Insbesondere ist eine weitere Besserung der pulmonalen Hämodynamik und der körperlichen Belastbarkeit für die Patienten durch die zusätzliche interventionelle Behandlung zu erreichen, was für Synergie-Effekte der beiden Therapiemodalitäten spricht.

4.2 Multimodale Therapie der operablen CTEPH

Wie bereits beschrieben, war die CTEPH lange Zeit eine rein chirurgisch behandelte

Erkrankung (39). Ziel der PEA ist eine akute Nachlastsenkung des rechten Ventrikels durch eine möglichst vollständige Desobliteration der Pulmonalarterien. Dies ist insofern bedeutsam, als dass die Letalität mit dem postoperativen PVR korreliert (22). Dabei bedeutet ein postoperativer PVR > 6,25 WU eine Mortalitätsrate von 30,6 % im Gegensatz zu 0,9 % bei Werten darunter (64). Dies sollte stets bei der Risikobewertung eines CTEPH Patienten und der Indikationsstellung zur PEA bedacht werden. Selten finden sich Patienten mit einseitig „noch“ operablen, auf der Gegenseite jedoch weit peripher gelegenen Veränderungen (siehe **Abbildung 23**) und gleichzeitig bestehender schwerer PH.

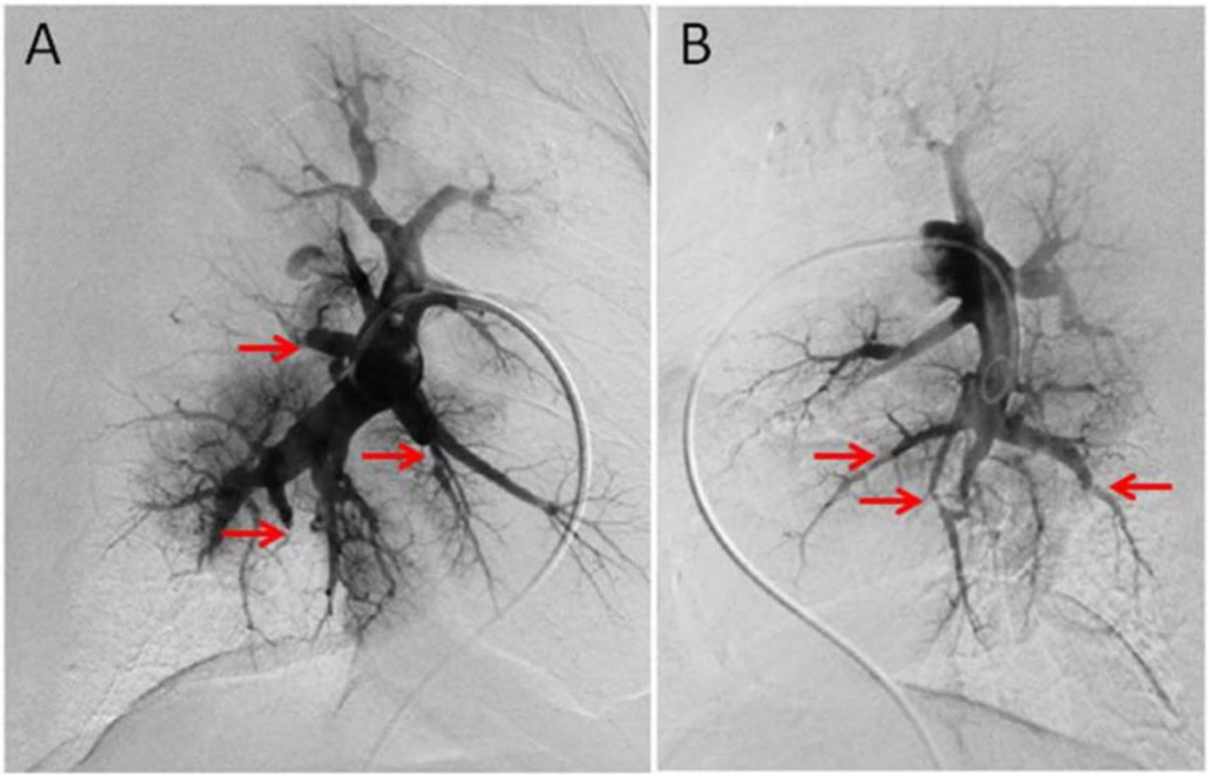

Abbildung 23: Pulmonalis-Angiographie eines 58-jährigen Patienten mit schwerer PH (PAPm 64 mmHg, PVR 10,65 WU). A zeigt die rechte Lungenarterie, B die linke Seite jeweils in 90° lateraler Projektion. Pfeilmarkiert einzelne stenosierte bzw. verschlossene Pulmonalarterienäste. Man erkennt linksseitig die weiter periphere Lokalisation der Läsionen.

Entsprechend der Erfahrung aus dem PEA Programm der Kerckhoff-Klinik findet sich bei der Operation häufig mehr obstruierendes Material, als entsprechend der bildgebenden Befunde (Pulmonalis-Angiographie und CT) zu vermuten war. Zudem kann häufig in einer zwar dünnen, aber stabilen Schicht präpariert werden, so dass auch weit peripher gelegenes Material zu entfernen ist. Entsprechend kann die PEA auch im oben beschriebenen Patientengut eine kurative Therapieoption sein. Die Unmöglichkeit der Desobliteration auf einer Seite würde jedoch hochwahrscheinlich zu einer unzureichenden Senkung der rechtsventrikulären Nachlast, entsprechend zum Fortbestehen einer schweren PH, zum akuten Rechtsherzversagen und damit zum Tod des Patienten führen. Nicht zuletzt auch aufgrund der wachsenden Erfahrung mit der BPA, wurde daher eine Kombination von PEA und, bei

Unmöglichkeit der chirurgischen Desobliteration einer Seite, intraoperativer BPA zur größtmöglichen Nachlastsenkung des rechten Ventrikels erwogen. Dies war Inhalt der siebten Publikation.

Dabei wurden die Verläufe von CTEPH Patienten zusammengefasst, die weltweit erstmalig intraoperativ zusätzlich interventionell behandelt wurden. **Abbildung 24** zeigt das Endarteriektomie-Präparat eines dieser Patienten. Man erkennt zahlreiche

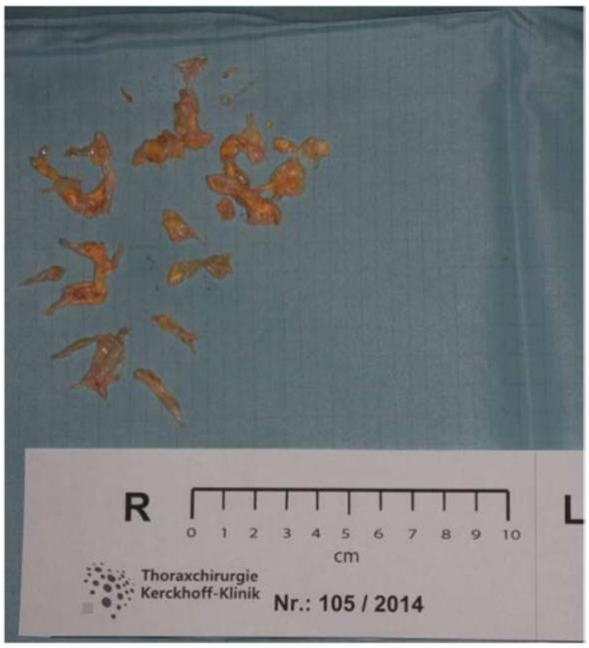

Abbildung 24: Endarteriektomie-Präparat des unter Abbildung 19 gezeigten Patienten. Es finden sich rein segmental-/subsegmentale Bindegewebszylinder aus der rechtsseitigen Lungenstrombahn. Linksseitig konnte kein Material entfernt werden.

Bindegewebszylinder, die aus Segment- und Subsegmentarterien entfernt wurden. Linksseitig konnte jedoch kein obstruierendes Gewebe entfernt werden. In enger interdisziplinärer Zusammenarbeit mit den in der BPA erfahrenen interventionell tätigen Radiologen und Kardiologen erfolgte unmittelbar die interventionelle Behandlung der wichtigsten linksseitigen Zielgebiete. Dies geschah während der Aufwärmphase, also bei bestehender extrakorporaler Zirkulation. Entsprechend konnten die Flussverhältnisse in der Lungenstrombahn an die Bedürfnisse des Interventionsteams angepasst werden (z. B. ausreichender Kontrastmittelfluss in den Subsegmentarterien). Ebenso wurden die Lungengefäße in ihrem Verlauf möglichst gestreckt durch Etablierung eines inspiratory hold durch den Anaesthesisten. Zugang war die zentrale Lungenarterie noch in ihrem intraperikardialen Verlauf. Ansonsten erfolgte die Intervention wie bereits beschrieben (siehe **Abbildung 25**).

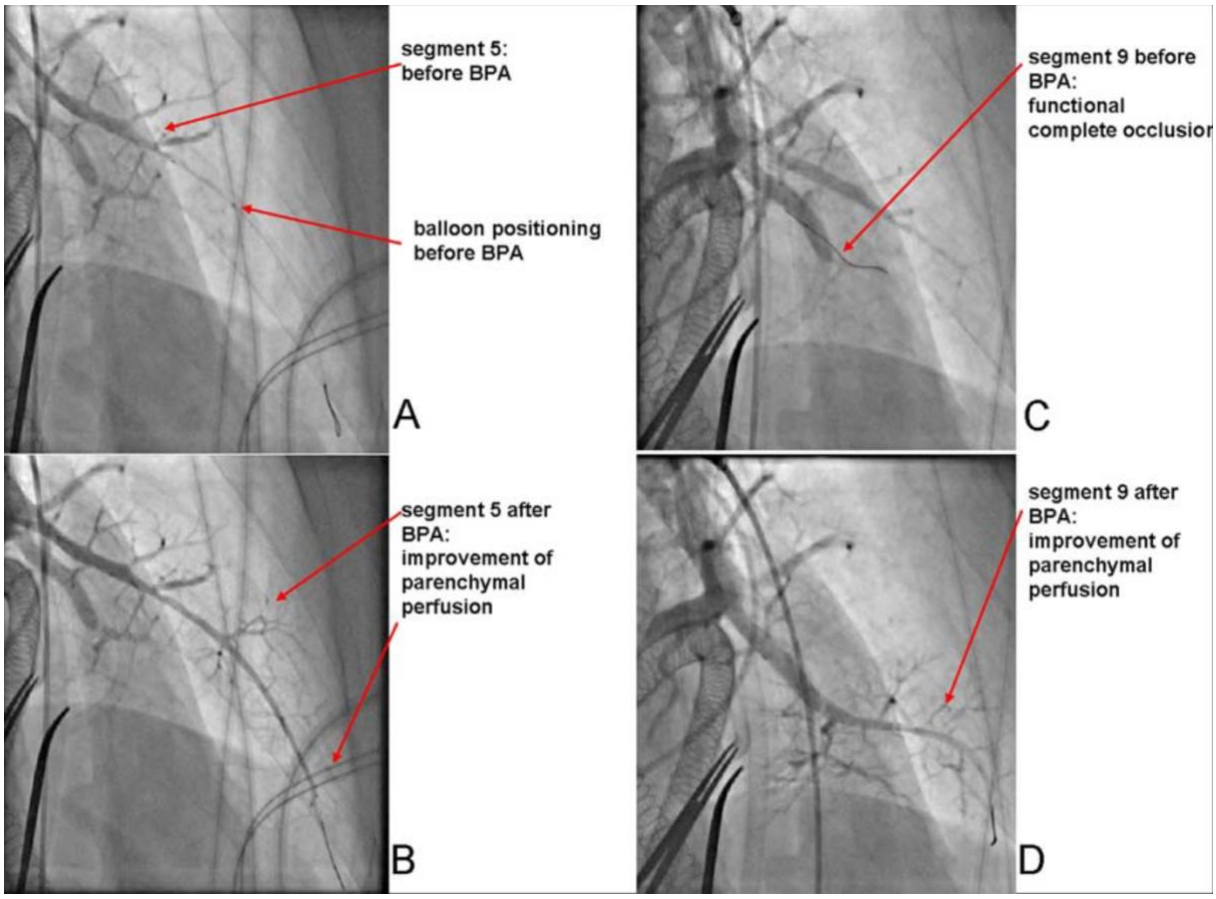

Abbildung 25: Intraoperative BPA der Segmente 5 und 9 links. Im Segment 5 findet sich vor der Intervention nur ein geringer antegrader Fluss mit schwacher Parenchymperfusion (A), nach der BPA deutliche Befundbesserung (B). In Segment 9 erkennt man einen Gefäßverschluss (C), der interventionell wiedereröffnet werden konnte (D). Man erkennt zudem jeweils am linken Bildrand die Aortenkanüle sowie zwei Klemmchen, die zur Befestigung der Kanüle dienen.

Abbildung 26 fasst die wesentlichen hämodynamischen Parameter vor dem Eingriff und am ersten postoperativen Tag sowie die WHO Funktionsklasse vor und 6 bis 10 Monate nach der Prozedur zusammen. Es konnte eine deutliche Besserung sowohl der pulmonalen Hämodynamik als auch der körperlichen Belastbarkeit erreicht werden. Dabei trat bei allen Patienten im postoperativen Verlauf ein Reperfusionsödem auf, welches bei zwei Patienten mittels nicht-invasiver Beatmung und Diuretikagabe behandelt werden konnte. Zudem kam es in zwei Patienten zu Vorhofflimmern, welches medikamentös in einen stabilen Sinusrhythmus konvertiert wurde. Weitere Komplikationen traten nicht auf.

	Mean PAP (mm Hg)		PVR (dyne · sec/cm^5)			WHO Functional Class	
Patient	Pre	Post	Pre	Post	Δ-PVR	Pre	Post (months)
1	65	38	1,600	605	995	4	2 (10)
2	65	45	1,630	601	1,029	3	1 (9)
3	64	30	852	350	502	4	1 (6)

Abbildung 26: Zusammenfassung der pulmonalarteriellen Mitteldrücke und des PVR unmittelbar vor dem Eingriff und am ersten postoperativen Tag. Zudem Darstellung der WHO Funktionsklasse vor und 6 bis 10 Monate nach der Prozedur.

4.2.1 Schlussfolgerung

Es konnte gezeigt werden, dass die Kombination aus PEA und BPA in einer Sitzung bei hochselektionierten Patienten sicher und machbar ist. Dieses komplexe Verfahren konnte in enger interdisziplinärer Zusammenarbeit etabliert und ohne Sterblichkeit eingesetzt werden. Die kurz- bis mittelfristigen Ergebnisse waren sehr gut.

5. Diskussion

Die gegenwärtige Behandlung der CTEPH fußt auf drei verschiedenen Modalitäten (pulmonale Endarteriektomie (PEA), gezielte medikamentöse Therapie und pulmonale Ballonangioplastie (BPA)), wobei die Therapiestrategie maßgeblich von der exakten Lokalisation der pulmonalarteriellen Läsionen abhängt. Wie bereits beschrieben, war die CTEPH lange Zeit eine rein chirurgisch behandelte Erkrankung, wobei das Resultat der Operation als kurativ gewertet wurde (39). Die zunehmende Wahrnehmung des Krankheitsbildes führte zu einer wachsenden Zahl an Patienten in den etablierten CTEPH-Zentren. Dazu kam die Verbesserung der bildgebenden Darstellung, so dass auch periphere, chirurgisch nicht erreichbare Veränderungen als CTEPH erkannt wurden. Parallel hierzu kam es, nicht zuletzt infolge mangelnder chirurgischer Expertise, zu einer Weiterentwicklung der interventionellen Therapie insbesondere in japanischen Zentren (33, 34). Fast zeitglich wurden auch die gezielte medikamentöse Therapie für inoperable CTEPH Patienten etabliert (28, 60, 61). Da die CTEPH im Spontanverlauf eine sehr ungünstige Prognose aufweist (10), änderte sich die fast ausschließlich chirurgisch ausgerichtete Sichtweise in den führenden westlichen CTEPH Zentren, was sich auch an den Veränderungen der Therapiealgorithmen der Weltkonferenz, der europäischen Leitlinie und den Empfehlungen der Kölner Konsensuskonferenz im Verlauf ablesen lässt (12-14, 19, 20).

Nicht zuletzt mit den Daten des internationalen CTEPH-Registers von 2011 wurde klar, dass für etwa ein Drittel aller CTEPH Patienten eine andere, nicht-chirurgische Behandlungsstrategie notwendig ist, da eine PEA üblicherweise aufgrund einer zu peripheren Lokalisation der pulmonalarteriellen Läsionen nicht in Frage kommt (15). Diese Rate an inoperablen Patienten konnte mit der ersten dieser Arbeit zugrundeliegenden Publikation auch für Deutschland bestätigt werden. Dies unterstreicht die Notwendigkeit einer Wiedereinführung der BPA in Deutschland zum damaligen Zeitpunkt.

Wie in der zweiten Publikation gezeigt, erscheinen die Ergebnisse der BPA insbesondere im Hinblick auf die pulmonale Hämodynamik in Deutschland weniger effektiv als in den japanischen Zentren (33-35), allerdings gut vergleichbar mit den Berichten aus anderen europäischen Einheiten (36, 67). Die Unterschiede lassen sich einerseits durch die bis heute fehlende Vereinheitlichung der Indikationsstellung zur BPA wie auch der Zielsetzung der Intervention, der technischen Durchführung und des Umganges mit der gezielten medikamentösen Therapie erklären (68).

Andererseits bestehen teils erhebliche Unterschiede in den Patientengruppen: so ist beispielsweise der Anteil weiblicher Patienten in den japanischen CTEPH Kohorten überproportional hoch (33-35), in bislang nicht veröffentlichten Registerdaten bei > 80 %, während das Geschlechterverhältnis in europäischen und nordamerikanischen CTEPH-Kohorten üblicherweise ausgeglichen ist (15).

Eine weitere Schwierigkeit stellt die langfristige Betreuung dieser chronisch kranken Patienten dar. Wird bei operablen Patienten eine invasive Kontrolle nach 6-12 Monaten empfohlen (13, 14), so bleibt ein Nachsorgekonzept bei inoperablen, interventionell behandelten Patienten bislang unklar. Aus diesem Grund war Inhalt der dritten und vierten Publikation die Etablierung von Biomarkern für die Beurteilung ebendieser Patienten. Vor dem Hintergrund der langfristigen Kontrolle von Patienten mit pulmonalarterieller Hypertonie (12) erschien insbesondere das NT-pro-BNP vielversprechend. Als weiteren Biomarker konnte in unserer Arbeitsgruppe auch das hochsensitive kardiale Troponin T etabliert werden (69). Im MRT war zudem der Nachweis der Korrelation der nativen T1 Zeiten mit der pulmonalen Hämodynamik in der Etablierung der nicht-invasiven Verlaufskontrolle wichtig. Bereits zuvor beschäftigte sich unsere Arbeitsgruppe mit dem Nachweis von unter Therapie rückläufigen Fibrosierungsarealen im interventrikulären Septum in inoperablen CTEPH Patienten vor und nach BPA (70) sowie Veränderungen im MRT vor und nach PEA bei operabler CTEPH (71, 72).

Neben der klar definierten CTEPH gibt es eine Gruppe von Patienten, die ebenfalls aufgrund von thrombembolischen Residuen Symptome, aber keine PH in Ruhe aufweisen. Entsprechend der letzten Weltkonferenz für PH von 2018 werden mittlerweile eine Untersuchung der pulmonalen Hämodynamik unter Belastung (PAPm/CO-slope > 3,0 WU), wie auch Befunde in der Spiroergometrie („Excluding ventilatory limitation, deconditioning“) und in der Echokardiographie („Excluding left ventricular myocardial or valvular disease“) gefordert, um die Diagnose einer chronisch thromboembolischen Erkrankung (CTED) zu verifizieren (20, **Abbildung 27**).

Diagnostic criteria	CTEPH	CTED
Symptoms	Exercise dyspnoea	Exercise dyspnoea
PH	*Present at rest*	*Absent at rest*
RHC at exercise		*mPAP/CO slope >3 mmHg·L^{-1}·min^{-1}*
***V/Q* scan**	Any mismatched perfusion defect	Any mismatched perfusion defect
Angiography (CTPA or DSA)	Typical findings of CTEPH	Typical findings of CTEPH
CPET		*Excluding ventilatory limitation, deconditioning*
TTE		*Excluding left ventricular myocardial or valvular disease*
Anticoagulation	At least 3 months	At least 3 months

Abbildung 27: Übersicht der zur Diagnosestellung benötigten Kriterien entsprechend der Empfehlung der Weltkonferenz für pulmonale Hypertonie von 2018 (20). Bei CTEPH werden neben einer symptomatischen PH in Ruhe ein Missverhältnis zwischen gestörter Perfusion und normaler Ventilation in der Lungenszintigraphie und/oder pulmonalarterielle Läsionen in den bildgebenden Verfahren (CT oder Pulmonalis-Angiographie) gefordert. Die Befunde dürfen dabei erst nach einer mindestens dreimonatigen Phase von effektiver Antikoagulation erhoben werden. Bei CTED findet sich keine PH in Ruhe. Hier werden daher eine Erhöhung des PAPm/CO-slope > 3,0 WU sowie der Ausschluss auf andere Erkrankungen hinweisender Befunde in der Spiroergometrie und der Echokardiographie gefordert. Dies ebenfalls nach dreimonatiger Antikoagulation.

Die CTED wird im klinischen Alltag ähnlich wie die CTEPH behandelt, d. h. überwiegend chirurgisch (21, 57, 58). Allerdings finden sich auch hier Patienten mit sehr peripheren pulmonalarteriellen Läsionen, die einer Operation nicht zugänglich sind. Eine gezielte medikamentöse Therapie ist für diese Patientengruppe nicht etabliert. Daher wurden mit der fünften Publikation die Ergebnisse einer interventionellen Therapie dieser inoperablen CTED Patienten untersucht. Zum Zeitpunkt der Studie wurde die CTED jedoch noch ohne die erwähnten Veränderungen der pulmonalen Hämodynamik definiert. Eine wichtige Einschränkung der Studie war daher das Fehlen von Belastungs-RHK-Daten. Dies erschwert den Vergleich mit in der Kerckhoff-Klinik operierten CTED Patienten (73), von denen postoperativ fast alle einen PAPm/CO-slope < 3,0 WU aufwiesen. Es konnte allerdings ein deutlicher Zugewinn an körperlicher Belastbarkeit bei einer sehr niedrigen Rate von Komplikationen nachgewiesen werden. Damit scheint die BPA ein sicheres und sinnvolles Therapiekonzept für inoperable CTED Patienten zu sein.

In den bisher vorgestellten (zugrundeliegenden) Publikationen wurden stets Befunde verglichen, die unmittelbar vor der ersten BPA (d. h. bei vorbehandelten Patienten unter mindestens 3 Monate laufender gezielter medikamentöser Therapie) und 6 Monate nach der letzten Intervention erhoben wurden. Inhalt der sechsten Publikation war, die inzwischen vorliegende Empfehlung der Leitlinie (20) nachzuzeichnen: so wurden therapienaive Patienten für mindestens 3 Monate mit Riociguat behandelt und nach erneuter Evaluation in das BPA Programm eingeschlossen. Hierbei konnten die Ergebnisse der zulassungsrelevanten Studie der medikamentösen Therapie mit Riociguat bestätigt werden (28). Darüber hinaus zeigten sich ausgeprägte additive Effekte der sequentiell durchgeführten BPA. Die Medikation blieb bis zur 6-Monats-Kontrolle unverändert. Die Studie weist verschiedene Einschränkungen auf: monozentrisch und nicht verblindet und nicht

placebo-kontrolliert angelegt, ist die Aussagekraft eingeschränkt. Auch kann die für die langfristige Behandlung dieser Patienten die wichtige Frage der Dauer der gezielten medikamentösen Therapie mit den vorhandenen Daten nicht beantwortet werden. Allerdings erscheint auch vor dem Hintergrund der Belastungs-RHK Daten dieser Patienten eine dauerhafte Fortsetzung der Medikation ratsam. In Zusammenschau der hier vorgestellten Arbeiten und der zunehmenden Zahl an Publikationen bleibt die Evidenz der BPA insbesondere bei Fehlen von validen Langzeitdaten und kontrollierten, randomisierten Studien begrenzt.

Im Hinblick auf operable CTEPH galten mögliche Kombinationen der PEA mit den beiden anderen Therapiemodalitäten lange als obsolet. Insbesondere der Einsatz der gezielten medikamentösen Therapie vor einer möglichen Operation sollte vermieden werden, um die Zeit bis zur kurativen Behandlung nicht zu verzögern und damit wiederum der Entwicklung einer sekundären Mikrovaskulopathie entgegenzuwirken. In internationalen Registerdaten war eine medikamentöse Vorbehandlung vor PEA sogar ein unabhängiger Prädiktor für ein schlechteres Outcome (23). Inzwischen wird jedoch bei schwerstkranken, operablen CTEPH Patienten eine präoperative Riociguat-Gabe in einer Placebo-kontrollierten Studie erprobt (NCT03273257). Rationale hierfür ist wiederum die Beeinflussung der sekundären Mikrovaskulopathie. Dies erscheint vor dem Hintergrund der Arbeit von Cannon und Kollegen mit einer Rate von 51 % von Patienten mit residueller PH nach PEA (definiert als PAPm ≥ 25 mmHg) besonders interessant. Bemerkenswert ist, dass nur in 5 der eingeschlossenen 880 Patienten die Entwicklung einer rekurrenten PH nach PEA nachgewiesen wurde, meist in Form einer erneuten CTEPH nach Lungenembolie. Als prognostisch relevant wurde eine bereits schwere Einschränkung der pulmonalen Hämodynamik beschrieben (PAPm > 38 mmHg; PVR > 5,3 WU) (24). Die BPA setzt wiederum, wie die PEA, an den endoluminalen Veränderungen an. Auch dieses Verfahren wurde mittlerweile bei Patienten mit residueller bzw. rezidivierender PH nach PEA eingesetzt, wobei die Datenlage hierzu noch sehr überschaubar ist (65, 66). Dabei wurde die BPA im Langzeitverlauf nach der Operation eingesetzt.

Ein hierzu sehr unterschiedliches Konzept war Inhalt der siebten Publikation. Ein grundlegendes Ziel der Operation ist die möglichst ausgeprägte Senkung der Nachlast des rechten Ventrikels durch eine möglichst vollständige Desobliteration der Lungenarterien. Bei Patienten mit einseitig klar operablem Befund, gegenseitig jedoch ausschließlich peripherem Befallsmuster und gleichzeitig bestehender schwerer PH ist die Festlegung eines Behandlungskonzeptes eine Herausforderung.

Einerseits ist entsprechend der chirurgischen Erfahrung bekannt, dass sich häufig eine stabile, wenn auch dünne Endarteriektomieschicht in den zentralen Gefäßabschnitten entwickeln lässt, die eine Desobliteration auch weit peripher gelegener Läsionen ermöglicht. Andererseits würde die Unmöglichkeit der vollständigen Desobliteration das Sterblichkeitsrisiko in dieser besonderen Patientengruppe deutlich erhöhen. Die Entscheidung gegen ein operatives Vorgehen bedeutet umgekehrt jedoch auch eine Abkehr von einem potentiell kurativen Ansatz. Aus diesem Grund wurde die PEA mit der Möglichkeit einer intraoperativen BPA durchgeführt. Publiziert wurden die ersten drei dieserart behandelten Patienten. Inzwischen wurden fast 20 dieser als Hybrid-Eingriff geplanten Prozeduren durchgeführt, wobei die BPA bei 9 Patienten notwendig wurde. Dies bedeutet, dass eine vollständige chirurgische Desobliteration in etwa 50 % der Patienten möglich war. Damit führte die Etablierung des Hybrid-Konzeptes auch zu einer Erweiterung der Indikation der PEA in hochselektionierten Patienten.

In den dieser Habilitationsschrift zugrundeliegenden Publikationen wurde nach Darstellung der chirurgischen CTEPH-Behandlung in Deutschland und den Ergebnissen der PEA im eigenen Zentrum einerseits die BPA als mögliche Therapie inoperabler CTEPH Patienten, andererseits verschiedene Möglichkeiten der Kombination der drei Therapiemodalitäten untersucht. Hierbei ist herauszustreichen, dass die Behandlung der CTEPH aufgrund der Komplexität der Diagnostik und Therapie nur durch ein entsprechend erfahrenes und interdisziplinäres Team erfolgen kann: eine enge Zusammenarbeit von PH-erfahrenen Pneumologen und Anästhesisten/Intensivmedizinern, interventionell tätigen Radiologen und Kardiologen sowie PEA-erfahrenen Chirurgen ist Grundvoraussetzung. Die Festlegung des therapeutischen Konzeptes, auch im Verlauf dieser chronischen Erkrankung, erfolgt im Idealfall im Rahmen einer multidisziplinären CTEPH-Konferenz. Die Leitlinien geben hier eine gute Orientierung, wobei die Entscheidung im Einzelfall sehr komplex sein kann.

Die CTEPH bietet in allen Aspekten weiterhin ein spannendes Forschungsgebiet: die Pathogenese, aber auch pathophysiologische Veränderungen im Verlauf der Erkrankung sind nicht vollständig verstanden. Zudem entwickelt sich auch die zugrundeliegende Diagnostik weiter. Insbesondere wird ein langfristiges Betreuungskonzept für diese Patienten benötigt, um einerseits eine mögliche residuelle oder rekurrente PH nach erfolgter PEA zu diagnostizieren und zu

behandeln, aber auch um eine langfristige Versorgung der inoperablen und heutzutage meist kombiniert medikamentös und interventionell behandelten Patienten sicherzustellen. Die allein in den letzten Jahren dramatische Entwicklung der drei Therapiemodalitäten bedeutet auch in dieser Hinsicht die Notwendigkeit weiterer Studien. Insbesondere multimodale Ansätze für die langfristige Behandlung der CTEPH bedürfen einer eingehenden Untersuchung.

6. Zusammenfassende Darstellung

Zur Behandlung der chronisch thromboembolischen pulmonalen Hypertonie (CTEPH) stehen drei Therapiemodalitäten zur Verfügung: etwa 2/3 der Patienten werden mit der pulmonalen Endarteriektomie (PEA) potentiell kurativ versorgt. Die inoperablen Patienten werden gezielt medikamentös mit Riociguat behandelt, mit oder ohne zusätzliche pulmonale Ballonangioplastie (BPA). Weltweit konzentriert sich die Behandlung der CTEPH auf einzelne spezialisierte Zentren. In Deutschland findet sich das größte CTEPH Programm an der Kerckhoff-Klinik. Die PEA wird dort mit vergleichsweise niedrigen Sterblichkeitszahlen durchgeführt. Daneben konnte mit der BPA ein interventionelles Verfahren etabliert werden, dessen kurz- bis mittelfristige Ergebnisse denen der anderen europäischen Zentren ähneln. Mit dem NT-pro-BNP und der Magnetresonanztomographie (MRT) wurden nicht-invasive Methoden zur Verlaufsbeurteilung etabliert. Auch wurde die BPA erfolgreich bei Patienten mit inoperabler chronisch thromboembolischer Erkrankung (CTED) eingesetzt.

Darüber hinaus wurden multimodale Therapiekonzepte für inoperable und operable CTEPH Patienten etabliert: einerseits die Kombination von gezielter medikamentöser Therapie und BPA, wobei sich deutliche additive Effekte der interventionellen Therapie fanden. Andererseits wurde die PEA erfolgreich mit der BPA verknüpft, um hochselektionierte Patienten mit schwerer CTEPH zu behandeln.

Aufgrund der Komplexität des Krankheitsbildes und der möglichen Therapien ist die Behandlung in einem entsprechend erfahrenen, interdisziplinären Team Grundvoraussetzung für eine möglichst optimale Versorgung dieser Patienten.

7. Abkürzungsverzeichnis

6MWD	6-Minuten-Gehstrecke
BPA	pulmonale Ballonangioplastie
CT	Computertomographie
CTED	chronisch thromboembolische Erkrankung
CTEPH	chronisch thromboembolische pulmonale Hypertonie
HZV	Herzzeit-Volumen
MRT	Magnetresonanztomographie
NT-pro-BNP	N-terminales pro-brain natriuretic peptide
PAPm	mittlerer pulmonalarterieller Druck
PAWP	pulmonalarterieller Verschlußdruck
PEA	pulmonale Endarteriektomie
PH	pulmonale Hypertonie
PVR	pulmonal vaskulärer Widerstand
RHK	Rechtsherzkatheter

V/P SPECT	ventilation/perfusion single photon emission computed tomography

8. Abbildungsverzeichnis

	Hauptsubsegmente eingebracht und die Bifurkation wird mit 2 Ballons gleichzeitig („kissing balloon“ Technik) aufgedehnt. Anschließend zeigt sich eine deutlich gebesserte Parenchymperfusion mit raschem venösem Rückstrom.	
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11. Zugrundeliegende Publikationen

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The Journal of Heart and Lung Transplantation
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ORIGINAL CLINICAL SCIENCE

Pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension

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KEYWORDS:
chronic thromboembolic pulmonary hypertension;
pulmonary endarterectomy;
balloon pulmonary angioplasty;
non–vitamin K–dependent oral anticoagulants;
prognosis

BACKGROUND: Management and outcome of patients with operable chronic thromboembolic pulmonary hypertension (CTEPH) who underwent pulmonary endarterectomy (PEA) at a large German referral center were investigated.

METHODS: In Germany, 394 PEAs were performed in 2014 and 2015 with an in-hospital mortality rate of 5.8%. Of these, 253 patients (64.2%) were treated at the Kerckhoff Clinic, Bad Nauheim, and 237 (93.7%; median age, 62 years [interquartile range [IQR], 52–72 years]; 46.0% female) were included in the present analysis.

RESULTS: On referral, 52 patients (22.0%) were treated with pulmonary arterial hypertension–specific drugs and 95 (40.4%) were treated with non–vitamin K–dependent oral anticoagulants, and 14 (5.9%) had mean pulmonary artery pressure <25 mm Hg and were classified as having chronic thromboembolic pulmonary vascular disease. PEA was feasible in 236 (99.6%) patients with median duration of surgery of 397 minutes (IQR, 363–431 minutes). Periprocedural (0%) and in-hospital (2.5%) mortality rates were very low. Forty-two patients (17.7%) had intraoperative complications, and 60 (25.3%) had post-operative complications. The duration of surgery was the only predictor of in-hospital mortality (≥ 500 minutes; odds ratio [OR], 32.0; 95% confidence interval [CI], 5.5–187.6) and the only independent predictor of intraoperative (≥ 440 minutes; OR, 10.8; 95% CI, 4.4–26.5) and post-operative (≥ 390 minutes; OR, 2.4; 95%CI, 1.1–5.7) complications. Only intraoperative complications independently predicted a longer duration of surgery (≥ 397 minutes; OR, 5.0; 95% CI, 2.2–11.2).

CONCLUSIONS: In an experienced center with multidisciplinary diagnostic and therapeutic approaches, PEA is safe. Prognosis was mainly determined by occurrence of intraoperative complications and duration of surgery rather than patients' pre-operative status.

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct form of pulmonary hypertension (PH), constituting group 4 of the clinical classification of PH.[1] The disease is characterized by fibrotic obstructions and occlusions of pulmonary arteries combined with a

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remodeling of the non-occluded, hyperperfused pulmonary vessel, similar to that observed in pulmonary arterial hypertension (PAH).[2] Although the exact pathogenesis of CTEPH is not completely understood, it is believed to result from incomplete resolution of thrombi after pulmonary embolism.[3] The increase in pulmonary vascular resistance (PVR) and pulmonary artery (PA) pressure leads to the development of right ventricular dysfunction and failure.

Historical data indicate a poor prognosis for patients with CTEPH if the disease is left untreated, with mortality rates of 90% after 3 years in patients with a mean PA pressure >50 mm Hg.[4] As the surgical removal of the obstructive fibrous material by a true pulmonary endarterectomy (PEA) constitutes a potentially curative treatment option, PEA is recommended as the gold standard by current guidelines.[1,5–8] Although early diagnosis remains challenging owing to the lack of specific symptoms, it is increasingly being recognized that chronic thromboembolic disease, defined as typical morphologic changes without elevation of the mean PA pressure >25 mm Hg at rest,[1] represents an early stage of the disease[1,3] that may also be beneficially treated with PEA.[9] PEA is a technically complex procedure requiring cardiopulmonary bypass (CPB) and phases of circulatory arrest in deep hypothermia. Experienced, high-volume centers perform PEA with low mortality rates and significant improvement of hemodynamic parameters, functional capacity, symptoms, and quality of life.[10–15] Despite an increasing number of PEAs worldwide (studies of ≥ 100 operated patients are summarized in Table S1, available in the online version of this article at www.jhltonline.org), data on patients with CTEPH who underwent PEA in Germany are limited. Thus, in the present study, we investigated the clinical presentation, functional characteristics, surgical management, and complications of patients with CTEPH who underwent PEA at a large national surgical referral center in Germany.

Methods

All patients admitted to the Kerckhoff Clinic, Bad Nauheim, Germany, for scheduled PEA between January 2014 and December 2015 were considered eligible for inclusion in the present prospective, non-interventional cohort study. The Kerckhoff Clinic serves as a national referral center for PEA, with >100 PEA procedures performed per year. The diagnosis of CTEPH was established by the referring physician (in most cases at national PH expert centers) according to current guidelines.[16] Operability was evaluated in a multidisciplinary conference including thoracic surgeons, cardiologists, pulmonologists, radiologists, anesthesiologists, and intensive care specialists. For patients classified as non-operable, readjudication by consulting an external expert PEA center (UC San Diego Health, San Diego, CA) was considered. Patients finally classified as non-operable were treated with PAH-specific medication, and balloon pulmonary angioplasty (BPA) was offered if target lesions had been detected (Figure 1); patients who underwent BPA are reported elsewhere.[17]

At admission for scheduled PEA, patients were asked to participate in the study and to sign the informed consent form. Patients who declined participation in the study, patients with a diagnosis of pulmonary artery sarcoma, and patients with missing data were excluded from the study (Figure 1). The study was approved by the ethics committee of the Justus-Liebig-University Giessen (AZ 44/14) and is in accordance with the Declaration of Helsinki. All treatment decisions were made by the caring physician and were not influenced by the study protocol at any time. Baseline and in-hospital follow-up data were collected using a standardized case report form by interviewing the patient and reviewing the medical records.

PEA was performed as previously reported.[7,8] Briefly, after sternotomy, CPB was established, and circulatory arrest in deep hypothermia $\leq 20^{\circ}$C was induced to allow good visibility in a bloodless surgical field down to the subsegmental branches. True endarterectomy, including the intima layer and parts of the media, was performed with the aim of removing all obstructive material from the pulmonary arteries. In selected patients, a hybrid procedure combining PEA and BPA, as previously reported,[18] or additional surgical procedures (e.g., coronary artery bypass graft surgery or valve replacement) were performed. Post-operative hemodynamics were measured at the end of PEA immediately before the transfer of the patient to the intensive care unit.

Intraoperative and post-operative complications and the cause of death were independently adjudicated by 2 of the authors (M.L. and V.K.) with disagreement resolved by a third author (S.G.). Major intraoperative bleeding was defined as need for additional surgical interventions, such as additional vascular sewing, use of patches, or use of fibrin glue, or need for venovenous or venoarterial extracorporeal membrane oxygenation (ECMO). Major post-operative bleeding was defined according to Schulman et al[19] (the complete definition is provided in the supplementary data, available in the online version of this article at www.jhltonline.org). Survival status was assessed at least 6 months after PEA by contacting the responsible residents' registration office.

In Germany, diagnoses coded according to the *International Classification of Diseases, 10th Revision with German Modification* and surgical or interventional procedures with OPS

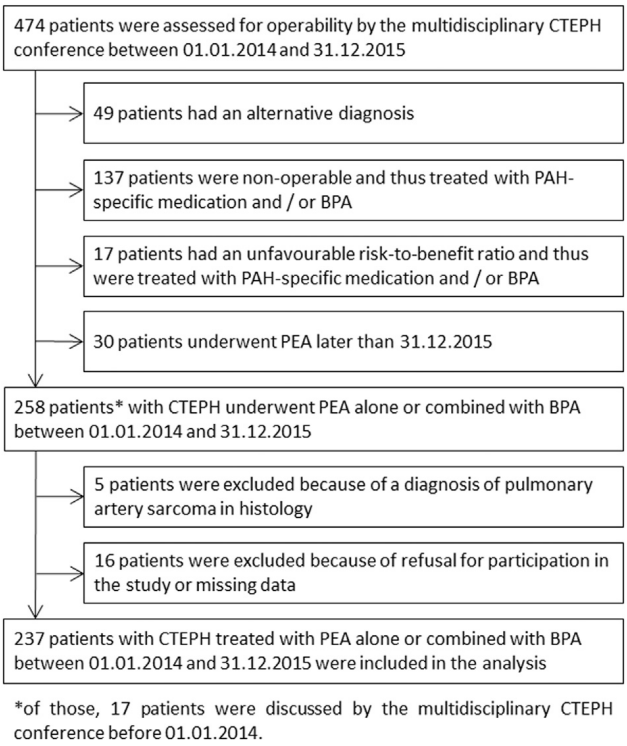

Figure 1 Study flowchart showing inclusion and exclusion criteria. BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.

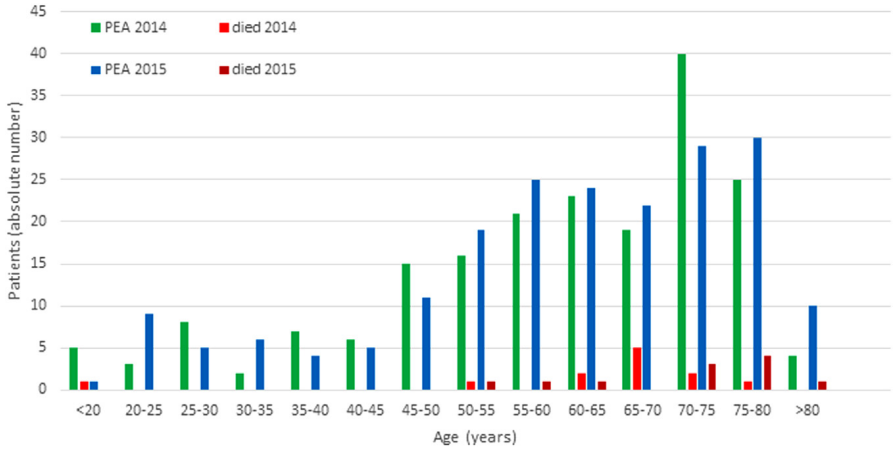

Figure 2 Absolute numbers of patients undergoing PEA (OPS number 5-381.42) and of in-hospital deaths in Germany in 2014 and 2015 as reported by the Federal Statistical Office of Germany (Statistisches Bundesamt).

(Operationen- und Prozedurenschlüssel) codes are collected in a national inpatient data resource (diagnosis-related groups data set) by the Federal Statistical Office of Germany (Statistisches Bundesamt). PEA is separately coded as OPS number 5-381.42. Information on the number, age, and in-hospital death of patients who underwent PEA in Germany in 2014 and 2015 was obtained from the Federal Statistical Office.

Statistical analysis

Categorical data are presented as numbers and percentages and were compared using Student's *t*-test or the chi-square test, as appropriate. Continuous data are presented as median with the corresponding interquartile range (IQR, 25th–75th percentile) and were compared using the Mann-Whitney *U* test or Wilcoxon test. To test the prognostic relevance of continuous variables with regard to intraoperative and post-operative complications and in-hospital death, receiver operating characteristic analyses were performed, and the area under the curve with corresponding 95% confidence interval (CI) was calculated. For variables associated with study outcomes, the optimal cutoff value was calculated using Youden index quantification. Categorical and dichotomous/dichotomized variables were included in univariable logistic and Cox regression analysis with calculation of odds ratio (OR) and hazard ratio, respectively, with corresponding 95% CI to assess their prognostic value with regard to study outcomes. Finally, variables identified as univariable predictors of outcomes, with data available for >80% of patients, were included in a multivariable logistic regression model using stepwise forward selection to identify independent predictors of intraoperative and post-operative complications. All statistical tests were 2-sided and used a significance level of 0.05. All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY).

Results

Patient cohort

Between January 1, 2014, and December 31, 2015, 253 patients with CTEPH underwent PEA (alone or in combination with BPA); 237 (93.7%) of these patients were included in the study (Figure 1). Patients excluded did not differ with regard to baseline characteristics, symptoms, functional status, medication, risk factors for CTEPH, comorbidities, and outcome (data not shown). Most of the patients (219 [92.4%]) were transferred to Bad Nauheim from centers in Germany, and 18 further patients were referred from other countries (6 patients from Switzerland; 3 from Greece; 3 from Russia; 2 from Austria; and 1 each from Belgium, Italy, United Arab Emirates, and Egypt). As reported by the Federal Statistical Office of Germany, 194 PEAs (OPS number 5-381.42) were performed in 2014, and 200 PEAs were performed in 2015 in Germany with in-hospital mortality rates of 6.2% and 5.5%, respectively (Figure 2). Thus, 64.2% of all PEAs in Germany were performed at the Kerckhoff Clinic.

The baseline characteristics, comorbidities, risk factors for CTEPH, symptoms, and functional status of the study patients are shown in Table 1. Although extreme overweight is still considered to be a relative contraindication for PEA, 61 patients (26.0%) had a body mass index >30 kg/m^2, 20 patients (8.5%) a body mass index >35 kg/m^2, and 30 patients (12.8%) had a body weight >100 kg. The median time from diagnosis of CTEPH to PEA was 129 days (IQR, 85–271 days), with a large range of 7 to 4,687 days; thus, 21 patients (8.9%) underwent PEA >2 years after the first diagnosis of CTEPH. In these cases, referral for PEA was prolonged mainly because of initial improvement of symptoms or functional limitations after initiation of PAH-specific treatment or refusal of surgery by the patient. At admission for scheduled PEA, most patients (72.2%) presented with symptoms they had had for >1 year. The predominant symptom was dyspnea (all but 1 patient [99.6%]), and 186 patients (78.5%) presented in New York Heart Association class III or IV. A 6-minute walk test was performed in 123 patients (51.9%), with a median distance walked of 387 m (IQR, 289–435 m). There were 93 patients (75.6%) with a walking distance of <440 m and 5 patients (4.1%) with a walking distance of <165 m. Transthoracic echocardiography (TTE) was performed in 229 patients (96.6%), and right heart catheterization (RHC) was performed in 233 patients (98.3%). Only the results of examinations performed <6 months before PEA (TTE, $n = 216$ [91.1%]; RHC, $n = 206$ [86.9%]) were considered suitable for analysis and are shown in Table 1. Echocardio-

Table 1 Baseline Characteristics, Comorbidities, and Risk Factors for CTEPH, Symptoms, and Functional Status of Patients With CTEPH Referred for PEA

	All study patients; $n = 237$
Age, years	62 (52–72); range, 18–84
Female sex	109 (46.0%)
BMI, kg/m^2	26.3 (23.8–30.4); range, 16.0–55.0; $n = 235$
Comorbidities and risk factors for CTEPH	
Active cancer[a]	6 (2.5%)
Chronic left heart failure	10 (4.2%); $n = 236$
Coronary artery disease	44 (18.6%)
Atrial fibrillation	25 (10.6%); $n = 236$
Diabetes mellitus	23 (9.7%)
Previous stroke	12 (5.1%)
Renal insufficiency[b]	63 (26.8%); $n = 235$
Anemia[c]	28 (11.9%); $n = 235$
Systemic inflammatory disease[d]	24 (10.1%)
Pulmonary disease	66 (27.9%)
Previous pulmonary embolism	203 (85.7%)
Thrombophilia[e]	46 (19.4%)
Previous splenectomy	10 (4.2%)
Hypothyroidism	43 (18.1%)
Symptoms at admission	
Symptom onset >1 year	169 (72.2%); $n = 234$
WHO function class I/II/III/IV	1 (0.4%)/51 (21.5%)/160 (67.5%)/25 (10.5%)
Dyspnea NYHA I/II/III/IV	1 (0.4%)/50 (21.1%)/160 (67.5%)/26 (11.0%)
Cough	50 (23.5%); $n = 213$
Hemoptysis	10 (4.7%); $n = 212$
Cyanosis/LTOT	34 (16.0%); $n = 212$/71 (35.1%); $n = 202$
Fatigue	40 (18.6%); $n = 215$
Chest pain	26 (12.1%); $n = 214$
Syncope at exercise/at rest	20 (9.4%); $n = 213$/10 (4.7%); $n = 214$
Peripheral edema	82 (38.7%); $n = 212$
TTE; $n = 216$	
Peak tricuspid regurgitation velocity, m/sec	4.2 (3.8–4.5); $n = 133$
>2.8 m/sec	126 (94.7%)
Estimated systolic PA pressure, mm Hg	82 (68–96); $n = 132$
RV dilatation	160 (76.2%); $n = 210$
D-sign	130 (62.8%); $n = 207$
TAPSE, mm	18 (14–22); $n = 183$
<16 mm	52 (28.4%)
RA area, cm^2	22.9 (16.6–31.2); $n = 160$
>18 cm^2	114 (94.7%)
LVEF $<60\%$	10 (5.8%); $n = 171$
Pericardial effusion	18 (8.6%); $n = 210$
RHC; $n = 206$	
Systolic PA pressure, mm Hg	74 (60–87); range, 21–125; $n = 168$
Mean PA pressure, mm Hg	43 (34–50); range, 13–73
PAWP, mm Hg	10 (8–13); range, 1–40; $n = 195$
PVR, Wood units	7.2 (5.0–10.3); range, 0.5–22.8; $n = 197$
Cardiac output, liters/min	4.5 (3.6–5.5); range, 2.0–9.2; $n = 197$
Cardiac index, liters/min/m^2	2.3 (1.9–2.7); range, 1.0–5.0; $n = 196$
Laboratory biomarkers	
NT-proBNP, ng/liter	792 (195–2,271); range, 13–27,617; $n = 200$
≥ 750 ng/liter	102 (51.0%)

"$n =$" refers to number of patients with data available; data are shown as median (interquartile range) or number (percentage).

BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; LTOT, long-term oxygen therapy; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RA, right atrium; RHC, right heart catheterization; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; WHO, World Health Organization.

[a]Defined as active or under treatment for the last 6 months.

[b]Defined as glomerular filtration rate <60 ml/min/1.73 m^2 (only 4 patients had a glomerular filtration rate <30 ml/min/1.73 m^2).

[c]Defined as hemoglobin concentration <13 g/dl in male patients and <12 g/dl in female patients.

[d]Defined as inflammatory bowel disease (e.g., ulcerative colitis or Crohn disease), rheumatic disorder (e.g., systemic lupus erythematosus, connective tissue disease, or vasculitis), or chronic systemic infections (e.g., owing to immunosuppressive therapy).

[e]Defined as antiphospholipid syndrome, heterozygous or homozygous factor V Leiden mutation, heterozygous or homozygous prothrombin mutation, or protein S or C deficiency.

Table 2 Medication of Patients With CTEPH Referred for PEA

	At admission: all study patients; $n = 237$	At discharge: survivors; $n = 231$
Therapeutic anticoagulation	235 (100%); $n = 235$	231 (100%)
Vitamin K antagonist	128 (54.5%)	119 (51.5%)
Rivaroxaban	90 (38.3%)	100 (43.3%)
Apixaban	2 (0.9%)	2 (0.9%)
Edoxaban	0	0
Dabigatran	3 (1.3%)	1 (0.4%)
Low-molecular-weight heparin	12 (5.1%)	9 (3.9%)
PAH-specific drugs	52 (22.0%); $n = 236$	2 (0.9%)
Riociguat	19 (8.1%)	1 (0.4%)
Sildenafil	23 (9.8%)	1 (0.4%)
Tadalafil	5 (2.1%)	0
Bosentan	10 (4.2%)	0
Macitentan	4 (1.7%)	0
Ambrisentan	3 (1.3%)	0
Prostacyclin	4 (1.7%)	0

CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy.

graphic signs of right ventricular dysfunction were present in most patients. Fourteen patients (6.8%) had a mean PA pressure <25 mm Hg in RHC and were classified as having chronic thromboembolic disease (details are provided in the supplementary data, available in the online version of this article at www.jhltonline.org).

As shown in detail in Table 2, all patients were receiving anti-coagulation therapy on referral (95 patients [40.4%] received non–vitamin K–dependent oral anticoagulants [NOACs]), and 10 patients (4.3%, $n = 235$) were treated additionally with acetylsalicylic acid. Fifty-two patients (22.0%, $n = 236$) were treated with PAH-specific drugs (e.g., phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, prostacyclins, or soluble guanylate cyclase stimulators); 19 (36.5%) of these patients were treated with riociguat, and 14 (26.9%) received combination therapy. Patients on PAH-specific drugs had a longer median time from CTEPH diagnosis to PEA (314 days [IQR, 117–825 days] vs 120 days [IQR, 76–187 days]; $p < 0.001$), a higher median mean PA pressure (47 mm Hg [IQR, 39–52 mm Hg] vs 42 mm Hg [IQR, 32–50 mm Hg]; $p = 0.049$), and a higher median PVR (8.6 Wood units [IQR, 6.0–12.0 Wood units] vs 6.8 Wood units [IQR, 4.8–9.8 Wood units]; $p = 0.041$) than patients without PAH-specific treatment.

Success rates and outcome after PEA

PEA was surgically (technical) feasible in 236 patients (99.6%). In 1 patient, PEA was impossible owing to a difficult thoracic access caused by injuries as a result of a serious traffic accident. Four patients (1.7%) were treated additionally with BPA (hybrid procedure), and 19 patients (8.0%) underwent additional surgical procedures (e.g., coronary artery bypass graft surgery, valve replacement). The median duration of surgery was 397 minutes (IQR, 363–431 minutes; range, 289–622 minutes), the median duration of CPB was 267 minutes (IQR, 245–290 minutes; range, 190–402 minutes), and the median time of circulatory arrest in deep hypothermia was 34 minutes (IQR, 26–40 minutes; range, 11–60 minutes). After PEA, median PVR was reduced to 4.8 Wood units (IQR, 3.5–6.4 Wood units; range, 0.3–16 Wood units; $n = 163$; $p < 0.001$ vs RHC performed before PEA), and median mean PA pressure was reduced to 29 mm Hg (IQR, 26–33 mm Hg; range 15–50 mm Hg; $n = 171$; $p < 0.001$ vs RHC performed before PEA).

A total of 86 patients (36.3%) had intraoperative complications (42 patients; complication rate, 17.7%) and/or post-operative complications (60 patients; complication

Table 3 Complications After PEA

	All study patients; $n = 237$
Intraoperative complications	
Major bleeding[a]	27 (11.4%)
Endobronchial/pulmonary bleeding	9 (3.8%)
Surgical bleeding	18 (7.6%)
Venoarterial/venovenous ECMO	10 (4.2%)/ 2 (0.8%)
Intraoperative death	0
Postoperative complications	
Reperfusion lung edema	23 (9.7%)
Requiring diuretics	10 (4.2%)
Requiring non-invasive/invasive mechanical ventilation	11 (4.6%)
Requiring venovenous ECMO	2 (0.8%)
Venoarterial/venovenous ECMO	4 (1.7%)/4 (1.7%)
Major bleeding[b]	13 (5.5%)
Surgical site bleeding	4 (1.7%)
Endobronchial/pulmonary bleeding	3 (1.3%)
Intracranial bleeding	3 (1.3%)
Other extrasurgical site bleeding	3 (1.3%)
Resternotomy <48 hours	7 (3.0%)
Pericardial tamponade requiring drainage or resternotomy	12 (5.1%)
Pneumothorax requiring drainage	10 (4.2%)
Acute/surgical abdomen	3 (1.3%)
Prolonged mechanical ventilation with tracheotomy	10 (4.2%)
CVVH or hemodialysis	13 (5.5%)
Sepsis	7 (3.0%)
Ischemic stroke	3 (1.3%)
Cardiopulmonary resuscitation	9 (3.8%)
In-hospital death	6 (2.5%)

CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; PEA, pulmonary endarterectomy.

[a]Major intraoperative bleeding was defined as the need for additional surgical interventions, such as additional vascular sewing, use of patches, or use of fibrin glue, or the need for venovenous or venoarterial ECMO.

[b]Major postoperative bleeding was defined according to Schulman et al.[19]

Table 4 Predictors of Intraoperative Complications During PEA ($n = 42$)

		Univariable model		Multivariable model[a]	
	n/N	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age ≥75 years[b] (AUC, 0.65; 95% CI, 0.56–0.74; $p = 0.046$)	42/237	4.0 (2.0–5.4)	<0.001	5.3 (2.0–13.6)	0.001
PVR ≥4.8 Wood units[b] (AUC, 0.60; 95% CI, 0.51–0.70; $p = 0.048$)	150/197	7.1 (1.6–30.8)	0.009	4.4 (1.0–20.2)	0.058
Duration of surgery ≥440 minutes[b] (AUC, 0.78; 95% CI, 0.70–0.87; $p < 0.001$)	47/237	10.0 (4.7–21.1)	<0.001	10.8 (4.4–26.5)	<0.001
Duration of circulatory arrest ≥40 minutes[b] (AUC, 0.62; 95% CI, 0.52–0.71; $p = 0.016$)	64/237	2.1 (1.1–4.3)	0.033		
Duration of CPB ≥260 minutes[b] (AUC, 0.70; 95% CI, 0.61–0.78; $p < 0.001$)	138/236	3.7 (1.6–8.4)	0.002		

AUC, area under the curve; CI, confidence interval; CPB, cardiopulmonary bypass; OR, odds ratio; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance.

[a]Univariable predictors were included the multivariable logistic regression model using stepwise forward selection as described in Methods.

[b]The optimal cutoff value was calculated using Youden index quantification based on receiver operating characteristic analysis as described in Methods. n/N and ORs refer to the calculated optimal cutoff value.

rate, 25.3%) (Table 3). Complication rates did not differ in patients treated with PAH-specific drugs or NOACs. Of 14 patients (5.9%) requiring intraoperative or post-operative venoarterial or venovenous ECMO, 4 patients (28.6%) died during the in-hospital stay. Predictors of intraoperative and post-operative complications are presented in Tables 4 and 5. In multivariable logistic regression models using stepwise forward selection, the duration of surgery was identified as the only independent predictor of both intraoperative complications (≥440 minutes; OR, 10.8; 95% CI, 4.4–26.5; $p < 0.001$) (Table 4) and post-operative complications (≥390 minutes; OR, 3.6; 95% CI, 1.4–9.3; $p = 0.009$)

Table 5 Predictors of Postoperative Complications After PEA (n=60)

		Univariable model		Multivariable model[a]	
	n/N	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Renal insufficiency[b]	63/235	2.1 (1.1–3.9)	0.021		
Fatigue	40/215	2.3 (1.1–4.8)	0.023		
Distance in 6-minute walk test <440 m	93/123	3.3 (1.0–10.1)	0.042	—	—
D-sign (on TTE)	130/207	3.5 (1.6–7.7)	0.002	3.3 (1.2–9.3)	0.025
TAPSE <16 mm (on TTE)	52/183	2.3 (1.1–4.6)	0.019	—	—
NT-proBNP ≥750 ng/liter[c] (AUC, 0.67; 95% CI, 0.59–0.76; $p < 0.001$)	102/200	3.3 (1.6–6.6)	0.001	2.9 (1.1–7.4)	0.030
Mean PA pressure ≥40 mm Hg[c] (RHC) (AUC, 0.61; 95% CI, 0.53–0.70; $p = 0.014$)	128/206	2.1 (1.1–4.0)	0.036		
Systolic PA pressure ≥65 mm Hg[c] (RHC) (AUC, 0.64; 95% CI, 0.55–0.73; $p = 0.045$)	115/168	5.1 (1.9–13.9)	0.001	—	—
PVR ≥9.0 Wood units[c] (RHC) (AUC, 0.61; 95% CI, 0.52–0.69; $p = 0.020$)	63/197	2.4 (1.3–4.7)	0.007		
Duration of surgery ≥390 minutes[c] (AUC, 0.62; 95% CI, 0.53–0.70; $p = 0.043$)	124/237	2.7 (1.5–5.1)	0.002	2.4 (1.1–5.7)	0.036
Duration of circulatory arrest ≥30 minutes[c] (AUC, 0.64; 95% CI, 0.57–0.72; $p = 0.001$)	158/237	2.8 (1.4–5.7)	0.005		
Duration of CPB ≥280 minutes[c] (AUC, 0.60; 95% CI, 0.51–0.68; $p = 0.029$)	289/236	1.9 (1.0–3.4)	0.038		

AUC, area under the curve; CI, confidence interval; CPB, cardiopulmonary bypass; NT-proBNP, N-terminal prohormone brain natriuretic peptide; OR, odds ratio; PA, pulmonary artery; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RHC, right heart catheterization; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography.

[a]Univariable predictors were included in the multivariable logistic regression model using stepwise forward selection as described in Methods.

[b]Defined as glomerular filtration rate <60 ml/min/1.73 m^2.

[c]The optimal cutoff value was calculated using Youden index quantification based on receiver operating characteristic analysis as described in Methods. n/N and ORs refer to the calculated optimal cutoff value.

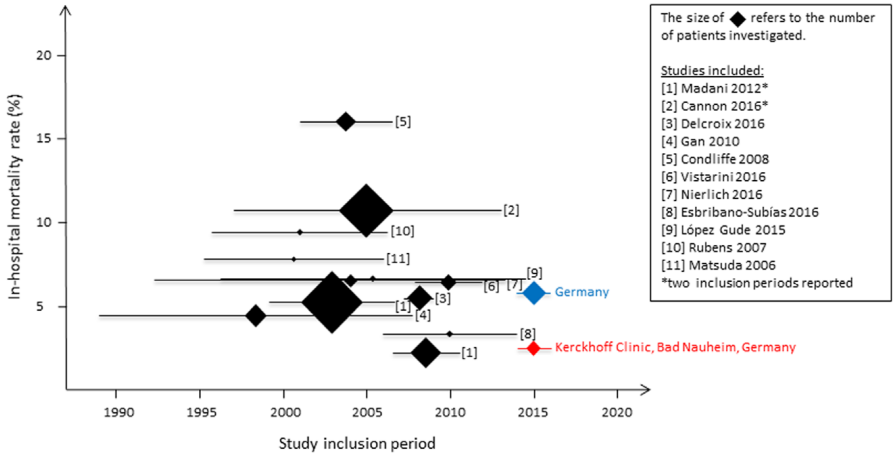

Figure 3 In-hospital mortality rates of patients with CTEPH undergoing PEA in relation to the study observation period. Only studies reporting on ≥100 patients are shown, and studies reporting on the same cohort (such as patients included in the international CTEPH registry or the UK PH registry) are excluded; in the latter case, the most recent publication is shown. Details on the studies shown are provided in Table S1, available in the online version of this article at www.jhltonline.org.

(Table 5). Six patients (2.5%) died during the hospital stay (range, 3–22 days after surgery) (Figure 3); all deaths were due to post-operative complications such as sepsis followed by multiorgan failure. Patients who died during the in-hospital stay had higher N-terminal prohormone brain natriuretic peptide plasma concentrations and more frequently a tricuspid annular plane systolic excursion <16 mm on TTE compared with survivors (Table S3, available in the online version of this article at www.jhltonline.org). Only the duration of surgery (area under the curve, 0.79; 95% CI, 0.61–0.97; $p = 0.016$; calculated optimal cutoff value, ≥500 minutes; OR, 32.0; 95% CI, 5.5–187.6; $p < 0.001$/hazard ratio, 12.1; 95% CI, 2.2–66.7; $p = 0.004$) was associated with an increased risk of in-hospital death in logistic and Cox regression analyses, whereas baseline characteristics, comorbidities, risk factors for CTEPH, symptoms, and functional status (listed in Table 1) and medication at admission (Table 2) were not of predictive value. The duration of surgery weakly correlated with age ($r = 0.16$; $p = 0.014$) and body mass index ($r = 0.16$; $p = 0.014$); however, only intraoperative complications were independently associated with a longer median duration of surgery (≥397 minutes; OR, 4.96; 95% CI, 2.20–11.15; $p < 0.001$) and CPB time (≥267 minutes; OR, 5.63; 95% CI, 2.32–13.65; $p < 0.001$). Baseline characteristics, duration of symptoms, hemodynamic status, pre-medication with PAH-specific drugs, or additional surgical procedures had no influence on the duration of surgery.

The median in-hospital stay was 15 days (IQR, 13–18 days; range, 5–42 days). At discharge, all patients received anti-coagulation therapy, and 21 patients (9.1%) were treated additionally with acetylsalicylic acid. Only 2 patients required treatment with PAH-specific drugs (Table 2) owing to persistent PH after PEA. During the observation period (median, 490 days; IQR, 343–697 days; range, 3–957 days; $n = 229$ patients [96.6%]), 7 patients died (overall mortality rate, 5.7%) after a median time of 233 days (IQR, 177–259 days) (Figure 4). Two patients died of right ventricular failure (day 226 and day 233), and 1 patient each died of complications after PEA (day 36), pneumonia (day 127), aortic dissection (day 256), myocardial infarction (day 262), and recurrent pulmonary embolism (day 566).

Discussion

PEA is the only potentially curative treatment for patients with CTEPH.[1,5–8] During the past decade, improvements in surgical techniques and supportive intensive care and, most importantly, understanding of the importance of interdisciplinary team approaches in experienced PEA centers have resulted in decreased in-hospital mortality rates after PEA. In the most recently operated patients, 2 of the largest PEA centers worldwide reported favorable in-hospital mortality rates of 2.2% and 2.4%, respectively.[12,20] The results of the present single-center study are in line with these observations. We demonstrate an in-hospital mortality rate of 2.5% in 237 patients with CTEPH undergoing PEA over a 2-year period in a German referral center, which was lower than that reported for the large international CTEPH registry (4.7%[11]) and for patients who underwent PEA >10 years ago (9.4% and 7.8%,

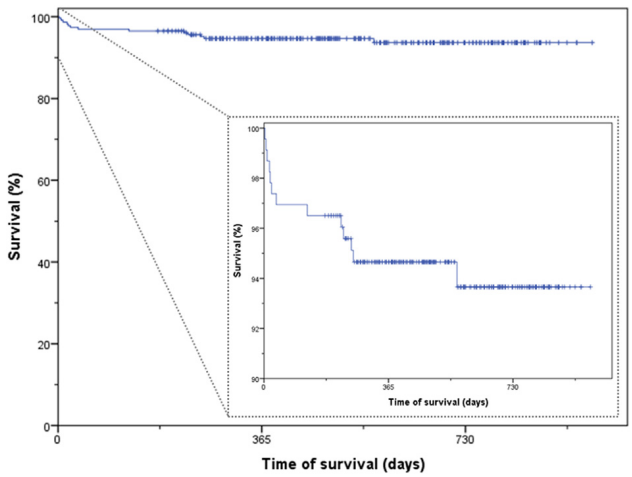

Figure 4 Probability of midterm survival of patients with CTEPH undergoing PEA.

respectively[21,22]) (Figure 3 and Table S1, available in the online version of this article at www.jhltonline.org).

Although numerous studies report on the beneficial hemodynamic effects of PEA (summarized by Jenkins[6] and Guth et al[7]), little is known about intraoperative and post-operative complications after PEA, and a definition of "PEA-related complications" is lacking. In the present study, we provide a detailed description of intraoperative and post-operative complications (listed in Table 3). Typical complications after PEA include reperfusion lung edema (requiring venovenous ECMO in the most severe cases), which affects approximately 10% of all patients (present study, 9.7%; international CTEPH registry, 9.6%[23]) and major bleeding. The numbers of patients with post-operative major bleeding are more difficult to compare, as different definitions are used. In the present study, we used the definition of the International Society on Thrombosis and Haemostasis[19] and observed a bleeding rate of 5.5% (hemorrhagic stroke in 1.3% of patients). Further relevant post-operative complications include pericardial tamponade requiring drainage or repeat sternotomy in 5.1%, renal failure requiring continuous venovenous hemofiltration or hemodialysis in 5.5%, and the need for venovenous or venoarterial ECMO in 3.4% (international CTEPH registry, 3.1%[23]).

Pre-operative risk assessment of patients with CTEPH presenting for PEA should focus not only on the risk of PEA-related death but also of PEA-related complications; however, most available studies have investigated predictors of mortality only. For example, in 239 patients with CTEPH of the UK PH registry who underwent PEA, a higher total pulmonary resistance ($\geq$1,000 dyne • sec • cm^{-5}) was associated with increased perioperative mortality, whereas higher cardiac index, longer 6-minute walk distance, and higher carbon monoxide transfer factor of the lungs were associated with better perioperative survival.[24] Similarly, an elevated PVR, New York Heart Association class IV, and low cardiac index were identified as predictors of 30-day mortality in 214 patients with CTEPH who underwent PEA in Vienna, Austria,[25] and a PVR $\geq$1,000 dyne • sec • cm^{-5}, World Health Organization functional class IV, and reperfusion lung injury were associated with increased mortality in 106 patients with CTEPH who underwent PEA in Madrid, Spain.[26] In contrast to these previous reports, in the present study, the duration of surgery was the only predictor of in-hospital mortality and the only independent predictor of both intraoperative and post-operative complications. Additionally, in these multivariable logistic regression models, age $\geq$75 years emerged as an independent predictor of intraoperative complications, and a D-sign (flattening of interventricular septum) on TTE and N-terminal prohormone brain natriuretic peptide $\geq$750 ng/liter emerged as independent predictors of post-operative complications. However, only intraoperative complications independently predicted a longer duration of surgery. Because a 6-minute walk test was available in only 123 patients (51.9%), final conclusions on its prognostic value require further investigation.

The introduction of novel treatment options for patients with CTEPH challenges pre-operative and post-operative therapeutic decision making. First, BPA is increasingly available in many countries, and evidence is accumulating that BPA is a feasible and safe treatment option for patients with non-operable distal disease.[27,28] In the present study, patients treated with BPA only were excluded and are reported separately,[17] and 4 patients underwent a hybrid procedure (PEA combined with BPA; described in detail elsewhere[18]). A differentiated approach combining surgical PEA and interventional BPA may further improve prognosis, symptoms, and quality of life of a subgroup of patients with CTEPH, but such an approach requires careful patient selection by an experienced multidisciplinary team. Second, the soluble guanylate cyclase inhibitor riociguat is the first drug approved for treatment of non-operable CTEPH or persisting PH after PEA and has been available in Germany since March 2014. In the present study, 22.0% of all patients were treated with PAH-specific drugs (listed in Table 2) before PEA; of those, 36.5% received riociguat. As reported previously,[23,28] patients treated with PAH-specific drugs had a higher PVR and mean PA pressure and a longer time from CTEPH diagnosis to PEA than patients not receiving PAH-specific drugs. Although "pre-treatment" with PAH-specific drugs before surgery may optimize pulmonary hemodynamics in "high-risk" patients, an unnecessary delay of the potentially curative surgery should be avoided, as "pre-treatment" has not been shown to improve prognosis. Only 2 patients required treatment with PAH-specific drugs at hospital discharge, indicating a good hemodynamic and symptomatic improvement after PEA that was also reflected by the post-operative decrease in PVR and mean PA pressure. Finally, NOACs are increasingly being used for therapeutic anti-coagulation of patients with pulmonary embolism. Although studies on the safety and efficacy of NOACs in patients with CTEPH are lacking, in the present study, 40.4% of patients were treated with NOACs at the time of admission for PEA, and 50.7% of patients were treated with NOACs at the time of discharge with no differences in the rates of intraoperative and post-operative complications (including bleeding events) or midterm survival. Thus, depending on individual risk-benefit analysis and pending confirmation of the efficacy and safety of NOACs by real-world data with longer observation periods, these novel agents may constitute a valuable treatment option for patients with CTEPH.

In conclusion, in an experienced German center with multidisciplinary diagnostic and therapeutic approaches, PEA is safe with a low in-hospital mortality rate of 2.5%. Prognosis after PEA was not influenced by baseline characteristics, comorbidities, or pre-operative hemodynamic status and was mainly determined by the occurrence of intraoperative complications and the duration of surgery.

Disclosure statement

None of the authors reports a conflict of interest related to the submitted work. The following authors report financial activities outside the submitted work: M.L. reports having received consultancy and lecture honoraria from Actelion, Bayer, Daiichi-Sankyo, MSD, Pfizer, and Bristol-Myers-Squibb C.L.

reports having received lecture honoraria from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, and Bristol-Myers-Squibb and payment for travel accommodation/meeting expenses from Bayer and Daiichi-Sankyo. S.K. reports having received consultancy and lecture honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, and Bristol-Myers-Squibb payment for travel accommodation/meeting expenses from Bayer; and institutional grants from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo. E.M. reports having received consultancy and lecture honoraria from Actelion, Bayer, GlaxoSmithKline, MSD, and Pfizer. C.B.W. reports having received lecture honoraria from Actelion, Bayer, and Pfizer. S.G. reports having received lecture honoraria from Actelion, Bayer, GlaxoSmithKline, and Pfizer.

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Supplementary data

Supplementary data are available online at www.jhltonline.org.

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Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience

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ABSTRACT Balloon pulmonary angioplasty (BPA) is an emerging treatment for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

We report on a prospective series of 56 consecutive patients who underwent 266 BPA interventions (median, five per patient) at two German institutions. All patients underwent a comprehensive diagnostic work-up including right heart catheterisation at baseline and 24 weeks after their last intervention.

BPA resulted in improvements in WHO functional class, 6 min walk distance (mean change, +33 m), right ventricular function and haemodynamics, including a decline in mean pulmonary artery pressure by 18% and in pulmonary vascular resistance by 26%. Procedure-related adverse events occurred in 9.4% of the interventions. The most common complications were related to pulmonary vascular injury and consecutive pulmonary bleeding. Most of these events were asymptomatic and self-limiting, but one patient died from pulmonary bleeding, resulting in a mortality rate of 1.8%.

BPA resulted in haemodynamic and clinical improvements but was also associated with a considerable number of complications, including one fatal pulmonary bleeding. As the effects of BPA on survival are unknown, randomised controlled outcome trials comparing BPA with approved medical therapies in patients with inoperable CTEPH are required to allow for appropriate risk–benefit assessments.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening disease caused by persistent obstruction of pulmonary arteries as a result of residual pulmonary emboli and consecutive small-vessel pulmonary vascular remodelling [1, 2]. Surgical pulmonary endarterectomy (PEA) is the standard treatment of CTEPH and potentially curative [3, 4]. However, about one-third of the patients are not operable, mostly because of peripheral location of pulmonary vascular obstructions or because of comorbidities [5]. In addition, up to 50% of patients undergoing pulmonary endarterectomy have residual pulmonary hypertension (PH), which is usually mild, but occasionally moderate-to-severe, requiring additional treatment [6, 7]. Drug therapy with riociguat, a soluble guanylate cyclase stimulator, improves haemodynamics and exercise capacity in patients with inoperable or residual CTEPH, but it is not curative [8–10].

An evolving interventional treatment option for patients with inoperable CTEPH is balloon pulmonary angioplasty (BPA). After a first case report in 1988 [11], a series of 18 patients was presented by Feinstein *et al.* in 2001 [12], followed by two additional cases from Germany in 2003 [13]. BPA initially did not get widespread attention as it was associated with serious and potentially fatal complications, most notably reperfusion oedema and pulmonary bleeding. Over the past couple of years, however, BPA has re-emerged after several centres, mainly from Japan, have optimised the interventional approach using modern imaging technology, a careful staged approach and undersizing of the balloons to minimise injury to the pulmonary vessels [14–16]. The initial peri-procedural mortality was 3–10% [16–18] but this figure has dropped to 0–1.5% in more recent reports [14, 15, 19–22]. At the same time, impressive haemodynamic and clinical improvements closely resembling those seen in pulmonary endarterectomy with normalisation or near-normalisation of pulmonary haemodynamics in up to 50% have been reported [14, 19]. In addition, hybrid procedures consisting of pulmonary endarterectomy surgery and intraoperative BPA have been described in highly selected cases with operable findings in one lung and inoperable findings in the contralateral lung [23].

Despite being a promising therapy for patients with CTEPH, BPA is not yet considered an established procedure [24–26]. So far, there are no long-term, multicentre data on the safety and efficacy of BPA and it is unclear if BPA improves survival in patients with inoperable CTEPH. In addition, BPA was initially developed in countries where pulmonary endarterectomy was not widely used. Hence, several patients who underwent BPA may have been considered operable in other countries. Only recently, BPA has been adopted by European and American centres with established surgical programmes. In these centres, BPA is offered exclusively to patients who are considered inoperable or who suffer from symptomatic residual PH after surgery. It is unclear if the results of BPA in centres that strictly restrict BPA to inoperable patients are comparable with the results of BPA in centres that offer this interventional approach to a broader population of patients with CTEPH.

In Germany, BPA was introduced in 2013 by two centres with established surgical programmes for CTEPH (Kerckhoff Clinic Bad Nauheim and Hannover Medical School). These two centres cooperate closely as members of the German Centre for Lung Research. Both centres hold regular multidisciplinary conferences to determine individual treatment strategies for patients with CTEPH and offer BPA only to patients who are deemed technically inoperable or at high surgical risk, respectively. The two centres utilise different imaging technologies and technical approaches but similar standardised follow-up programmes for patients undergoing BPA to allow comparative analysis. Here, we present the results of the first 56 consecutive patients who underwent BPA in these two centres.

Methods

Patient selection

The two participating centres hold weekly conferences of a multidisciplinary team consisting of experienced PEA surgeons, interventional radiologists, cardiologists and/or pneumologists, and anaesthesiologists, if required. Inoperable patients were selected for BPA based on a comprehensive assessment of haemodynamics, comorbidities and imaging findings.

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Per protocol, PH-targeted medication was introduced at least 12 weeks prior to BPA and remained unchanged during the study.

All patients were informed verbally and in writing about the innovative nature of the procedure including potential risks and benefits. This prospective study was approved by the ethics committees of both institutions and all patients provided written informed consent.

Clinical assessment

All patients underwent structured pre-specified assessment at baseline, *i.e.* prior to the first BPA, before each consecutive intervention and 24 weeks after the last BPA. Assessment at baseline and at week 24 after intervention included the WHO functional class (FC), the 6 min walk test (6MWT), the Borg dyspnoea index obtained directly after the 6MWT, pulmonary function testing including the lung diffusion capacity for carbon monoxide (D_{LCO}), serum levels of creatinine (with calculation of the estimated creatinine clearance) and the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), echocardiography (including right ventricular end diastolic diameter, right ventricular free wall diameter, tricuspid annular plane systolic excursion, right atrial dilation, defined as right atrial diameter >43 mm in the four-chamber view) and right heart catheterisation to determine right atrial pressure, pulmonary arterial pressures, pulmonary arterial wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR) and mixed-venous oxygen saturation (S_{vO_2}). Assessment between the BPAs consisted of WHO FC, 6MWT and laboratory studies as described above.

Balloon pulmonary angioplasty

Both centres used a staged approach targeting a limited number of segmental or subsegmental pulmonary arteries during each intervention with intervals of 4–6 weeks between each session. All procedures were performed under local anaesthesia.

Bad Nauheim

In Bad Nauheim, all patients received direct-acting oral anticoagulants (DOACs) for the intervention period. One day prior to BPA, DOACs were replaced with low molecular weight heparin (LMWH). LMWH was not administered on the day of BPA. During the procedure, unfractionated heparin was used intravenously at 100 IU·kg^{-1} to maintain an activated clotting time >250 s.

BPA was performed in a series of staged procedures over a 6-month period using a femoral or jugular access. A 6F sheath (Johnson & Johnson Vista Brite Tip, Milpitas, CA, USA) was placed in the pulmonary artery using fluoroscopy (Siemens Axiom artis zee, Siemens, Erlangen, Germany), and a 6F guiding catheter (Medtronic multi-purpose, Judkins right 4, Medtronic, Dublin, Ireland) was inserted in the pulmonary artery to intubate the segmental arteries. The guide wire (Runthrough NS-PTCA Guide Wire, Terumo Europe, Leuven, Belgium) was placed into the target subsegmental arteries, whose diameters had been determined by fluoroscopy. Subsequently, the target subsegmental branches were dilated by multiple balloon inflations using semi-compliant balloons (Emerge 2.0/20 mm and 4.0/20 mm, Boston Scientific, Marlborough, MA, USA). To avoid pulmonary arterial rupture, slightly undersized balloons were used in all cases. A final pulmonary angiography documented the post-procedural morphologic result.

Hannover

In Hannover, BPA procedures were conducted as described previously [27]. All patients received anticoagulation with rivaroxaban, which was paused for the intervention day (without LMWH bridging). During the procedure, patients received 5000–10 000 IU of unfractionated heparin intra-arterially. A 6F sheath (Destination – Peripheral guiding sheath, Terumo Europe, Leuven, Belgium) was placed in the main pulmonary artery of interest and a selective C-Arm CT (CACT) was acquired using a 5F pigtail catheter (Optitorque, Terumo Europe) as described elsewhere [27, 28]. The target lesions were localised by selective digital subtraction angiography (DSA) and CACT. Based on these images, centre-lines indicating the course of the pulmonary arteries were drawn, BPA positions were identified and marked by coloured lines in the CACT dataset [27]. Both images could be superimposed on the live fluoroscopic image during intervention for individual navigation. Subsequently, a 6F guiding catheter (MACH 1, Boston Scientific, Marlborough, MA, USA) was advanced into the targeted pulmonary artery segment and a hydrophilic 0.014-inch guide-wire (V-14, Boston Scientific) was used to cross the target lesions. Based on the measured vessel diameter in CACT, appropriate rapid exchange balloon catheters (1.2–4 mm, Emerge, Boston Scientific) were selected. The balloons were advanced through the pulmonary lesion and inflated for 15–60 s by hand using an inflation device. BPA results were documented by selective pulmonary angiograms.

Statistical analysis

The IBM SPSS Statistics 24.0 (IBM Corp, Armonk, NY, USA) and STATA 13.0 (State Corp LP, College Station, TX, USA) statistical software were used to analyse the data. Categorical variables are shown as numbers (n) and percentages (%). Continuous variables are shown as mean±SD, unless indicated otherwise. For comparisons, Fisher's exact test, Chi-squared test, Mann–Whitney U test, McNemar's test or two-sided paired t-test were used as appropriate. All reported p-values are two-sided unless indicated otherwise; p-values <0.05 were considered statistically significant.

Results

Baseline characteristics, effects of BPA and procedures

Between August 2013 and January 2016, 56 consecutive patients were enrolled into this study: 31 in Hannover and 25 in Bad Nauheim. Only patients undergoing hybrid procedures, *i.e.* PEA surgery and BPA at the same time [23], were excluded. The demographics and baseline characteristics of these patients are depicted in tables 1 and 2. Follow-up ended in July 2016. The median duration between CTEPH diagnosis and first BPA was 14 months; in 34% of the patients this interval exceeded 2 years. Most patients received PH-targeted therapies, which were introduced at least 3 months prior to baseline assessment and kept unchanged during the study.

A total of 266 interventions were performed: 155 in Hannover and 111 in Bad Nauheim. In both centres, the median number of interventions per patient was five (range, 3–8). The median number of vessels targeted per intervention was two (range, 1–4). The median duration from first BPA to the 24-week follow-up assessment was 13.8 months.

Treatment response

The effects of BPA on haemodynamics, right ventricular (RV) function, serum NT-proBNP and exercise capacity are presented in table 2. WHO FC improved in 33 (59%) patients and remained unchanged in 22 (41%) patients; it did not deteriorate in any patients. The 6-min walk distance improved by an average of 33 m (about 9% from baseline) accompanied by a reduction in the Borg dyspnoea index. Haemodynamic assessment showed improvements in right atrial pressure, mean pulmonary artery pressure (PAPm) and PVR, while CO, CI and S_{vO_2} remained unchanged. NT-proBNP improved and so did several echocardiographic measurements of RV function including right atrial diameter, RV diameter and tricuspid annular plane systolic excursion. Arterial oxygen tension (increased while D_{LCO} remained unchanged, as did serum creatinine and creatinine clearance.

TABLE 1 Characteristics of patients at time of inclusion

	Last measurement prior to first intervention
Patients	56 (100)
Age years	65 (55–74)
Females	34 (61)
BMI kg·m^{-2}	26±4
Post PEA	7 (13)
History of VTE	32 (57)
Interval between CTEPH diagnosis and first BPA months	14 (5–36)
Pulmonary function	
TLC % pred	97±14
FVC % pred	88±17
FEV_1 % pred	77±16
Pulmonary hypertension therapy	
Riociguat	8 (14)
PDE5 inhibitor	33 (59)
ERA	10 (18)
Prostacyclin *i.v.*	1 (2)

Data are presented as n (%), median (interquartile range) and mean±SD. BMI: body mass index; PEA: pulmonary endarterectomy; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension; BPA: balloon pulmonary angioplasty; TLC: total lung capacity; % pred: % predicted; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PDE5: phosphodiesterase-5; ERA: endothelin receptor antagonist.

TABLE 2 Changes from baseline to week 24

	Baseline		Week 24		p-value
	Subjects n	Value	Subjects n	Value	
Exercise capacity					
WHO functional class	56		55		<0.001
I		0 (0)		6 (13)	
II		9 (15)		33 (60)	
III		40 (70)		16 (25)	
IV		7 (15)		0 (0)	
6 min walking distance m	55	358±108	53	391±108	0.001
Borg dyspnoea scale (1–10)	55	4.7±2.0	53	3.1±2.0	<0.001
Haemodynamics and NT-proBNP					
Right atrial pressure mmHg	55	8±5	55	6±4	0.001
PAPm mmHg	56	40±12	55	33±11	<0.001
PAPsyst mmHg	56	66±20	55	55±19	<0.001
PAPdiast mmHg	56	23±9	55	19±8	<0.001
PAWP mmHg	56	10±3	55	9±3	0.738
DPG mmHg	55	14±8	55	10±8	<0.001
TPG mmHg	56	30±11	55	23±10	<0.001
CO $L \cdot min^{-1}$	56	4.4±1.1	55	4.6±1.2	0.071
CI $L \cdot min^{-1} \cdot m^{-2}$	56	2.4±0.6	55	2.5±0.6	0.259
PVR $dyn \cdot s \cdot cm^{-5}$	56	591±286	55	440±279	<0.001
S_{vO_2} %	55	64±8	55	69±6	<0.001
HR bpm	56	72±12	55	69±11	0.123
NT-proBNP	56	504 (233–1676)	55	242 (109–555)	0.002
Echocardiographic findings					
RVED diameter mm	51	38±9	49	34±8	0.002
RV free wall diameter mm	31	6.6±1.2	31	6.5±1.0	0.917
TAPSE mm	51	19±5	44	21±5	<0.001
RA dilation	50	38 (76)	49	19 (39)	<0.001
Blood gas analysis and pulmonary function					
P_{aO_2} mmHg	53	62±9	53	66±10	0.001
S_{aO_2} %	53	93±3	53	94±3	0.004
P_{aCO_2} mmHg	53	34±3	53	34±6	0.801
D_{LCO} % pred	53	57±16	53	58±19	0.261
Laboratory findings					
Creatinine $\mu mol \cdot L^{-1}$	55	87±36	55	87±26	0.746
eGFR $mL \cdot min^{-1}$	56	62±15	55	64±17	0.343

Data are presented as n (%), mean±SD and median (interquartile range). WHO: World Health Organization; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; PAPm: mean pulmonary artery pressure; PAPsyst: systolic pulmonary artery pressure; PAPdiast: diastolic pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; DPG: diastolic pressure gradient; TPG: transpulmonary gradient; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; HR: heart rate; RVED: right ventricular end diastolic diameter; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; RA: right atrium; P_{aO_2}: arterial oxygen tension; S_{aO_2}: arterial oxygen saturation; P_{aCO_2}: arterial carbon dioxide tension; D_{LCO}: lung diffusion capacity for carbon monoxide; eGFR: estimated glomerular filtration rate based on serum creatinine.

Supplementary table S1 shows the effects of BPA on haemodynamics, RV function, serum NT-proBNP and exercise capacity in the two centres.

Complications

A total of 25 procedure-related complications (Hannover, n=9; Bad Nauheim, n=16) occurred during the 266 interventions (9.4% of all interventions, 32% of all patients; figure 1 and table 3). Most of these adverse events were related to pulmonary vascular injury by wire perforation resulting in parenchymal bleeding with or without haemoptysis, the majority of which were mild and did not require intervention. There was, however, one episode of fatal pulmonary bleeding. In that patient, wire perforation of a subsegmental right lower lobe artery occurred during the intervention. The patient was initially asymptomatic and had no haemoptysis. Chest fluoroscopy showed mild parenchymal bleeding which appeared to have stopped spontaneously without further therapeutic measures. The patient was discharged

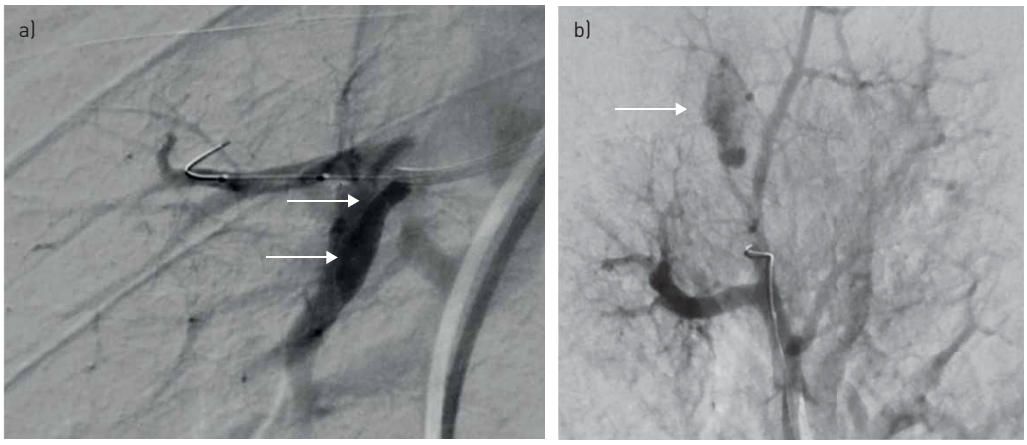

FIGURE 1 a) Digital subtraction angiography of the middle lobe arteries in a 63-year-old man with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) showing a pulmonary artery dissection (arrows) after manipulation with the guiding catheter. b) Digital subtraction angiography of the right upper lobe arteries in a 72-year-old woman with inoperable CTEPH showing pulmonary haemorrhage (arrow) after guide wire perforation.

from the hospital after 1 week in apparently good health but was admitted 14 days after the intervention to another hospital with shock, respiratory distress and a large right-sided haemothorax. The patient could not be stabilised and died from haemorrhagic shock.

Discussion

The present study supports the notion that BPA is potentially an effective interventional treatment for patients with inoperable CTEPH. We saw improvements in pulmonary haemodynamics, RV function, serum NT-proBNP, WHO functional class and 6 min walk distance in most of our patients, but this did not come without risks. In the present series of 266 interventions in 56 patients, adverse events occurred in 9.4% of the interventions; 32% of the patients had at least one procedure-related event. Reperfusion oedema, which was the predominant adverse event in previous series [12, 15–17], was rare, occurring only in two patients. By far the most common complication in our series was pulmonary bleeding because of pulmonary vascular injury. In the majority of cases, bleeding was mild, asymptomatic and required no intervention. One patient, however, died from pulmonary bleeding, resulting in a mortality rate of 1.8%.

The average haemodynamic improvement observed with BPA in our study was moderate with an 18% drop in PAPm (from 40 mmHg to 33 mmHg) and a 26% decrease in PVR (from 591 to 440 dyn·s·cm^{-5}). These haemodynamic improvements were less pronounced than in previous publications from Japanese centres, which reported reductions in PAPm and PVR between 31–49% and 45–69%, respectively [14, 15, 18–20, 22]. There are several possible explanations for these differences. 1) One might argue that Japanese centres are more experienced in BPA than German centres; however, both German centres developed BPA in close collaboration with Japanese centres and used basically the same interventional approach; in addition the overall number of 266 interventions in our series makes lack of experience an unlikely explanation; finally, the number of patients and interventions reported from Japanese centres was in the

TABLE 3 Complications related to balloon pulmonary angioplasty

	Total	Hannover	Bad Nauheim
Interventions[#] n	266	155	111
Pulmonary arterial dissection without bleeding	2 (0.8)	1 (0.6)	1 (0.9)
Vascular lesions with pulmonary bleeding but without haemoptysis	3 (1.1)	1 (0.6)	2 (1.8)[¶]
Vascular lesions with haemoptysis	15 (5.6)	5 (3.2)	10 (9)
Reperfusion oedema	2 (0.8)	0 (0)	2 (1.8)[+]
Others	3 (1.1)	2 (1.3)	1 (0.9)
Total	25 (9.4)	9 (5.8)	16 (14.4)

Data are presented as n (%), unless otherwise stated. [#]: others were groyne haematoma (n=1), peripheral arteriovenous fistula (n=1), induction of atrial fibrillation, self-limiting (n=1); [¶]: one event was fatal, see text for details; [+]: both patients recovered after noninvasive ventilation.

same range as in our series [14, 16]. 2) We studied a prospective cohort of consecutive patients treated in two centres whereas previous reports were based on single-centre series, so that the possibility of selective reporting cannot be excluded. 3) PEA surgery is well established in Germany but it is used less frequently in Japan; some of the patients who underwent BPA in Japan would have been deemed operable in Germany, but we selected for BPA only patients with inoperable disease or residual PH after surgery; hence, patient populations were not comparable. 4) The majority of patients in our series had a relatively long interval between CTEPH diagnosis and first BPA (median 14 months; 34% of the patients >2 years). It is possible that some of these patients had developed peripheral pulmonary vasculopathy, which would mitigate the haemodynamic effects of upstream interventions such as BPA.

The haemodynamic effects of BPA observed in our study were inferior to the effects of PEA surgery, which decreases PAPm by approximately 40% and PVR by approximately 60% [3, 6], but are similar to the effects of riociguat, which decreases PAPm by approximately 11% and PVR by approximately 31% in patients with inoperable CTEPH [8].

The profile of the haemodynamic changes observed with BPA, however, was different from the haemodynamic changes observed with medical therapy as we saw improvements in PAPm and PVR with very small changes in cardiac output. Medical therapy, in contrast, tends to improve mostly cardiac output, but the effects on PAPm are usually modest [8, 29]. One possible reason for this observation may have been that most patients in our study had normal or near normal cardiac output at baseline, perhaps because almost all of them were already pre-treated with PH medications. The baseline haemodynamics of our patients were similar to the on-treatment haemodynamics reported with riociguat in the CHEST-1 study [8]. In addition, it is possible that the increase in cardiac output observed with most medical therapies is partly mediated by systemic vasodilation, an effect that would be absent with BPA. This hypothesis is supported by the haemodynamic effects of inhaled nitric oxide, a selective pulmonary vasodilator, which also lowers PAPm with little effect on cardiac output [30].

As stated above, adverse events occurred in 9.4% of the interventions and in 32% of the patients. The observed mortality rate of 1.8% (1 of 56 patients) is similar to more recent publications from Japanese centres that reported mortality rates between 0 and 1.5% [14, 15, 19, 22]. However, the rate of pulmonary vascular injury with or without pulmonary bleeding was higher in our series, possibly because we recorded all episodes of parenchymal bleeding, even if they did not require interventions. The rate of adverse events tended to be higher in Bad Nauheim than in Hannover, which might have been partly related to the fact that Bad Nauheim used conventional contrast-enhanced DSA to guide the interventional procedures whereas DSA and CACT imaging were used in Hannover. CACT provides more detailed imaging of peripheral pulmonary arteries, allowing for a more reliable assessment of accessibility, vessel morphology and diameter, adequate balloon size and procedural guidance [27, 28]. In addition, LMWH bridging in patients receiving DOACs may have been associated with an increased bleeding risk in Bad Nauheim, as has been reported from other patient populations [31, 32].

Our study has several limitations. Firstly, although this was one of the largest prospective series of BPA, the number of patients was still small. Secondly, there was no control group. Thirdly, efficacy measures such as 6MWT, WHO FC and haemodynamics were not obtained by blinded study personal. Finally, long-term outcome data were not available. Despite these limitations, our data may provide a realistic perspective on the risks and benefits associated with the introduction of a BPA programme in referral centres with an established surgical programme for CTEPH.

In conclusion, our results confirm previous reports demonstrating that BPA improves haemodynamics, RV function and exercise capacity in patients with inoperable CTEPH or residual PH after PEA surgery. However, like any other interventional procedure, BPA is associated with potentially life-threatening complications. Further studies need to determine whether CACT-guided BPA is safer than DSA-guided BPA. Most importantly, as it remains unknown if BPA improves survival, our data call for a large, prospective, multicentre study comparing long-term outcomes in patients receiving medical therapy and BPA with medical therapy alone.

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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

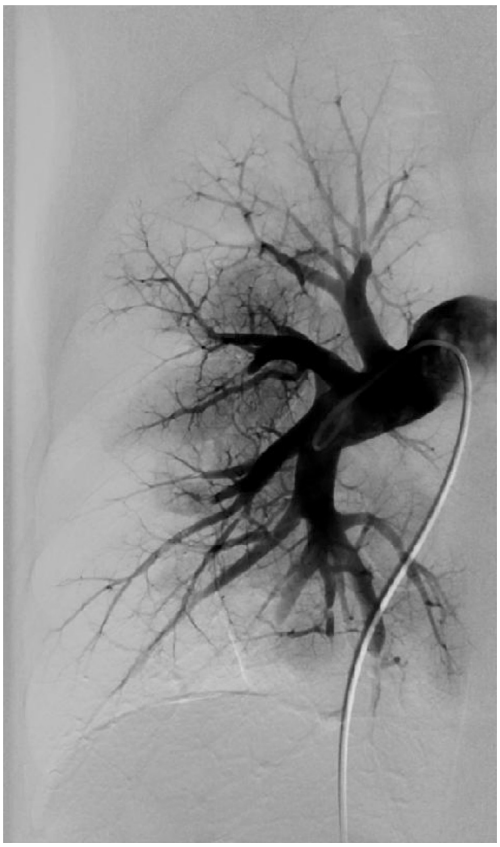

Figure 1 Illustration of multiple peripheral target lesions in a CTEPH patient.

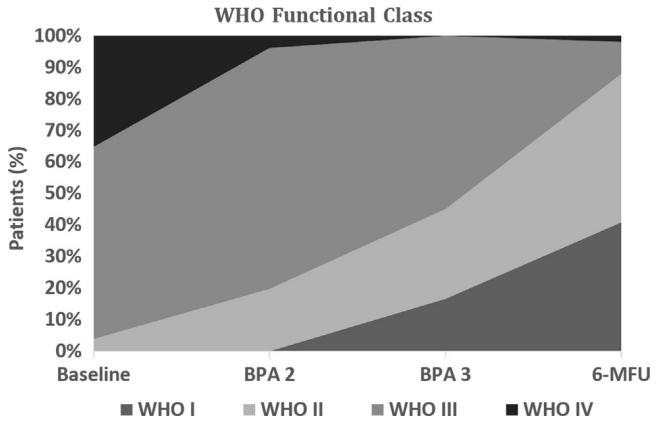

Figure 2 Development of WHO FC during staged BPA procedure (BPA = balloon pulmonary angioplasty; WHO = World Health Organization).

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%.

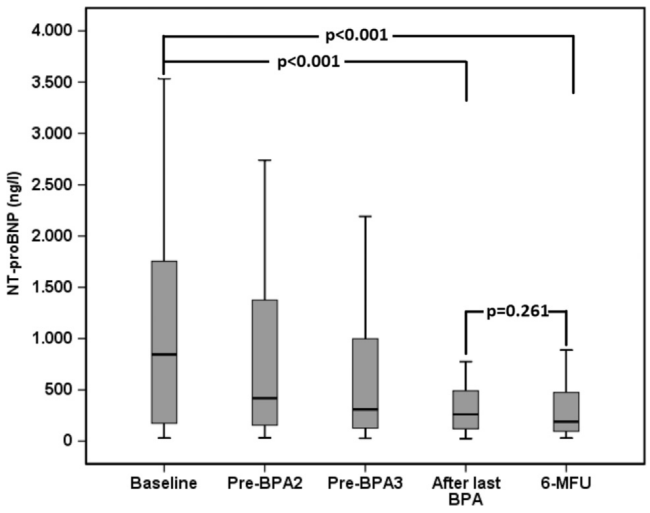

Figure 3 Analysis of the time course of NT-proBNP levels during staged BPA procedure (BPA = balloon pulmonary angioplasty; NT-proBNP = N-terminal pro–B-type natriuretic peptide).

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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CARDIAC

Correlation of native T1 mapping with right ventricular function and pulmonary haemodynamics in patients with chronic thromboembolic pulmonary hypertension before and after balloon pulmonary angioplasty

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Abstract

Objectives The aim of this study was to assess native T1 mapping in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) before and 6 months after balloon pulmonary angioplasty (BPA) and compare the results with right heart function and pulmonary haemodynamics.

Methods Magnetic resonance imaging at 1.5 T and right heart catheterisation were performed in 21 consecutive inoperable CTEPH patients before and 6 months after BPA. T1 values were measured within the septal myocardium, the upper and lower right ventricular insertion points, and the lateral wall at the basal short-axis section. In addition, the area-adjusted septal native T1 time (AA-T1) was calculated and compared with right ventricular function (RVEF), mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR).

Results The mean AA-T1 value decreased significantly after BPA (1,045.8 ± 44.3 ms to 1,012.5 ± 50.4 ms; $p < 0.001$). Before BPA, native T1 values showed a moderate negative correlation with RVEF ($r = -0.61$; $p = 0.0036$) and moderate positive correlations with mPAP ($r = 0.59$; $p < 0.01$) and PVR ($r = 0.53$; $p < 0.05$); after BPA correlation trends were present ($r = -0.21$, $r = 0.30$ and $r = 0.35$, respectively).

Conclusions Native T1 values in patients with inoperable CTEPH were significantly lower after BPA and showed significant correlations with RVEF and pulmonary haemodynamics before BPA. Native T1 mapping seems to be indicative of reverse myocardial tissue remodelling after BPA and might therefore have good potential for pre-procedural patient selection, non-invasive therapy monitoring and establishing a prognosis.

Key Points

- *BPA is a promising treatment option for patients with inoperable CTEPH*
- *Native septal T1 values significantly decrease after BPA and show good correlations with right ventricular function and haemodynamics before BPA*
- *Prognosis and non-invasive therapy monitoring might be supported in the future by native T1 mapping*

Keywords Magnetic resonance imaging · Pulmonary hypertension · Pulmonary embolism · Angioplasty

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Abbreviations

AA-T1	Area-adjusted native T1 time
BPA	Balloon pulmonary angioplasty
CMR	Cardiac magnetic resonance imaging
CTEPH	Chronic thromboembolic pulmonary hypertension
EDD	End-diastolic diameter
EDV	End-diastolic volume
EF	Ejection fraction
ESD	End-systolic diameter
ESV	End-systolic volume
LV	Left ventricle
mPAP	Mean pulmonary arterial pressure
PA	Pulmonary artery
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RVEF	Right ventricular function
RVIP	Right ventricular insertion point
RV	Right ventricle
SV	Stroke volume

Introduction

Pulmonary hypertension (PH) is defined as elevation of the mean pulmonary artery (PA) pressure (mPAP) beyond 25 mmHg [1]. Different aetiologies of PH are known and have been categorised according to the Nice classification [2]. Thus, chronic thromboembolic pulmonary hypertension (CTEPH) is defined as PH with persistent perfusion defects after a single or recurrent pulmonary embolism [3]. It is a rare but underdiagnosed disease with an estimated incidence between 0.5% and 3.8% after acute pulmonary embolism and 10% after recurring embolism [4–7]. The persistence of thrombotic material leads to fibrotic obstruction of pulmonary arteries that is compounded by secondary inflammation, cell proliferation and vascular remodelling [8–10]. As a result, elevated mPAP and pulmonary vascular resistance (PVR) ensue, which lead to long-term impairment of right heart function accompanied by poor prognosis and high mortality [11, 12].

CTEPH is potentially curable by surgical pulmonary endarterectomy (PEA) [13–15]. PEA surgery leads to normalisation of pulmonary haemodynamics in most patients [16], and the long-term survival rate is excellent [14]. However, up to one-third of all CTEPH patients are not amenable to surgery, mostly due to the presence of peripherally located lesions [3]. For these patients, targeted medical treatment with riociguat, a stimulator of soluble guanylate cyclase which improves not only pulmonary haemodynamics but also physical capacity of CTEPH patients [17–19], is recommended [8], and balloon pulmonary angioplasty (BPA), an emerging interventional treatment option [8, 20, 21], should also be considered.

Non-invasive assessment with cardiac magnetic resonance imaging (CMR) is widely used to assess RV structure, function and morphology. For example, CMR was used by Kreitner et al [22] and Rolf et al [23] to investigate effects of PEA in CTEPH patients and Van Wolferen et al [24] likewise investigated effects of medical treatment on biventricular heart function in patients with idiopathic PH. Recently, Sato et al [25] and Yamasaki et al [26] investigated effects of BPA in patients with inoperable CTEPH via CMR and showed improvements in biventricular function, pulmonary flow and interventricular dys-synchrony.

Native cardiac T1 mapping provides useful diagnostic information in many cardiac diseases [27–30], permitting parametric tissue characterisation without the need for contrast agents. Initial results in patients with different causes of PH are promising and have shown good correlations with right ventricular function and pulmonary haemodynamics [31–33]. Furthermore, the results of a recent study by Garcia-Alvarez et al [34] in an experimental animal model suggest that native T1 mapping might be suitable as a non-invasive method to assess fibrosis of the upper and lower right ventricular insertion point (RVIP) in chronic PH, as T1 times increase with the degree of fibrosis (myocardial collagen content). In order to determine the potential of native T1 mapping as an imaging biomarker, the aims of our study were to assess native T1 values in patients with inoperable CTEPH before and 6 months after BPA and to examine how well they correlate with right heart function and pulmonary haemodynamics.

Methods

Patient population

A total of 21 consecutive CTEPH patients (12 women) with a mean age of 63.4 ± 10.6 years (± standard deviation [SD]) and a mPAP of 40.9 ± 12.6 mmHg were enrolled in this prospective cohort study from January 2014 to February 2015. The primary diagnosis of CTEPH was based on ventilation-perfusion scintigraphy, right heart catheterisation and biplanar pulmonary angiography. Pre- and post-procedural management of these patients has been recently published [17, 35, 36]. In brief, all patients were assessed by CMR and right heart catheterisation (RHC) as part of their pre-and post-interventional routine workup (assessment of RV function and pulmonary arteries).

Contraindications for CMR and exclusion criteria in all patients were renal failure (glomerular filtration rate below 30 ml/min/1.73 m^2), incompatible cochlear or metallic implants, known gadolinium intolerance, claustrophobia, or the inability to lie supine for the duration of the protocol due to dyspnoea.

All patients gave written informed consent, and the local ethics committee approved the study.

CMR 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 (CV), three-CV, four-CV and stacked transaxial and short-axis (SA) from base to apex, black-blood (T2 turbo spin echo [TSE]), native T1 mapping and late gadolinium enhancement (LGE) (T1 gradient echo [GE] with inversion recovery) imaging. Gadobenate dimeglumine (Gd-BOPTA; Bracco Imaging, Milan, Italy) was injected at a dose of 0.15 mmol/kg. LGE imaging was performed 12 min after contrast media injection. SSFP imaging parameters were: slice thickness 8 mm; field of view: 300 × 400 mm; matrix 256 × 154; TR 59.62 and TE 1.15. LGE imaging parameters were: slice thickness 8 mm; field of view: 293 × 360 mm; matrix: 256 × 156; TR 843.2 and TE 3.19. Black-blood T2 images were not used for analysis.

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 LV and RV were obtained by manual tracing with exclusion of papillary muscles and trabeculae from the cavity. Ventricular volumes were estimated using the Simpson rule. The ejection fraction (EF) was calculated as [end-diastolic volume (EDV) – end-systolic volume (ESV)]/EDV**,** end-systolic diameter (ESD), and end-diastolic diameter (EDD) measurements were made using basal short-axis images. The post-processing was performed with the ARGUS software package (Siemens Syngo MMWP Version VE40A; Siemens Healthineers).

T1 mapping images were acquired at basal, mid-ventricular, and apical short-axis sections by using an optimised modified Look-Locker inversion-recovery (MOLLI) sequence, with three images in the first two Look-Locker segments and five images for the third inversion (known as the "3-3-5" standard protocol) [37]. Finally, 11 images were acquired during 17 heartbeats, and in-line motion correction and map generation were performed. Imaging parameters were [32]: slice thickness, 8 mm; spatial resolution, 2.2 mm × 1.8 mm × 8 mm; 6/8 partial Fourier acquisition; field of view, 240 × 340 mm; matrix, 192 × 124; flip angle, 35°; TR, 740; TE, 1.06; TI, 100 ms; TI increment, 80 ms; trigger delay, 300 ms; inversions, 3; acquisition heartbeats, 3, 3, 5; scan time, 17 heartbeats.

Qualitative and quantitative image assessment

All original images were assessed for artefacts due to susceptibility, cardiac, diaphragmatic or respiratory motion. Each motion-corrected series was evaluated for correct image alignment, and each map was carefully checked for signal loss due to misalignment and motion [32].

Image assessment and measurement of native T1

After image acquisition T1 maps were generated after in-line motion correction from the MR workstation [38]. T1 times were measured for myocardium at the basal short-axis section before and after BPA. Basal short-axis slices were chosen to facilitate proper T1 measurements caused by a greater septal myocardial diameter compared to midventricular and apical slices. Thus, a total of four regions of interest (ROIs) were drawn manually at the following locations: septum, upper and lower RVIP, and the lateral wall. ROIs were drawn carefully to exclude the myocardial borders, avoiding partial volume-averaging artefacts and registration errors with gradual T1 value changes that are present at the borders. In addition to the T1 values, the size of the ROIs was also compared and evaluated before and after BPA for each patient to exclude size-dependent differences. Moreover, a total area-adjusted septal native T1 value (AA-T1) was calculated that consisted of the mean T1 values and areas measured for the septum and the RVIPs [32]. The measured T1 values of the septum, the upper and lower RVIP were therefore added up to a sum and divided by the sum of the corresponding ROI areas. All measurements were performed by two experienced radiologists independently (G.K., 20 years of experience, and F.R., 7 years of experience), who were blinded to patient demographics, and LGE assessment was performed blinded to T1 maps and CINE images and vice versa. All studies were used for assessment of inter- and intra-rater variability.

Right heart catheterisation

RHC was performed as a part of the diagnostic workup [8]. RHC was repeated 6 months after the final BPA procedure in all patients. RHC was performed routinely via the right internal jugular vein using a 6-F sheath and a standard Swan-Ganz catheter. The medication of the patients was not modified prior to or during RHC.

Balloon pulmonary angioplasty

As described before [20], BPA was performed as staged procedure under smooth sedation using femoral or jugular access.

Table 1 Demographic data for CTEPH patients before and after BPA

	Pre-BPA	Post-BPA	*p* value
Patients (*n*)	21	21	
Age (years)	58.8 ± 12.2		
Sex (male:female)	9:12		
BSA (m^2)	1.8 ± 0.2		
mPAP (mmHg)	40.9 ± 12.6	34.4 ± 15.4	0.0016
PVR (dyn × s/cm^5)	538.2 ± 246.3	402.6 ± 190.5	0.0001
PCWP (mmHg)	10.3 ± 3.5	9.2 ± 2.6	
CO (l/m)	4.6 ± 1.3	5.0 ± 1.1	0.1649
Treated pulmonary segments (*n*)		10.0 ± 3.2	

Values are mean ± SD or absolute values

BPA balloon pulmonary angioplasty, *BSA* body surface area, *CO* cardiac output, *CTEPH* chronic thromboembolic pulmonary hypertension, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *SD* standard deviation

A 6-F sheath (Vista britetip; Cordis, Johnson & Johnson, New Brunswick, NJ, USA) was placed in the pulmonary artery, and a 6-F guiding catheter (in most cases multi-purpose; Medtronic, Minneapolis, MN, USA) was inserted into the pulmonary artery to intubate the target segmental arteries. During the procedure, patients received heparin intravenously to maintain an activated clotting time >250 s. The guide wire (Runthrough NS-PTCA Guide Wire; Terumo, Tokyo, Japan) was placed into the subsegmental arterial branches, passing the obstructing endoluminal material. Subsequently, the subsegmental branches were dilated by multiple inflations of semi-compliant balloons (Emerge™ 2.0/20 mm and 4.0/20 mm; Boston Scientific, Voisins-le-Bretonneux, France). Final fluoroscopy imaging documented the post-procedural morphological results. Expected results were improvement of parenchymal perfusion as well as a quick venous return, which were used to indicate successful intervention. Signs of successful interventions were seen in most patients.

Statistical analysis

Statistical analysis was performed using SPSS statistical software version 20 (SPSS, IBM, Armonk, New York, USA). Patient characteristics were described by mean ± standard deviation (SD). All data were tested for normal distribution using the Shapiro-Wilk test. In cases of normal distribution Student's *t*-test was used, and if the data were not distributed normally the Wilcoxon signed rank test (non-parametric) was used. Intra- and inter-observer variability was tested with simple linear regression analysis. Linear regression analysis was also used for assessing the correlation of native T1 and functional parameters. The correlation coefficient k was interpreted according to Hinkle et al [39], where $r > 0.5$ would be considered a moderate correlation, $r > 0.7$ a strong correlation, and $r > 0.9$ very strong correlation. An $r > 0.5$ would therefore be considered to have clinical impact. Strengths of correlations were tested using the Pearson correlation coefficient. All results were tested at a 5% level of significance and we accepted an alpha error of less than 0.05 as statistically significant.

Results

Table 1 presents patient demographics, RHC measurements and the mean number of treated pulmonary segments. A total of 10.0 ± 3.2 pulmonary segments were treated by BPA per

Table 2 Functional analysis before and after BPA (CMR)

n = 21		Pre-BPA	Post-BPA	*p* value
LV function				
	EF (%)	65.4 ± 10.3	66.5 ± 6.2	0.5603
	EDV (ml)	100.4 ± 24.9	115.4 ± 23.1	0.0187
	ESV (ml)	35.0 ± 13.5	39.3 ± 12.7	0.05
	SV (ml)	65.5 ± 18.4	76.1 ± 13.6	0.0295
	EDD (mm)	42.5 ± 5.8	46.6 ± 4.5	0.0002
	ESD (mm)	24.7 + 6.5	27.5 ± 4.3	0.01
RV function				
	EF (%)	38.2 ± 11.7	47.9 ± 7.6	0.001
	EDV (ml)	191.1 ± 66.3	161.6 ± 52.5	0.0093
	ESV (ml)	124.8 ± 50.2	85.5 ± 38.7	0.0003
	SV (ml)	71.0 ± 17.7	75.9 ± 19.4	0.4168
Wall thickness				
	Septal (mm)	7.3 ± 1.0 mm	7.5 ± 0.9 mm	0.548

Values are mean ± SD or absolute values

BPA balloon pulmonary angioplasty, *CMR* cardiac magnetic resonance imaging, *CTEPH* chronic thromboembolic pulmonary hypertension, *EF* ejection fraction, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *EDD* end-diastolic diameter, *ESD* end-systolic diameter, *LV* left ventricular, *RV* right ventricular

Table 3 Native T1 mapping in CTEPH patients before and after BPA

	Pre-BPA (n = 21) ms	Mean ROI size mm^2	Post-BPA (n = 21) ms	Mean ROI size mm^2	p value
Upper RVIP	1,059.0 ± 49.4	44.6	1,012.1 ± 67.4	37.4	0.0004
Lower RVIP	1,087.9 ± 78.2	38.7	1,062.5 ± 78.9	32.0	0.0637
Septum	1,008.3 ± 41.8	113.3	987.9 ± 40.1	106.8	0.0215
AA-T1	1,045.8 ± 44.3	97.3	1,012.5 ± 50.4	109.4	0.0009
Lateral wall	965 ± 44.3	116.5	972 ± 41.7	114.6	0.43

Values are mean ± SD

BPA balloon pulmonary angioplasty, *CTEPH* chronic thromboembolic pulmonary hypertension, *RVIP* right ventricular insertion point, *AA-T1* area-adjusted T1 time, *ROI* region of interest

patient. The mPAP decreased from 40.9 ± 12.6 mmHg before BPA to 34.4 ± 15.4 mmHg after BPA ($p < 0.01$), and PVR decreased from 538.2 ± 246.3 (dyn × s/cm^5) to 402.6 ± 190.5 (dyn × s/cm^5) ($p < 0.001$). Pulmonary capillary wedge pressure and cardiac output were not significantly affected by BPA.

Pre- and post-procedural LV and RV function as determined by CMR are displayed in Table 2. Before and after BPA all patients had normal LV function regarding EF but stroke volume (SV), EDV and ESV were significantly higher after BPA ($p = 0.0187$, $p = 0.05$ and $p = 0.0295$, respectively). Moreover, BPA resulted in significantly higher RV EF ($p = 0.001$) and significantly lower RV EDV and RV ESV ($p = 0.0093$ and 0.0003, respectively). The RV SV was not significantly different. The end-diastolic and end-systolic LV diameters were significantly higher after BPA ($p = 0.0002$ and 0.01, respectively). Seventeen of the 21 patients (81.0%) displayed typical LGE in the RVIPs pre- and post-procedurally with partially triangular extension to the septum.

The pre- and post-procedural T1 mapping values are presented in Table 3. Significant differences were observed for the septum ($p < 0.05$), the upper RVIP ($p < 0.001$) and for the AA-T1 values ($p < 0.001$), whereas the mean T1 values of the lower RVIP ($p > 0.06$) and the lateral wall ($p = 0.43$) were not significantly different. In addition, the ROIs in all areas measured were not significantly different in size, which means that comparable areas within the myocardium were measured before and after BPA. The inter-observer (upper RVIP, $r = 0.919$; lower RVIP, $r = 0.934$; septum, $r = 0.963$; lateral wall, $r = 0.947$; AA-T, $r = 1$ 0.935; all $p < 0.001$) and intra-observer ($r = 0.937$; $r = 0.939$; $r = 0.976$; $r = 0.939$; $r = 0.956$; all $p < 0.001$) variability for native T1 was very low in all areas.

Figure 1 shows the pre- and post-procedural native T1 maps and corresponding LGE images in a patient who was successfully treated by BPA and demonstrated improved right ventricular function and pulmonary haemodynamics. The T1 measurements were performed within ROIs (white borders) in the native T1 maps pre- and post-BPA and revealed significant decreases for the upper RVIP (1,090 ms to 1,043 ms), for the lower RVIP (1,063 ms to 1,023 ms), for the septum (1,022 ms to 1,005 ms), and for the lateral wall (997 ms to 982 ms). Correlations of native T1 mapping with RV function (RVEF) and pulmonary haemodynamics (mPAP and PVR) are given in Table 4 and corresponding scatter plots are presented in Fig. 2. Before BPA there were moderate significant positive correlations between native T1 values and mPAP ($r = 0.59$; $p < 0.01$) or PVR ($r = 0.53$; $p < 0.05$) and a moderate negative correlation between native T1 values and RVEF ($r =$

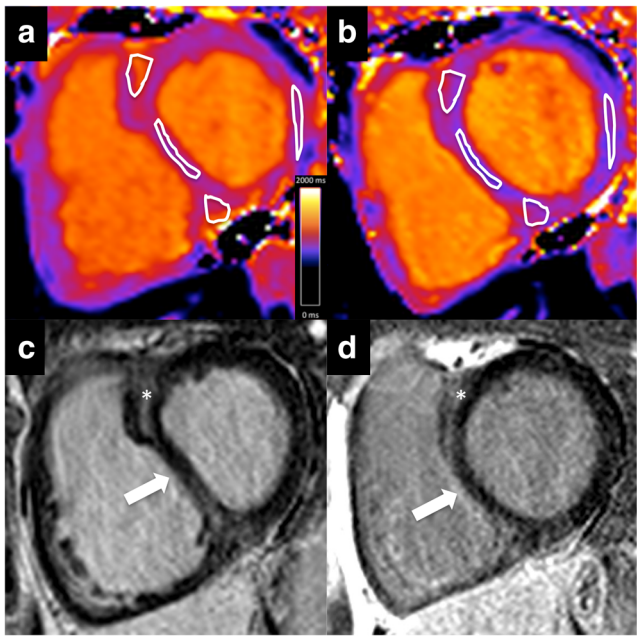

Fig. 1 Native T1 maps and LGE images at basal short axis section in a CTEPH patient pre-and post-BPA. Native T1 maps pre-BPA (**a**) and post-BPA (**b**) and corresponding LGE images pre-BPA (**c**) and post-BPA (**d**) in a 55-year-old man with CTEPH at the basal short-axis level. Pre-procedurally the patient had a mPAP of 51 mmHg at rest and an RVEF of 23.3%. Post-procedurally, mPAP decreased to 35 mmHg and RVEF increased to 45.4%. The patient had a PH-typical LGE pattern in the upper and lower RVIP (*white asterisk*), but the inversed septum receded after BPA (*white arrow*). Consequently, the left and right heart chamber sizes normalised

Table 4 Parameter correlations

	r	CI 95%	*p* value
RVEF to AA-T1			
Pre-BPA	-0.6064	-0.8227 to -0.2367	0.0036
Post-BPA	-0.2105	-0.5887 to 0.2433	0.3596
AA-T1 to mPAP			
Pre-BPA	0.5854	0.2057 to 0.8119	0.0053
Post-BPA	0.3013	-0.1499 to 0.6486	0.1844
AA-T1 to PVR			
Pre-BPA	0.5327	0.1311 to 0.7841	0.0129
Post-BPA	0.3545	-0.0911 to 0.6818	0.1149

Values are mean ± SD or absolute values

BPA balloon pulmonary angioplasty, *mPAP* mean pulmonary artery pressure, *PVR* pulmonary vascular resistance, *RVEF* right ventricular ejection fraction, *SD* standard deviation, *AA-T1* area-adjusted T1 time

-0.61; $r < 0.01$). Six months after BPA these correlations were no longer significant, but a trend towards positive and negative correlation levels still existing ($r = -0.21$, $r = 0.30$ and $r = 0.35$, respectively).

Discussion

To the best of our knowledge, this is the first study to determine the effects of BPA in inoperable CTEPH patients on native T1 time and to correlate the results with RV function and pulmonary haemodynamics. The changes in native T1 times and the moderate correlations with RV function (RVEF) and haemodynamics (mPAP and PVR) in our study are in line with results of previous investigations [31–33]. The increase in RVEF and the decrease in mPAP and PVR were accompanied by significantly decreased T1 times of

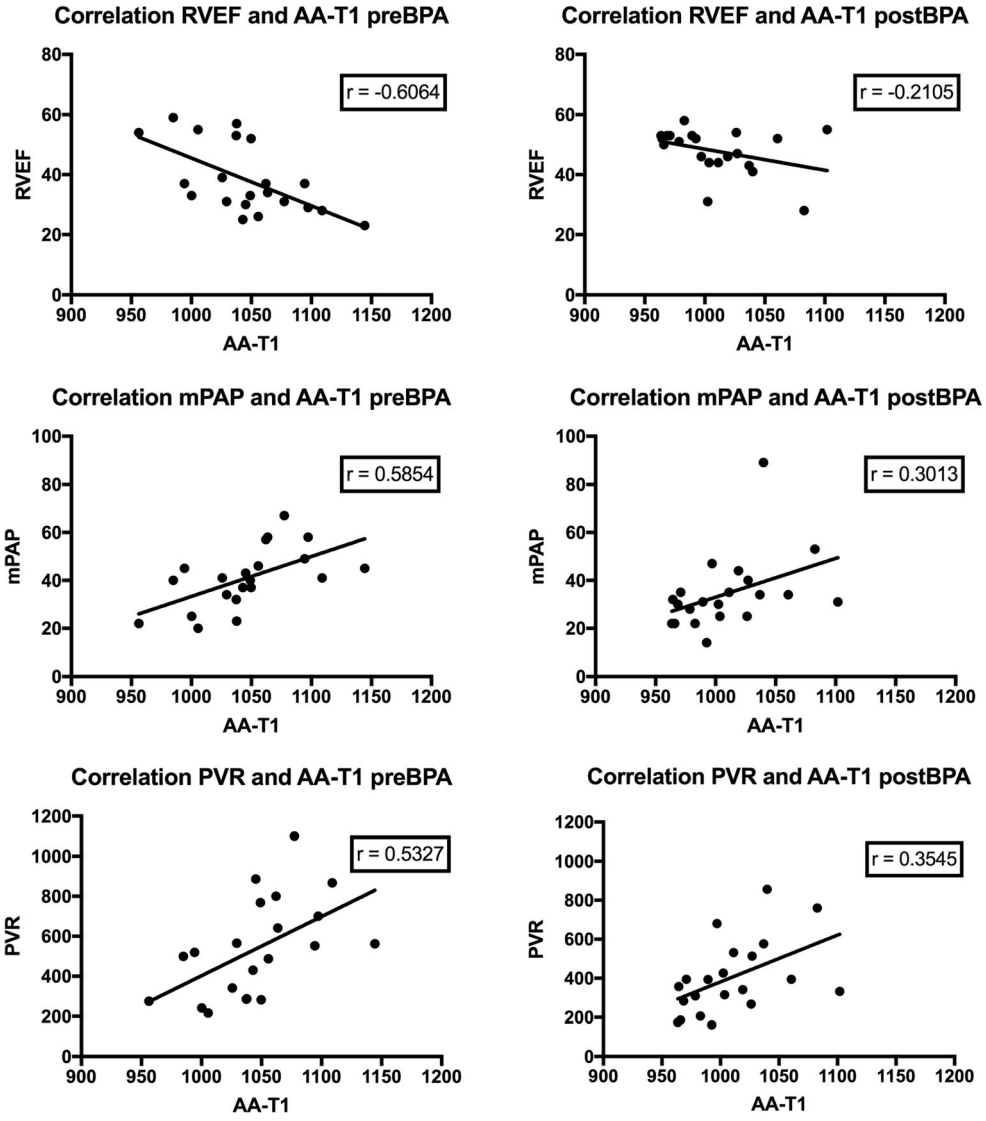

Fig. 2 Scatter plots showing the correlations of AA-T1 to RVEF, mPAP and PVR before and after BPA

the septum, suggesting reverse remodelling of the RV. Septal myocardial remodelling might be explained or rather triggered by possible mechanisms including traction, compression and shear forces due to the RV overload, deterioration and dyskinesia. Normal T1 values could be observed for the RV lateral wall, which therefore might not to be affected [32]. Interestingly, the post-procedural native septal T1 times still correlated weakly with RV function and haemodynamics.

Up to one-third of all CTEPH patients are not eligible for PEA due to the presence of peripherally located lesions [3]. BPA is considered an emerging interventional treatment option for these patients [20, 21, 40]. Non-invasive CMR is useful in PH to assess RV structure, function and morphology. In MRI follow-up studies with CTEPH patients undergoing PEA and BPA, promising results showing enhanced biventricular function and pulmonary flow [25] and improved interventricular dys-synchrony [26] have been reported.

Although improvements in right ventricular function and haemodynamics are well documented for PEA and BPA, little is known about therapy-related cardiac tissue remodelling. LGE in the RVIPs and the septum, which is frequently present in patients with PH [41, 42], is associated with worse outcome in several cardiac diseases [43–46]. However, LGE is only a dichotomous parameter that requires at least 15% of focal matrix expansion to display a myocardial scar [47]; therefore, LGE is limited for characterisation of diffuse tissue alterations, which makes it unsuitable for assessment of treatment effects in diffusely diseased right ventricles. In contrast, mapping techniques (parametric imaging) are increasingly being used within CMR protocols with promising results due to their ability to characterise and to quantify myocardial tissue on a pixel-by-pixel basis.

Native T1 mapping enables characterisation (with characteristics related to the whole myocardium) and visualisation of fundamental myocardial disease processes caused by alterations of tissue composition and structure without the need for contrast agent. Initial results in patients with pre-capillary PH or CTEPH showed good correlations between native T1 mapping and RV function and haemodynamics [31–33]. Since follow-up studies are still lacking, we asked whether the effects of treatment might be assessable via native T1 mapping at the tissue level.

The main limitation of the study is the relatively small number of patients. However, our pre-procedural native T1 mapping results and pre- and post-procedural functional and haemodynamic results are in good agreement with previously published studies [31–33], and experienced cardiac radiologists performed all measurements. Measurement and analysis of post-contrast T1 times and extracellular volume calculation might have provided additional information on the underlying nature of tissue alterations.

Conclusions

Our results suggest two primary conclusions: (1) native T1 measurements of the septal wall reflect tissue alterations that are associated with PH, especially against the background that native T1 values significantly decrease and haemodynamics return to almost normal after successful BPA; (2) BPA not only improves pulmonary arterial haemodynamics but also causes reverse remodelling of the right ventricular myocardium, which is paralleled by improved RV function. These assumptions are based on previous findings that T1 times reflect the myocardial collagen content and hence the degree of fibrosis [34]. Therefore, native T1 mapping holds promise to distinguish patients who will develop reverse remodelling after BPA and those who will not. Further research employing large-scale trials is needed to corroborate these findings.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- prospective
- prognostic study/observational/experimental
- performed at one institution

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Research Article

Pulmonary Circulation

Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic disease

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Abstract

Symptomatic patients with residual pulmonary perfusion defects or vascular lesions but no pulmonary hypertension at rest are diagnosed with chronic thromboembolic disease (CTED). Balloon pulmonary angioplasty (BPA) is an emerging treatment for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), but data regarding the safety and efficacy of BPA in patients with CTED are lacking. We report a prospective series of ten consecutive patients with CTED who underwent 35 BPA interventions (median of four per patient) at two German institutions. All patients underwent a comprehensive diagnostic workup at baseline and 24 weeks after their last intervention. BPA was safe, with one pulmonary vascular injury and subsequent self-limiting pulmonary bleeding as the only complication (2.9% of the interventions, 10% of the patients). After the procedures, World Health Organization functional class, 6-min walking distance, pulmonary vascular resistance, and pulmonary arterial compliance improved, and NT-proBNP concentrations declined in 9/10 patients. BPA may be a new treatment option for carefully selected patients with CTED. A larger, prospective, international registry is required to confirm these results.

Keywords

chronic thromboembolic disease, chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty

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Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as symptomatic pulmonary hypertension (PH) due to non-resolving pulmonary emboli with a mean pulmonary arterial pressure (mPAP) of at least 25 mmHg, normal pulmonary arterial wedge pressure (PAWP; ≤15 mmHg), and perfusion defects that persist despite at least three months of anticoagulation.[1] It is assumed that PH develops due to an obstruction of at least 40–60% of the pulmonary vasculature,[2] but the role of the ensuing

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small-vessel pulmonary vascular remodeling remains unclear.[3,4] In addition, patients may be symptomatic with persistent pulmonary perfusion defects but no PH at rest. These patients are referred to as having chronic thromboembolic disease (CTED).[5]

Surgical pulmonary endarterectomy (PEA) is the gold-standard treatment for CTEPH and is potentially curative.[6,7] Successful PEA has also been reported in patients with CTED, with perioperative mortality rates in the range of 0–0.9%.[6,8,9] Due to the low risk of the procedure, PEA surgery is the treatment of choice for operable, symptomatic patients with CTED.[10]

Approximately one-third of all CTEPH patients are inoperable, however, mostly due to peripheral localization of pulmonary vascular obstructions.[11] These findings can probably be extrapolated to CTED patients. Currently, an increasing number of inoperable CTEPH patients are treated with balloon pulmonary angioplasty (BPA) in addition to targeted medical therapy.[12–17] Hence, BPA may also be considered a treatment option for patients with inoperable CTED,[11] but data on the application of BPA in this population are lacking.

Here, we present the results of the first ten consecutive CTED patients who underwent BPA in Germany.

Methods

Patient selection

The two centers participating in this study (Hannover Medical School and the Kerckhoff Clinic, Bad Nauheim) hold weekly conferences of a multidisciplinary team consisting of experienced PEA surgeons, interventional radiologists, cardiologists and/or pulmonologists, and anesthesiologists, if required, to discuss particular cases.[15] CTED was diagnosed in symptomatic patients in at least World Health Organization (WHO) functional class (FC) II with pulmonary vascular lesions on computed tomography (CT) or PA angiography but with mPAP < 25 mmHg at rest.[5] Patients were deemed inoperable based on a comprehensive assessment of imaging findings for peripherally located lesions that were not surgically approachable.[18] Per protocol, PH-targeted medication was not introduced before BPA.

All patients were informed in detail about the innovative nature of the procedure, including potential risks and benefits, and gave written consent to participate. The ethics committees of both institutions approved this prospective observational study.

Clinical assessment

As previously described,[15] all patients underwent standardized assessment before the first BPA and six months after the last intervention. Assessment included WHO FC, 6-min walking distance (6MWD) with Borg dyspnea index, pulmonary function testing including lung diffusion capacity for carbon monoxide (DLCO), serum levels of creatinine (with calculation of the estimated creatinine clearance) and of the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), echocardiography, and right heart catheterization to determine right atrial pressure, pulmonary arterial pressures, PAWP, cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR), pulmonary arterial compliance (PAC), and mixed-venous oxygen saturation (SvO_2). Cardiac magnetic resonance imaging (MRI) was used in the majority of patients to assess right ventricular (RV) function.

Balloon pulmonary angioplasty

BPA was performed as a staged procedure, with treatment of a limited number of pulmonary segments during each session. All procedures were performed in conscious patients with local anesthesia. The two centers used a common standard procedure:[15] a detailed plan for all interventions was established before the first session using angiographic und CT findings with the aim to treat all target lesions. Short-term web-like stenoses and long-segment obstructions in sub- and sub-subsegmental pulmonary arterial branches were considered as target lesions. Using a femoral or jugular access, a sheath was placed in the pulmonary artery and a guiding catheter was inserted into the target segmental arteries. The guidewire was then inserted into the target subsegmental branches, which were subsequently dilated by multiple balloon inflations. Based on the measured vessel diameter in CT and angiography slightly undersized balloons were used in all cases to avoid pulmonary arterial rupture. A final pulmonary angiogram documented the post-procedural morphologic result. In Hannover, selective C-Arm CT was also used to localize the target lesions.[17]

Statistical analysis

All data for continuous variables are expressed as mean $\pm$ 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. Within-subject comparisons are made across repeated observations without correction for multiple comparisons. The CTED 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 be statistically significant.

Results

Baseline characteristics, effects of BPA, and procedures

Between August 2013 and June 2017, ten consecutive CTED patients were treated with BPA; three in Hannover and seven in Bad Nauheim. In the same time period, 33 CTED

Table 1. Characteristics of patients at time of inclusion.

	Last measurement before first intervention
Patients (n (%))	10 (100)
Age (years) (median (IQR))	69 (52–75)
Female (n (%))	9 (90)
Body mass index (kg/m^2) (median (IQR))	28 (25–30)
History of VTE (n (%))	4 (40)
Interval between CTED diagnosis and first BPA (months) (median (IQR))	16 (4–35)
Pulmonary function	
TLC (% pred)	102 ± 9
FVC (% pred)	96 ± 9
FEV_1 (% pred)	94 ± 10
PH therapy	
Tadalafil (n (%))	2 (20)
Anticoagulation	
Vitamin K antagonist (n (%))	3 (30)
FXa inhibitor (n (%))	7 (70)

Values are given as mean ± SD unless otherwise indicated.
IQR, interquartile range; VTE, venous thromboembolism; CTED; chronic thromboembolic pulmonary disease; BPA, balloon pulmonary angioplasty; TLC, total lung capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

patients underwent PEA: four in Hannover and 29 in Bad Nauheim. The demographics and baseline characteristics of the patients who underwent BPA are depicted in Table 1. The majority (9/10) were women. Follow-up ended in June 2017. The median duration between CTED diagnosis and first BPA was 16 (IQR = 4–35) months.

All patients were treated with anticoagulants at least three months before diagnosis. Despite mPAP < 25 mmHg at the time of diagnosis, two patients received PH-targeted medical therapy with the phosphodiesterase 5 inhibitor sildenafil that was introduced at least three months before baseline assessment and kept unchanged during the study. Neither of these patients experienced improvement of their physical capacity under medication.

A total number of 35 interventions were performed: ten in Hannover and 25 in Bad Nauheim. In both centers, the median number of interventions per patient was four (range = 1–5). The median number of vessels targeted in all interventions was ten (range = 2–14). The median duration from first BPA to the 24-week follow-up assessment was 11 months (IQR = 9–14 months).

Treatment response

The effects of BPA on hemodynamics, RV function, serum NT-proBNP, and exercise capacity are presented in Table 2. The WHO FC improved in nine (90%) patients and remained unchanged in one (10%) patient. The 6MWD improved by an average of 31 m (about 8.5% from baseline) and this was accompanied by a reduction in the Borg dyspnea index. Hemodynamic assessment showed improvement in CO and SvO_2, whereas mPAP was unchanged. There was a distinct decrease in PVR. Furthermore, PAC improved after BPA. DLCO and pO_2 increased somewhat, but these changes were not statistically significant. RV function was unchanged on MRI before and after treatment.

Complications

One procedure-related complication (Hannover, n = 0; Bad Nauheim, n = 1) occurred during the 35 interventions (2.9% of all interventions, 10% of the patients). This adverse event was caused by wire perforation of the pulmonary vasculature, resulting in parenchymal bleeding with mild hemoptysis; intervention was not required. All of the patients were alive at the end of the observation period.

Discussion

The observations presented here focus on the use of BPA in inoperable symptomatic CTED patients. We demonstrate individual improvements in exercise capacity (6MWD, WHO FC) and pulmonary hemodynamics (PVR, PAC). Furthermore, we show that BPA is feasible and relatively safe in this particular group of patients.

CTED was only described recently and there are only a few reports addressing treatment of these patients. In 13 years, only 42 out of 1019 patients undergoing PEA in a UK cohort were diagnosed with CTED.[8] PEA programs worldwide have shown excellent results, with functional improvements and low mortality rates.[5,7–9] Taboada et al. reported improvements in WHO FC, 6MWD, and PVR in 39 CTED patients before and six months after PEA: 20 patients were in WHO FC II and 22 in FC III before PEA; 16 patients were in WHO FC I, 21 in II, and two in FC III after PEA.[8] The 6MWD improved from 372 m to 413 m, and the PVR at rest decreased from 164 dynes to 128 dynes. These findings are in line with van Kan et al. who described changes in physical capacity and pulmonary hemodynamics in nine CTED patients one year after PEA: all patients were regrouped into WHO FC I after PEA and the 6MWD improved from 517 m to 548 m.[19] Therefore, PEA has become an accepted therapeutic strategy for symptomatic CTED patients, who potentially represent the lower border of the wide spectrum of CTEPH patients.[10] Based on experiences with CTEPH, however, it can be speculated that around one-third of all CTED patients are deemed inoperable. Previous data indicated that BPA may be feasible and effective in patients with lower mPAP.[19]

Our preliminary results suggest that BPA may be an effective interventional treatment for patients with inoperable CTED, leading to improvements in WHO FC and pulmonary hemodynamics in the majority of the patients. The mean PVR reduction of 67 dynes*s/cm^5 is comparable to the results published for PEA procedures.[7–9]

Table 2. Changes from baseline to week 24.

	n	Baseline	n	Week 24	*P* value
Exercise capacity					
WHO functional class (n (%))	10		10		
I		0 (0)		4 (40)	**0.004**
II		1 (10)		5 (50)	
III		9 (90)		1 (10)	
IV		0 (0)		0 (0)	
6MWD (m)	10	365 ± 139	10	396 ± 142	0.11
Borg dyspnea scale (1–10)	6	4.0 ± 1.0	6	1.8 ± 0.9	0.13
Hemodynamics and NT-proBNP					
Right atrial pressure (mmHg)	10	4 ± 2	10	6 ± 3	0.12
mPAP (mmHg)	10	21 ± 2	10	20 ± 3	0.74
systPAP (mmHg)	10	35 ± 6	10	31 ± 7	0.31
diastPAP (mmHg)	10	10 ± 4	10	11 ± 2	0.38
PAWP (mmHg)	10	8 ± 3	10	10 ± 2	**0.02**
DPG (mmHg)	10	3 ± 3	10	1 ± 1	0.20
TPG (mmHg)	10	12 ± 3	10	9 ± 3	**0.02**
CO (L/min)	10	4.3 ± 0.5	10	4.5 ± 0.7	0.32
CI (L/min/m^2)	10	2.4 ± 0.3	10	2.5 ± 0.4	0.38
PVR (dyn·s·cm^{-5})	10	234 ± 68	10	167 ± 40	**0.004**
PAC (mL/mmHg)	10	3.2 ± 2.1	10	4.1 ± 1.7	**0.027**
SvO_2 (%)	10	65 ± 9	10	69 ± 4	0.22
HR (bpm)	10	65 ± 9	10	64 ± 8	0.66
NT-proBNP, ng/L (median (IQR))	10	144 (60–227)	10	109 (87–194)	0.56
Blood gas analysis and pulmonary function					
PaO_2 (mmHg)	7	68 ± 13	7	71 ± 7	0.69
SaO_2 (%)	7	95 ± 3	7	96 ± 1	0.94
$PaCO_2$ (mmHg)	7	34 ± 3	7	35 ± 3	0.38
DLCO (% predicted)	7	60 ± 11	7	69 ± 18	0.19
MRI findings					
LV-EF (%)	6	68 ± 9	6	69 ± 5	0.88
LV-SV (mL)	6	76 ± 3	6	76 ± 8	0.81
LV-EDV (mL)	6	114 ± 18	6	112 ± 15	0.63
LV-ESV (mL)	6	39 ± 15	6	36 ± 10	0.44
RV-EF (%)	6	55 ± 1	6	55 ± 4	0.99
RV-SV (mL)	6	75 ± 16	6	68 ± 10	0.31
RV-EDV (mL)	6	135 ± 26	6	125 ± 22	0.19
RV-ESV (mL)	6	60 ± 10	6	57 ± 14	0.38
Laboratory findings					
Creatinine (μmol/L)	10	76 ± 25	8	82 ± 23	0.99
eGFR (mL/min)	8	81 ± 28	8	67 ± 19	0.56

Values are given as mean ± SD unless otherwise indicated.

WHO, World Health Organization; mPAP, mean pulmonary artery pressure; systPAP, systolic pulmonary artery pressure; diastPAP, diastolic pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; DPG, diastolic pressure gradient; TPG, transpulmonary gradient; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; SvO_2, mixed venous oxygen saturation; HR, heart rate; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PaO_2, partial pressure of oxygen; SaO_2, oxygen saturation; $PaCO_2$, partial pressure of carbon dioxide; DLCO, lung diffusion capacity for carbon monoxide; MRI, magnetic resonance imaging; LV, left ventricular; RV, right ventricular; EF, ejection fraction; SV; stroke volume; EDV, end diastolic volume; ESV, end systolic volume; eGFR, estimated glomerular filtration rate based on serum creatinine.

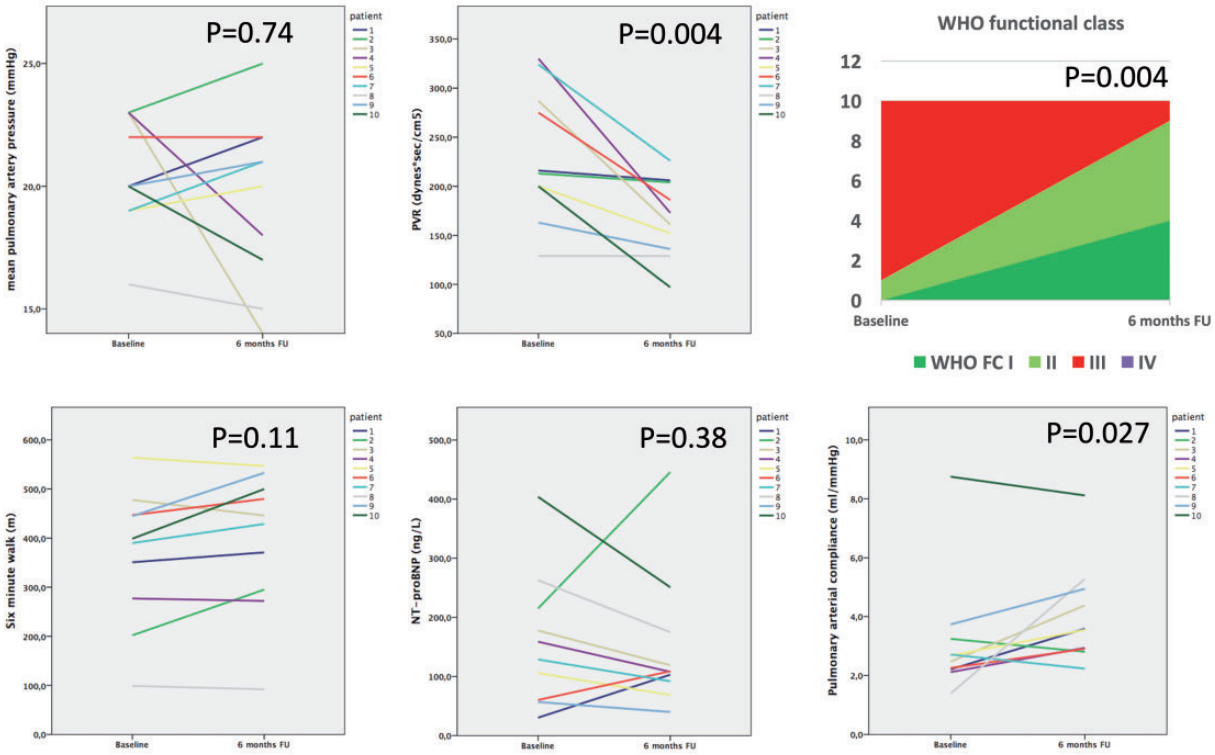

Fig. 1. Individual effects of balloon pulmonary angioplasty on mPAP, PVR, functional capacity, 6MWD, and NT-proBNP. NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance.

Furthermore, we observed a distinct improvement in PAC, which is believed to be one of the most important markers of prognosis in P(A)H patients.[20] However, its meaning in CTED remains unclear.

In our study, 6/10 patients increased their 6MWD and 7/10 patients had a lower NT-proBNP level 6 months after treatment. Overall, however, the changes in 6MWD and NT-proBNP were not statistically significant, potentially due to the low number of patients studied. Nevertheless, 9/10 patients had an improvement in WHO FC, a change that was significant for the cohort as a whole. MRI revealed that RV function was not affected by treatment; these findings before and after treatment. However, these findings could be explained by the absence of PH in this particular group of patients.

The small number of patients enrolled in this study is a major limitation that must be considered. In addition, there was no control group and long-term data are missing. The findings are nevertheless sufficient to demonstrate improvement in physical capacity and PVR. Furthermore, our data may provide a realistic perspective on the treatment of CTED patients in referral centers with an established surgical and interventional program for CTEPH.

Little is known about CTED and it is still being discussed whether it is an early stage in the development of CTEPH. PEA is an accepted surgical treatment for CTED patients, but there is no established treatment for inoperable patients. Our observation is the first to describe the effects of BPA in this particular group of patients. Improvements in physical capacity as well as pulmonary vascular resistance were achieved without severe complications. These data add important new information for the treatment of inoperable CTED patients. However, we have no data concerning prognostic implications of BPA in inoperable CTED patients. The development of a comprehensive therapeutic concept for CTED patients will require additional data and individualized decision-making based on multidisciplinary experience.

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Conflict of interest

The author(s) declare the following conflicts of interest: CB Wiedenroth has received speaker fees or consultant honoraria from Actelion, Bayer AG, BTG, MSD, and Pfizer. KM Olsson has received speaker fees from Actelion, Bayer, GSK, Pfizer, and United Therapeutics. S Guth has received speaker fees from Actelion, Bayer, GSK, and Pfizer. E Mayer has received speaker fees and/or honoraria for consultations from Actelion, Bayer, GSK, MSD, and Pfizer. 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. BC Meyer has received speaker fees from Bayer, MSD, and Siemens Healthineers. C Liebetrau has received speaker fees from Abbott, Astra Zeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Daiichi Sankyo, Elixir Medical, and Pfizer. The rest of the authors have nothing to disclose.

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Research Article

Pulmonary Circulation

Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension

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Abstract

Riociguat is the treatment of choice for inoperable patients with chronic thromboembolic pulmonary hypertension (CTEPH). We addressed here whether additional balloon pulmonary angioplasty (BPA) provides further benefits. A prospective series of 36 consecutive patients with inoperable CTEPH were treated with riociguat at least three months before BPA. All patients underwent diagnostic workup at baseline, before BPA treatments, and six months after final intervention. The main outcome measures were pulmonary hemodynamic parameters and World Health Organization (WHO) functional class (FC). Significant improvements in pulmonary hemodynamics and physical capacity were observed for riociguat treatment, and subsequent BPA interventions yielded further benefits. With targeted medication, WHO FC improved by at least one class in 13 (36.1%) patients ($P = 0.01$). Hemodynamic assessment showed significant improvements in mean pulmonary arterial pressure (mPAP) (49 ± 12 mmHg vs. 43 ± 12 mmHg; $P = 0.003$) and PVR (956 ± 501 dyn·s·cm^{-5} vs. 517 ± 279 dyn·s·cm^{-5}; $P = 0.0001$). Treatment with a combination of targeted medication and BPA resulted in WHO FC improvement in 34 (94.4%) patients. Hemodynamic assessment showed significant improvement in mPAP (43 ± 12 mmHg vs. 34 ± 14 mmHg; $P = 0.0001$) and PVR (517 ± 279 dyn·s·cm^{-5} vs. 360 ± 175 dyn·s·cm^{-5}; $P = 0.0001$). These findings provide, for the first time, support for the therapeutic strategy recommended by current guidelines.

Keywords

chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, targeted medication, riociguat

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Approximately one-third of all patients with diagnosed chronic thromboembolic pulmonary hypertension (CTEPH) are not amenable to surgical pulmonary endarterectomy (PEA), mainly due to peripheral localization of pulmonary vascular obstructions.[1] Several pulmonary arterial hypertension (PAH) therapies have been considered for use

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in CTEPH patients: bosentan, an endothelial receptor antagonist,[2] and sildenafil, an inhibitor of phosphodiesterase-5,[3] were found to improve pulmonary hemodynamics, but there was no significant change in patients' physical capacity, and randomized controlled trials (RCT) failed to meet their primary endpoint. Riociguat, a stimulator of soluble guanylate cyclase, is the first drug that improves not only pulmonary hemodynamics but also the physical capacity of inoperable CTEPH patients, and it is the first drug that has been approved for this indication.[4–6]

An increasing number of inoperable CTEPH patients are currently being treated with balloon pulmonary angioplasty (BPA), but the use of targeted medical treatment differs among various centers.[7–13] As the evidence for BPA is still scarce, with a lack of long-term data and/or controlled clinical trials, this interventional therapy is not clearly recommended in current guidelines. Moreover, guidelines describe BPA as a further, additional treatment option for inoperable CTEPH patients (IIb C) after initiating riociguat without any evidence to support this recommendation.[14]

Therefore, the aim of the present study was to determine the effects of riociguat treatment in inoperable CTEPH patients with BPA-feasible target lesions determined by angiography. Furthermore, additional effects of BPA on top of medical treatment were investigated.

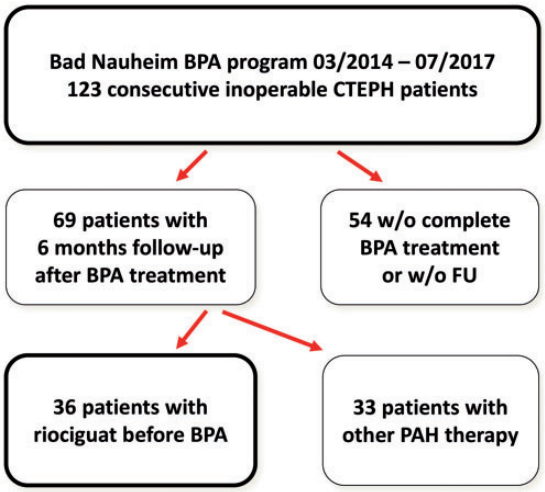

Fig. 1. Flow chart describing the balloon pulmonary angioplasty program in Bad Nauheim showing patient selection.

Methods

Patient selection

Patients admitted to the Kerckhoff Clinic, Bad Nauheim, Germany, who, after evaluation in a multidisciplinary CTEPH conference, were scheduled for BPA between March 2014 and July 2017 were considered eligible for inclusion in the present prospective, observational cohort study. The Kerckhoff Clinic serves as an international reference center for CTEPH, with >150 PEA and >200 BPA procedures performed per year. CTEPH was diagnosed in symptomatic patients who presented in at least World Health Organization (WHO) functional class (FC) II with a mean pulmonary arterial pressure (mPAP) of at least 25 mmHg at rest and with pulmonary vascular lesions on computed tomography and conventional biplanar pulmonary artery angiography. Patients were deemed technically inoperable based on a comprehensive assessment of imaging findings; they were included in the study if they were considered to be amenable to BPA. Patients were treated with riociguat and BPA was offered after a period of at least three months of targeted medication if WHO FC was still ≥II.

A total of 123 consecutive patients underwent BPA treatment. Follow-up after six months was completed in 69 patients. Of these, 36 patients were without targeted medication at the time of referral (Fig. 1); these patients served as the study cohort.

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 patients included were also enrolled in the New International CTEPH Database of the International CTEPH Association (NCT02656238).

Clinical assessment

All patients underwent standardized assessment: (1) before initiation of medical treatment; (2) before the first BPA; and (3) six months after the last intervention. Assessment included WHO FC, 6-min walking distance (6MWD), serum levels of creatinine (with calculation of the estimated creatinine clearance) and of the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), and right heart catheterization to determine right atrial pressure (RAP), pulmonary arterial pressures (PAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), and pulmonary vascular resistance (PVR) (Fig. 2).

Targeted medical therapy

Targeted medical therapy with riociguat was initiated in an outpatient setting. The initial dose was 1 mg three times daily, which was increased to the maximally tolerated dose (up to 2.5 mg three times daily) within 4–6 weeks.

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 (and light sedation, if required). The standard procedure has been described previously.[13] Briefly,

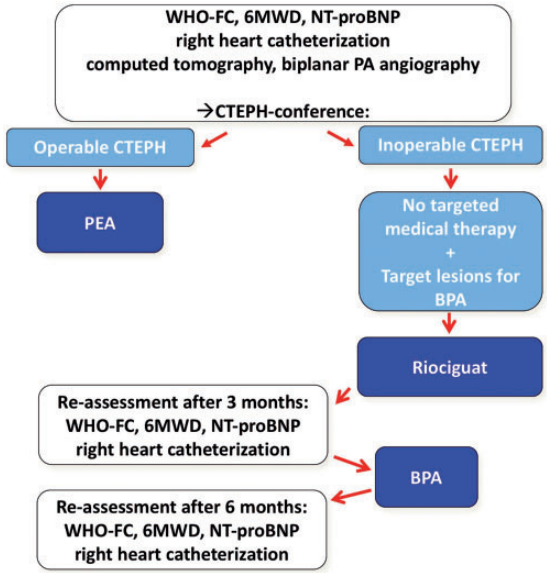

Fig. 2. Study flow chart for the 36 patients included in the study.

using femoral or jugular access, a sheath was placed in the pulmonary artery and a guiding catheter was inserted into the target segmental arteries. The guide wire was then advanced into the target subsegmental branches, which were subsequently dilated by multiple balloon inflations. Final pulmonary angiography documented the post-procedural morphological result.

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. Longitudinal comparisons were made across repeated observations without correction for multiple comparisons. 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.

Results

Baseline characteristics and procedures

A total of 36 consecutive patients underwent BPA after initiation of targeted medication with riociguat. The demographics and baseline characteristics of these patients before riociguat administration are given in Table 1. The hemodynamics and functional capacity before riociguat are shown in Table 2. The follow-up was concluded in July 2017.

All patients were treated with riociguat and medical therapy was continued even after the six-month follow-up.

Table 1. Baseline characteristics of patients at time of inclusion.

	Last measurement before riociguat treatment
Patients (n (%))	36 (100)
Age (years) (median (IQR))	62 (50–71)
Female (n (%))	14 (38.9)
Body mass index (kg/m^2) (median (IQR))	24 (23–27)
History of VTE (n (%))	10 (27.8)
Interval between first symptoms to CTEPH diagnosis (months) (median (IQR))	16 (6–44)
Pulmonary function	
TLC (% pred)	97 ± 25
FVC (% pred)	84 ± 20
FEV_1 (% pred)	83 ± 22
Anticoagulation	
Vitamin K antagonist (n (%))	6 (16.7)
FXa inhibitor (n (%))	30 (83.3)

Values are given as mean ± SD unless otherwise indicated.
IQR, interquartile range; VTE, venous thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; BPA, balloon pulmonary angioplasty; TLC, total lung capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

Table 2. Baseline functional capacity and hemodynamics of patients at time of inclusion.

	n	Last measurement before riociguat treatment
Exercise capacity		
WHO FC (n (%))	36	
I		0 (0)
II		0 (0)
III		19 (52.8)
IV		17 (47.2)
6MWD (m)	26	389 ± 108
Hemodynamics and NT-proBNP		
mPAP (mmHg)	36	49 ± 12
PAWP (mmHg)	36	9 ± 4
CO (L/min)	36	4.3 ± 1.3
CI (L/min/m^2)	36	2.2 ± 0.6
PVR (dyn·s·cm^{-5})	36	956 ± 501
NT-proBNP (ng/L) (median (IQR))	31	1137 (283–2142)

Values are given as mean ± SD unless otherwise indicated.
WHO, World Health Organization; FC, functional class; 6MWD, 6-min walking distance; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide.

Table 3. Functional capacity and hemodynamics with riociguat and 6 months after BPA.

	n	Under riociguat	n	6 months after BPA	*P* value
Exercise capacity					
WHO FC (n (%))	36		36		0.0001
I		0 (0)		18 (50.0)	
II		7 (19.4)		16 (44.4)	
III		18 (50.0)		2 (5.6)	
IV		11 (30.6)		0 (0)	
6MWD (m)	32	409 ± 102	30	467 ± 95	0.0001
Hemodynamics					
Right atrial pressure (mmHg)	36	7 ± 4	36	6 ± 3	0.02
mPAP (mmHg)	36	43 ± 12	36	34 ± 14	0.0001
sPAP (mmHg)	36	74 ± 21	36	59 ± 25	0.0001
dPAP (mmHg)	36	25 ± 7	36	18 ± 8	0.0001
PAWP (mmHg)	36	10 ± 3	36	10 ± 3	0.92
DPG (mmHg)	36	15 ± 7	36	8 ± 8	0.0001
TPG (mmHg)	36	33 ± 11	36	24 ± 13	0.0001
CO (L/min)	36	5.0 ± 1.5	36	5.5 ± 1.3	0.0001
CI (L/min/m^2)	36	2.6 ± 0.7	36	2.9 ± 0.6	0.02
PVR (dyn·s·cm^{-5})	36	517 ± 279	36	360 ± 175	0.0001
PAC (mL/mmHg)	36	1.4 ± 0.6	36	2.3 ± 1.0	0.0001
HR (bpm)	36	78 ± 12	36	70 ± 11	0.001
Laboratory findings					
NT-proBNP (ng/L) (median (IQR))	29	1,010 (128–1,887)	35	150 (75–385)	0.0001
Creatinine* (mg/dL)	28	0.98 ± 0.31	36	0.91 ± 0.28	0.02
eGFR (mL/min)	28	82 ± 28	36	94 ± 59	0.05

Values are given as mean ± SD unless otherwise indicated.
*To convert mg/dL to mmol/L divide by 11.3.
WHO, World Health Organization; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; DPG, diastolic pressure gradient; TPG, transpulmonary gradient; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; HR, heart rate; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

In eight patients, the full dose could not be administered due to side effects (e.g. arterial hypotension, gastrointestinal disorders). The interval between initiation of targeted medication to first BPA was five months (range = 2–18 months). A total number of 195 interventions were performed. The median number of sessions per patient was five (range = 5–6). The median number of pulmonary segments targeted in all interventions was 11 (range = 8–13). The median duration from first BPA to the six-month follow-up assessment was 14 months (IQR = 12–16 months).

Response to treatment with targeted medication

The effects of targeted medical treatment with riociguat on hemodynamics, serum NT-proBNP, and exercise capacity (WHO FC, 6MWD) in comparison with baseline are presented in Table 3 and Fig. 3. The WHO FC improved by at least one class in 13 (36.1%) patients and remained unchanged in 23 (63.9%) patients ($P = 0.01$). The 6MWD improved by an average of 20 m (5% from baseline; range = 1–17%), but this was not a significant change ($P = 0.88$). Hemodynamic assessment showed significant improvements in mPAP (49 ± 12 mmHg vs. 43 ± 12 mmHg; $P = 0.003$) and PVR (956 ± 501 dyn·s·cm^{-5} vs. 517 ± 279 dyn·s·cm^{-5}; $P = 0.0001$). NT-proBNP levels were significantly decreased (baseline = 1137 ng/L [IQR = 283–2142] vs. under riociguat = 1010 ng/L [IQR = 128–1887]; $P = 0.02$).

Response to treatment with a combination of targeted medication and BPA

The effects of BPA on hemodynamics, serum NT-proBNP, and exercise capacity in comparison with the assessment after at least three months of riociguat are presented in Table 3 and Fig. 3. The WHO FC improved in 34 (94.4%) patients and remained unchanged in two (5.6%) patients. The 6MWD after BPA improved by an average of 58 m (12.5%; range = 2–46%) compared with riociguat (riociguat = mean 409 ± 102 m vs. after BPA = 467 ± 95 m;

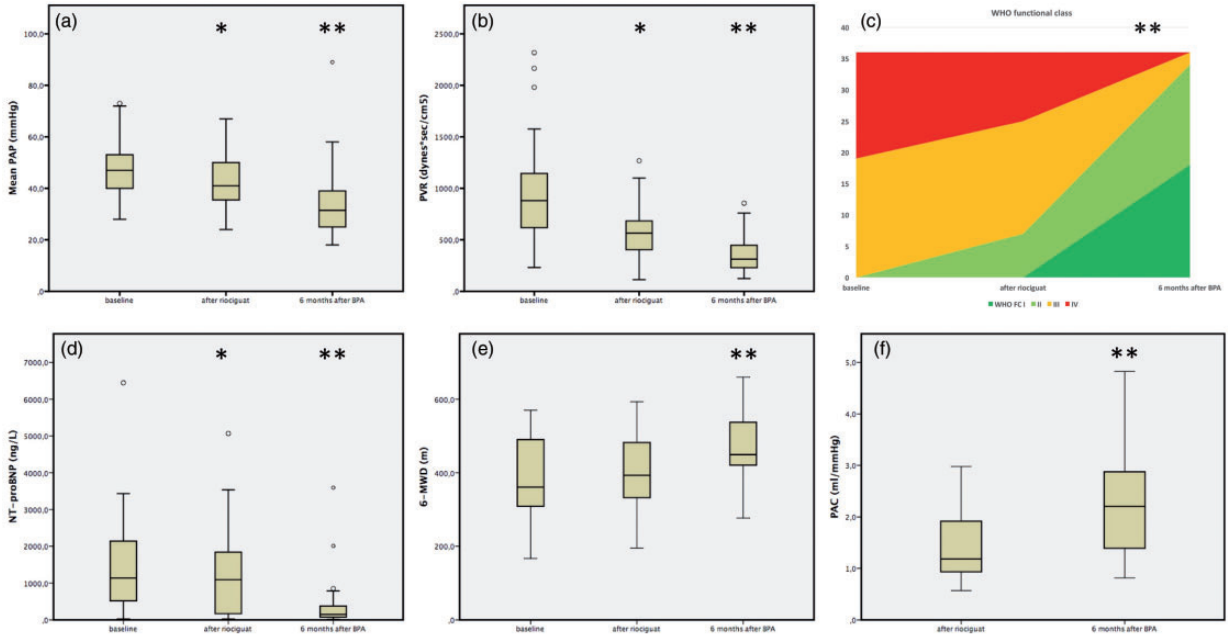

Fig. 3. Effects of riociguat and BPA on (a) mPAP, (b) PVR, (c) WHO FC given in mean values, (d) NT-proBNP, (e) 6MWD, and (f) PAC. The asterisk indicates the significance level (*$P < 0.05$; **$P < 0.001$).

$P = 0.0001$). Hemodynamic assessment showed significant improvement in mPAP and PVR. NT-proBNP was significantly decreased six months after BPA.

Complications of BPA

Twenty-seven procedure-related complications occurred during the 195 interventions (13.8% 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. Seven patients developed reperfusion edema with clinical symptoms (coughing of frothy secretion, desaturation) and consolidations in chest X-ray during the post-procedural period of 6–24 h (3.6% of all interventions). Non-invasive ventilation, which is routinely used even after mild hemorrhage according to the local standard protocol, was performed in 11 patients. Invasive ventilation was not necessary. All of the patients were alive at the end of the observation period.

Discussion

There is incremental evidence from smaller and mid-sized case series that BPA exerts beneficial effects on pulmonary hemodynamics and physical capacity in inoperable CTEPH patients. The impact of administering riociguat, the only approved treatment for inoperable CTEPH, before BPA has not yet been elucidated. Here, we detail the changes in hemodynamics and exercise capacity induced by riociguat and describe the effects of treating with BPA in addition to this targeted medication. The main findings of this study are: (1) targeted medication with riociguat improves hemodynamics and physical capacity in inoperable CTEPH patients amenable to BPA; (2) the additional interventional treatment of these patients by BPA leads to further improvements; (3) the combination of riociguat and BPA is feasible and safe in this particular group of patients. These findings strengthen the evidence for the current recommendation by the guidelines.[14]

The changes in physical capacity and pulmonary hemodynamics under targeted medication are in line with published data.[4] Based on the results of the CHEST-1 study, Ghofrani et al. reported a mean reduction in PVR of 226 (±248) dyn·s·cm^{-5} and WHO FC improved in 33% of the patients; in our present cohort, there was also a mean PVR reduction of 439 dyn·s·cm^{-5} and an improvement in WHO FC in 36.1% of the patients. Furthermore, there were no severe side effects observed and a discontinuation of the medication was not required in any patient; however, full dose acceptance was achieved in 77% of patients.

The outcome measures WHO FC, NT-proBNP, and 6MWD are associated with overall survival at baseline and follow-up,[15] and 6MWD changes from baseline are clearly correlated with survival as reported in the CHEST-2 trial.[6] In the current study, the 6MWD increased by a mean of 20 m after riociguat treatment and a further 58 m after BPA, clearly indicating the benefits of the sequential treatment with riociguat and BPA.

The changes in physical capacity and pulmonary hemodynamics after BPA in our cohort are comparable to the results of other European groups[11,16] but are less distinct than those of Japanese observations.[8–10] This has been discussed previously by our working group[13] and may be due to an especially well-established program of PEA in

Germany that is used less frequently in Japan; thus, some of the patients who underwent BPA in Japan would have been deemed operable in Germany. In our study, patients selected for BPA comprised only those with inoperable disease; hence, patient populations were not comparable. Furthermore, there are no clear data on the use of targeted pretreatment in CTEPH patients treated interventionally. As Lang et al. brought together in their very recent review,[16] there is no consensus for the use of PAH therapies in CTEPH patients. Only one center has presented data from their BPA program in which 40% of the patients treated interventionally were on riociguat;[17] the authors mainly described changes in MRI findings and did not discriminate hemodynamic changes before and during targeted medication and BPA. Just recently, Aoki et al. reported long-term results of their BPA program: PAH medical therapies were administered in 96% of all patients before BPA.[18] However, the use of targeted medication was not standardized: only 17% of all patients received riociguat, which, in fact, represents the best standard of care according to evidence-based criteria; six months after the last intervention the proportion of patients undergoing any targeted treatment was decreased to 68%.[18]

Our results suggest that the combination of targeted medication with riociguat and BPA is an effective treatment for patients with inoperable CTEPH, leading to significant improvements in physical capacity (WHO FC, 6MWD) and pulmonary hemodynamics. These findings support the recommendations for the treatment of inoperable CTEPH patients available in the latest European guidelines.[14] Decreasing PAPs before performing an interventional treatment may be a reasonable concept for avoiding severe complications. However, the observed complication rate is comparable to that of recently published trials.[8–12,16,17] The higher rate of non-invasive ventilation can be explained by the routine use of short-term ventilation even after mild bleeding.

Some limitations to this study must be considered. This is a single-center study of an observational nature. Due to the highly selected population of CTEPH patients, there is no matched control group. However, our analysis reflects "real-world" treatment in an international reference center for CTEPH with high-volume surgical and interventional programs. In addition, this study is the first to investigate the sequential treatment with riociguat and BPA in inoperable CTEPH patients.

This is the first observation focusing on the sequential combination of riociguat and BPA in inoperable CTEPH patients. Despite it being a single-center experience, our study provides a realistic perspective on the management of CTEPH patients in a German referral center with an established surgical and interventional CTEPH program. The combination of targeted medical and interventional treatment shows positive effects on physical capacity and pulmonary hemodynamics in inoperable CTEPH patients. A RCT is required to confirm this concept.

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Conflict of interest

CBW has received speaker fees or consultant honoraria from Actelion, Bayer AG, BTG, MSD, and Pfizer. HAG 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. AR has received a research grant from Pfizer and speaker fees and/or honoraria from Servier, St. Jude Medical, Actelion and Novartis. EM has received speaker fees and/or honoraria for consultations from Actelion, Bayer, GSK, MSD, and Pfizer. SG has received speaker fees from Actelion, Bayer, GSK, and Pfizer. CL has received speaker fees from Abbott, Astra Zeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Daiichi Sankyo, Elixir Medical, and Pfizer. MSDA, AB, MH, CWH, and SK have nothing to disclose.

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FEATURED PAPERS

Combined pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension

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KEYWORDS:
pulmonary endarterectomy; pulmonary hypertension; thromboembolic; unilateral disease; balloon pulmonary angioplasty

BACKGROUND: Pulmonary endarterectomy (PEA) is a curative treatment option for more than 60% of patients with chronic thromboembolic pulmonary hypertension (CTEPH). For selected inoperable patients, interventional balloon pulmonary angioplasty (BPA) has recently been established in addition to medical treatment. This approach disrupts scar tissue occluding the pulmonary arteries, leading to an improvement in parenchymal perfusion. CTEPH is occasionally heterogeneous, with operable disease on one side but peripheral, inoperable changes on the contralateral side. Performing unilateral PEA (on the operable side only) in these patients may lead to a worse hemodynamic outcome and increased mortality compared with patients who that can be surgically corrected bilaterally. We sought to determine the feasibility, safety, and benefits of BPA applied to the contralateral lung in several patients with predominantly unilateral disease that was amenable to treatment by PEA.
METHODS: Standard unilateral PEA in deep hypothermic circulatory arrest was performed in 3 CTEPH patients with poor pulmonary hemodynamics, and inoperability of the contralateral pulmonary artery obstructions was confirmed. The inoperable side was treated by BPA. The intervention was performed during the rewarming phase of cardiopulmonary bypass.
RESULTS: A dramatic improvement in pulmonary hemodynamics, with a mean reduction in pulmonary vascular resistance of 842 dyne · sec/cm^5, was achieved in all patients. World Health Organization Functional Class was also significantly improved at the midterm follow-up.
CONCLUSIONS: The combination of surgical PEA and interventional BPA is a new treatment option for highly selected high-risk CTEPH patients. A multidisciplinary CTEPH expert team is a basic pre-requisite for this complex concept.
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Chronic thromboembolic pulmonary hypertension (CTEPH) is a common form of pulmonary hypertension.[1]

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Up to 4% of patients who survive an episode of acute pulmonary embolism will develop CTEPH.[2,3] Proximal and distal stenoses and occlusions of pulmonary artery (PA) branches lead to PH with consecutive deterioration of right ventricular (RV) function and right heart failure. Increased PA pressure (PAP) and hyperperfusion of the patent vessels cause a secondary microvasculopathy and further clinical deterioration.[4] This vicious circle compromises the pulmonary and systemic circulation and is associated with a poor prognosis.

Patients with CTEPH should be examined and treated in a high-volume center by a specialized team of experts.[1,5–9] The gold standard treatment for CTEPH is pulmonary endarterectomy (PEA). This complex surgical intervention is often curative, with post-operative normalization of the pulmonary hemodynamics, and can be accomplished with a low risk for the patients in experienced centers.[5,6] However, up to 37% of the patients are deemed inoperable.[7] In many countries, medical treatment with the soluble guanylate cyclase stimulator riociguat has been approved for patients with inoperable CTEPH.[10,11]

In 2001, Feinstein et al[12] reported balloon pulmonary angioplasty (BPA) as a new treatment option for patients with inoperable CTEPH.[12] Recently, the procedure has been refined, mostly by Japanese centers, with improved clinical and hemodynamic results with a mean reduction of mean PAP (mPAP) from 43 mm Hg to 25 mm Hg.[13–17]

BPA is performed as a staged procedure to reduce the risk of reperfusion edema and to minimize the amount of injected contrast medium, depending on the patient's actual pulmonary hemodynamics and the number of PA lesions. However, BPA is not a competitive treatment option for operable CTEPH patients but seems to be a promising therapeutical tool for inoperable patients with sub-segmentally located net-like structures or strands ("webs and slits") obstructing PA branches.[15,16]

There are rare cases, however, of technically operable obstructions on one side (mostly right-sided) that could be treated surgically combined with distal contralateral lesions not amenable to surgery that could be target areas for BPA. Depending on the severity of PH, low-risk patients may undergo PEA, and if needed, BPA during follow-up. For patients with very poor pulmonary hemodynamics, however, a staged procedure might carry an extreme peri-operative risk of right heart complications and death. Therefore, PEA in combination with BPA of the inoperable side as a hybrid procedure might be a new therapeutic option for a carefully selected group of high-risk patients to instantly achieve a maximum reduction in RV afterload and to decrease the risk of RV failure after weaning from extracorporeal circulation. We report here 3 patients with severe CTEPH who were treated by combined PEA and BPA.

Pre-operative assessment

All patients were assessed by an experienced multidisciplinary team in an international CTEPH reference center. Clinical history, physical examination, 12-lead electrocardiogram, laboratory tests, echocardiography, cardiopulmonary exercise test, 6-minute walk distance, coronary angiography, right-sided heart catheterization, ventilation and perfusion scintigraphy, computed tomography (CT) angiography, and pulmonary angiography were performed. The results were assessed for all patients.

The 3 patients had bilateral distal PA obstructions that were considered technically operable on the right side with a high likelihood of technical inoperability of the sub-segmental arteries of the left lower lobe. PEA was planned for all 3 patients with the possibility of combined BPA if surgical inaccessibility of the left-sided distal obstructions was confirmed.

Patient 1

A 68-year-old man with inoperable CTEPH was diagnosed in 2011, and combined PH-specific medication was initiated. After further clinical deterioration (World Health Organization Functional Class [WHO FC] IV), the patient was referred to our center for a second opinion. Pulmonary angiography showed lesions in almost every segmental branch of the right PA. On the left side, there were only a few subsegmental obstructions in the lower lobe. Right-sided heart catheterization revealed severe CTEPH (mPAP, 65 mm Hg; pulmonary vascular resistance [PVR], 1,600 dyne • sec/cm^5). The procedure was planned as an endarterectomy of the right PA branches and BPA of the left posterobasal segment if these lesions were deemed inoperable.

Patient 2

A 70-year-old woman with severe progressive dyspnea for 5 years was diagnosed with CTEPH in 2009. She denied further assessment of operability at that time, and PH-specific medication was initiated. Owing to further worsening of her clinical condition (WHO FC III), she was referred to our center. As in Patient 1, pulmonary angiography showed surgically accessible lesions in the right PA and sub-segmentally located obstructions in the left lower lobe with poor pulmonary hemodynamics (mPAP, 65 mm Hg; PVR, 1,630 dyne · sec/cm^5). A complete endarterectomy of 7 segmental arteries of the right side and BPA of the anterobasal and posterobasal segments (8 and 10) of the left PA was planned.

Patient 3

A 58-year-old man (WHO FC IV) was diagnosed with severe CTEPH (mPAP, 64 mm Hg; PVR 852 dyne · sec/cm^5). Comorbidity was significant, with a history of stroke and coronary artery disease. Pulmonary angiography showed exclusively segmental obstructions of the right PA with sub-segmental lesions located in the left lower lobe and lingular PA branches (Figure 1). Endarterectomy of the right side for complete disobliteration with BPA of 3 segments of the left lower lobe (segment 8–10) and 1 lingular segment (segment 5) was planned. Coronary intervention or bypass was not indicated according to findings of the pre-operative coronary angiography.

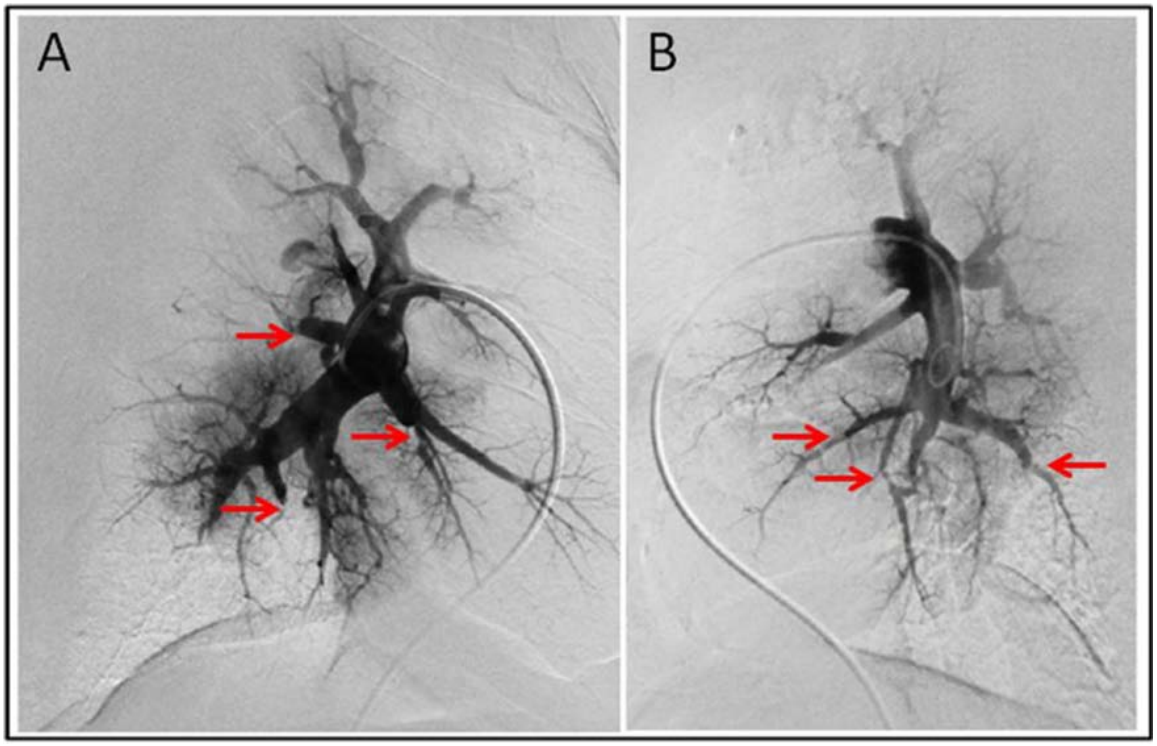

Figure 1 Pre-procedural pulmonary angiography (lateral projections) in Patient 3. (A) Right pulmonary artery with surgically removable lesions (arrows); (B) left side with very distally located lesions (arrows).

Procedural characteristics

All patients were repeatedly informed in detail about the planned treatment options and possible risks. All gave written consent and agreed to the analytic processing of their data. Surgery was accomplished using the San Diego technique, with periods of deep hypothermic circulatory arrest of up to 20 minutes. Right-sided PEA was successfully performed with circulatory arrest times of 43 minutes in 3 periods (Patient 1), 28 minutes in 2 periods (Patient 2), and 38 minutes in 2 periods (in Patient 3; Figure 2).

The left PA was incised for inspection and eventual endarterectomy. Because an adequate endarterectomy plane could not be developed during another period of deep hypothermic circulatory arrest and the obstructions were located distally to the areas of visibility, endarterectomy was considered impossible and the PA incision was closed. Reperfusion was initiated and rewarming of the patient was started after release of the aortic cross clamp.

BPA of the left PA branches was performed during rewarming (Figure 3). This phase generally takes between 1 and 1.5 hours, offering a useful time-slot for angioplasty. In all 3 patients, no further time was needed for the intervention. Two purse-string sutures were placed into the anterior pulmonary trunk, and a 6F sheath (Terumo) was inserted and navigated to the left main PA. A 6F multipurpose guiding catheter (Medtronic) was passed through the left PA to intubate the obstructed segments under fluoroscopy. The cardiopulmonary bypass flow was reduced to achieve a systolic pulmonary pressure of 30 mm Hg. At the same time, an inspiratory hold was generated by the ventilator.

During angiography, guiding in a 30° lateral projection, 2 guidewires (Runthrough NS-PTCA Guide Wire, Terumo; Galeo ES PTCA Guide Wire, Biotronik) were placed into the subsegmental arteries that had been previously identified as target lesions for angioplasty, and the diseased sub-segmental branches were dilated by multiple balloon inflations (Emerge, 2.0/20 mm, 4.0/20 mm, and 5.0/20 mm; Boston Scientific;

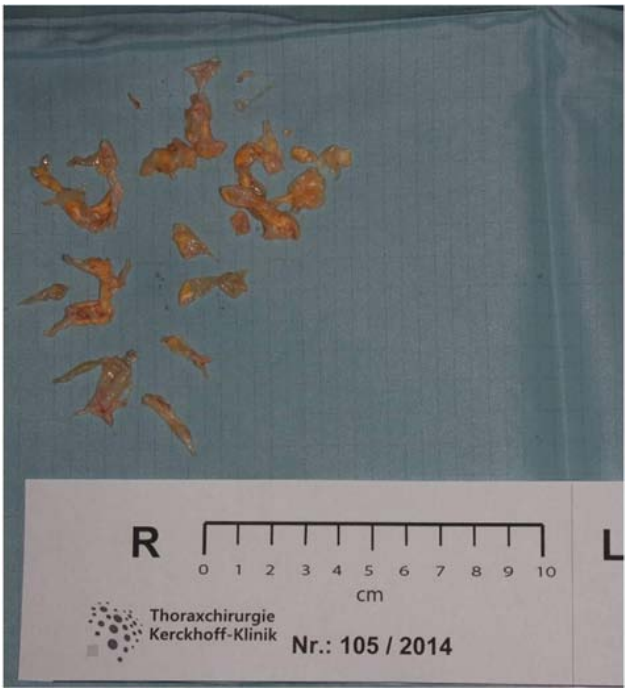

Figure 2 The surgically removed obstructing tissue from the right pulmonary artery in Patient 2.

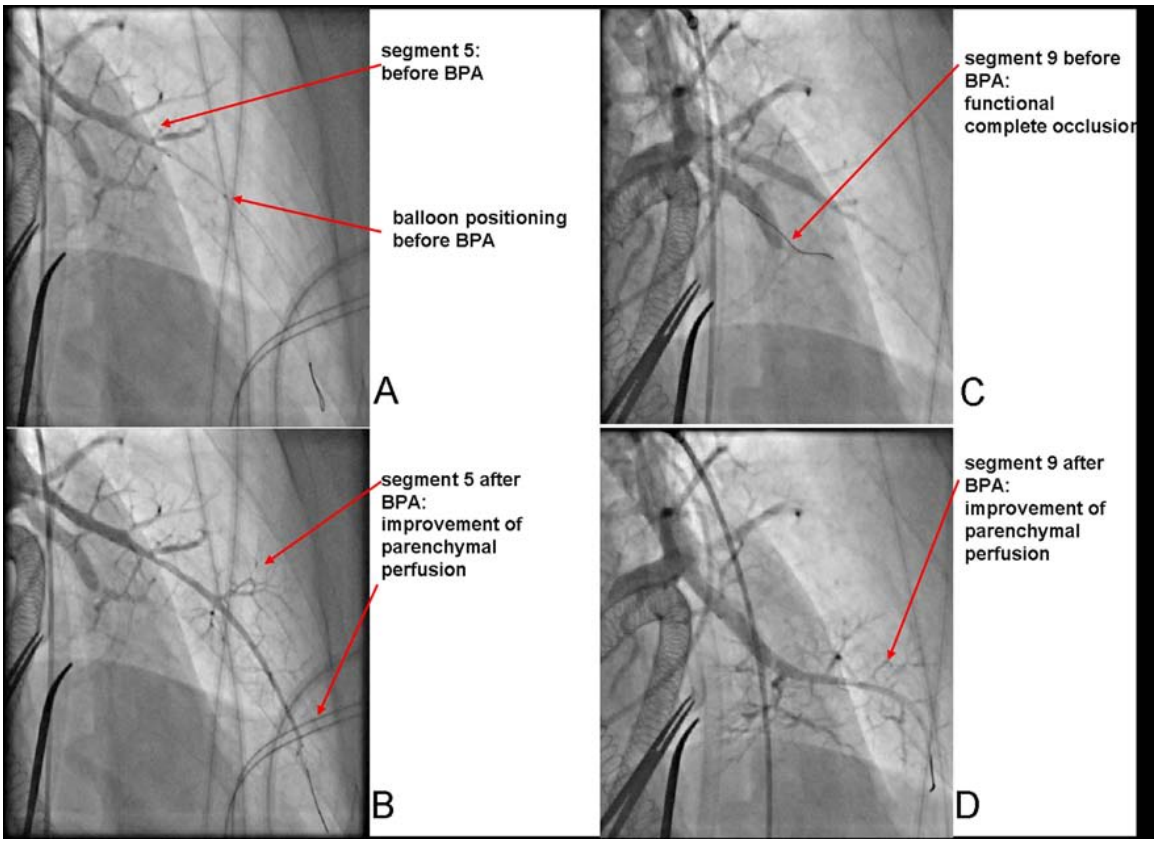

Figure 3 (A–D) Peri-procedural pulmonary angiography during balloon pulmonary angioplasty (BPA) of the left pulmonary artery in Patient 2.

Figure 3). Balloon size had been determined before the procedure using CT imaging. As in conventional BPA, in case of uncertainty, the smaller-sized balloon was used. Two segmental arteries with their sub-segmental branches were dilated in Patients 1 and 2, and 4 segmental arteries were successfully treated in Patient 3. The final pulmonary angiography showed an improvement of parenchymal perfusion, with excellent run-off in the venous phase.

After normal core temperature was re-established, patients were weaned from cardiopulmonary bypass, and the chest was closed according to standard clinical practice. Simultaneously, inhaled iloprost was administered and continued for the first 6 hours after surgery,[18] which follows our standard protocol for patients with high pre-operative PVR and poor RV function.

Post-procedural observations

On the first post-operative day, pulmonary hemodynamic variables were measured at 07:00 A.M., before removal of the PA catheter. A mean reduction of PVR of 842 dyne · sec/cm^5 was observed (Table 1). All patients were extubated on the morning of the first post-operative day. Radiographic signs of reperfusion edema in the endarterectomized lung (in all 3 patients) and also in the interventionally treated lung in Patient 3 were seen within the first 4 post-operative days. Two patients required non-invasive ventilation for 2 and 3 days, respectively. In addition, 2 patients developed intermittent atrial fibrillation, which was treated medically. No further complications were observed.

All patients were discharged from hospital after 14 days in good general condition. At 10 (Patient 1), 9 (Patient 2), and 6 (Patient 3) months after the intervention, all patients are alive with a significant improvement of exercise capacity (WHO FC II [Patient 1] and I [Patients 2 and 3]). To date, no further interventional treatment has been performed.

Discussion

We report use of a hybrid procedure combining PEA and BPA to treat 3 patients with CTEPH. Experience in both therapeutic strategies is limited to very few centers worldwide.

Table 1 Pulmonary Hemodynamics and World Health Organization Functional Classes of All Patients[a]

	Mean PAP (mm Hg)		PVR (dyne · sec/cm^5)			WHO Functional Class	
Patient	Pre	Post	Pre	Post	Δ-PVR	Pre	Post (months)
1	65	38	1,600	605	995	4	2 (10)
2	65	45	1,630	601	1,029	3	1 (9)
3	64	30	852	350	502	4	1 (6)

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; WHO, World Health Organization

[a]Hemodynamic variables were assessed in the initial phases of the operation ("pre") and on postoperative day 1 ("post"), with the difference in the PVR values (-PVR) indicated. The WHO Functional Class assessed preoperatively ("pre") months after the procedure ("post"), as indicated.

Operability assessment is the key point in the management of CTEPH patients. The pattern of PA obstructions and the impairment of right heart function and pulmonary hemodynamics are of particular importance. Early mortality after PEA is increased in patients with high pre-operative PVR [8,19] or post-operative PVR $>$ 500 dyne $\cdot$ sec/cm^5.[9] De Perrot et al[20] recently reported an elevated risk for PEA in patients with poor RV function.

Patients with obstructions amenable to surgery on one side and only sub-segmental lesions (i.e., surgically inaccessible) on the opposite side are rare. In 2014, 220 CTEPH patients were evaluated in our department: 152 were considered operable, and 8 with poor pulmonary hemodynamics were classified as possible hybrid candidates. All of these patients underwent surgery, and only in the 3 patients presented here was a unilateral PEA with intraoperative BPA on the opposite side performed. A complete bilateral PEA was possible in the remaining 5 patients considered for the hybrid procedure.

The use of PEA and BPA as a hybrid procedure is a completely new approach for severely ill CTEPH patients with poor hemodynamics and PA obstructions that are only partially accessible by surgery. This approach might reduce the early mortality rate in this high-risk group of patients. The decision for such a procedure certainly depends on the experience of the center. Because surgical removal of the obstructive material was not possible in all 3 patients, BPA was considered as the best option for an additional RV afterload reduction.

The overall survival among patients with severe CTEPH is similar to that of a malignant disease.[21] For operable patients, PEA provides a safe and often curative treatment option.[7] Most patients with inoperable disease are treated medically for PH, and there is a wide spectrum of treatment outcomes.[22] In specialized centers, inoperable CTEPH patients are screened for the additional treatment option of BPA. In selected cases, BPA might be a promising therapeutic option with a limited peri-procedural risk. To date, however, there are only limited studies that have addressed the outcome of BPA,[14–17] and long-term data are lacking.

The indication for treatment in the patients presented here was based on an interdisciplinary decision considering the localization of the obstructions in the PAs shown by pulmonary angiography and CT scan and the severity of PH. It was assumed that PEA alone might not lead to sufficient reduction in RV afterload, with a high risk of post-operative right heart failure and death, because one side was rated as inoperable in all 3 patients due to a high amount of peripheral occlusions. The combined removal of obstructive tissue within segmental vessels on one side and the interventional opening of sub-segmental arterial branches in more peripheral territories on the contralateral side was expected to result in a sufficient decrease in RV afterload. The intraoperative situation (invasive ventilation, cardiopulmonary bypass, possibility of inspiratory hold, no coughing, adjustable flow conditions in the PA, direct access to the PA) presents ideal conditions for BPA. The risk of vascular injury might also be reduced due to low pressures in the pulmonary vasculature.

The risk of post-interventional reperfusion edema is probably lower than in conventional BPA because of the expected abrupt improvement in pulmonary hemodynamics after contralateral PEA and the continual invasive ventilation with high positive end-expiratory pressure during the first night. For this reason, more target areas can be treated in the same session. The concept of image-guided BPA was preferred to direct BPA with an open PA because more precise deployment of the balloon catheter within the sub-segmental branches of the left lower lobe arteries was possible.

The hybrid procedure of PEA and BPA for well-selected, high-risk CTEPH patients may be a useful addition to the surgical and interventional spectrum of procedures in experienced CTEPH centers. Centrally localized thromboembolic material can still be targeted for surgical removal, and peripheral lesions can be dilated during the same session. Vessels that have been previously insufficiently surgically treated should not be dilated due to the increased risk of bleeding from guidewire perforation. An experienced multidisciplinary CTEPH team is mandatory for this complex procedure.

Disclosure statement

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

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