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Innovationen in der Evaluation und Therapie der chronisch thromboembolischen pulmonalen Hypertonie (CTEPH)

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Inhaltsverzeichnis

1 Der Arbeit zugrundeliegende Publikationen

Diese kumulative Habilitationsschrift basiert auf den folgenden Publikationen:

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2 Einleitung

Die pulmonale Hypertonie (PH) ist definiert als ein mittlerer pulmonalarterieller Druck (MPAP) von 25 mmHg (3,3 kPa) oder darüber [1]. Die Gründe für eine pulmonale Hypertonie sind vielfältig und prinzipiell muss unterschieden werden, ob eine prä- oder postkapilläre Form beziehungsweise eine Kombination aus beiden vorliegt, da dieses entscheidend für die weitere Diagnostik und Therapie ist [2].

Bei der präkapillären PH ist die chronisch thromboembolische pulmonale Hypertonie (CTEPH) eine der Formen der PH, für die unterschiedliche Therapieansätze von der Operation der pulmonalen Endarteriektomie [3], über die medikamentöse Therapie [4-6] bis zur Ballonangioplastie der Lungenarterien [7-11] existieren. Hierbei stellt die pulmonale Endarteriektomie für einen großen Anteil der Patienten eine kurative Behandlung dar [3, 12] und dies unterscheidet die CTEPH wesentlich von den meisten anderen Formen der PH und betont die Wichtigkeit der diagnostischen Verfahren und der kontinuierlichen Verbesserung der Therapieoptionen.

An der Abteilung Thoraxchirurgie der Kerckhoff-Klinik in Bad Nauheim werden neben dem üblichen Spektrum der thoraxchirurgischen und onkologischen Erkrankungen der Lunge und des Thorax vor allem auch Patienten mit CTEPH behandelt [13]. Die Diagnostik und Therapie der CTEPH stellt ein wesentliches Teilgebiet der Klinik dar, in dem Patienten aus ganz Deutschland und aus dem Ausland behandelt werden. Auf diesem Gebiet kooperiert unsere Klinik eng mit dem Zentrum für Thrombose und Hämostase der Johannes Gutenberg-Universität Mainz, der Medizinischen Klinik II Schwerpunkt Pneumologie der Justus-Liebig-Universität Gießen, der Thoraxklinik Heidelberg der Universität Heidelberg, der Klinik III für Innere Medizin der Universitätsklinik Köln und der Medizinischen Klinik mit Schwerpunkt Kardiologie des Campus Virchow- Klinikum der Charité sowohl im klinischen als auch im wissenschaftlichen Bereich. Zusätzlich ist die Klinik im Sonderforschungsbereich 1312 eingebunden. Unsere Abteilung gehört mittlerweile zu den weltweit 4 größten Zentren, die sich auf die Behandlung dieses Krankheitsbild spezialisiert haben [3, 14, 15].

Die Pathophysiologie der Entwicklung einer CTEPH ist derzeit weiterhin nur zum Teil verstanden [16]. Weder für die Inzidenz der Erkrankung noch für den Ablauf von der Lungenembolie über die unvollständige Thrombolyse bis zur fibrotischen Organisation der Thromben und Ausbildung der pulmonalen Hypertonie existieren schlüssige Konzepte und es werden viele Anstrengungen unternommen, um den Nebel über diesen Vorgängen zu lichten [17]. Anhand von

Blutproben, die vor und nach der pulmonalen Endarteriektomie abgenommen wurden und auf der Grundlage von während der Operation gewonnenen Gewebeproben wurden weiterführende histologische und analytische Untersuchungen zur Pathophysiologie der CTEPH initiiert, um mögliche Ansatzpunkte zur Prävention dieser Erkrankung zu gewinnen.

Eine weitere Patientengruppe mit chronisch obstruktiven Veränderungen der Pulmonalarterien, die aber laut Definition noch keine PH aufweisen, da ihr mittlerer pulmonalarterieller Druck < 25 mmHg ist, weisen unter Belastung eine deutliche Dyspnoesymptomatik auf. Diese Patienten, die zumeist jüngeren Alters sind, erfahren hierdurch eine erhebliche Einschränkung ihrer Lebensqualität. Sie werden gegenwärtig unter dem Begriff der chronisch thromboembolischen Erkrankung (CTED) subsummiert und ihnen wird ebenfalls die operative Therapie und selten auch die BPA angeboten [18-20].

Diese Gruppe der CTED-Patienten hat auch in unserer Klinik das Interesse an Belastungsuntersuchungen und hier insbesondere an Rechtsherzkatheter-Untersuchungen unter Belastung in den Fokus gerückt [21-24]. Denn neben der postulierten vermehrten Totraumventilation, welche Patienten mit CTED (und CTEPH) sicherlich aufweisen, stellt man für dieses Patientenkollektiv eine erheblich veränderte Belastungshämodynamik fest, die ebenfalls für die massive Belastungsdyspnoe mitverantwortlich gemacht werden muss. Wir konnten für dieses Patientenkollektiv vor und nach der PEA deutliche Verbesserungen in den belastungsabhängigen Untersuchungen wie Spiroergometrie und RHK aufzeigen, die bestätigen, dass der Benefit für die Patienten vor allem mit einer verbesserten Hämodynamik einhergeht [18]. Die Werte für den totalen pulmonalen Widerstand (TPR) sowie für die Steigung der MPAP-Herzzeitvolumen (HZV)-Relation zeigen hierbei eine gute Übereinstimmung mit dem Konzept der pulmonalarteriellen Hypertonie unter Belastung [22].

Die pulmonale Endarteriektomie (PEA) ist weiterhin der „Gold-Standard“ in der Therapie der CTEPH. Dieses komplexe Verfahren, welches eine Ausschälung von fibrotischem Material aus den Pulmonalarterien bedeutet, wird in unserer Abteilung 150-mal im Jahr angewandt mit international vergleichbarer Prozess- und Ergebnisqualität [13]. Ausschlaggebend hierfür sind eine bildgebende Diagnostik auf höchster Qualität [25] und eine optimierte intra- und postoperative Behandlung [26], die den Hauptfokus auf das Management schwerwiegender und damit lebensbedrohlicher Komplikationen legt. Hier konnte durch ein neu aufgestelltes intraoperatives Therapiekonzept eine entscheidende Verbesserung des Überlebens der operierten Patienten erreicht werden. Es handelt sich hierbei um den gezielten Einsatz des extrakorporalen Membranoxygenation- (ECMO) Verfahrens, welches auch schon früher bei Patienten mit speziellen Komplikationen bei PEA zum Einsatz kam, aber erstmalig in einem kleinen Patientenkollektiv in einem innovativen Ansatz angewendet wurde [27].

Eine weitere Innovation neben der medikamentösen Therapie, die zur Erweiterung des Behandlungsspektrums der CTEPH in unserer Klinik etabliert wurde, ist die pulmonale Ballonangioplastie (BPA), welche für inoperable Patienten in Frage kommt [7, 11, 28]. Diese ist ein kathetergestütztes interventionelles Verfahren, um Patienten mit distalen und somit durch die Chirurgie nicht erreichbaren Obstruktionen mechanisch zu behandeln. Auch hier liegt die Erfahrung unseres Zentrums mittlerweile bei über 200 Patienten. Mit der Einführung der BPA haben sich ganz neue Therapiemöglichkeiten entwickelt, so dass durch unsere Klinik erstmalig in ausgewählten Fällen die Behandlung schwerkranker Patienten durch simultane PEA und BPA zur Anwendung kam [29]. Weiterhin werden Patienten mit persistierender oder rekurrenter CTEPH mittels gezielter medikamentöser Therapie und BPA behandelt [6].

Im Rahmen dieser Habilitationsarbeit werden die verschiedenen innovativen Aspekte der Pathophysiologie, der Diagnostik und Therapie der CTEPH, die sich parallel mit dem Ausbau unseres Zentrums entwickelt haben, aufgezeigt und in den Kontext mit dem aktuellen Stand rund um die CTEPH eingeordnet.

3 Chronisch thromboembolische pulmonale Hypertonie

3.1 Pulmonale Hypertonie

Die pulmonale Hypertonie (PH) ist definiert als ein mittlerer pulmonalarterieller Druck (MPAP) von 25 mmHg (3,3 kPa) oder darüber [1]. Dieser Wert wurde während des ersten Weltsymposiums für pulmonale Hypertonie (1st World Symposium on Pulmonary Hypertension, WSPH) 1973 in Genf „willkürlich" festgelegt, um eine eindeutige Schwelle zwischen normalen hämodynamischen Werten in der Lungenstrombahn und den pathologischen Werten bei PH zu definieren [30]. Anhand der Rechtsherzkatheteruntersuchung mit Bestimmung des pulmonalarteriellen Mitteldrucks, des pulmonalarteriellen Verschlussdrucks (PAWP) und des Herzzeitvolumens (HZV) und daraus folgender Berechnung des pulmonalvaskulären Widerstands (PVR) lässt sich zwischen einer prä- und einer postkapillären pulmonalen Hypertonie unterscheiden. Die präkapilläre Hypertonie zeichnet sich neben einem MPAP von $\geq$ 25 mmHg durch einen PAWP $\leq$ 15 mmHg und einen PVR > 3 Wood-Einheiten ($\triangleq$ 240 dyn $*$ s $*$ cm^{-5}) aus [1]. Zu dieser Form der pulmonalen Hypertonie zählt auch die chronisch thromboembolische pulmonale Hypertonie ([31], Gruppe IV der Nizza-Klassifikation).

Seit dem 6. und letzten WSPH 2018 in Nizza wurde diese Definition nun in Frage gestellt. Zum einen gibt es Daten, die zeigen, dass bei Rechtsherzkatheter (RHK)-Untersuchungen gesunder Probanden der pulmonalarterielle Mitteldruck (MPAP) 14,0 ± 3,3 mmHg beträgt, so dass mit 2 Standardabweichungen ein MPAP > 20 mmHg als das obere Limit des Normalen betrachtet werden könnte [31]. Die Einbeziehung des pulmonalvaskulären Widerstands (PVR = (MPAP-PAWP)/HZV) in der Definition der präkapillären PH ist hierbei essentiell, da dadurch zwischen der pulmonalarteriellen PH durch vaskuläre Obstruktionen (Querschnittsveränderungen) und der PH durch erhöhten pulmonalarteriellen Wedgedruck (PAWP), d.h. durch postkapilläre Nachlasterhöhung bzw. durch erhöhtes Herz-Zeit-Volumen, unterschieden werden kann. Seit dem 4. WSPH 2008 in Dana Point (USA) ist die präkapilläre PH definiert als ein MPAP ≥ 25 mmHg bei einem normalen PAWP ≤ 15 mmHg und einem erhöhten PVR ≥ 3 Wood Units (WU) [1, 32, 33]. Der Wert von 3,0 WU ist ebenfalls willkürlich festgelegt und es gibt durchaus Daten, die bereits einen PVR > 2 WU als krankhaft ansehen [34]. Somit lässt sich feststellen, dass ein PVR ≥ 3,0 WU eine eher konservativ gewählte Schwelle in der Definition einer präkapillären PH darstellt. Dieses Maß ist klinisch relevant und man weiß, dass beispielsweise die Korrektur eines kongenitalen Shuntvitiums ab Überschreitung dieser Schwelle sehr fragwürdig und riskant wird [2], bzw. herztransplantierte Patienten ein schlechteres Überleben aufweisen [35]. Somit wurde während des 6. Weltsymposiums zur pulmonalen Hypertonie von der Task Force 4 vorgeschlagen, das Kriterium PVR ≥ 3,0 WU nicht nur für die Gruppe 1 der PH (s.u.) zu definieren, sondern für alle Formen der präkapillären PH zu nutzen. Für die CTEPH konnte durch ein großes internationales Register gezeigt werden, dass im Regelfall ein schwere präkapilläre PH vorliegt mit einem MPAP von 47 mmHg und einem PVR von 8,9 WU und dass für Patienten mit milder Erhöhung des MPAP (20-24 mmHg) im Regelfall der PVR > 3,0 WU beträgt [14].

Die Einteilung der pulmonalen Hypertonien erfolgt seit 2008 nach der Dana-Point-Klassifikation, die die pulmonale Hypertonie bereits in fünf Kategorien einteilte. Seit dem „6th World Symposium on Pulmonary Hypertension", das 2018 in Nizza stattfand, werden nach der Nizza-Klassifikation aktuell weiterhin fünf Klassen der pulmonalen Hypertonie unterschieden, die diskrete Änderungen gegenüber der Dana-Point-Klassifikation aufweisen [31]:

1. Pulmonalarterielle Hypertonie (PAH)
2. Pulmonale Hypertonie bei Linksherzversagen
3. Pulmonale Hypertonie bei Lungenerkrankungen und/oder Hypoxie
4. Pulmonale Hypertonie durch pulmonalarterielle Obstruktionen
    a. Chronisch thromboembolische pulmonale Hypertonie
    b. Andere pulmonalarterielle Obstruktionen
5. Pulmonale Hypertonie aufgrund eines unklaren oder multifaktoriellen Mechanismus

Patienten mit pulmonaler Hypertonie weisen zunächst unspezifische Symptome wie Dyspnoe, Leistungsminderung und Müdigkeit auf. Im Verlauf der Erkrankung kommt es unabhängig von der Ursache des Lungenhochdrucks zu einer Rechtsherzbelastung mit zunehmenden Beschwerden und Einschränkung der Leistungsfähigkeit. Die CTEPH ist eine progressive Erkrankung, die unbehandelt regelmäßig zu einem Rechtsherzversagen führt [2, 36].

Die mit der Erkrankung der pulmonalen Hypertonie einhergehenden Symptome mindern zunehmend die Lebensqualität der Patienten. Lange Zeit gab es nur eine eingeschränkte Möglichkeit die subjektive Lebensqualität von PH-Patienten zu erfassen und zu quantifizieren, da die spezifischen durch Lungenhochdruck verursachten Einschränkungen in den gängigen Scores nicht adäquat abgebildet waren. Mit Einführung des CAMPHOR-Fragebogens im Jahr

2006 und der Anpassung und Validierung für den Gebrauch im deutschsprachigen Raum 2012 wurde ein Werkzeug bereitgestellt, um die Auswirkungen einer PH auf die Lebensqualität der Patienten besser beurteilen zu können und somit den oben genannten Limitationen Rechnung zu tragen [37, 38].

3.1.1 Definition einer pulmonalen Hypertonie unter Belastung

Die PH unter Belastung war ursprünglich mit einem Ruhewert des MPAP < 25 mmHg und einem Belastungswert > 30 mmHg definiert. Auf dem 4. WSPH in Dana Point wurde die Belastungskomponente aus der Definition gestrichen, da viele offene Fragen im Zusammenhang mit dem Alter, Änderungen des Herz-Zeit-Volumens unter Belastung und der pulmonalvaskulären Physiologie bestanden. Diese spezielle Fragestellung der Belastungs-PH wurde wieder auf dem letzten WSPH 2018 in Nizza aufgegriffen.

Einige Anstrengungen zur frühzeitigen Entdeckung einer pulmonalvaskulären Erkrankung wurden unternommen, um Patienten in einem möglicherweise besser behandelbaren Stadium zu erkennen [39]. Dazu eignen sich Belastungsuntersuchungen, denn Patienten klagen zu Beginn meistens über eine Belastungsdyspnoe im Rahmen ihrer Erkrankung [40, 41]. Es wurden Belastungs-RHK-Studien durchgeführt, um die MPAP-HZV-Relationen in Mehrpunktdiagrammen darzustellen. Hierbei zeigte sich, dass für gesunde Probanden der MPAP ≥ 1 mmHg pro 1 Liter HZV ansteigt, während bei einer pulmonalvaskulären Erkrankung diese Steigerung meist ≥ 3 mmHg beträgt [24]. Da diese Daten nur durch einen höheren Aufwand gemessen werden können, sind sie nicht Teil der klinischen Routine und werden nur an wenigen Zentren erhoben.

Kontroversen in diesem Konzept sind begründet einerseits in physiologischen Veränderungen, die altersbedingt zu sein scheinen, und andererseits in der Abhängigkeit zwischen HZV und MPAP, wobei insbesondere trainierte Athleten eine HZV-Steigerung bis zu 30-40 $L \cdot min^{-1}$ erreichen können und hierbei auch MPAP-Werte über 30 mmHg entwickeln, womit der obere Referenzpunkt überschritten wird [42]. Die größte Schwierigkeit bei den Belastungstests ist der Fakt, dass unter Belastung auch der PAWP ansteigt und das umso ausgeprägter im Falle einer Linksherzerkrankung. Da der PVR = (MPAP-PAWP) / HZV ist, muss auch unter Belastung eine PAWP-Messung zwingend erfolgen [31].

3.2 Chronisch thromboembolische Erkrankung

Patienten mit einer chronischen thromboembolischen Erkrankung (CTED) weisen die gleichen Symptome und die gleichen Obstruktionen in der Bildgebung wie bei CTEPH auf, aber in Ruhe liegen deren Werte für den MPAP < 25 mmHg. Für die Limitationen unter Belastung in dieser Kohorte werden zum einen die Belastungs-PH mit zunehmender Steigung der MPAP/HZV-Relation sowie eine zunehmende Totraumventilation mit gesteigerten Ventilationsäquivalenten für Kohlendioxid verantwortlich gemacht [19, 43]. Weiterhin klagen viele Patienten nach einer überstandenen Lungenembolie über zunehmende Dyspnoe und nach einer akuten Lungenembolie weisen 30-50% der Patienten persistierende Perfusionsdefekte auf, was somit die Diagnosestellung der CTED anspruchsvoll macht [44-46]. Gut selektierte Patienten mit CTED profitieren von einer PEA. So zeigte eine Serie von 42 Patienten aus Großbritannien eine deutliche Verbesserung der postoperativen Symptomatik, Funktionsklasse und Lebensqualität [20]. Diese Ergebnisse wurden durch weitere Fallserien untermauert [18, 19]. Obwohl die PEA zum Ziel hat, dem Fortschreiten der Erkrankung bei einer CTEPH vorzubeugen, können derzeit keine Aussagen zum natürlichen Verlauf einer CTED gemacht werden, insbesondere dahin gehend, ob sich daraus eine CTEPH entwickeln könnte. Für diese Patientengruppe mit CTED muss die Forschung noch intensiviert werden.

4 Pulmonale Endarteriektomie (PEA)

Die pulmonale Endarteriektomie (PEA) ist bei gegebener technischer Operabilität die Therapie der Wahl, falls keine schwerwiegenden Kontraindikationen (Komorbiditäten) vorliegen. Die PEA ist derzeit das einzige Verfahren mit kurativer Intention. Hierbei ist die Erfahrung des Chirurgen der wichtigste prognostische Faktor sowohl für den perioperativen Verlauf als auch für das Langzeitergebnis. Bildmaterial von hoher Qualität, individuelle Patientenevaluation und –selektion, chirurgische Expertise sowie ein zielgerichtetes postoperatives Management sind Voraussetzungen für den erfolgreichen operativen Eingriff [47, 48]. Proximale Obstruktionen auf Lappen- und Segmentebene sind ideale Indikationen zur Operation, wohingegen die „distalen“ Obstruktionen (wobei „distal“ nicht definiert ist und die Einschätzung vor allem von der Expertise des Chirurgen abhängt) meist in Kombination mit einem erhöhten PVR [49] das operative Risiko für den Patienten erhöhen. Die PEA hat ihr kuratives Potential für Patienten mit schwerer CTEPH bewiesen und weltweit wurden bis jetzt etwa 10.000 Operationen durchgeführt. Die größten Erfahrungen weisen hierbei 4 große PEA-Programme in Europa (Hôpital Marie Lannelongue, Université Paris-Sud, Paris, Royal Papworth Hospital, Cambridge; Kerckhoff-Klinik, Bad Nauheim) und den USA (University of California San Diego) auf [3, 13, 50-52].

Das Ziel der PEA ist es, möglichst alle fibrösen Obstruktionen, die bindegewebig transformiertem Thrombusmaterial entsprechen, vollständig zu beseitigen, um die pulmonale Perfusion und damit das normale Ventilations-Perfusionsverhältnis wiederherzustellen. Dies führt zur Senkung der rechtsventrikulären Nachlast und durch die sofortige perioperative Widerstandsminderung der pulmonalen Strombahn verbessert oder normalisiert sich die Hämodynamik. Die drohende sekundäre Mikrovaskulopathie bleibt aus oder kann sich, falls bereits vorhanden, wieder zurückbilden.

Das Verfahren der PEA ist komplex. Es handelt sich hierbei um eine Endarteriektomie, mit der das bindegewebige Material aus den Pulmonalarterien herausgeschält wird. Hierzu werden die Patienten an die Herz-Lungen-Maschine angeschlossen, um im hypothermen Kreislaufstillstand (ca. 18-20°C Körperkerntemperatur) ein blutfreies Operationsfeld bis auf Segment- und Subsegmentniveau zu garantieren, ohne das die Endarteriektomie nicht vollständig gelingen kann [15, 48, 53]. Die Kreislaufstillstandszeit pro Lungenseite dauert ca. 10 bis maximal 20 Minuten, welche sich in schwierigen Fällen kumulativ auf 60 oder mehr Minuten ausweiten kann. In einer Arbeit konnte hierbei gezeigt werden, dass die neurokognitiven Funktionen durch die profunde Hypothermie effektiv geschützt werden [54].

Die Problematik des Eingriffs besteht in der Tatsache, dass die präoperative bildgebende Diagnostik nur einen Anhalt bezüglich der Operabilität des Patienten zulässt und dass die Schwierigkeit des Eingriffs erst mit Präparation des Dissektionszylinders in der Pulmonalarterie ersichtlich wird.

Im Gegensatz zu den meisten anderen herz-thoraxchirurgischen Operationen, bei denen die Aufmerksamkeit der linksventrikulären Funktion und dem Systemkreislauf gilt, stehen sowohl bei der Entwöhnung von der extrakorporal[55, 56]en Zirkulation als auch im weiteren postoperativen Verlauf die Rechtsherzfunktion und die Pulmonalzirkulation im Vordergrund. Die postoperativen Probleme konzentrieren sich auf die residuale pulmonale Hypertonie, die rechtsventrikuläre Dysfunktion und die reperfusionsbedingte Ödementwicklung in den endarteriektomierten und damit wiedereröffneten Lungenarealen. Diese gefürchtete Komplikation ist selten, kann aber die Unterstützung durch ein venovenöses ECMO-System notwendig werden lassen. Eine seltenere, aber häufig fatale Situation stellt die intraoperative endobronchiale Blutung dar. Hier kann die Situation entweder durch den endoskopischen Verschluss des betroffenen Segmentbronchus oder bei diffuser Blutung nur mit einer venoarteriellen ECMO-Unterstützung stabilisiert werden mit danach ungewissem Ausgang.

Sowohl die mittel- als auch die langfristigen Ergebnisse hinsichtlich Belastungsfähigkeit, Hämodynamik, Lebensqualität und des Überlebens von Patienten nach PEA sind in PEA-Zentren mit entsprechender Expertise exzellent, verglichen mit dem natürlichen Verlauf der CTEPH [15, 51, 57]. Ein Expertenzentrum für PEA-Chirurgie liegt vor, wenn mindestens 50 Operationen im Jahr bei einer Letalität unter 5% durchgeführt werden und mindestens eine Erfahrung für dieses operative Verfahren von 5 oder mehr Jahren vorliegt. Hochvolumige Zentren (>100 PEA-Operationen / Jahr) berichten über Letalitäten unter 5% [3, 16]. Aufgrund dieser Ergebnisse stellt auch die Lungentransplantation keine sinnvolle Alternative zur PEA dar, da für inoperable Patienten sowohl die gezielte medikamentöse Therapie als auch die Ballonangioplastie als weitere Therapieoptionen zur Anwendung kommen.

5 Pulmonale Ballonangioplastie

Für CTEPH-Patienten, die aufgrund zu distaler Veränderungen in den Pulmonalarterien als inoperabel eingestuft werden, gibt es neben der gezielten medikamentösen Therapie seit jüngster Zeit die pulmonale Ballonangioplastie (BPA) als interventionelles Verfahren zur Reduktion des pulmonalarteriellen Widerstands und somit zur Entlastung des rechten Ventrikels [16].

Artikel zur BPA wurden seit 2012 vorwiegend aus Japan veröffentlicht und führten weltweit zur Erweiterung des Behandlungsalgorithmus der CTEPH [10, 58, 59]. Durch die BPA verbesserten sich die Hämodynamik, die Symptome, die Belastungsfähigkeit und die rechtsventrikuläre Funktion bei einer gleichzeitig signifikant geringeren Komplikationsrate verglichen mit der Erstbeschreibung einer Fallserie durch Feinstein und Mitarbeiter im Jahr 2001 [60-63]. Nachfolgend wurde ähnliche Daten aus Europa berichtet [64-66]. Aus Deutschland wurden durch unser Zentrum sowie das Zentrum Hannover ebenfalls BPA-Ergebnisse publiziert, wobei erstmalig diese Programme parallel zu laufenden PEA-Programmen etabliert wurden [7]. Hierbei wurden vergleichbare Komplikationsraten dargestellt, aber bezüglich der hämodynamischen Veränderungen (z.B. Reduktion des PVR) waren die Ergebnisse weniger ausgeprägt verglichen mit denen der japanischen Zentren.

Bei der BPA werden über in die Leistenvene eingebrachte Schleusen Führungskatheter, Führungsdrähte und Ballonkatheter in die betroffenen Pulmonalarterien platziert, um durch Dilatation von der Periphere nach zentral die fibrösen Obstruktionen in den Gefäßen aufzubrechen und damit eine Perfusionsverbesserung zu erreichen [10, 58, 59]. Im Unterschied zur PEA wird hierbei das fibröse Material nicht entfernt, sondern verbleibt in den Gefäßen. Die Patienten werden mehrfach behandelt und es müssen hierfür zumeist 4 bis 8 Sitzungen durchgeführt werden.

6 Darstellung der eigenen Arbeit

6.1 Inzidenz und Charakteristik der chronisch thromboembolischen pulmonalen Hypertonie in Deutschland

Die publizierten epidemiologischen Daten zur chronisch thromboembolischen pulmonalen Hypertonie (CTEPH) sind sehr different. Die jährliche Inzidenz einer akuten Lungenembolie wird mit 750 bis 2700 pro 1 Mio. Erwachsener angegeben [67-69]. Unterschiedliche Studien beschreiben das Risiko der Entwicklung einer CTEPH der Überlebenden einer Lungenembolie im Bereich von 1 bis 9% [70-73]. Eine kürzlich veröffentlichte Metaanalyse schätzt die Inzidenz auf 3% [74]. Basierend auf diesen Schätzungen müsste eine Inzidenz der CTEPH im Bereich von 22,5 bis 81 pro 1 Mio. Erwachsenen angenommen werden. Für Großbritannien wird hierbei aber nur eine Inzidenz von 1,75 pro 1 Mio. und für Spanien eine Inzidenz von 0,9 pro 1 Mio. angegeben [75, 76].

In dieser Studie haben wir prospektiv die Inzidenz und die Charakteristik der CTEPH für das Jahr 2016 in Deutschland erfasst.

Hierzu wurden die Daten der drei größten deutschen CTEPH-Zentren (Kerckhoff-Klinik, Bad Nauheim; Medizinische Hochschule Hannover; Medizinisches Universitätszentrum des Saarlandes, Homburg/Saar), die auch pulmonale Endarteriektomien durchführen, prospektiv gesammelt und zusätzlich Daten vom COMPERA-Register (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) berücksichtigt. Dieses ist ein europäisches Register für pulmonale Hypertonie (PH), das erwachsene PH-Patienten mit allen Formen der PH, welche eine gezielte medikamentöse Therapie erhalten, einschließt [77]. Das COMPERA-Register ist das offizielle deutsche PH-Register mit einem umfassenden Patienteneinschluss aus deutschen PH-Zentren. Wir haben aus diesem Register alle deutschen Patienten mit der im Jahr 2016 neu gestellten Diagnose CTEPH selektiert, die nicht in einem der oben genannten Zentren behandelt wurden.

Für diese Studie wurden alle Patienten ≥ 18 Jahre eingeschlossen, die zwischen 1. Januar und 31. Dezember 2016 die Neu-Diagnose CTEPH gestellt bekamen. Die Diagnosekriterien der gültigen europäischen Leitlinie für pulmonale Hypertonie wurden angewandt. Patienten aus dem Ausland wurden nicht berücksichtigt. Um postoperative Verläufe der im Jahr 2016 diagnostizierten Patienten zu erfassen, wurde die Datenbank erst am 30. Juni 2017 geschlossen.

Die Studie wurde durch die lokalen Ethikkommissionen der teilnehmenden Zentren genehmigt und anschließend registriert (clinical trials.gov, Nummer: NCT02660463).

Alle Daten wurden über Excel-Tabellen von den teilnehmenden Zentren zur Verfügung gestellt und mit den Daten aus COMPERA zusammengeführt. Im Jahr 2016 wurden insgesamt 392 Patienten in Deutschland mit einer CTEPH diagnostiziert. Der Patienteneinschluss war wie folgt: Bad Nauheim N=234 (59,7%), Homburg N=69 (17,6%), Hannover N=57 (14,5%) und COMPERA N=32 (8,2%).

Tabelle 1: Patientencharakteristik zum Zeitpunkt der Diagnose

	n = 392
Age (years), *N* = 392	63.5 ± 15.0
Female/male (%), *N* = 392	50.8/49.2
Body mass index (kg/m²); *N* = 389	28.1 ± 6.5
6 min walk distance, *N* = 156	326 ± 121
WHO functional class, *N* = 305	I, 1 (0.3%)
	II, 76 (24.9%)
	III, 182 (59.7%)
	IV, 46 (15.1%)
RAP (mmHg), *N* = 306	9 ± 45
PAPm (mmHg), *N* = 374	43 ± 10
PAWP (mmHg), N = 357	11 ± 4
CO (l/min), *N* = 315	4.6 ± 1.4
CI (l/min/m²), *N* = 345	2.5 ± 1.9
PVR (dyn s cm⁻⁵), *N* = 345	652 ± 396
SvO_2 (%), *N* = 235	64 ± 8

RA = rechtsatrialer Druck, PAPm = mittlerer pulmonalarterieller Druck, CO = Herzzeitvolumen, CI = Herzindex, PVR = pulmonalvaskulärer Widerstand, SvO2 = gemischtvenöse Sauerstoffsättigung.

Anhand der Anzahl der Erwachsenen von 68,6 Mio. in Deutschland (http://www.destatis.de, Webseite wurde am 18. Oktober 2017 aufgerufen) berechnet sich eine jährliche Inzidenz von 5,7 pro 1 Mio. Erwachsene. Die Patientencharakteristika sind in Tabelle 1 dargestellt. Das mittlere Alter lag bei 63,5 Jahren und das Geschlechterverhältnis war ausgeglichen. Das mittlere Alter aus COMPERA war 71 Jahre und somit um 8 Jahre älter.

Der Behandlungsweg der Patienten ist in Abbildung 1 dargestellt. Insgesamt wurden 197 (50,3%) der Patienten mittels PEA operiert: 148 (75,1%) in Bad Nauheim, 30 (15,2%) in Homburg und 19 (9,6%) in Hannover. Die perioperative Letalität war 4/148 (2,7%) in Bad Nauheim, 0 (0%) in Homburg und 1/19 (5,3%) in Hannover.

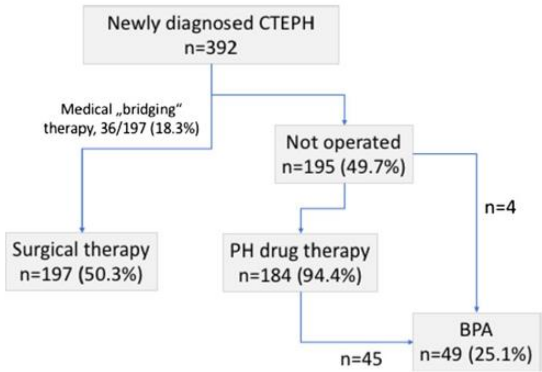


Abbildung 1: Behandlungspfad von 392 neu diagnostizierten CTEPH-Patienten; PH = pulmonale Hypertension, BPA = pulmonale Ballonangioplastie

Eine gezielte medikamentöse Therapie erhielten 36 von 197 (18,3%) Patienten, die später operiert wurden und 184 von 195 (94,4%) Patienten, die keine PEA erhielten.

Neunundvierzig Patienten (12,5%) wurden mittels pulmonaler Ballonangioplastie therapiert ohne periinterventionelle Letalität.

6.1.1 Schlussfolgerung

Nach dieser Datenerhebung wurden im Jahr 2016 für Deutschland 392 Patienten mit einer neu diagnostizierten CTEPH in Deutschland gezählt. Somit liegt die Inzidenz für Deutschland bei 5,7 pro 1 Mio. Erwachsene. Diese ist deutlich höher als die Zahlen, die für Großbritannien (1,75 pro 1 Mio.) und Spanien (0,9 pro 1 Mio.) vorliegen. Andererseits reflektiert sie die Ergebnisse Frankreichs mit 300 Patienten pro Jahr, die mit CTEPH diagnostiziert werden und somit eine Inzidenz von 5-6 pro 1 Mio. Erwachsene ergeben. Für Deutschland ist diese Erhebung eine eher konservative Schätzung der CTEPH-Inzidenz, dennoch ergeben die Zahlen höhere Inzidenzen als bis jetzt angenommen wurde. Etwa die Hälfte der Patienten wurden einer pulmonalen Endarteriektomie unterzogen, was etwas weniger war als im internationalen europäischen Register, das eine PEA-Rate von 56,8% beschrieb [14]. Die nicht operierten Patienten erhielten eine gezielte medikamentöse Therapie und einige der Patienten wurden mittels pulmonaler Ballonangioplastie behandelt.

6.2 Pulmonale Hämodynamik unter Belastung bei Patienten mit chronisch thromboembolischer pulmonaler Hypertonie vor und nach pulmonaler Endarteriektomie

Der rechte Ventrikel (RV) adaptiert sich an eine erhöhte Nachlast zunächst durch Hypertrophie (adaptives Remodeling), gefolgt durch eine maladaptive Dilatation [78] nach unterschiedlicher Dauer. Die Prognose der Patienten ist vor allem davon abhängig, wie der RV auf Belastung reagiert [79, 80]. Die pulmonale Endarteriektomie verbessert die Hämodynamik, die Belastungsfähigkeit und das Überleben [57, 81-83]. Die Prädiktoren für das perioperative Überleben sind bekannt [84, 85], aber die Prädiktoren für das langfristige Outcome sind weniger gut definiert. Eine residuale oder rekurrente PH stellt meist eine Kombination aus Mikrovaskulopathie, inkompletter PEA und unterschiedlicher Erholung des RV dar [86]. Ein weiterer Faktor ist die sich entwickelnde bronchiale Hyperperfusion, die möglicherweise zusätzlich zum mikrovaskulären Remodeling beiträgt [87, 88]. Hierbei korreliert die Ruhehämodynamik im Rechtsherzkatheter (RHK) vor der PEA nicht mit der Hämodynamik nach der PEA [89]. Für die idiopathische pulmonalarterielle PH (IPAH, Gruppe I der Nizza-Klassifikation [31]) zeigten kürzlich publizierte Daten zum Belastungs-RHK eine bessere prognostische Aussage [90]. In einer kleinen CTEPH-Kohorte bestehend aus Patienten mit persistierender Belastungsdyspnoe nach PEA, aber normaler Hämodynamik in Ruhe, waren eine verminderte arterielle Compliance unter Belastung ein starker Prädiktor für eine eingeschränkte Funktion [91]. Weiterhin zeigten Blumberg et al. [92], dass in einer heterogenen Gruppe von IPAH und inoperablen CTEPH-Patienten die Beziehung zwischen MPAP und HZV ein Prädiktor für das Überleben darstellt.

Somit lautete die Hypothese, dass der Belastungs-RHK (RHK_{ex}) mit der Erfassung der MPAP/HZV-Beziehung bei operablen CTEPH-Patienten möglicherweise die hämodynamischen Verbesserungen nach der PEA vorhersagt.

Zwischen Januar 2011 und Dezember 2013 wurden 299 PEA-Operationen an der Kerckhoff-Klinik durchgeführt. Aus dieser Kohorte konnten insgesamt 16 Patienten identifiziert werden (Abbildung 2), für die ein prä- sowie postoperativer Belastungs-Rechtsherzkatheter in unserem Zentrum durchgeführt wurde. 114 Patienten erhielten präoperativ einen RHK_{ex} vor der PEA und von den 62 Patienten, die zur 1-Jahres-Kontrolle wieder zurückkamen, konnte von 16 Patienten sowohl ein prä- als auch ein postoperativer RHK_{ex} ausgewertet werden. Als eine residuale PH wurde hierbei ein MPAP > 25 mmHg und ein PVR ≥ 240 $dyn \cdot s \cdot cm^{-5}$ definiert.

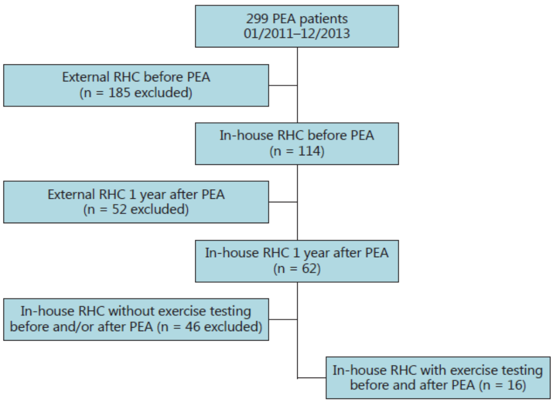


Abbildung 2: Flussdiagramm zur Patientenselektion

Während des RHK wurden in Ruhe und unter Belastung folgende Parameter erfasst: mittlerer, systolischer, diastolischer pulmonalarterieller Druck (MPAP, SPAP, DPAP), pulmonalarterieller Wedge-Druck (PAWP) und das Herzzeitvolumen durch Thermodilution. Berechnet wurden Herzindex (CI) und pulmonalvaskulärer Widerstand (PVR). Die Belastungsuntersuchungen wurden an konstanten Belastungsstufen von 25, 50 oder 75 Watt durchgeführt. Berechnet wurden folgende Werte: transpulmonaler Gradient (TPG) = MPAP-PAWP, diastolischer pulmonaler Gradient (DPG) = DPG-PAWP und die Steigungen der verschiedenen Parameter bezogen auf das HZV: (MPAP/HZV, PVR/HZV, SPAP/HZV, DPAP/HZV, PAWP/HZV, S_vO_2/HZV, TPG/HZV, DPG/HZV).

Das mittlere Alter der Patienten lag bei 60,8 Jahren zum Zeitpunkt der PEA. Die meisten Patienten fanden sich präoperativ in den WHO-Funktionsklassen (FC) III und IV, während postoperativ alle Patienten außer einem sich in den WHO-FC I und II wiederfanden.

Tabelle 2: Baseline-Charakteristik

	Before PEA	One year after PEA
Patients, n	16	
Male/female	10/6	
Age, years	60.8±14.8	61.9±14.4
BMI	24.7±4.6	25.9±5.2**
WHO functional class, n (%)		
I	–	4 (23)
II	3 (18)	12 (71)
III	12 (71)	1 (6)
IV	2 (11)	–
NT-proBNP, pg/ml	1,419.8±1,093.1	413.7±369.7**
Peak VO_2, ml·kg^{-1}·min^{-1}	13.6±5.9	17.9±4.6**
TAPSE, mm	17.7±5.5	18.8±3
PASP, mm Hg	81.7±19.8	43.4±8.7#
6MWD, m	345.6±117.5	485.6±105.9#
Targeted PAH therapy, n (%)	1 (6)	–
Phosphodiesterase type 5 inhibitors, n (%)	1 (6)	–
Therapy naive, n (%)	15 (94)	–
Jamieson type, n (%)		–
I	2 (13)	
II	9 (56)	
III	5 (31)	

Werte entsprechen Mittelwerten ± SD, falls nicht anderseits angegeben. # p < 0,001 (Wilcoxon signed-rank test), ** p < 0,01; (gepaarter t-Test) vs. Baseline. VO_2 = Sauerstoffaufnahme; BMI = Body-Mass-Index

In den Tabellen 3 und 4 sind die hämodynamischen Parameter in Ruhe und unter Belastung sowie die absoluten Änderungen präoperativ sowie 1 Jahr postoperativ mit den zugehörigen Steigungen aufgeführt. Man erkennt präoperativ einen deutlichen Anstieg des MPAP von 35,8 ± 7,6 auf 53,8 ± 5,1 mmHg, während das HZV lediglich von 4,4 ± 0,8 auf 6,5 ± 1,9 l/min ansteigt. Somit ergibt sich eine steile Steigung in der MPAP/HZV-Beziehung von 13,3 ± 10,8 mmHg.

Tabelle 3: Hämodynamische Parameter in Ruhe und unter Belastung

	Before PEA		One year after PEA	
	rest	exercise	rest	exercise
sPAP, mm Hg	64.5±13.3	94.2±8.5#	39±10.8*	70.9±15.5*,#
mPAP, mm Hg	35.8±7.6	53.8±5.1#	23.7±6.6*	43.2±7.1*,#
dPAP, mm Hg	21.5±5.6	30.3±9.6#	14.1±6.4*	23.7±5.4**,#
RA, mm Hg	5.9±2.1	13±3.4#	5.8±2.8	14.7±4.6#
PAWP, mm Hg	7.3±2.9	11.8±4.8#	10.4±3.6***	19.1±6.1**,#
TPG, mm Hg	28.9±6.8	44.3±8.8#	13.3±6.9*	24.1±7.9*,#
DPG, mm Hg	14.6±4.9	20.7±12.7†	3.6±6.9††	4.6±6.8
PVR, dyne·s/cm^5	522.6±151.2	529.8±161.5	213±117.3*	246.2±113.6*
CO, l/min	4.4±0.8	6.5±1.9#	5.1±0.9***	8.4±1.9*,#
CI, l/min/m^2	2.4±0.5	3.5±1.2#	2.6±0.5	4.7±1.9**,#
SvO_2, %	66.6±6.2	41.7±14.2#	72.8±5.4*	39.5±5.9#
HR, beats/min	74±15	96±15#	75.7±10.6	104.3±15.7***,#
SpO_2, %	93.9±3.1	88.5±4.8#	96.1±2.5***	92.3±3.1***,##
Workload, W	–	32±16.4	–	44±20.2†††

Werte entsprechen Mittelwerten ± SD. * p < 0.001, ** p < 0.01, *** p < 0.05 versus Werten vor PEA, # p < 0.001, ## p < 0.01 versus Ruhewerte n(*,# = paired t test), † < 0.01 versus Ruhewerten, †† p < 0.001, ††† p < 0.01 versus Werten vor PEA († = Wilcoxon signed-rank-Test). RA = Rechtes Atrium; HR = Herzfrequenz; SpO2 = arterielle Sauerstoffsättigung.

Tabelle 4: Absolute Änderungen (Δ) der hämodynamischen Parameter von Ruhe zur Belastung und Bezug zum Herzzeitvolumen (CO) in l/min

	Before PEA		One year after PEA	
	Δ	slope (CO)	Δ	slope (CO)
sPAP, mm Hg	29.7±12.1	19.9±12.6	31.9±8.7	12.5±8.8***
mPAP, mm Hg	18.1±7	13.3±10.8	19.4±4.6	6.4±2.6†††
dPAP, mm Hg	8.8±8	7.7±13.2	9.6±4.9	3.4±2.5
PAWP, mm Hg	5.1±4.9	4.4±5.1	8.7±4.6***	3.5±2.7
RA, mm Hg	7.1±2.9	5.9±6.3	9±3.6***	5.8±4.5
PVR, dyne·s/cm^5	26.1±66.2	16.4±122.3	25.8±62.5	11.5±36.7
SvO_2, %	−27.9±14.3	−23.4±20.6	−33.4±5.9	−25.1±17.5
TPG, mm Hg	15.4±9.5	19.7±20.6	10.8±5.5	6.6±4.9***
DPG, mm Hg	6.1±11	5.1±14.3	0.9±5.4	0.6±3.4
CO, l/min	2.1±1.7	–	3.3±1.5***	–

Werte entsprechen Mittelwerten ± SD. *** p < 0.05 versus Werten vor PEA (paired t test), ††† p < 0.01 versus Werten vor PEA (Wilcoxon signed-rank-Test). RA = Rechtes Atrium.

Parallel zum MPAP stiegen ebenso SPAP, DPAP, PAWP, rechtsatrialer Druck (RAP), TPG und DPG deutlich an und es resultierten somit steile Steigungen dieser Parameter in Bezug zum HZV (Abbildung 3, Tabelle 4).

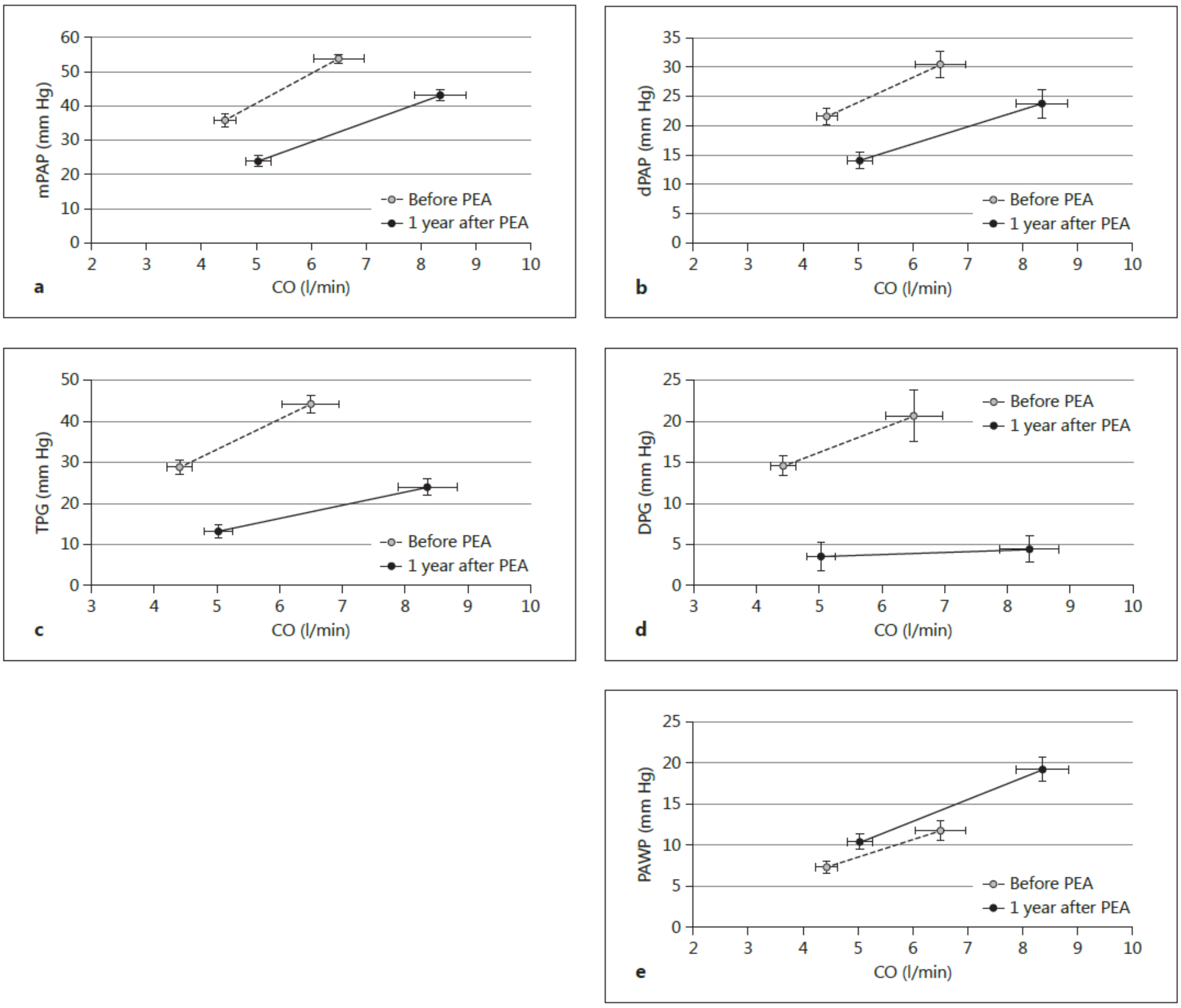


Abbildung 3: Lineare Druck-Fluss-Beziehung vor und nach PEA während konstanter Belastung. a MPAP/HZV-Steigung; b DPAP/HZV-Steigung; c TPG/HZV-Steigung; d DPG/HZV-Steigung; e PAWP/HZV-Steigung. Werte entsprechen Mittelwerten ± Standardfehler des Mittelwertes.

Für 7 Patienten wurde eine residuale PH in Ruhe von 30,3 ± 3,1 mmHg festgestellt und unter Belastung stieg der MPAP auf 49,6 ± 4,5 mmHg an. Diese Patienten zeigten steilere Steigungen in der MPAP/HZV-, DPAP/HZV- und TPG/HZV-Beziehung verglichen mit den Patienten ohne residuale PH, aber diese Unterschiede waren nicht signifikant.

Weiterhin zeigte sich, dass die präoperativen Steigungen der DPAP/HZV- sowie der DGP/HZV-Beziehung signifikant mit den Ruhewerten von PVR und MPAP nach der PEA korrelierten, während dies für MPAP/HZV, SPAP/HZV und TPG/HZV nicht zutraf (Abbildung 4). MPAP/HZV wies eine signifikante Korrelation mit den ein Jahr postoperativen NT-proBNP Spiegeln (Spearman r = 0,59, p = 0,03) auf sowie SPAP/HZV mit der erreichten Strecke im 6-Minuten-Gehtest (Spearman r = -0,7, p = 0,02).

Tabelle 5: Parameter bezüglich der residualen pulmonalen Hypertonie ein Jahr nach pulmonaler Endarteriektomie

	Nonresidual PH (n = 9, 56%)		Residual PH (n = 7, 44%)	
	rest	exercise	rest	exercise
mPAP, mm Hg	18.7±2.6*	30.3±3.1*	30.3±3.1	49.6±4.5
dPAP, mm Hg	9.6±3.3*	20.2±3.6*	19.9±4.1	28.1±3.9
PAWP, mm Hg	9.7±3.7	19.3±6.9	11.4±3.4	18.9±5.2
TPG, mm Hg	9±4.1*	18.9±6.2*	18.8±6	30.7±3.4
DPG, mm Hg	2.5±2.8	3.0±4.7###	7.8±4.1	8.4±6.5
PVR, dyne·s/cm^5	130.6±50.3#	161.1±35.2*	319±88.1	365.4±56.7
CO, l/min	5.3±0.9	9.1±1.9	4.6±0.8	7.4±1.5
HR, beats/min	76±11	105±15	75±10	103±17
mPAP/CO, mm Hg/l/min	5.8±2.5		7.2±2.7	
dPAP/CO, mm Hg/l/min	3.2±1.7		3.7±3.3	
TPG/CO, mm Hg/l/min	4.8±3.8		9.1±5.4	
DPG/CO, mm Hg/l/min	0.6±2.5		0.5±4.6	
NT-proBNP, pg/ml	159.1±122.5##		753.2±303.9	
6MWD, m	511±111.1		454±94	
Jamieson type, n (%)				
I	2 (22)			
II	5 (56)		4 (57)	
III	2 (22)		3 (43)	

Werte entsprechen Mittelwerten ± SD, falls nicht andererseits angegeben. * p < 0,05; ## p < 0,01; ** p < 0,05; *** p < 0,05 versus Werten bei residualer PH (* = zweiseitiger t-Test, # = Mann-Whitney U test).

Ein Jahr nach der PEA waren der MPAP, SPAP, DPAP sowie TPG und DPG deutlich niedriger sowohl unter Ruhe als auch während Belastung. Ein Jahr nach PEA stieg das HZV signifikant stärker unter Belastung an als vor der PEA. Somit zeigten die Steigungen der SPAP/HZV-, MPAP/HZV- und TPG/HZV-Beziehung eine deutliche Abflachung der Steigungen. Für die DPAP/HZV-, PAWP/HZV-, PVR/HZV-, S_vO_2/HZV-, und DPG/HZV-Beziehung waren die Abnahmen nachweisbar, aber nicht statistisch signifikant.

Mit dieser Studie wurde erstmalig für CTEPH-Patienten eine Abhängigkeit der postoperativen Hämodynamik ein Jahr nach PEA von der präoperativen Belastungshämodynamik aufgezeigt. Es konnte weiterhin dargestellt werden, dass die unter Belastung zu beobachtenden Druck/Fluss-Beziehungen vor der PEA sich ein Jahr nach der PEA deutlich verbesserten, das heißt einen flacheren Verlauf aufwiesen, und dass sie besser mit dem hämodynamischen Outcome ein Jahr nach PEA korrelierten, verglichen mit den Ruhewerten. Dies ist die erste Studie, die RHK_{ex}-Daten ausgewählter CTEPH-Patienten untersuchte und ihren Zusammenhang mit postoperativen Hämodynamikuntersuchungen nach PEA nachwies.

Verglichen mit früheren Studien, zeigte diese Patientenkohorte eine ähnliche Ruhehämodynamik mit einer eingeschränkten rechtsventrikulären Funktion mit hohem PVR und pulmonalarteriellen Drücken. Wie erwartet verbesserten sich MPAP, HZV und PVR signifikant ein

Jahr nach der PEA, aber dennoch wiesen 7 Patienten eine residuale PH auf. Diese Ergebnisse stehen im Einklang mit früheren Publikationen, Unterschiede zeigten sich jedoch im Anteil der symptomatischen Patienten von 10-24% sowie bei einem Anteil der residualen PH mit bis zu 35%.

Das Pulmonalgefäßsystem ist physiologisch gesehen ein „Hochfluss-“ und „Niedrigwiderstandssystem“ und weist somit ein flache MPAP/HZV-Steigung während körperlicher Belastung auf [93]. Das Ausmaß der Mikrovaskulopathie und eine limitierte Vasodilatation bzw. Rekrutierung von nicht perfundierten Gefäßarealen während zunehmenden HZVs zeigt sich in steileren Druck/Fluss-Relationen, was auch bei heterogenen Gruppen von PAH-Patienten gefunden wurde [93-96]. Somit sind hämodynamische Belastungsuntersuchungen, die möglicherweise den Anteil an Mikrovaskulopathie erfassen, prädiktiv für den langfristigen Outcome nach PEA.

Zusätzlich gibt es Hinweise dafür, dass Belastungsuntersuchungen zur Hämodynamik möglicherweise einen stärkeren Prädiktor für das Outcome bei PAH-Patienten darstellen als Messungen der Ruhehämodynamik [90, 92, 97, 98]. In einer vorhergehenden Studie zeigte sich, dass die pulmonalarterielle Compliance (C_{pa}) unter Belastung mit der maximalen V_{O2} bei chirurgisch behandelten CTEPH-Patienten korrelierte und einen starken Prädiktor für postoperative körperliche Belastbarkeit nach PEA darstellte [91].

In dieser Studie wurde weiterhin deutlich, dass die Abflachung der Steigungen der verschiedenen Druck/Fluss-Beziehungen eine verbesserte Compliance der pulmonalen Strombahn bzgl. des gesteigerten HZV anzeigt. Weiterhin ergab sich für die Patienten ohne residuale PH eine numerische größere Abnahme dieser Werte. Hervorzuheben sind die abflachenden Steigungen der DPG/HZV- und der DPAP/HZV-Beziehung, die signifikant mit den verbesserten hämodynamischen Werten ein Jahr nach PEA verknüpft sind. Ähnliches findet man für die Steigung der SPAP/HZV-Relation mit dem 6-MGT und der Konzentration des NT-proBNP.

In einer weiteren Studie wurde die rechtsventrikuläre(RV)-Reserve, definiert als die Fähigkeit des RV, die Ejektionsfraktion bzw. das Schlagvolumen unter Belastung zu erhöhen, als Prognosefaktor für Patienten mit PAH beschrieben, wohingegen die C_{pa} (Schlagvolumen/(MPAP-DPAP)) eine prognostische Bedeutung für CTEPH-Patienten aufwies [91, 99]. Die Abflachung der Steigungen der Druck/Fluss-Beziehungen spiegelt somit die verbesserte rechtsventrikuläre kontraktile Reserve und die pulmonalarterielle Compliance wieder.

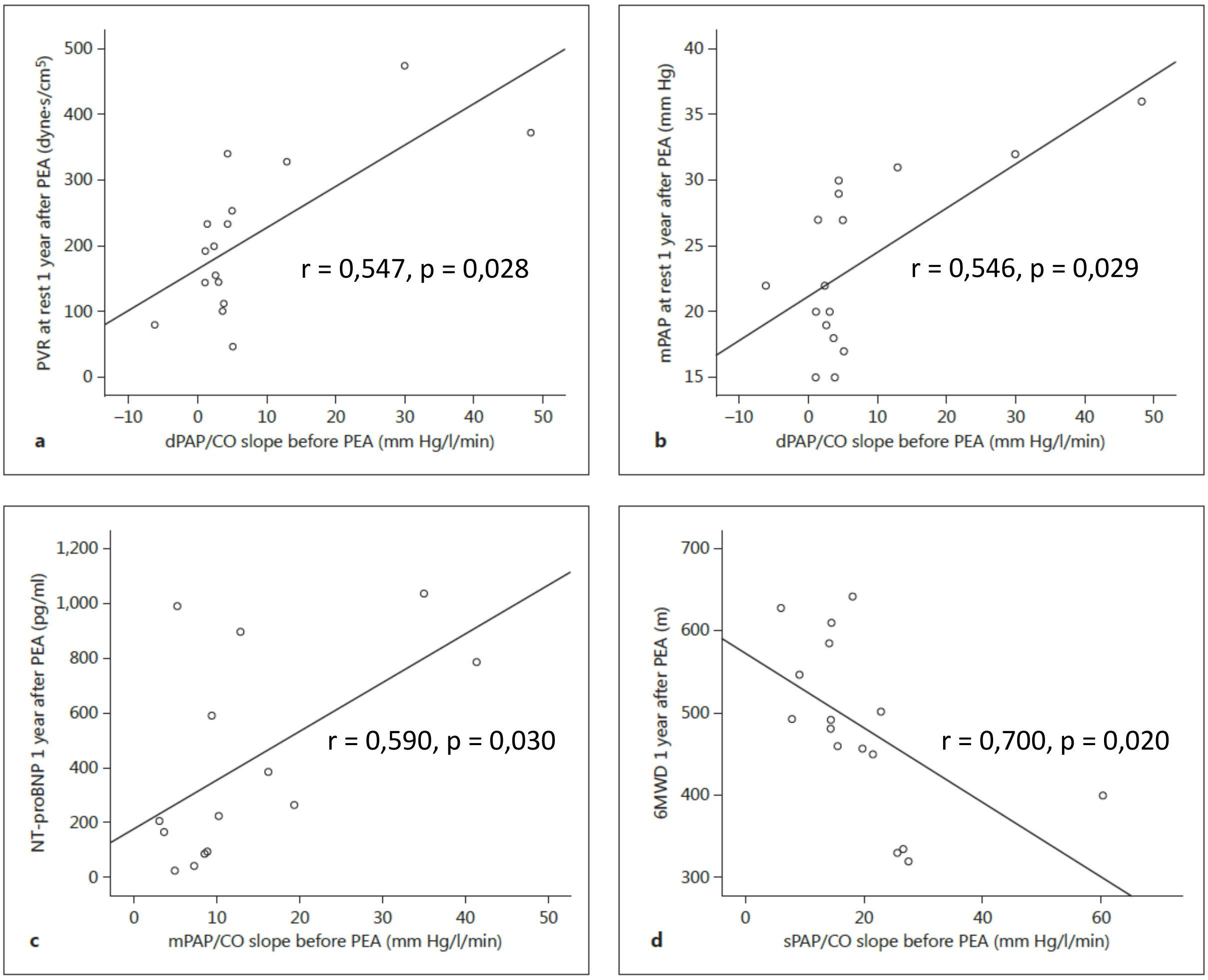


Abbildung 4: Zusammenhang zwischen der DPAP/HZV-Steigung vor PEA und PVR in Ruhe nach PEA (a), zwischen der DPAP/HZV-Steigung vor PEA und MPAP in Ruhe nach PEA (b), zwischen der MPAP/HZV-Steigung vor PEA und NT-proBNP nach PEA (c) und zwischen der SPAP/HZV-Steigung vor PEA und dem 6-MGT nach PEA (d).

6.2.1 Schlussfolgerung

Dies ist die erste Studie, in der hämodynamische Untersuchungen mittels Rechtsherzkatheter unter Einschluss von submaximaler Belastung in CTEPH-Patienten durchgeführt wurden. Diese Daten legen nahe, dass bei der CTEPH die RHK-Daten unter Belastung vor der PEA besser mit den postoperativen Hämodynamikdaten nach einem Jahr korrelieren verglichen mit RHK-Messungen, die nur auf Ruhewerte zurückgreifen. Die Abflachung der Steigungen der verschiedenen Druck/Fluss-Beziehungen spiegelt eine verbesserte Compliance der pulmonalen Strombahn in Bezug auf die RV-Kontraktilität wieder, was auch eine bessere Aufnahme des steigenden HZV unter Belastung anzeigt. Jedoch sind für weiterreichende Aussagen bzgl. der Druck/Fluss-Beziehungen Studien an größeren Patientenkollektiven nötig.

6.3 Belastungs-Rechtsherzkatheter vor und nach pulmonaler Endarteriektomie bei Patienten mit chronisch thromboembolischer Erkrankung

Bei Patienten mit CTEPH (MPAP ≥ 25 mmHg) findet eine bindegewebige Transformation der Blutgerinnsel in den Pulmonalarterien statt und dieses führt mit zunehmender Mikrovaskulopathie zu einer Zunahme des pulmonalvaskulären Widerstands (PVR) [2, 55, 100]. Die pulmonale Endarteriektomie (PEA) ist hierbei der Gold-Standard der Therapie [51]. Patienten mit persistierenden Gefäßobstruktionen, aber ohne pulmonale Hypertonie (PH, MPAP < 25 mmHg) erhalten heute die Diagnose der chronisch thromboembolischen Erkrankung (CTED) [1, 101]. Diese Patienten haben Dyspnoe während Belastung und zeigen dieselben Symptome wie CTEPH-Patienten der WHO-Funktionsklassen (FC) II bis III. CTED-Patienten weisen hierbei eine inadäquate Hämodynamikantwort unter Belastung auf [19, 20, 43]. Diese Patienten wurden erfolgreich mittels (PEA) operiert [19, 20]. Durch die Operation werden die Lebensqualität und die Belastungsfähigkeit wieder verbessert oder normalisiert. Zusätzlich können potentielle Langzeitkomplikationen wie eine sekundäre Mikrovaskulopathie und Rechtsherzversagen vermieden werden [51, 102, 103].

Es besteht eine laufende Diskussion über die Definition einer PH unter Belastung, die derzeit nicht durch Leitlinien abgedeckt wird [1, 21, 24, 93]. Kovacs et al. definieren Belastungs-PH als einen MPAP in Ruhe <25 mmHg und einen MPAP >30 mmHg unter Belastung bei einem gleichzeitig bestehenden totalen pulmonalen Widerstand (TPR) > 3 Wood Units (WU) [22]. CTED-Patienten zeigen einen steileren Anstieg im MPAP/HZV-Verhältnis verglichen zu gesunden Probanden [19, 22]. Naeije et al. [24] und Lewis et al. [93] haben vorgeschlagen, dass der TPR und die MPAP/HZV-Steigung nicht den Wert von 3.0 WU unter maximaler Belastung bei Gesunden übersteigen sollten. Die klinische Herausforderung des Konzepts der Belastungs-PH wurde kürzlich zusammengefasst [21].

Unsere Gruppe hat bereits Daten zur Hämodynamik unter Belastung vor und 1 Jahr nach PEA publiziert und die Verbesserungen dargestellt [104]. Für CTED lagen bis jetzt noch keine diesbezüglichen Daten vor. Unsere Hypothese hierbei lautete, dass durch die PEA die Hämodynamik unter Belastung wieder TPR-Werte bzw. MPAP/HZV-Steigungen ≤ 3.0 WU aufweisen würde.

Von Januar 2010 bis März 2016 wurden insgesamt 664 Patienten mittels PEA operiert. Die Hospitalletalität betrug 3,6% (24 Patienten). 32 Patienten hatten eine CTED (Baseline-Charakteristik in Tabelle 6) und hiervon lagen für 12 Patienten sowohl prä- als auch postoperative RHK unter Belastung vor (Abbildung 5). 8 Patienten waren hierbei in der WHO-FC II und 4 in der FC III. Bei 9 Patienten traten keine perioperativen Komplikationen auf, 2 Patienten hatten leichte Komplikationen und 1 Patient, bei dem eine Re-Operation nach operativer Embolektomie durchgeführt wurde, entwickelte postoperativ Krampfanfälle, wahrscheinlich in Zusammenhang mit einer Hirnhypoxie aufgrund einer Gasembolisation. Im Verlauf erholte sich der Patient ohne Folgeschäden.

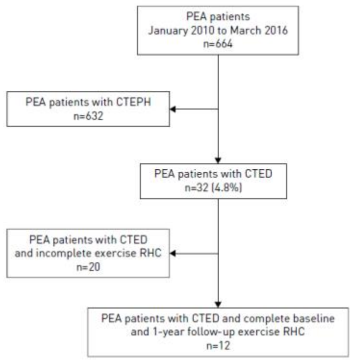


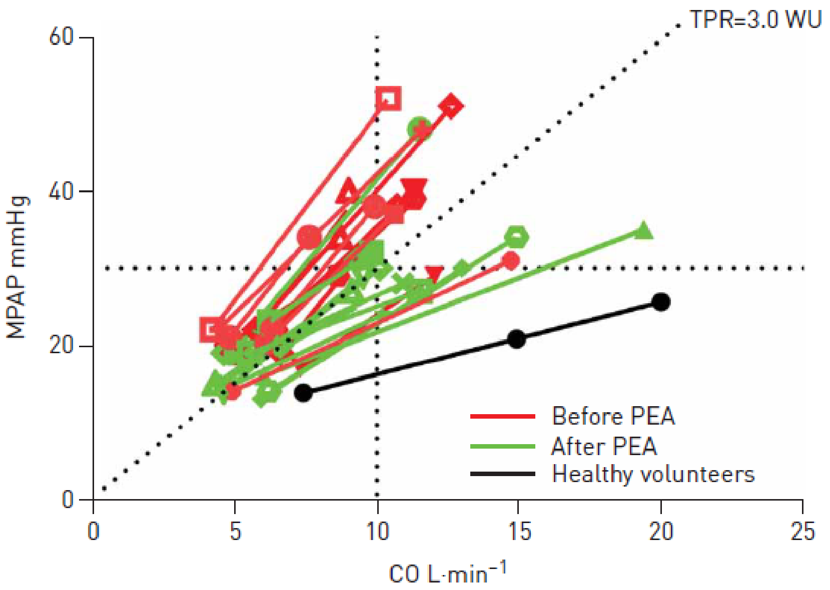
Abbildung 5: Flussdiagramm zur Patientenselektion; PEA = pulmonale Endarteriektomie; CTEPH = chronisch thromboembolische pulmonale Hypertonie; CTED = chronisch thromboembolische Erkrankung; RHC = Rechtsherzkatheter

Tabelle 6: Baseline-Charakteristik von 12 Patienten mit chronisch thromboembolischer Erkrankung mit Belastungsrechtsherzkatheter-Untersuchungen, die einer PEA unterzogen wurden.

Baseline characteristics	
Age years	34 (24–60)
Sex	
Male	6
Female	6
Height cm	175±7
Weight kg	81±17
BMI kg·m^{-2}	26.6±4.9
Pulmonary function	
FVC L	3.9±0.8
FVC % pred	91±11
FEV$_1$ L	3.1±0.8
FEV$_1$ % pred	83±11
FEV$_1$/FVC %	78±6
T_{LCO} % pred	72±18
NT-proBNP ng·L^{-1}	68 (25–147)

Werte entsprechen Medianen (Interquartilspanne), n oder Mittelwert ± Standardabweichung. BMI = Body-Mass-Index; FVC = forcierte Vitalkapazität; FEV1 = forcierte Ein-Sekundenkapazität; TLCO = Transferfaktor der Lunge für Kohlenmonoxid; NT-proBNP = N-terminale pro-Brain natriuretisches Peptid.

Belastungsuntersuchungen vor und ein Jahr nach PEA (Abbildung 6) ergaben für 9 Patienten mit einem MPAP > 30 mmHg eine MPAP/HZV-Steigung sowie einen TPR > 3.0 WU. Ein Patient mit einem TPR von 3,0 WU erreichte nur einen MPAP von 29 mmHg. Ein Jahr nach PEA erfüllten noch 3 Patienten die Kriterien für eine Belastungs-PH (MPAP > 30 mmHg und TPR > 3,0 WU). Hinsichtlich der MPAP/HZV-Steigung wiesen 11 Patienten einen Wert < 3.0 WU auf und bei einem Patienten erhöhte sich die Steigung von 3,5 auf 4,3 WU. Abbildung 7 zeigt einerseits die individuellen Änderungen des TPR und der Steigung vor und nach der PEA. Weiterhin erkennt man, dass der mittlere TPR (3,6 ± 0,8 auf 2,7 ± 0,7 WU, p = 0,0040) und die mittlere MPAP/HZV-Steigung (3,6 ± 1,0 auf 2,3 ± 0,8 WU; p = 0,0024) nach der PEA abnehmen. Patienten mit Werten > 3,0 WU zeigten hierbei einen deutlicheren Abfall der Werte.



Before PEA WU	After PEA WU
3.7	1.4
4.8	2.5
1.8	1.7
3.6	1.7
4.4	1.3
4.6	2.5
4.2	2.9
4.6	2.6
3.5	2.3
2.3	2.0
3.5	4.3
2.5	2.4

Abbildung 6: Mittlerer pulmonalarterieller Druck (MPAP) / Herzzeitvolumen (CO) Beziehung von 12 Patienten mit Belastungsrechtsherzkatheter vor und 1 Jahr nach pulmonaler Endarteriektomie (PEA). TPR: totaler pulmonaler Widerstand; WU: Wood Units. Die Werte der individuellen Steigungen sind in der Tabelle angegeben. Die schwarze Linie beschreibt die mittlere Steigung (0,94 WU) gesunder Probanden von Kovacs et al. [105].

Die weiteren hämodynamischen Veränderungen sind in Tabelle 7 dargestellt. Der MPAP in Ruhe zeigte eine Abnahme von 20 ± 3 auf 17 ± 3 mmHg (p = 0,006). Weitere Abnahmen wurden für den SPAP, den transpulmonalen Gradienten (TPG), PVR und TPR beobachtet. Für den PAWP fand sich ein Anstieg von 8 ± 3 auf 11 ± 4 mmHg (p = 0,02). Während des Belastungs-RHK ergab sich eine deutliche Verbesserung der Hämodynamik, wobei für das HZV und den HI keine Veränderungen zu sehen waren. Der TPG nahm bei allen Patienten ein Jahr nach der PEA ab. Interessanterweise nahm die mittlere pulmonalarterielle Compliance (C_{Pa}) während der Belastung von 2,6 ± 1,1 auf 3,6 ± 0,8 ml·mmHg^{-1} (p = 0,03) 1 Jahr nach der PEA zu.

Tabelle 7: Parameter im Rechtsherzkatheter vor und 1 Jahr nach PEA

	Before PEA	After PEA	p-value#
Rest			
SPAP mmHg	33±7	29±5	0.04
MPAP mmHg	20±3	17±3	0.006
DPAP mmHg	10±3	9±4	0.4
PAWP mmHg	8±3	11±4	0.02
RAP mmHg	4.3±2.4	6.5±3.0	0.1
TPG mmHg	12±4	7±4	0.004
PVR WU	2.1±0.9	1.5±0.5	0.01
CO $L \cdot min^{-1}$	5.6±1.0	5.6±0.7	0.9
CI $L \cdot min^{-1} \cdot m^{-2}$	2.7±0.3	2.9±0.5	0.39
C_{pa} $mL \cdot mmHg^{-1}$	3.9±1.6	4.0±1.0	0.86
SV $mL \cdot min^{-1}$	70±15	77±12	0.72
Heart rate $beats \cdot min^{-1}$	72±9	73±7	0.77
Maximal exercise			
SPAP mmHg	62±15	51±14	0.04
MPAP mmHg	39±8	31±6	0.02
DPAP mmHg	19±5	16±5	0.05
PAWP mmHg	11±5	11±4	>0.9
TPG mmHg	26±8	18±6	<0.0001
PVR WU	2.7±1.1	1.8±1.0	0.001
CO $L \cdot min^{-1}$	10.9±1.8	11.6±3.0	0.52
Exercise pulmonary hypertension	9	3	0.04
CI $L \cdot min^{-1} \cdot m^{-2}$	5.4±1.6	6.2±1.8	0.17
C_{pa} $mL \cdot mmHg^{-1}$	2.6±1.1	3.6±0.8	0.03
SV $mL \cdot min^{-1}$	102±14	113±29	0.4
Heart rate $beats \cdot min^{-1}$	106±23	106±9	>0.9

Werte entsprechen Mittelwert ± Standardabweichung oder n, falls nichts anderes angegeben ist. SPAP = systolischer pulmonalarterieller Druck; MPAP = mittlerer pulmonalarterieller Druck; DPAP = diastolischer pulmonalarterieller Druck; PAWP = pulmonalarterieller Wedgedruck; RAP = rechtsatrialer Druck; TPG = transpulmonaler Druckgradient; PVR = pulmonalvaskulärer Widerstand; WU = Wood Units; CO = Herzzeitvolumen; CI = Herzindex; C_{pa} = pulmonalarterielle Compliance; SV = Schlagvolumen. # = $p < 0,05$ als signifikant betrachtet

Für die nichtinvasive Spiroergometrie und die Lebensqualität abgefragt durch den „Cambridge pulmonary hypertension outcome review“ (CAMPHOR) zeigte sich parallel dazu eine signifikante Verbesserung der Leistungsfähigkeit und der Symptomwahrnehmung (Tabelle 8). Nach der PEA nahmen die erreichte maximale Arbeitsleistung, die höchste Sauerstoffaufnahme und der maximale Sauerstoffpuls verglichen mit den Baseline-Werten zu. Die ventilatorischen Äquivalente für das Kohlendioxid (V'_E/V'_{CO_2}) nahmen ab. Der Mittelwert für die WHO-FC (Abbildung 8) reduzierte sich von 2,3 ± 0,5 auf 1,4 ± 0,5 ($p < 0,001$) und für die CAMPHOR-Werte zeigte sich eine Verbesserung sowohl für den Gesamt-Score als auch für die Scores aller Teilbereiche (Symptome, Aktivität, Lebensqualität).

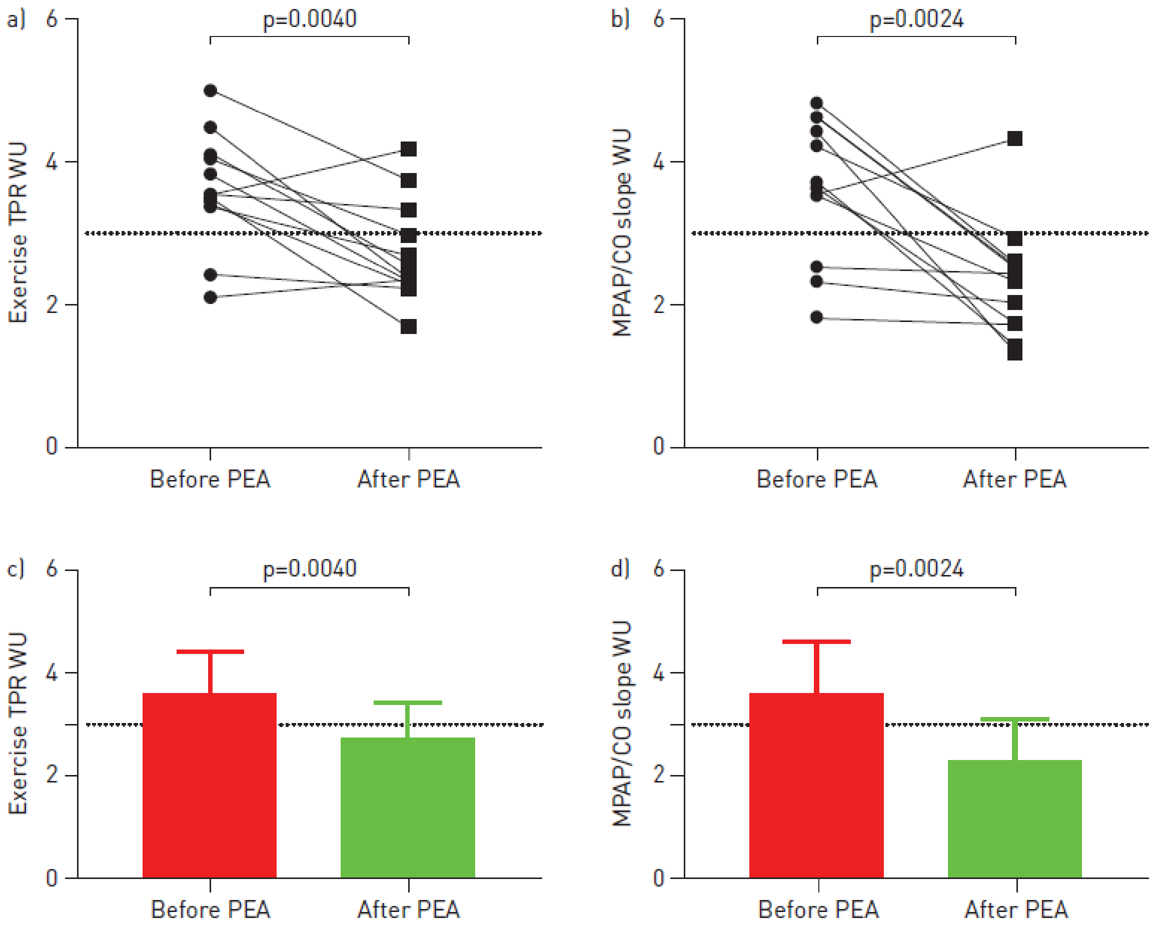


Abbildung 7: a, b) Individuale und c, d) Mittelwerte ± SD- Änderungen für a, c) totaler pulmonaler Widerstand TPR unter Belastung sowie b, d) Steigungen des mittleren pulmonalarteriellen Drucks (MPAP) / Herzzeitvolumen (CO) Beziehung von 12 Patienten mit Belastungsrechtsherzkatheter vor und 1 Jahr nach pulmonaler Endarteriektomie (PEA). WU: Wood Units. Die gepunktete Linie zeigt 3,0 WU an, was als oberer Referenzwert des Normalen von Naeije et al. vorgeschlagen wurde [24].

Tabelle 8: Noninvasive Parameter bei chronisch thromboembolischer Erkrankung, Pulmonary Hypertension Outcome Review (CAMPHOR) Scores und 6-Minuten-Gehtest (6MWD) vor und 1 Jahr nach pulmonaler Endarteriektomie (PEA).

	Before PEA	After PEA	p-value#
Functional parameters			
Maximal workload W	109±31	131±42	0.01
$V'O_2$ peak L·min^{-1}	1.24±0.36	1.54±0.26	0.01
$V'O_2$ peak % pred	64±16	81±22	0.02
Maximal heart rate beats·min^{-1}	142±23	133±30	0.13
$V'E/V'CO_2$ at peak	39±2	30±2	0.002
$V'E/V'CO_2$ slope	38±3	30±4	0.006
Peak oxygen pulse mL·beat^{-1}	10±2	12±3	0.02
CAMPHOR scores			
Total score	23 (14–33)	6 (2–4)	<0.001
Symptoms	8 (4–12.5)	2 (1–3)	0.001
Activity	8 (4–9.5)	3 (0.5–6)	0.001
Quality of life	7 (3.5–12)	2 (0.5–3)	0.002
6MWD m	437±105	498±64	0.2

Werte entsprechen Mittelwert ± Standardabweichung oder Median (Interquartilspanne), falls nicht anderes angezeigt ist. VO_2 = Sauerstoffaufnahme; V'E = Minutenvolumen; $V'CO_2$ = Kohlendioxidabgabe.
#: p < 0,05 als signifikant betrachtet

Die optimale Behandlung von CTED-Patienten wird immer noch diskutiert[19, 20]. Nach akuter Lungenembolie reichen die Veränderungen bzw. Symptome von Patienten mit „nur“ nachweisbaren Perfusionsdefekten (30-50%) bis zu schwer kranken CTEPH-Patienten[46, 106]. Die Rationale, dass CTED-Patienten eine PEA angeboten wird, ist in der Tatsache begründet, dass diese Patienten die gleiche Pathophysiologie aufweisen, die zur Belastungsintoleranz führt wie CTEPH-Patienten. Erstmalig wurden prä- und postoperative Belastungs-RHK-Daten für dieses Patientenkollektiv erhoben.

Die Hauptergebnisse dieser Studie sind: 1) CTED-Patienten weisen eine Abnahme im MPAP und im TPR unter Belastung ein Jahr nach PEA auf. 2) Die mittleren Werte vom TPR und der MPAP/HZV-Steigung sinken auf Werte < 3,0 WU, welche als obere Grenze des „Normalen“ unter Belastung angesehen werden. 3) Die Patienten weisen wieder eine verbesserte ventilatorische Effizienz und Belastungstoleranz sowie eine Zunahme der Lebensqualität auf.

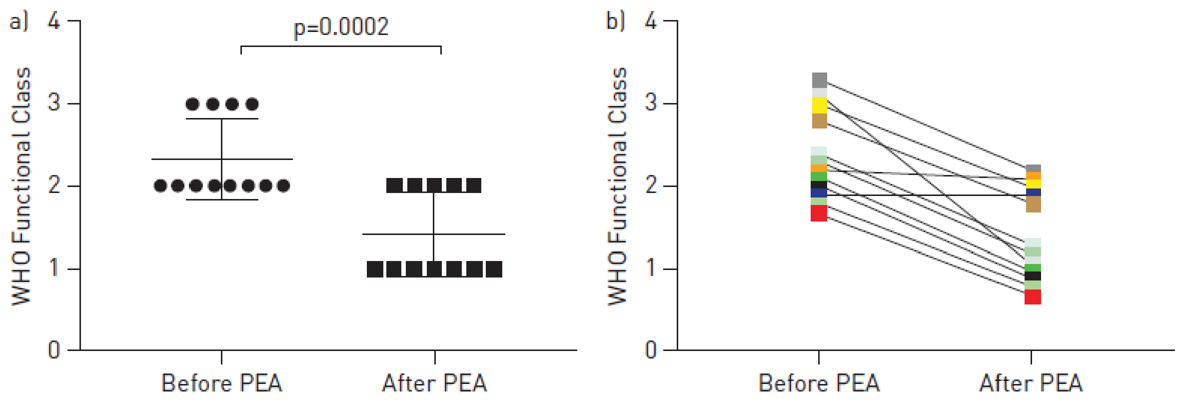


Abbildung 8: Änderungen in der WHO-Funktionsklasse von 12 Patienten vor und 1 Jahr nach pulmonaler Endarteriektomie (PEA). a) gestreutes Punktediagramm der Verteilung der WHO-Funktionsklasse als Mittelwert ± Standardabweichung vor und nach PEA. b) Individuelle Änderungen der WHO-Funktionsklasse vor und nach PEA.

Kürzlich publizierte Studien über CTED-Patienten durch Taboada et al.[20] und van Kan et al.[19] beschrieben ebenfalls positive Effekte bzgl. Belastungsuntersuchungen, WHO-FC und CAMPHOR-Scores. So zeigte sich eine Verbesserung im Gesamt-Score von 40 (Baseline) auf 11 nach 6 Monaten und 1 Jahr, eine Abnahme des MPAP von 21 auf 18 mmHg und eine Abnahme des PVR von 164 auf 128 dyn·s·cm^{-5} [20]. Van Kan et al. stellten zusätzlich die Steigerungen im Sauerstoffpuls und die Abnahme der maximalen Herzfrequenz fest sowie der V'_E/V'_{CO_2}, und zwar sowohl an der anaeroben Schwelle als auch unter maximaler Belastung[19]. Daten zum Belastungs-RHK vor und nach der PEA lagen in diesen zwei Publikationen jedoch nicht vor.

Wir fanden ähnliche Verbesserungen dieser Werte (Tabelle 8), vor allem auch Verbesserungen der Belastungshämodynamik (Tabelle 7) nach der PEA gemessen im RHK. Weiterhin konnten wir eine signifikante Abnahme des PVR sowohl in Ruhe als auch unter Belastung nach der PEA feststellen. Zusätzlich war eine Zunahme der C_{Pa} unter Belastung zu sehen, die als unabhängiger Prädiktor der Belastungsfähigkeit bei CTEPH-Patienten gilt[91]. Übereinstimmend betonten dazu Claessen et al., dass die MPAP/HZV-Beziehung und die C_{Pa} empfindliche Parameter der resistiven und pulsatilen pulmonalvaskulären Funktion darstellen[107].

6.3.1 Definition der pulmonalen Belastungshypertonie (PH_{ex}) und eigene Daten

CTED-Patienten erfüllen nicht die Kriterien der PH, leiden aber trotzdem unter erheblichen Belastungseinschränkungen (Belastungsdyspnoe). Eine sinnvolle Definition der PH_{ex} sollte einen TPR oder eine MPAP/HZV-Steigung > 3,0 WU enthalten. Das bedeutet für einen MPAP > 30 mmHg muss das HZV < 10 $L{\cdot}min^{-1}$ sein. In unserer Studie erfüllten 9 der 12 Patienten präoperativ diese Definition, wobei 5 Patienten sogar Steigungswerte > 4,0 WU aufwiesen. Die Mittelwerte für den TPR und die MPAP/HZV-Steigung lagen bei 3,6 WU.

Nach der PEA ergab sich bei 11 von 12 Patienten eine Reduktion der MPAP/HZV-Steigung unter 3,0 WU, wohingegen der TPR für drei Patienten bei über 3,0 WU verblieb. Der mittlere TPR sank auf 2,7 WU und somit hatten anhand dieses Kriteriums 9 von 12 Patienten keine pulmonale Belastungshypertonie mehr. Da die Mittelwerte ein Jahr nach der PEA unter die Schwelle von 3,0 WU absanken, erscheint uns die neue Definition der PH_{ex} sinnvoll und sollte daher auch angewandt werden. Kovacs et al. veröffentlichten in diesem Zusammenhang Daten von Patienten mit unerklärter Beastungsdsypnoe und konnten hierbei aus 141 Patienten 32 mit einer sogenannten „Borderline-PH“ (MPAP 21-24 mmHg) identifizieren, die wiederum eine deutlich höhere MPAP/HZV-Steigung von 5,2 WU aufwiesen. Dieses Patientenkollektiv, welches vor allem auch Sklerodermie-Patienten umfasste, wies eine höhere Mortalität auf.

6.3.2 Schlussfolgerung

Patienten mit CTED weisen eine überschießende Steigerung des MPAP und eine steilere Steigung der MPAP/HZV-Beziehung im RKH auf, welche mit einer schlechteren Belastungsfähigkeit und Belastungsdyspnoe einhergeht. Die Mittelwerte des TPR und der MPAP/HZV-Steigung waren > 3,0 WU, aber nach erfolgreicher PEA verbesserte sich die Hämodynamik signifikant und die Werte für den TPR reduzierten sich auf 2,7 WU und für die MPAP/HZV-Steigung auf 2,3 WU. Somit lagen diese Werte unterhalb der Obergrenze von 3,0 WU, was von einer Verbesserung der Belastungsfähigkeit und Lebensqualität begleitet wurde.

6.4 Rechtsventrikuläre Anpassung an die pulmonale Nachlast vor und nach pulmonaler Endarteriektomie bei Patienten mit chronisch thromboembolischer pulmonaler Hypertonie

Bei Patienten mit pulmonaler Hypertonie ist das rechtsventrikuläre Remodeling eine wichtige Anpassung und entscheidend für die Prognose der Patienten [108]. Der rechte Ventrikel (RV) ist längere Zeit in der Lage, die ansteigende Nachlast durch Zunahme der Kontraktilität zu kompensieren. Die RV-Funktion verschlechtert sich jedoch rasch, sobald eine Entkopplung („Uncoupling“) zwischen der rechtsventrikulären Elastizität von der Elastizität der pulmonalarteriellen Strombahn einsetzt [108, 109].

Andererseits zeigt der rechte Ventrikel im Gegensatz zum linken Ventrikel eine rasche funktionelle Erholung, was bei der Wiederherstellung eines normalen ventrikuloarteriellen Couplings der Fall ist. Die chronisch thromboembolische Hypertonie stellt ein ideales Krankheitsbild dar, um diese Zusammenhänge zu untersuchen, da durch die pulmonale Endarteriektomie (PEA) eine sofortige Nachlastminderung und somit eine weitestgehende Normalisierung der pulmonalen Hämodynamik einsetzt. Es wurde bereits über das Reverse-Remodeling nach PEA durch D’Armini berichtet, die im Langzeitverlauf zeigen konnte, dass sich die RV-Volumina zumeist normalisierten [57].

Mittels Konduktanzkatheter zur Erfassung von Druck/Volumen-Schleifen können sowohl die Nachlast als auch die Last als unabhängiger Kontraktilitätsparameter des RV gemessen werden. Hierbei beschrieben Kuehne et al. [109] ein Verfahren, das die Messung mit der Konduktanzmethode über die Kombination einer RHK-Messung und von Volumetriedaten ausreichend gut annähern kann. Anhand dieser Methode wurden aus den Routine-RKH-Daten und den prä- sowie postoperativen Magnetresonanztomographie (MRT)-Daten die pulmonal-arterielle Elastance ($E_{a\text{-}pulm\_i}$), die Elastance des rechten Ventrikels ($E_{es\text{-}RV\_i}$) und deren Coupling im zeitlichen Verlauf erfasst.

Die Elastance ist definiert als eine Druckänderung bezogen auf eine bestimmte Volumenänderung: $E_{a\text{-}pulm} \approx RVESP / SV$, wobei RVESP der endsystolische Druck im rechten Ventrikel und SV das Schlagvolumen ist. Der RVESP kann annähernd durch den mittleren pulmonalarteriellen Druck (MPAP) beschrieben werden: $RVESP \approx MPAP$, und somit ergibt sich $E_{a\text{-}pulm} \approx MPAP / SV$.

$E_{a\text{-}pulm}$ ist somit das Maß für die rechtsventrikuläre Nachlast. Ebenso lässt sich die Elastance des rechten Ventrikels als Maß der Kontraktilität approximieren: $E_{es\text{-}RV} \approx MPAP / ESV$.

Für eine effiziente Energieübertragung vom rechten Ventrikel in die pulmonalarterielle Strombahn sollte das Verhältnis beider Größen nahe 1 liegen. Mit zunehmendem Anstieg der $E_{a\text{-}pulm}$, die die Elastance des RV deutlich übertrifft, entsteht das sogenannte Uncoupling, das durch den rapiden Funktionsverlust des RV gekennzeichnet ist [110].

Für 57 Patienten lagen sowohl komplette prä- als auch postoperative Daten vor (Tabelle 9). Das mittlere Alter lag bei 56 ± 16 Jahren, wobei das Geschlechterverhältnis ausgeglichen war. Die Patienten befanden sich überwiegend in der NYHA-Klasse III und IV und die mittlere 6-Minuten-Gehstrecke betrug präoperativ 386 ± 116 m. Der MPAP vor der PEA lag bei 47 ± 12 mmHg und reduzierte sich nach der PEA auf 25 ± 9 mmHg (p = 0,0001).

Die präoperativen Kardio-MR-(CMR) Messungen wurden im Median 1 Tag vor der PEA und im Median 12 Tage postoperativ durchgeführt. Präoperativ war die RV-Nachlast $E_{a\text{-}pulm}$ deutlich erhöht und normalisierte sich nach der PEA fast vollständig. Die $E_{es\text{-}RV}$ wies eine leichte Abnahme auf. Aufgrund dessen konnte vor der PEA ein erhebliches Uncoupling gemessen werden, welches sich bereits 12 Tage postoperativ normalisierte. Dies war begleitet von einer signifikanten Reduktion der RV-Volumina, wie in Tabelle 9 und Abbildung 9 und 10 dargestellt.

Tabelle 9: Patientencharakteristik, Remodeling und hämodynamische Parameter vor und nach PEA

	Before PEA	After PEA	p value
Mean age (years)	56.7 ± 16		
Female gender (%)	28(43)		
BSA (m^2)	1.96 ± 0.22		
NYHA class II(%)	7(11)		
NYHA class III(%)	48(74)		
NYHA class IV(%)	10(15)		
6 minute walking distance	386 ± 116	399 ± 120	0.48
mPAP (mmHg)	47 ± 12	25 ± 9	0.0001
PVR (dyn*sec/cm^5)	531 ± 176	331 ± 278	0.01
PCWP mmHg	8.7 ± 3.7	10.7 ± 5.7	0.19
CO (l/min)	4.7 ± 1.5	4.6 ± 1.3	0.7
EDVi (ml/m^2)	92 ± 32	72 ± 23	0.0001
ESVi (ml/m^2)	69 ± 31	41 ± 18	0.0001
SVi (ml/m^2)	22 ± 10	32 ± 9	0.0001
RVMASSi (ml/m^2)	32 ± 9	30 ± 9	0.03
EF (%)	25 ± 12	46 ± 10	0.0001
$E_{a\text{-}pulm\_i}$ (mmHg/ml/m^2)	2.8 ± 2.1	0.85 ± 0.4	0.0001
$E_{es\text{-}RVi}$ (mmHg/ml/m^2)	0.72 ± 0.27	0.66 ± 0.3	0.13
$E_{a\text{-}pulm}/E_{es\text{-}RV}$	4.2 ± 3	1.4 ± 0.6	0.0001

CTEPH-Patienten können nach erfolgreicher PEA wieder eine normalisierte pulmonale Hämodynamik erlangen. Dies unterscheidet CTEPH-Patienten von Patienten mit anderen Ätiologien der PH. In Studien konnte gezeigt werden, dass sich der RV postoperativ wieder vollständig regenerieren kann [57, 111, 112]. Diese Studie vergleicht erstmalig die Änderung der Nachlast-Parameter mit dem Reverse-Remodeling des rechten Ventrikels. Hierzu wurden die $E_{a\text{-}pulm\_i}$ und $E_{es\text{-}RV\_i}$ sowohl aus den MR-Daten als auch aus den RHK-Daten approximiert.

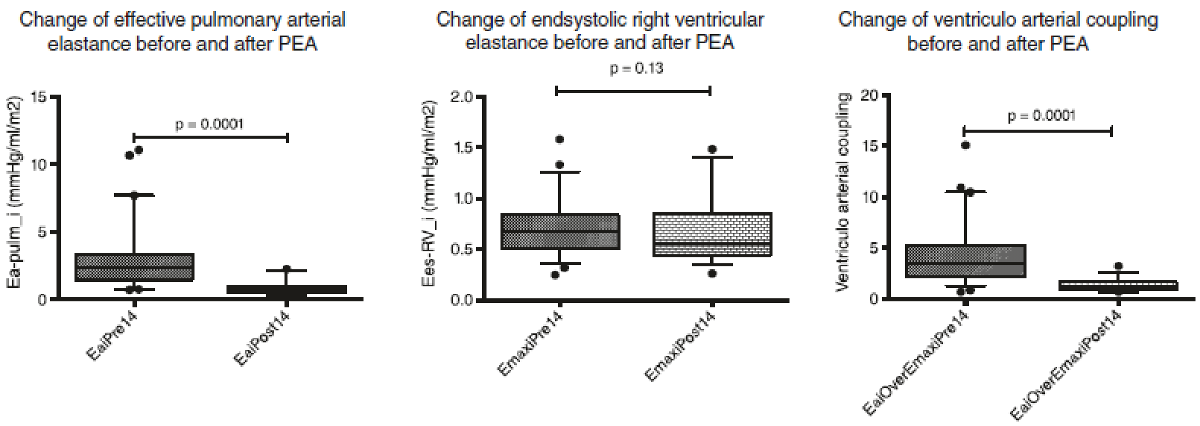


Abbildung 9: Änderung der pulmonalarteriellen Nachlast ($E_{a\text{-}pulm}$), der rechtsventrikulären Kontraktilität ($E_{es\text{-}RV}$) und des ventrikuloarteriellen Couplings. Aufgrund der abnehmenden Nachlast nach der PEA kommt es zur Normalisierung des Couplings, obwohl eine noch reduzierte Kontraktilität vorliegt.

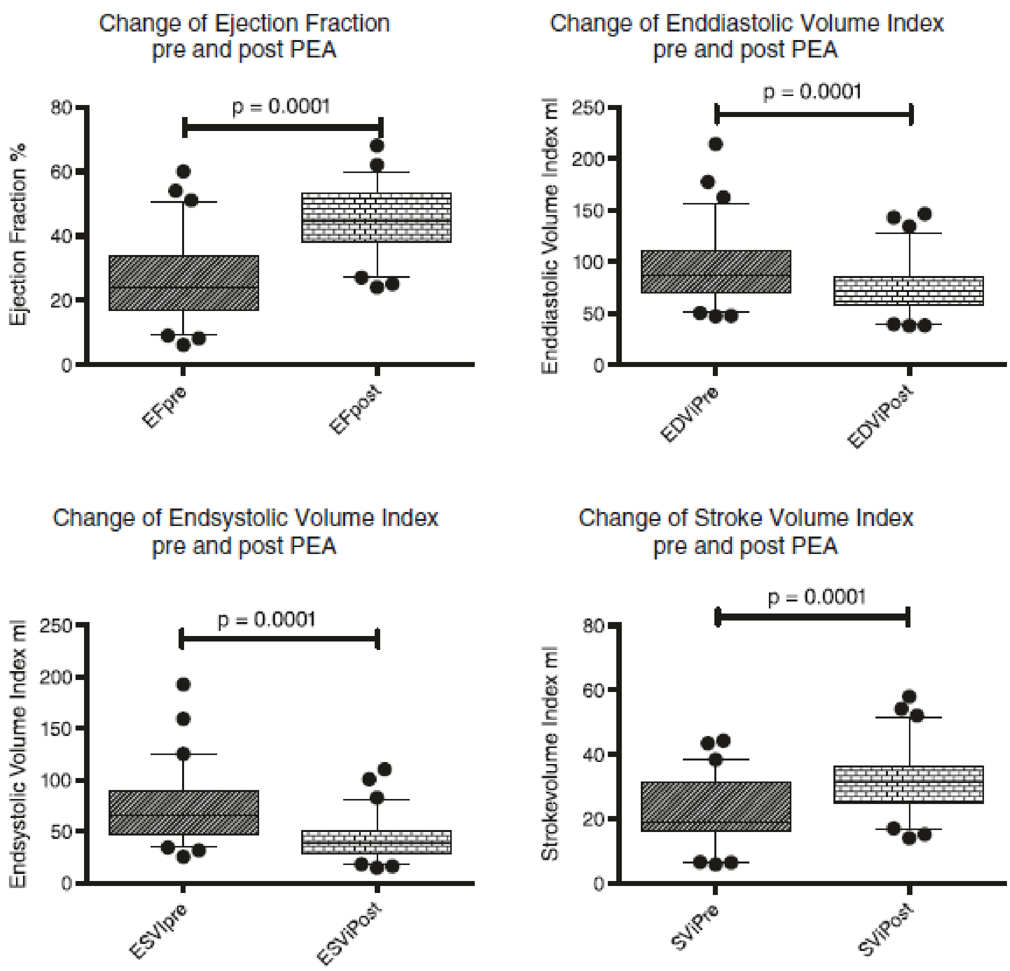


Abbildung 10: Änderung der Ejektionsfraktion und des Volumens. Der rechte Ventrikel zeigt bereits 10 Tage nach der PEA ein reverses Remodeling.

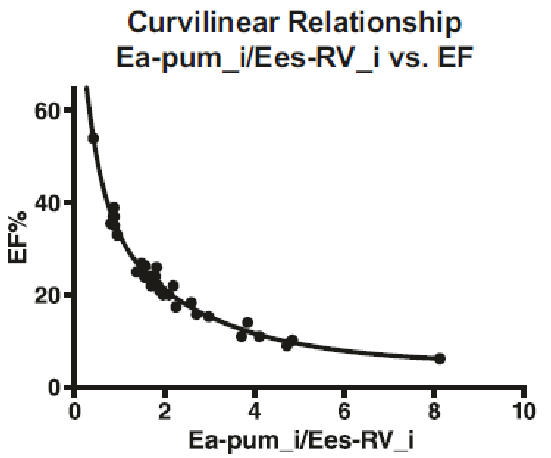


Abbildung 11: Hyperbolische Beziehung zwischen dem ventrikuloarteriellen Coupling und der Ejektionsfraktion

Es gibt wenig publizierte Referenzwerte für $E_{a\text{-pulm\_i}}$. Setzt man aber für die MPAP-Werte einen Bereich von 10 - 20 mmHg voraus und wählt einen normalen Schlagvolumenindex von 55 ml·m^{-2}, so berechnet sich daraus ein $E_{a\text{-pulm\_i}}$ von 0,3 mmHg·ml^{-1}·m^{-2}. Unsere CTEPH-Patienten wiesen hierbei einen Wert von 2,8 mmHg·ml^{-1}·m^{-2} auf. Sanz et al. publizierten für Patienten mit unterschiedlicher PH-Ätiologie einen Wert von 0,88 mmHg·ml^{-1}·m^{-2} [113]. In dieser Studie waren jedoch lediglich 3 CTEPH-Patienten enthalten mit im Mittel deutlich höheren Schlagvolumina. Mehr übereinstimmende Werte wurden lediglich in einer Studie von Kuehne et al. [109] berichtet mit Werten im Mittel von 0,75 mmHg·ml^{-1}·m^{-2}. Dies betont nochmals die massiv erhöhte Nachlast für den RV in der Kohorte unserer CTEPH-Patienten. Damit im Einklang zeigte sich eine erhebliche Kontraktilitätseinschränkung des rechten Ventrikels, die unmittelbar postoperativ keine wesentliche Verbesserung zeigte. Für eine energetische Effizienzbetrachtung muss neben der $E_{es\text{-RV\_i}}$ ebenfalls die $E_{a\text{-pulm\_i}}$ betrachtet werden und somit das effektive ventrikuloarterielle Coupling berechnet werden. Dieser Wert war vor der PEA mit 4,2 ± 3 massiv erhöht als Zeichen für ein schweres Uncoupling zwischen RV und pulmonalarterieller Strombahn. Postoperativ ergab sich wenige Tage später im Mittel ein Wert von 1,4 ± 0,6 und somit eine Normalisierung des Couplings, was als ein Hinweis für die Ökonomisierung der RV-Schlagarbeit und somit des Energietransfers angesehen werden kann. Auch hierzu fehlen noch gültige Referenzwerte und es wurden Werte im Bereich von 0,6 – 1,2 angegeben [114, 115]. Man kann jedoch festhalten, dass mit der Abnahme des Coupling-Wertes auf ein Drittel des präoperativen Wertes, unmittelbar postoperativ eine deutliche Tendenz zur Normalisierung dieser Größe zu erkennen ist.

Betrachtet man die Relation zwischen RV-EF und $E_{a\text{-pulm\_i}}$ / $E_{es\text{-RV\_i}}$, zeigt sich ein streng hyperbolischer Verlauf (Abbildung 11) mit initial steilem Abfall der RV-EF bei zunehmendem Uncoupling.

6.4.1 Schlussfolgerung

Die Kombination aus Routinedaten aus dem RHK-Labor mit volumetrischen Daten aus der kardialen MRT-Messung für CTEPH-Patienten lässt eine Quantifizierung der RV-Kontraktilität und der pulmonalarteriellen Nachlast zu. In dieser Studie ließ sich zeigen, dass die RV-Funktion vor allem durch die Nachlast bestimmt ist und dass mit Wiederherstellung eines effizienten ventrikuloarteriellen Couplings nach PEA sich sowohl die RV-Dimensionen als auch die RV-Funktion sich wieder normalisieren.

6.5 Minimierung der Thrombusentstehung an der Spitze des Pulmonaliskatheters durch systemische Heparingabe im Rahmen der pulmonalen Endarteriektomie bei CTEPH: eine randomisierte Doppelblindstudie.

Zentrale Venenkatheter (ZVK) und Pulmonalarterienkatheter (PAK) werden häufig in der Behandlung von Hochrisikopatienten während komplexer operativer Eingriffe und auf Intensivstationen eingesetzt. Dabei wird mit einer Häufigkeit von 12,5 bis zu 29% eine Thrombusentwicklung an den Kathetern beobachtet [116-118]. Bei einer pulmonalen Endarteriektomie von Patienten mit einer chronisch thromboembolischen pulmonalen Hypertonie (CTEPH) wird regelmäßig ein PAK eingeschwemmt. Bei diesem Patientenkollektiv sind häufig Störungen im Gerinnungssystem anzutreffen, wobei das Antiphospholipidsyndrom das höchste Risiko für Thrombenbildungen aufweist [14, 119].

Während der PEA besteht die seltene Möglichkeit nach Öffnen der Lungenarterie direkt den PAK inspizieren zu können, da er regelmäßig aus der Arterie luxiert werden muss. Das Ziel dieser Studie war es, die Thrombusformation in Abhängigkeit von einer niedrigen Heparindosis vor Einlage des Katheters zu untersuchen und mit dem Standardprotokoll dieser Operation zu vergleichen, bei dem erst vor der Kanüleneinlage für den Anschluss an die extrakorporale Zirkulation die volle Heparindosis verabreicht wird.

Im Zeitraum von September 2013 bis Februar 2015 wurden insgesamt 288 Patienten mittels PEA operiert. Von diesen wurden 60 Patienten in die Studie miteingeschlossen. Die Patienten wurden verblindet kontrolliert randomisiert, je nachdem ob sie niedrigdosiert Heparin (Heparin-Gruppe) oder ein Placebo (NaCl-Lösung 0,9%, Kontroll-Gruppe) erhielten. Im Fall von Heparin wurden 17,5% der zu verabreichenden Zieldosis von 400 U/kg (ca. 5000 U) anstatt Kochsalzlösung appliziert. Weiterhin durften bei den Patienten keine Voroperationen am Thorax oder Herzen vorliegen und eine Heparin-induzierte Thrombozytopenie musste ausgeschlossen sein.

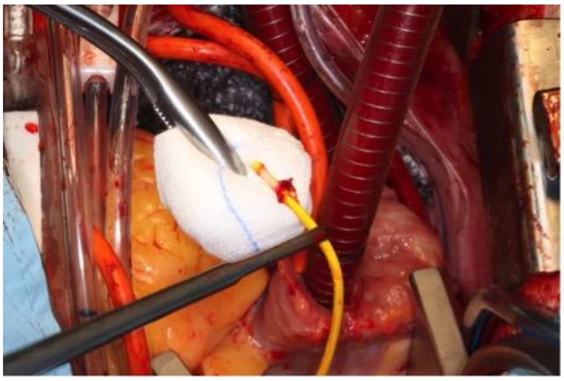


Abbildung 12: Thrombus am PA-Katheter

Der primäre Endpunkt war der Unterschied bei der Thrombusbildung zwischen den beiden Gruppen. Sekundäre Endpunkte waren Thrombusgewicht und Gerinnungsparameter: aktivierte Gerinnungszeit (ACT), Antifaktor-Xa-Spiegel (anti-Xa), Antithrombin-3-Spiegel (AT3), die international normalisierte Ratio (INR) und die D-Dimere.

An der Studie nahmen 30 Männer und 30 Frauen mit einem mittleren Alter von 62 (Spanne: 19-85) Jahren teil (Tabelle 10). 12 Patienten (20%) wiesen eine Gerinnungsstörung auf, davon waren 4 Patienten in der Kontrollgruppe und 8 Patienten in der Heparingruppe.

Es gab weder perioperative Blutungskomplikationen noch Unterschiede in der perioperativen Transfusion von Erythrozyten, Thrombozyten oder Frischplasmen.

Die Spitze des PA-Katheters lag bei 51 Patienten (85%) in der rechten Pulmonalarterie und die Zeiten von der PAK-Einlage bis zur Inspektion der Katheterspitze sowie die Heparingabe und die Gerinnungswerte sind in Tabelle 11 angegeben. Die mittleren Heparindosen lagen bei 31860 ± 5960 U für die Kontrollgruppe und bei 33080 ± 7280 U für die Heparingruppe. In der Heparingruppe waren die Werte für die ACT, PTT, Anti-Xa und INR, wie zu erwarten war, erhöht.

In der Kontrollgruppe wurde bei 17 Patienten (56,7%) und in der Heparingruppe bei 6 Patienten (20%) Thrombusmaterial am PAK gefunden (p < 0,001, Abbildung 12 und 13). Die Thrombusgewichte waren ebenfalls signifikant unterschiedlich (p < 0,001): Kontrollgruppe 27 mg (IQR 12 – 53 mg) und Heparingruppe 10 mg (IQR 4 – 16 mg).

Tabelle 10: Patientencharakteristik

	Control group[a] (n=30)	Heparin group[a] (n=30)	p value
Age (years)	63.7 ± 14	60.3 ± 14	0.832
Sex (female/male)	12/18	18/12	0.196
Mean PA pressure (mmHg)	42 ± 12	43 ± 10	0.543
Mean PA occlusion pressure (mmHg)	11 ± 4	11 ± 3	0.816
Cardiac output (l/min)	5.0 ± 1.2	4.6 ± 1.3	0.450
Pulmonary vascular resistance (dyn*sec/cm^5)	617 ± 323	702 ± 471	0.465
WHO functional class	2.9 ± 0.5	2.8 ± 0.6	0.351

Alle Werte sind Mittelwerte ± Standardabweichung aller 30 Patienten in jeder Gruppe. PA = pulmonalarterieller

Zentrale Venenkatheter werden häufig in der täglichen Routine eingesetzt und Komplikationen wie Thrombusentstehung bzw. Infektionen sind häufig und gefährden die Patienten [116]. Ducatman et al. beschreiben eine Inzidenz von 29% katheterinduzierten Rechtsherzthromben in einer prospektiven Serie von 141 Autopsien [118] und Gilon et al. wiesen eine Inzidenz von 12,5% in einer prospektiven Studie bei 55 Patienten nach [117]. In einem weiteren Report von Torbicki et al. wurde eine Lungenembolie in 6% der Patienten mit einem zentralen Venenkatheter aufgezeigt und man fand bei Patienten mit rechtsventrikulären Thromben eine signifikant höhere Letalität nach 3 Monaten von 29% verglichen mit 16% ohne Thrombusnachweis [116].

PA-Katheter sind wichtig im perioperativen Monitoring der PEA und die Effekte der niedrigdosierten Heparinisierung vor der PAK-Einlage wurden evaluiert. Die Hauptergebnisse dieser Studie waren: 1. Die niedrigdosierte Heparinisierung reduzierte die Rate der Thrombusbildung am PAK; 2. Die Thrombusgewichte waren signifikant niedriger bei Heparingabe; 3. Die frühzeitige Heparingabe führte nicht zu einer erhöhten Blutungsrate.

Tabelle 11: Gerinnungsparameter beider Gruppen

	Control group[a] (n = 30)	Heparin group[a] (n = 30)	p value*
Total heparin dose (IU)	31,860 ± 5,956	33,080 ± 7,280	0.480
D1 = duration from PA catheter insertion to full heparin dose administration (min)	47 ± 21	39 ± 16	0.097
D2 = duration from full heparin dose administration to luxation of PA catheter (min)	74 ± 21	83 ± 25	0.154
D3 = duration from PA catheter insertion to luxation (min)	122 ± 19	122 ± 31	0.945
ACT at T1 (sec)	124 ± 11	129 ± 14	0.130
ACT at T2 (sec)	127 ± 13	184 ± 18	<0.001
PTT at T1 (sec)	33 ± 4	34 ± 8	0.300
PTT at T2 (sec)	31 ± 4	193 ± 18	<0.001
Anti-Xa at T1 (IE/ml)	0.29 ± 0.18	0.37 ± 0.22	0.118
Anti-Xa at T2 (IE/ml)	0.25 ± 0.17	1.52 ± 0.32	<0.001
AT3 at T1 (IE/ml)	84 ± 11	84 ± 10	0.884
AT3 at T2 (IE/ml)	81 ± 11	82 ± 9	0.677
INR at T1	1.1 ± 0.1	1.1 ± 0.1	0.785
INR at T2	1.1 ± 0.1	1.2 ± 0.1	0.002
D-dimers at T1 (mg/l)	105 (223)	87 (82)	0.156
D-dimers at T2 (mg/l)	117 (245)	95 (91)	0.075

Alle Werte sind Mittelwerte ± Standardabweichung von jeweils 30 Patienten jeder Gruppe mit Ausnahme des D-Dimers, dessen Werte Mediane mit Interquartilsspanne [IQR] sind. *p Werte sind mit dem t-Test berechnet, außer für das D-Dimer, bei denen der Mann-Whitney U Test angewendet wurde. PA = Pulmonalarterie, ACT = Aktivierte Gerinnungszeit, PTT = partielle Thromboplastinzeit, anti-Xa = anti-Faktor-Xa-Spiegel, AT3 = Antithrombin 3, INR = International normalisierte Ratio, T1 = Baseline, T2 = nach Medikationsgabe (Plazebo oder Heparin)

Die PEA ermöglicht exklusiv die routinemäßige Inspektion der PA-Katheterspitzen, wodurch diese Studie erst ermöglicht wurde. PEA-Patienten können nicht direkt mit Patienten auf Intensivstationen mit einliegenden zentralen Kathetern verglichen werden, da PEA-Patienten bis zu 40% eine Gerinnungsstörung und somit eine erhöhte Thromboseneigung aufweisen [14]. Dies mag auch die hohe Zahl der Thromben insgesamt erklären. Interessant hierbei ist, dass die Thromben trotz der Vollheparinisierung 42 min nach Einlage des PAK und für eine Dauer von ca. 80 min bis zur Luxation in diesem Ausmaß nachweisbar waren. Aber Patienten auf Intensivstationen, die zentralvenöse Katheter benötigen, befinden sich zumeist in kritischem Zustand mit erhöhtem Thromboserisiko und der ZVK per se ist bereits ein Stimulus für das Gerinnungssystem zur Thrombenentwicklung [120, 121].

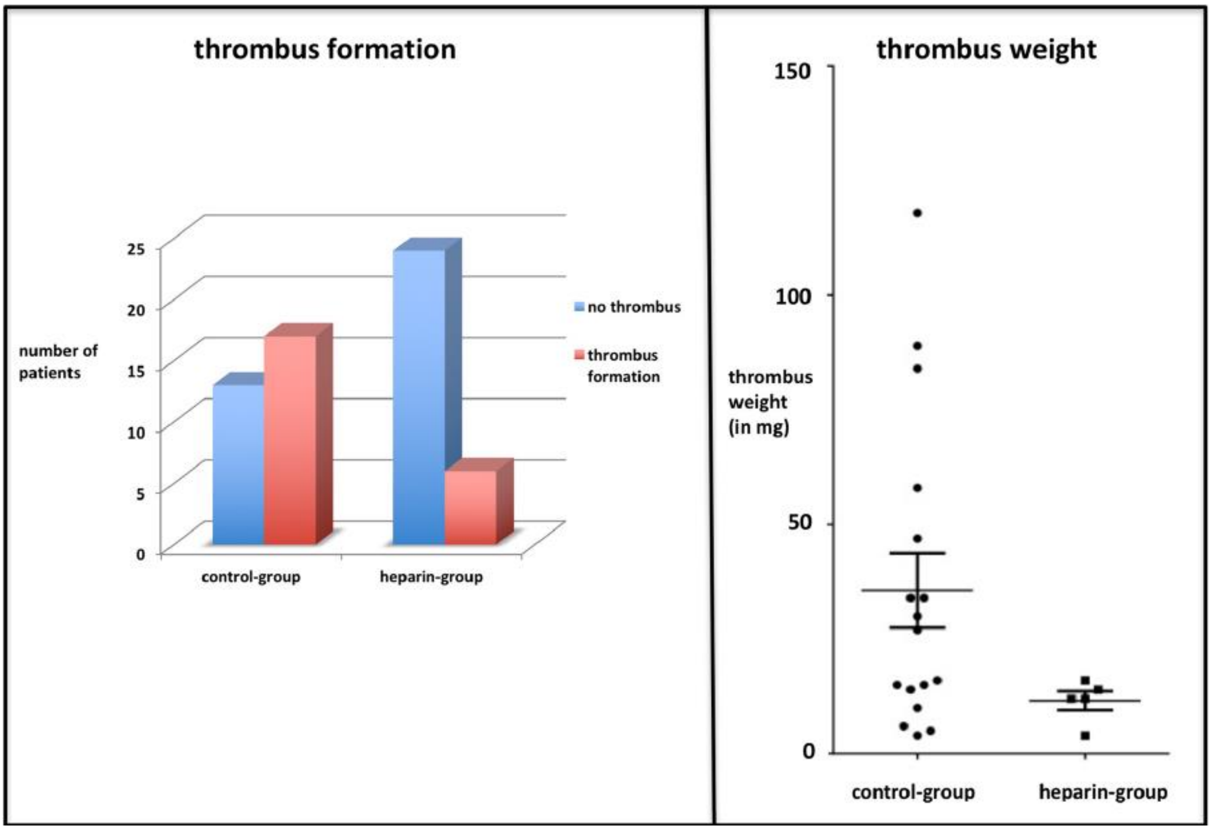


Abbildung 13: Thrombusformation nach Anzahl und Gewicht

6.5.1 Schlussfolgerung

Für PEA-Patienten zeigte diese Studie eine hohe Inzidenz an Thromben am PA-Katheter, die durch frühzeitige Gabe von niedrigdosiertem Heparin sowohl in Anzahl und Gewicht signifikant reduziert werden konnte. Dieses Ergebnis führte zu einer Änderung unseres Protokolls im Rahmen der PEA-Operationen, um die Thrombusbildung zu minimieren. In weiteren Studien sollte die Indikation zur Heparinisierung für Patienten auf Intensivstationen evaluiert werden.

6.6 Kurzzeitige venoarterielle extrakorporale Membranoxygenierung (ECMO) bei massiver endobronchialer Blutung nach pulmonaler Endarteriektomie

Die pulmonale Endarteriektomie (PEA) ist die vielversprechendste Therapieoption für Patienten mit chronisch thromboembolischer pulmonaler Hypertonie (CTEPH). Mit zunehmender Erfahrung wurden weltweit hervorragende Ergebnisse publiziert [13, 15, 51, 54, 122]. Ein Hauptrisikofaktor für einen letalen Ausgang nach einer PEA stellt ein hoher pulmonalvaskulärer Widerstand (PVR) dar, insbesondere wenn der PVR größer 12,5 WU (1000 dyn·s·cm^{-5}) ist [49]. Patienten mit vorwiegend distalen Veränderungen weisen ebenfalls eine höhere Letalität auf, da sie ein höheres Risiko für eine persistierende postoperative PH aufweisen [123]. Die schwerwiegendsten Komplikationen nach einer PEA umfassen Reperfusionsschäden der Lunge mit eingeschränkter Oxygenierung, persistierende postoperative PH, rechtsventrikuläres Versagen und endobronchiale Blutungen. Diese intra- oder frühoperativen Komplikationen verursachen die meisten perioperativen Todesfälle, wobei die endobronchiale Blutung im Regelfall die kritischste ist.

Die extrakorporale Membranoxygenierung (ECMO) ist ein gut etabliertes Verfahren, um Patienten mit einer kritischen Oxygenierung im Notfall zu oxygenieren und um die Zirkulation zu unterstützen. Die ECMO wird sowohl venovenös [124] als auch venoarteriell [125] angeschlossen. Insbesondere für endobronchiale Blutungen nach einer PEA wurde die ECMO als lebensrettendes Verfahren beschrieben, welches im Regelfall für mehrere Tage lang angewandt wurde [126, 127]. Aber insbesondere der längere venoarterielle ECMO-Einsatz zieht weitere Komplikationen wie Thrombozytopenie, systemische Embolisation und Rethrombosierungen der Pulmonalisstrombahn nach sich. Deshalb ist eine möglichst kurzfristige ECMO-Unterstützung zu präferieren.

Ein großer Vorteil des heparinbeschichteten ECMO-Systems gegenüber der konventionellen extrakorporalen Zirkulation (EKZ) während der PEA ist die Tatsache, dass das Gerinnungssystem, welches durch Heparingabe außer Kraft gesetzt wurde, wieder durch Gabe von Protamin in seiner Funktion normalisiert werden kann, ohne eine Thrombosierung des Oxygenators zu riskieren. 2014 änderten wir unser Konzept des Managements endobronchialer Blutungen mit kurzfristiger venoarterieller ECMO-Unterstützung unter sofortiger Wiederherstellung der Blutgerinnung.

Von Januar 2014 bis Dezember 2016 wurden 396 Patienten (216 Männer, 180 Frauen) einer PEA unterzogen. Die Tabelle 12 zeigt die präoperativen demographischen und hämodynamischen Daten sowie die Jamieson-Klassifikation aller 396 Patienten.

Das mittlere Alter betrug 60 ± 18 Jahre mit fast ausgeglichener Geschlechterverteilung. Der MPAP betrug 45 ± 13 mmHg.

Tabelle 12: Hämodynamik aller Patienten, die einer pulmonalen Endarteriektomie unterzogen wurden

Characteristics	
n	396
Age, y	60 ± 18
Male, n (%)	216 (54.5)
Pre-CPB sPAP, mm Hg	70 ± 23
Pre-CPB mPAP, mm Hg	45 ± 13
Pre-CPB dPAP, mm Hg	29 ± 16
Pre-CPB PVR, $dynes \cdot s \cdot cm^{-5}$	620 ± 320
Pre-CBP SVR, $dynes \cdot s \cdot cm^{-5}$	1220 ± 440
Pre-CPB CVP, mm Hg	10.9 ± 4.7
Pre-CPB CO, $L \cdot min^{-1}$	4.8 ± 2.0
Jamieson type	I (34.5%), II (34.2%), III (31.3%)

Alle Werte sind Mittelwerte ± Standardabweichung oder n (%), CBP = Kardiopulmonaler Bypass; sPAP = systolischer pulmonalarterieller Druck; mPAP = mittlerer pulmonalarterieller Druck; dPAP = diastolischer pulmonalarterieller Druck; PVR = pulmonalvaskulärer Widerstand; SVR = systemvaskulärer Widerstand; CVP = zentralvenöser Druck; CO = Herzzeitvolumen.

Die perioperative Letalität lag bei 2,3% (9/396 Patienten). Insgesamt 16 Patienten wurden mit ECMO-Unterstützung behandelt, wovon 8 Patienten aufgrund einer schweren endobronchialen Blutung mittels venoarterieller (va) ECMO behandelt wurden. Es handelte sich hierbei um 6 Frauen und 2 Männer, welche im Mittel 67 ± 11 Jahre alt waren. Diese ECMO-Patienten wiesen präoperativ ein niedrigeres HZV (3,7 ± 1,1 L/min) und einen höheren PVR (857 ± 553 $dyn \cdot s \cdot cm^{-5}$) auf. Diese Patienten hatten eine Bypass-Zeit von 308 ± 45 min mit einer Aortenabklemmzeit von 103 ± 32 min und einer totalen Kreislaufstillstandszeit von 38 ± 8 min. Die niedrigste Körperkerntemperatur lag bei 18,6 ± 1,2 °C. Einer der 8 Patienten starb aufgrund eines postoperativen Multiorganversagens. Die Charakteristika der Patienten mit der Kurzzeit-ECMO sind in Tabelle 13 dargelegt. Bei allen Patienten wurde intraoperativ von der extrakorporalen Zirkulation auf die Kurzzeit-ECMO gewechselt, nachdem eine schwere endobronchiale Blutung bronchoskopisch festgestellt wurde.

Tabelle 13: ECMO nach pulmonaler Endarteriektomie (kurzzeitige venoarterielle ECMO)

Characteristics	
n	8
Age, y	67 ± 11
Male, n (%)	2 (25)
Jamieson Classification I, n (%)	3 (38)
Jamieson Classification II, n (%)	1 (13)
Jamieson Classification III, n (%)	4 (50)
Cardiopulmonary bypass time, min	308 ± 45
Aortic crossclamp time, min	103 ± 32
Circulatory arrest time, min	38 ± 8
Lowest core temperature, °C	18.6 ± 1.2
Duration of va ECMO, min	49 ± 13
Weaned, n (%)	8 (100)
Discharged from hospital, n (%)	7 (88)
Blood products	
pRBCs, U	7.0 ± 3.2
FFP, U	7.9 ± 3.8
Platelets, U	1.7 ± 1.3

Alle Werte sind Mittelwerte ± Standardabweichung oder n (%), vaECMO = venoarterielle extrakorporale Membranoxygenierung; pRBCs = Erythrozytenkonzentrate; FFP = gefrorene Frischplasmen

Nach Wiederherstellung der Gerinnung mittels Protamin konnten im Mittel nach 49 ± 13 min (20 – 113 min) alle Patienten vom vaECMO-System entwöhnt werden. Ein Patient benötigte 6 h später aufgrund schlechter Oxygenierung eine venovenöse ECMO-Unterstützung.

Die detaillierten Daten für die einzelnen Patienten sind nachfolgend in Tabelle 14 dargestellt.

Tabelle 14: Klinischer Verlauf nach ECMO

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y	71	54	70	81	75	75	61	50
Sex	Female	Female	Male	Female	Male	Female	Female	Female
WHO FC	III	III	III	III	III	III	III	III
Duration of ECMO support, min	29	50	70	35	20	36	25	104
Ventilator support, h	206	113	43	27	102	335	34	146
Bronchus block (fibrin glue)	X		X					X
Parenchymal lesion in CT	S8 RLL		S2 RUL, S8/S9 RLL	S5 lingula	S5 ML, S9 RLL, S1 LUL	S5 ML		S2, S5, S6
ICU, d	11	10	9	9	8	16	2	12
Hospital stay, d	22	22	16	13	15	19	26	14
pRBCs, U	8	6	7	4	9	12	2	10
FFP, U	14	6	10	3	6	12	6	4
Platelets, U	0	2	4	2	2	0	2	2
Discharged from hospital	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

WHO FC = Welt-Gesundheits-Organisation Funktionsklasse; ECMO = extrakorporale Membranoxygenierung; CT = Computertomographie; S = Segment; RLL = rechter Unterlappen; RUL = rechter Oberlappen; ML = Mittellappen; LUL = linker Oberlappen; ICU = Intensivstation; pRBCs = Erythrozytenkonzentrate; FFP = gefrorene Frischplasmen

Alle Patienten benötigten perioperativ signifikant mehr Blutprodukte mit 6,8 ± 3,0 Erythrozytenkonzentraten, 8,1 ± 3,7 Einheiten an Frischplasma und 1,7 ± 1,3 Thrombozytenkonzentraten. Alle Patienten befanden sich präoperativ in der WHO-Funktionsklasse (FC) III und in der Computertomographie zeigten sich in 6 Fällen parenchymale Läsionen. Die Operationszeiten (489 ± 36 vs. 416 ± 65 min, $P < 0{,}0001$), Beatmungszeiten (164 ± 139 vs. 52 ± 76 h, $P < 0{,}0001$), sowie die Zeiten auf der Intensivstation (9,4 ± 1,1 vs. 3,6 ± 3,1 d, $P < 0{,}0001$) und der Krankenhausaufenthalt (15 ± 5 vs. 12 ± 20 d, $P = 0.0102$) insgesamt waren signifikant länger verglichen mit Patienten ohne ECMO-Therapie. Sieben Patienten konnten aus dem Krankenhaus entlassen werden. Alle Patienten sind am Leben (mittleres Follow-up von 2,6 Jahren): 3 in WHO-FC I, 3 in WHO-FC II und einer in WHO-FC III. Ein Jahr nach der Operation wiesen die Patienten sowohl eine erhebliche Verbesserung ihrer Lebensqualität als auch eine signifikante Verbesserung der pulmonalen Hämodynamik auf (Tabelle 15).

Tabelle 15: Hämodynamische Änderungen und prä- und postoperative WHO-Funktionsklasse bei Patienten mit kurzfristiger venoarterieller ECMO

Characteristics	Preoperative	1-year postoperative	
WHO FC	3.1 ± 0.4	1.7 ± 0.8	(P = .0027)
mPAP, mm Hg	45 ± 14	24 ± 10	(P = .0424)
CI, L/min/m^2	2.3 ± 0.3	2.5 ± 0.2	(P = .3236)
PVR, dynes·s·cm^{-5}	671 ± 272	296 ± 211	(P = .0242)

Alle Werte sind Mittelwerte ± Standardabweichung, WHO FC = WHO-Funktionsklasse; mPAP = mittlerer pulmonalarterieller Druck; CI = Herzindex; PVR = pulmonalvaskulärer Widerstand.

Abbildung 14 vergleicht das Überleben von Patienten mit schwerer endobronchialer Blutung in 2 Zeiträumen: Zeitraum 1 geht von 2009 bis 2013 mit 2 Überlebenden und 6 Verstorbenen und Zeitraum 2 geht von 2014 bis 2016 mit 7 Überlebenden und einem Verstorbenen.

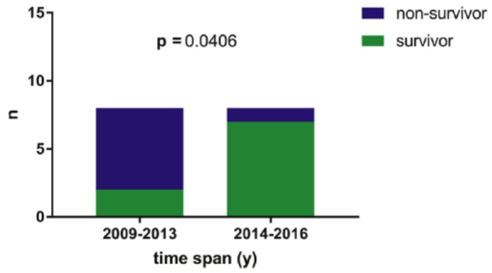


Abbildung 14: Überlebensvergleich zwischen 2 verschiedenen Konzepten der ECMO-Unterstützung. Dargestellt werden die Langzeit-Unterstützung von 2009 bis 2013 und die kurzzeitige Unterstützung von 2014 bis 2016. Grün steht für überlebende und Blau für verstorbene Patienten.

Diese Arbeit beschreibt ein neues Konzept der kurzfristigen venoarteriellen ECMO-Unterstützung zur Behandlung schwerer endobronchialer Blutungen, welches das Entwöhnen von der extrakorporalen Zirkulation nach Antagonisierung der Voll-Heparinisierung ermöglicht.

Alle großen PEA-Zentren (> 100 PEA-Operationen pro Jahr) haben aufgrund der zunehmenden Expertise die Indikationsstellung zur PEA erweitert. Hierbei müssen seltene, aber lebensbedrohliche Komplikationen wie Reperfusionsödeme, persistierende PH und endobronchiale Blutungen suffizient therapiert werden, um die Letalität der Operation zu minimieren [15].

In den meisten Fällen zeigt sich die endobronchiale Blutung zu Beginn der Entwöhnung von der extrakorporalen Zirkulation, wenn der MPAP wieder ansteigt. Durch Abnahme des Tidalvolumens bei druckgesteuerter Ventilation ist dies bereits frühzeitig erkennbar. Bronchoskopisch wird die Blutung verifiziert und falls diese lokalisierbar ist, wird versucht den betroffenen Bronchus zum Beispiel mittels Fibrin zu blockieren.

In Fällen massiver Blutung wird zunehmend die extrakorporale Unterstützung favorisiert: venovenös [124],wenn vorwiegend die Lungenfunktion unterstützt werden muss, und venoarteriell [125] , wenn auch eine kardiale Unterstützung notwendig wird. Früher wurden Patienten mit dieser Komplikation ohne ECMO therapiert mit zum Teil hoher Letalität [128, 129]. Zuletzt wurden zahlreiche Fallberichte veröffentlicht, die die ECMO-Unterstützung zur Behandlung einer massiven endobronchialen Blutung beschreiben. Hierbei war die Art der Anwendung sehr unterschiedlich und die mittlere Unterstützungsdauer betrug 3½ Tage. Insbesondere die längere venoarterielle Unterstützung kann zur Stase des Blutes in der Pulmonalarterie mit Rethrombosierung führen. Diese fatale Komplikation trat bei einem unserer Patienten auf, so dass wir über einen alternativen Ansatz nachdachten.

Bei einer schweren endobronchialen Blutung muss die Gerinnung wieder normalisiert werden. Das gelingt aber nicht an der Herz-Lungen-Maschine, da hier der Oxygenator zugerinnt und somit das System zur Kreislaufunterstützung zum Stillstand kommt. Somit ergab sich die Überlegung, von der Herz-Lungen-Maschine intraoperativ direkt auf ein ECMO-System zu wechseln, da dessen Komponenten heparinbeschichtet sind und dadurch die volle Dosis an Protamin zur Antagonisierung der Heparinwirkung verabreicht werden kann. Darunter gelang es, alle Patienten nach Stabilisierung der Blutung noch im Operationssaal wieder von der ECMO-Unterstützung zu entwöhnen und die Operation wie üblich zu beenden.

6.6.1 Schlussfolgerung

Diese Arbeit beschreibt nicht zum ersten Mal die ECMO-Unterstützung bei massiver endobronchialer Blutung [126, 127, 130, 131], aber unseres Wissens nach zum ersten Mal eine kleine Fallserie, welche dieses Kurzzeit-Management zur Behandlung einer endobronchialen Blutung im Operationssaal einsetzt. Alle anderen Fallberichte beschreiben eine ECMO-Unterstützung von 2-4 Tagen, wobei die meisten ECMO-Systeme nach der Entwöhnung von der Herz-Lungen-Maschine gestartet wurden. Durch die Anwendung des neuen Konzepts der kurzzeitigen vaECMO-Unterstützung gelang es, die Letalität dieser Komplikation dramatisch zu reduzieren.

6.7 Pulmonale Endarteriektomie bei chronisch thromboembolischer pulmonaler Hypertonie

Historische Daten belegen die schlechte Prognose (Letalität nach 3 Jahren um 90%) einer unbehandelten CTEPH, wenn der MPAP > 50 mmHg ist [132]. Da eine PEA als eine wirkliche Endarteriektomie von fibrotischem Material eine kurative Therapieoption darstellt, wird die pulmonale Endarteriektomie (PEA) als Gold-Standard der CTEPH-Behandlung durch die gültigen Leitlinien empfohlen [2, 51, 133, 134]. Die PEA ist ein komplexes operatives Verfahren, das eine extrakorporale Zirkulation sowie Phasen tiefer hypothermer Kreislaufstillstände benötigt. Erfahrene hochvolumige Zentren führen die PEA mit niedriger Letalität und signifikanten Verbesserungen von Hämodynamik, Symptomatik und Lebensqualität aus [14, 75, 82, 122, 135]. Daten bzgl. der PEA-Patienten in Deutschland sind rar und deshalb fokussiert sich diese Arbeit auf die Klinik, die funktionellen Einschränkungen, das chirurgische Management und die Komplikationen der operierten CTEPH-Patienten.

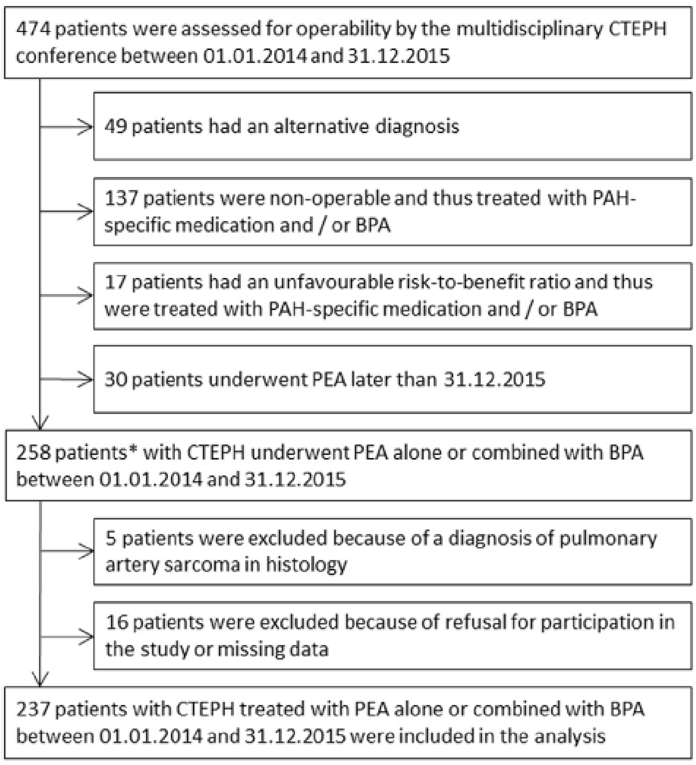


Abbildung 15: Flussdiagramm zum Ein- und Ausschluss von Patienten. BPA = pulmonale Ballonangioplastie; CTEPH = chronisch thromboembolische pulmonale Hypertonie; PEA = pulmonale Endarteriektomie.

Alle Patienten, die sich zwischen Januar 2014 bis Dezember 2015 einer PEA unterzogen, wurden in diese prospektive Kohortenstudie eingeschlossen. Die Kerckhoff-Klinik ist mit > 100 Operationen pro Jahr ein nationales Zuweisungszentrum für die operative Behandlung der CTEPH. Abbildung 15 zeigt den Auswahlprozess. Von 474 Patienten zur Abklärung einer CTEPH blieben 237 operierte und zu untersuchende Patienten übrig.

Zwischen 1. Januar 2014 und 31. Dezember 2015 wurden 253 CTEPH-Patienten einer PEA unterzogen (auch als Hybrid-Eingriff mit pulmonaler Ballonangioplastie). 237 Patienten wurden in diese Studie eingeschlossen, wobei 219 Patienten (92,4%) von anderen Zentren in Deutschland überwiesen wurden und 18 Patienten aus dem Ausland kamen. Nach Angaben des statistischen Bundesamtes (Abbildung 16) wurden in Deutschland im Jahr 2014 194 und 2015 200 PEA-Operationen durchgeführt. Die Krankenhaus-Letalität betrug hierbei jeweils 6,2% und 5,5%. Von diesen Patienten wurden 64,2% in der Kerckhoff-Klinik mit einer Letalität von 2,5% operiert.

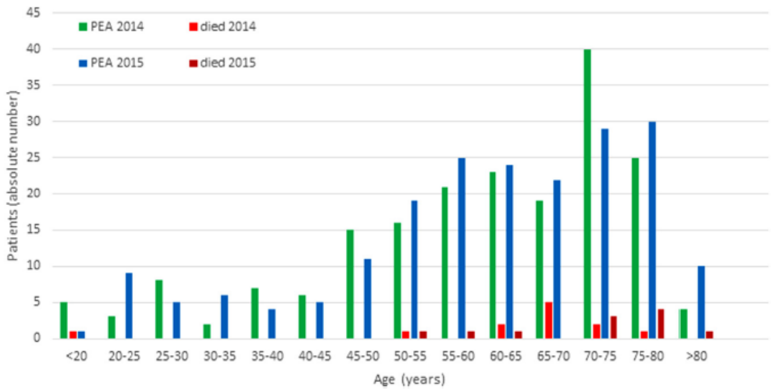


Abbildung 16: Anzahl der Patienten, die in den Jahren 2014 und 2015 einer PEA (OPS-Code: 5-381.42) unterzogen wurden und deren Hospitalletalität laut Statistischem Bundesamt.

In Tabelle 16 sind die Baseline-Charakteristika, Komorbiditäten, Risikofaktoren für eine CTEPH, Symptome sowie der funktionelle Status der Patienten zusammengefasst. Obwohl extremes Übergewicht immer noch als eine Kontraindikation für die PEA erwogen wird, hatten 61 Patienten (26,0%) einen Body-Mass-Index (BMI) > 30 kg·m^2, 20 Patienten (8,5%) einen BMI > 35 kg·m^2 und 30 Patienten (12,8%) wogen mehr als 100 kg. Der zeitliche Median von der Diagnosestellung der CTEPH bis zur PEA betrug 129 Tage (IQR 85-271 Tage) mit einer Spanne von 7 bis 4687 Tagen. 21 Patienten (8,9%) wurden nach mehr als 2 Jahren operiert. Die meisten Patienten (72,2%) wiesen seit mehr als einem Jahr Symptome auf, wobei das Hauptsymptom Dyspnoe bis auf einen Patienten bei allen anderen (99,6%) vorhanden war. 186 Patienten (78,5%) befanden sich in der New York Heart Association- (NYHA) Funktionsklasse 3 oder 4. Ein 6-Minuten-Gehtest lag für 123 Patienten (51,9%) vor mit einer medianen Gehstrecke von 387 m (IQR 289-435). Eine transthorakale Echokardiographie wurde bei 229 Patienten (96,6%) und eine Rechtsherzkatheteruntersuchung bei 233 Patienten (98,3%) durchgeführt. Bezüglich der Antikoagulation und der gezielten medikamentösen Therapie (Tabelle 17) sieht man, dass zum einen mehr als die Hälfte der Patienten Vitamin-K-Antagonisten (54,5%) einnahm und bei nicht-Vitamin-K-abhängiger oraler Antikoagulation (NOAK) zumeist Rivaroxaban (38,3%) angewendet wurde.

Tabelle 16: Baseline Charakteristik, Komorbiditäten und Risikofaktoren für CTEPH, Symptome und funktioneller Status von CTEPH-Patienten vor der pulmonalen Endarteriektomie

	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 = bezieht sich auf die Anzahl der Patienten mit verfügbaren Daten; Werte sind Mediane (Interquartilspanne) oder Anzahl (Prozent). BMI = Body-Mass-Index; CTEPH = chronisch thromboembolische pulmonale Hypertonie; LTOT = Langzeit-Sauerstofftherapie; LVEF = linksventrikuläre Ejektionsfraktion; NT-proBNP = N-terminales pro B-Typ natriuretisches Peptid; NYHA = New York Heart Association; PA = Pulmonalarterie; PAWP = pulmonalarterieller Verschlussdruck; PEA = pulmonale Endarteriektomie; PVR = pulmonalvaskulärer Widerstand; RA = rechtes Atrium; RHC = Rechtsherzkatheter; RV = rechter Ventrikel; TAPSE = systolische Exkursion der Ebene des Trikuspidalklappenanulus; TTE = transthorakale Echokardiographie; WHO = Weltgesundheitsorganisation.

[a] Als aktiv oder unter Behandlung während der letzten 6 Monate definiert.

[b] Definiert als eine glomeruläre Filtrationsrate < 60 ml/min/1,73 m^2.

[c] Definiert als Hämoglobinkonzentration < 13 g/dl für Männer und < 12 g/dl für Frauen.

[d] Definiert als entzündliche Darmerkrankung, Erkrankung des rheumatischen Formenkreises oder einer chronischen systemischen Entzündung.

[e] Definiert als Antiphospholipidsyndrom, hetero- oder homozygote Faktor-V-Leiden Mutation, hetero- oder homozygote Prothrombinmutation oder Protein S- bzw. C- Mangel

Tabelle 17: Medikation der CTEPH-Patienten

	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 = chronisch thromboembolische pulmonale Hypertonie; PAH = pulmonalarterielle Hypertonie; PEA = pulmonale Endarteriektomie.

Etwa 1/5 der Patienten erhielten vor der Operation eine gezielte medikamentöse Therapie, wobei Riociguat (8,1%) und Sildenafil (9,8%) am häufigsten verschrieben wurden.

Außer einem Patienten konnten 236 mittels PEA operiert werden. Bei 4 (1,7%) Patienten wurde ein Hybrid-Eingriff mit PEA und gleichzeitiger BPA durchgeführt und bei 19 Patienten (8,0%) wurde die Operation durch zusätzliche Prozeduren (z.B. koronare Bypass-Operation oder Herzklappenersatz) erweitert. Die mittlere Operationszeit lag bei 397 min (IQR 363-431 min) und die mediane kardiopulmonale Bypass-Zeit lag bei 267 min (IQR 245-290 min) sowie die mediane Kreislaufstillstandszeit bei 34 min (IQR 26-40 min). Direkt nach der PEA fiel der PVR im Median auf 4,8 WU (IQR 3,5-6,4 WU, p<0,001 vs. präoperativ) und der MPAP auf 29 mmHg (IQR 26-33 mmHg, p<0,001 vs. präoperativ).

Tabelle 18: Komplikationen nach 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 = kontinuierliche venovenöse Hämofiltration; ECMO = extrakorporale Membranoxygenierung; PEA = pulmonale Endarteriektomie.

[a] Eine Majorblutung wurde definiert bei zusätzlichen chirurgischen Interventionen (Übernähungen ohne/mit Patch, Anwendung von Fibrinkleber oder bei venoarterieller ECMO.

[b] Eine postoperative Majorblutung wurde definiert nach Schulmann et al. [136].

Insgesamt gab es bei 86 Patienten (36,2%) intraoperative und/oder postoperative Komplikationen (Tabelle 18), wobei keine Unterschiede zu erkennen waren für Patienten mit gezielter medikamentöser Therapie oder NOAK-Therapie. Bei 14 Patienten (5,9%) wurde eine venoarterielle oder venovenöse ECMO-Therapie benötigt, wobei 4 Patienten (1,6% vom Gesamtkollektiv) in der Klinik verstarben.

Prädiktoren für eine intra- und/oder postoperative Komplikation sind in den Tabellen 19 und 20 aufgeführt.

Tabelle 4

Tabelle 19: Prädiktoren für intraoperative Komplikationen währende der 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 = Fläche unter der Kurve; CI = Konfidenzintervall; CPB = kardiopulmonaler Bypass; OR = Chancenverhältnis; PEA = pulmonale Endarteriektomie; PVR = pulmonalvaskulärer Widerstand.
[a] Univariate Prädiktoren werden in das multivariate logistische Regressionsmodell integriert (s. Methoden)
[b] Der optimale „Cutoff"-Wert wurde anhand der Quantifikation des Youden-Index berechnet (s. Methoden)

Tabelle 20: Prädiktoren für postoperative Komplikationen nach der 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, Fläche unter der Kurve; CI, Konfidenzintervall; CPB, kardiopulmonaler Bypass; NT-proBNP, N-terminales pro B-Typ natriuretisches Peptid; OR, Chancenverhältnis; PA, Pulmonalarterie; PEA, pulmonale Endarteriektomie; PVR, pulmonalvaskulärer Widerstand; RHC, Rechtsherzkatheter; TAPSE, systolische Exkursion der Ebene des Trikuspidalklappenanulus; TTE, transthorakale Echokardiographie.
[a] Univariate Prädiktoren werden in das multivariate logistische Regressionsmodell integriert (s. Methoden)
[b] Definiert als eine glomeruläre Filtrationsrate < 60 ml/min/1,73 m2.
[c] Der optimale „Cutoff"-Wert wurde anhand der Quantifikation des Youden-Index berechnet (s. Methoden)

Unter Anwendung des multivariaten logistischen Regressionsmodells war nur die Operationszeit als unabhängige Variable sowohl mit intraoperativen (≥440 min; OR = 10,8; 95% CI 4,4-26,5, p<0,001) als auch postoperativen (≥390 min; OR = 3,6; 95% CI 1,4-9,3; p=0.009) Komplikationen verknüpft. Sechs Patienten (2,5%) verstarben im Krankenhaus (3-22 Tage nach der

PEA) aufgrund postoperativer Komplikationen, wie z.B. Sepsis mit nachfolgendem Multiorganversagen (Abbildung 17). Patienten, die verstarben, hatten präoperativ höhere NT-proBNP-Spiegel und eine häufiger reduzierte TAPSE (tricuspid annular plane systolic excursion) < 16 mm im TEE verglichen mit nicht verstorbenen Patienten.

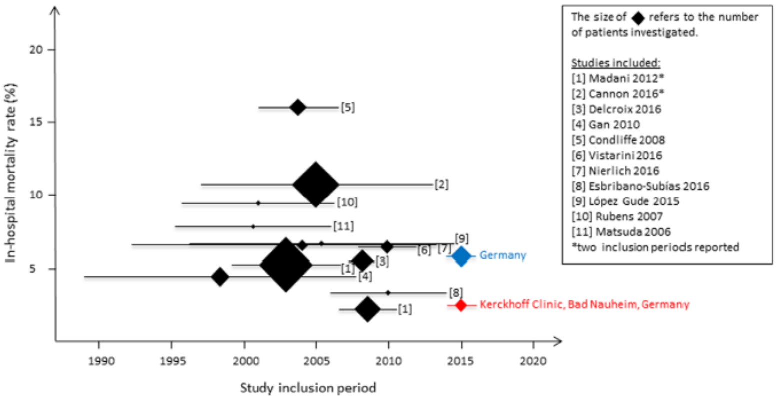


Abbildung 17: Die Hospitalletalität von CTEPH-Patienten nach einer PEA bezogen auf die jeweilige Studie und den Beobachtungszeitraum. Es wurden nur Studien mit ≥ 100 Patienten berücksichtigt.

Die pulmonale Endarteriektomie ist die einzige potentiell kurative Therapie für CTEPH [2, 3, 51, 55, 133]. Durch Verbesserungen der chirurgischen Techniken, der Behandlungen von Komplikationen und der Intensivtherapie konnte die Letalität der PEA deutlich unter 5% gesenkt werden. Zwei der größten PEA-Zentren weltweit berichten von einer Hospitalletalität zwischen 2,2% und 2,4% [50, 51]. Die Ergebnisse dieser monozentrischen Studie stimmen damit überein. Unser Zentrum erreichte als ein Zuweisungszentrum für CTEPH bei 237 Patienten über einen Zeitraum von 2 Jahren eine Letalität von 2,5%. Diese liegt unterhalb der berichteten Letalitätsrate des ersten großen internationalen CTEPH-Registers (4,7%) [122] sowie für Patientenserien, die vor mehr als 10 Jahren einer PEA unterzogen wurden und Raten von 9,4% und 7,8% [137, 138] aufwiesen.

Erstmalig wurden für eine größere Kohorte detailliert sowohl die intraoperativen als auch die postoperativen Komplikationen aufgelistet, wobei die Hauptkomplikationen Reperfusionsödeme (9,7%, internationales CTEPH-Register 9,6% [15]) und Blutungen umfassen.

6.7.1 Schlussfolgerung

Im Rahmen eines multidisziplinären diagnostischen wie auch therapeutischen Ansatzes in einem erfahrenen PEA-Zentrum in Deutschland ist die PEA ein sicheres Verfahren zur Behandlung schwer kranker Patienten mit CTEPH bei einer niedrigen Hospitalletalität von 2,5%. Die

Prognose der Patienten nach einer PEA war hierbei nicht beeinflusst durch Baseline-Charakteristika, Komorbiditäten oder die präoperative Hämodynamik. Die Prognose wurde im Wesentlichen durch die intraoperativen Komplikationen und die daraus bedingte Länge der Operationszeit bestimmt.

6.8 Sequentielle Behandlung mit Riociguat und pulmonaler Ballonangioplastie bei inoperabler chronisch thromboembolischer pulmonaler Hypertonie (CTEPH)

Aufgrund der peripheren Lokalisation chronisch thromboembolischer Obstruktionen können ca. 1/3 der Patienten mit einer CTEPH nicht der operativen Desobliteration durch pulmonale Endarteriektomie zugeführt werden [14]. Verschiedene Medikamente für die gezielte pulmonalarterielle Blutdrucksenkung wie Bosentan [139] oder Sildenafil [140] wurden getestet, konnten aber in kontrollierten randomisierten Studien (RCT) den primären Endpunkt der Therapieverbesserung nicht erreichen. Riociguat, ein Stimulator der löslichen Guanylatzyklase war die erste Substanz, die nicht nur die pulmonale Hämodynamik verbesserte, sondern auch die physische Belastbarkeit gemessen am 6-Minuten-Gehtest signifikant steigerte und wurde deshalb als erstes Medikament für die Behandlung der inoperablen CTEPH zugelassen [6, 141, 142].

Weltweit werden zunehmend inoperable CTEPH-Patienten mit der pulmonalen Ballonangioplastie (BPA) behandelt, aber die zusätzliche gezielt medikamentöse Therapie ist zentrumsabhängig und somit unterschiedlich [7, 10, 58-60, 64, 143]. Weiterhin ist die Evidenzlage für die BPA in der Behandlung der CTEPH nach wie vor gering mit fehlenden Langzeitdaten bzw. Daten aus randomisierten Studien. Bis jetzt wird diese interventionelle Therapie in den Leitlinien nicht empfohlen. Die Leitlinien beschreiben die BPA als mögliche Ergänzung einer medikamentösen Therapie ohne wirkliche Evidenz dieser Empfehlung [2].

Somit war das Ziel dieser Studie, zunächst den medikamentösen Effekt von Riociguat auf die Behandlung von Patienten mit inoperabler CTEPH, aber Vorliegen von BPA-zugänglichen Obstruktionen zu erfassen und dann auch den zusätzlichen Effekt der nachfolgenden BPA-Sitzungen zu untersuchen. Zwischen März 2014 und Juli 2017 wurden > 150 PEA-Operationen und > 200 BPA-Prozeduren durchgeführt. Es handelte sich um symptomatische Patienten mit CTEPH, die sich mindestens in der WHO-Funktionsklasse (FC) II befanden, bei denen ein mittlerer pulmonalarterieller Druck ≥ 25 mmHg in Ruhe gemessen wurde und die in der Pulmonalisangiographie in der DSA-Technik vaskuläre Obstruktionen aufwiesen. In diese Studie wurden alle inoperablen Patienten eingeschlossen, die für eine BPA geeignet erschienen und die sich nach einer medikamentösen Vorbehandlung mit Riociguat für mindestens 3 Monate immer noch in einer WHO-FC ≥ 2 befanden. Es wurden insgesamt 123 Patienten mit BPA behandelt (Abbildung 18). Das Follow-up nach 6 Monaten war für 69 Patienten komplettiert und von diesen waren 36 ohne gezielte medikamentöse Therapie. Diese wurden für die Studie ausgewählt.

Alle Patienten wurden über die Studie aufgeklärt und haben schriftlich ihre Einwilligung bekundet. Die Ethikkommission erteilte für diese Studie ein positives Votum (AZ 43/14, Fachbereich Medizin der Justus-Liebig-Universität, Gießen).

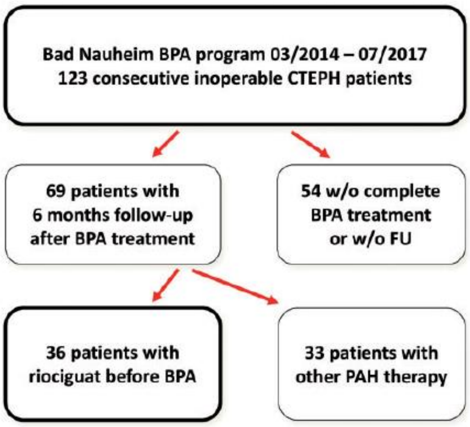


Abbildung 18: Flussdiagramm, das die Patientenselektion des BPA-Programms in Bad Nauheim beschreibt.

Abbildung 19 stellt den diagnostischen und therapeutischen Ablauf für die Patienten dieser Studie dar.

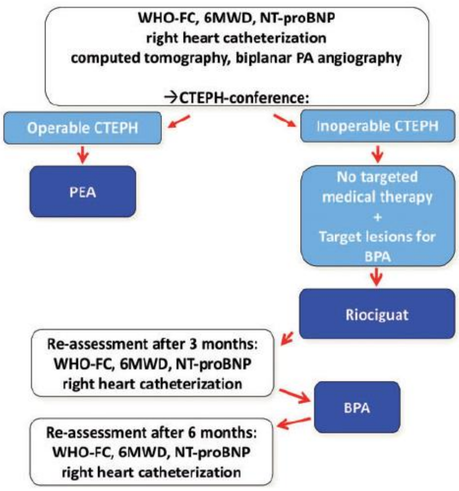


Abbildung 19: Flussdiagramm der 36 Studienpatienten

Vor der Initiierung der medikamentösen Therapie wurden alle standardisierten diagnostischen Untersuchungen durchgeführt. Danach wurde für mindestens 3 Monate Riociguat verabreicht. Vor der ersten BPA erfolgte wiederum eine komplette Diagnostik, welche nochmals 6 Monate nach der letzten BPA abschließend erfolgte. Zu den Untersuchungen zählten das Erfassen der WHO-FC, der 6-Minuten-Gehtest (6MGT), der Serumkonzentration des Kreatinins und des N-terminalen pro B-Typ natriuretischen Peptids (NT-proBNP), der Rechtsherzkatheter (RHK) zur Messung des rechtsatrialen Drucks (RAP), des pulmonalarteriellen Drucks (PAP), des pulmonalarteriellen Wedge-Drucks (PAWP), des Herz-Zeit-Volumens (HZV,CO), des Herzindex (HI,CI) und des pulmonalvaskulären Widerstands (PVR).

Die Tabelle 21 gibt Aufschluss über die Baseline-Charakteristik der Patienten. Tabelle 22 zeigt die hämodynamischen Daten sowie die funktionelle Kapazität vor der Gabe von Riociguat.

Bei 8 Patienten wurde die Zieldosis (3 x 2,5 mg/d) aufgrund von Nebenwirkungen nicht erreicht. Das Intervall zwischen Beginn der gezielten Medikation bis zur 1. BPA war 5 Monate (Spanne 2-18 Monate). Insgesamt wurden 195 BPAs durchgeführt, im Median

5 und hierbei im Median 11 Segmente (Spanne 8-13).

Tabelle 21: Baseline-Charakteristik der Patienten

	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)

Werte sind Mittelwerte ± Standardabweichung, falls nicht anderes angegeben ist. IQR = Interquartilspanne; VTE = venöse Thromboembolie; CTEPH = chronisch thromboembolische pulmonale Hypertonie; BPA = pulmonale Ballonangioplastie; TLC = totale Lungenkapazität; FVC = forcierte Vitalkapazität; FEV_1 = forcierte Einsekundenkapazität.

Tabelle 23 und Abbildung 20 stellen die Effekte der gezielten medikamentösen Therapie bezüglich Hämodynamik, Serumkonzentration des NT-proBNP sowie körperlicher Belastung dar. Bei 13 Patienten (36,1%) konnte eine Verbesserung der WHO-FC um eine Stufe erreicht werden, die restlichen 23 Patienten (63,9%) zeigten keine Änderung. Der 6MGT nahm gering um 20 m zu. Hämodynamisch konnten signifikante Abnahmen für den MPAP (49 ± 12 vs. 43 ± 12 mmHg, P=0,003), PVR (956 ± 501 vs. 517 ± 279 dyn·s·cm^{-5}, P=0,0001) sowie den NT-proBNP-Spiegel (1137 [IQR = 283-2142] vs. 1010 [IQR = 128-1887], P=0,02) gemessen werden.

Tabelle 22: Belastungsfähigkeit und Hämodynamik der Patienten zur Baseline

	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)

Werte sind Mittelwerte ± Standardabweichung, falls nichts anderes angegeben ist. WHO = Weltgesundheitsorganisation 6MWD = 6-Minuten-Gehstrecke; mPAP = mittlerer pulmonalarterieller Druck; PAWP = pulmonalarterieller Verschlussdruck; CO = Herzzeitvolumen; PVR = pulmonalvaskulärer Widerstand; NT-proBNP = N-terminales pro B-Typ natriuretisches Peptid.

Die Ergebnisse der Kombinationstherapie bestehend aus gezielter Therapie mit Riociguat und 6 Monate nach der letzten BPA sind ebenfalls in Tabelle 23 und Abbildung 20 dargestellt. Die WHO-FC hat sich nochmals gebessert und blieb nur bei 2 Patienten unverändert. Der 6MGT hat sich verglichen mit der alleinigen Riociguat-Behandlung im Mittel um weitere 58 m (12,5%) gesteigert (P = 0,0001). Für die hämodynamischen Parameter ergaben sich signifikante Verbesserungen für den MPAP und PVR.

Tabelle 23: Belastungsfähigkeit und Hämodynamik unter Riociguat und 6 Monate nach 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

Werte sind Mittelwerte ± Standardabweichung, falls nichts anderes angegeben ist.
[a] Konvertierung von mg/dl → mmol/l dividiert durch 11,3
WHO = Weltgesundheitsorganisation 6MWD = 6-Minuten-Gehstrecke; mPAP = mittlerer pulmonalarterieller Druck; sPAP = systolischer pulmonalarterieller Druck; dPAP = diastolischer pulmonalarterieller Druck; PAWP = pulmonalarterieller Verschlussdruck; DPG = diastolischer pulmonaler Gradient; TPG = transpulmonaler Gradient; CO = Herzzeitvolumen; CI = Herzindex; PVR = pulmonalvaskulärer Widerstand; PAC = pulmonalarterielle Compliance; HR = Herzfrequenz; NT-proBNP = N-terminales pro B-Typ natriuretisches Peptid; eGFR = geschätzte glomeruläre Filtrationsrate.

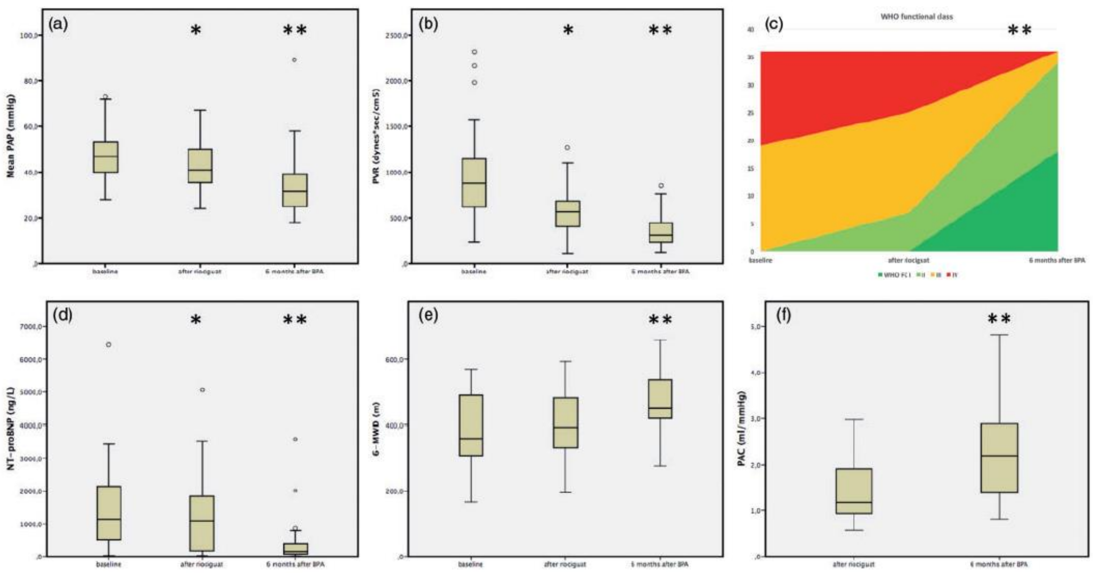


Abbildung 20: Effekt von Riociguat und nachfolgender BPA auf a) MPAP, b) PVR, c) WHO-FC, d) NT-proBNP, e) 6-Minuten Gehstrecke (6-MWD) und f) pulmonalarterielle Compliance (PAC). Sternchen zeigen die Signifikanz an (* P < 0,05; ** P < 0,001).

Es gibt zunehmend kleine und mittlere Fallserien, die für Patienten nach einer BPA die positiven Auswirkungen dieser Behandlung auf die pulmonale Hämodynamik sowie körperliche Leistungsfähigkeit beschreiben [7, 9, 10, 64, 143]. Die Auswirkung der gezielten medikamentösen Therapie mit Riociguat, dem einzigen zugelassenen Medikament für die inoperable CTEPH, wurde bis jetzt nicht evaluiert. Dies wurde explizit mit dieser Arbeit untersucht.

Die Hauptergebnisse sind wie folgt: 1. Riociguat verbessert die Hämodynamik und die körperliche Leistungsfähigkeit für inoperable, aber BPA-fähige Patienten. 2. Die zusätzlichen Interventionen mittels BPA führen zu weiterer Verbesserung. 3. Die Kombination von Riociguat und BPA ist für bestimmte Patienten geeignet und sicher. Somit werden die momentan gültigen Leitlinien durch diese Arbeit unterstützt [2].

Die Änderungen durch die Riociguat-Gabe entsprechen den bereits durch Ghofrani et al. publizierten Daten [6]. In der CHEST-1 Studie wurde eine PVR-Reduktion von 226 (±248) $dyn \cdot s \cdot cm^{-5}$ sowie eine Verbesserung der WHO-FC bei 33% der Patienten beschrieben. In diesem Kollektiv wurde eine PVR-Abnahme um 439 $dyn \cdot s \cdot cm^{-5}$ und eine Verbesserung der WHO-FC bei 36,1% der Patienten gefunden. Die Chest-2 Studie konnte eine Korrelation zwischen dem Patientenüberleben und den Parametern WHO-FC, NT-proBNP und 6-MGT aufzeigen [142]. In dieser Studie steigerte sich der 6-MGT nach Riociguat im Mittel um 20 m und nach BPA im Mittel um weitere 58 m und belegt somit klar den Benefit der Kombination beider Verfahren.

Die positiven Veränderungen bei der physischen Belastbarkeit und der pulmonalen Hämodynamik in unserer Kohorte sind vergleichbar mit den Ergebnissen andere europäischer Zentren [64, 144], aber weniger ausgeprägt im Vergleich mit japanischen Veröffentlichungen [10, 58, 59]. Dieser Fakt wurde bereits durch unsere multizentrische Arbeitsgruppe diskutiert [7] und könnte beeinflusst sein durch die Tatsache, dass in Deutschland hoch-spezialisierte CTEPH/PEA-Zentren existieren, was für Japan nicht gilt. So werden in Japan Patienten mittels BPA therapiert, die in Deutschland eher eine PEA erhalten würden. Da in diesem Kollektiv nur inoperable Patienten eingeschlossen wurden, sind die Ergebnisse mit Japan aufgrund unterschiedlicher Patientenkohorten nicht vergleichbar. In einem Review beschrieben Lang et al., dass bzgl. der medikamentösen Therapie bei BPA kein Konsens besteht [144]. Nur ein Zentrum veröffentlichte Daten und gab an, dass 40% der Patienten mit Riociguat behandelt wurden [145]. Die Autoren beschrieben aber nicht die Veränderungen im Rahmen der Riociguat-Applikation. Aoki et al. beschrieben Langzeitdaten ihres BPA-Programmes [146]: 96% der Patienten erhielten vor der

BPA eine medikamentöse Therapie, es wurden jedoch nur 17% mit Riociguat behandelt. 6 Monate nach der letzten Therapie waren noch 68% unter einer medikamentösen Therapie.

6.8.1 Schlussfolgerung

Dieser Artikel beschreibt erstmalig systematisch die Effekte der sequentiellen Therapie mit Riociguat gefolgt von einer BPA für inoperable CTEPH-Patienten. Diese Daten beleuchten die realen Therapiealgorithmen eines hochvolumigen CTEPH-Zentrums in Deutschland. Die Kombinationstherapie hat deutliche positive Auswirkungen auf die physische Belastbarkeit und auf die pulmonale Hämodynamik der Patienten. Mit kontrolliert randomisierten Studien sollte mehr Evidenz für diesen Therapieansatz gefunden werden.

6.9 Kombinierte pulmonale Endarteriektomie und pulmonale Ballonangioplastie bei Patienten mit chronisch thromboembolischer CTEPH

Nach akuter Lungenembolie entwickeln bis zu 4% der Patienten eine chronisch thromboembolische pulmonale Hypertonie (CTEPH) [72, 147]. Dabei führen sowohl die proximale als auch die distale Stenosierung bzw. Verschlüsse der pulmonalarteriellen Äste und die zusätzliche Mikrovaskulopathie zur PH mit konsekutivem Rechtsherzversagen [80]. Die Behandlung von CTEPH-Patienten sollte in spezialisierten CTEPH-Zentren erfolgen, in denen pulmonale Endarteriektomien (PEA) in einem hohen Volumen durchgeführt werden [14, 15, 48, 55, 103, 148]. Dieses komplexe chirurgische Verfahren ist für viele Patienten kurativ (Normalisierung der pulmonalen Hämodynamik) und wird mit einem niedrigen Letalitätsrisiko in erfahrenen Zentren durchgeführt. Jedoch werden bis zu 37% der Patienten als inoperabel eingestuft [14], für die die gezielte medikamentöse Therapie mit Riociguat nun in vielen Ländern zugelassen ist [6, 139].

Die pulmonale Ballonangioplastie wurde erstmalig 2001 durch Feinstein et al. in einem kleinen Patientenkollektiv als neue Therapieoption für inoperable CTEPH vorgestellt [60]. Dieses Verfahren wurde zuletzt vor allem durch japanische Zentren weiterentwickelt, die ebenfalls über erhebliche Reduktionen des pulmonalarteriellen Mitteldrucks (MPAP) von 43 auf 25 mmHg berichten [10, 58, 59, 64, 149]. Für die seltenen Fälle, in denen der Patient für eine Seite als operabel erachtet wird (meistens rechts), aber inoperabel für die Gegenseite, kann bei schwerer hämodynamischer Beeinträchtigung und damit hohem perioperativen Letalitätsrisiko ein Kombinationseingriff, bestehend aus einer PEA der operativen Seite und einer BPA der Gegenseite, erwogen werden, um eine maximal mögliche Reduktion der rechtsventrikulären Nachlast zu erreichen. Wir berichten über 3 Patienten, bei denen dieser Hybridansatz ausgeführt wurde.

In Abbildung 21 wird die Angiographie eines typischen Falles (Patient 3) dargestellt. Man erkennt für die rechte Seite, dargestellt durch die Pfeile, chirurgisch erreichbare Obstruktionen, während für die linke Seite nur sehr distale Veränderungen zur Darstellung kommen, deren chirurgische Erreichbarkeit nicht gegeben ist. Bei allen drei Patienten wurde jeweils für die rechte Seite eine PEA durchgeführt mit drei hypothermen Kreislaufstillständen von 43 min für Patient 1, zwei Kreislaufstillständen von 28 min für Patient 2 und 2 Kreislaufstillständen von 38 min für Patient 3 (Abbildung 27). Die linke Pulmonalarterie (PA) wurde immer eröffnet, um die Möglichkeit einer PEA zu evaluieren.

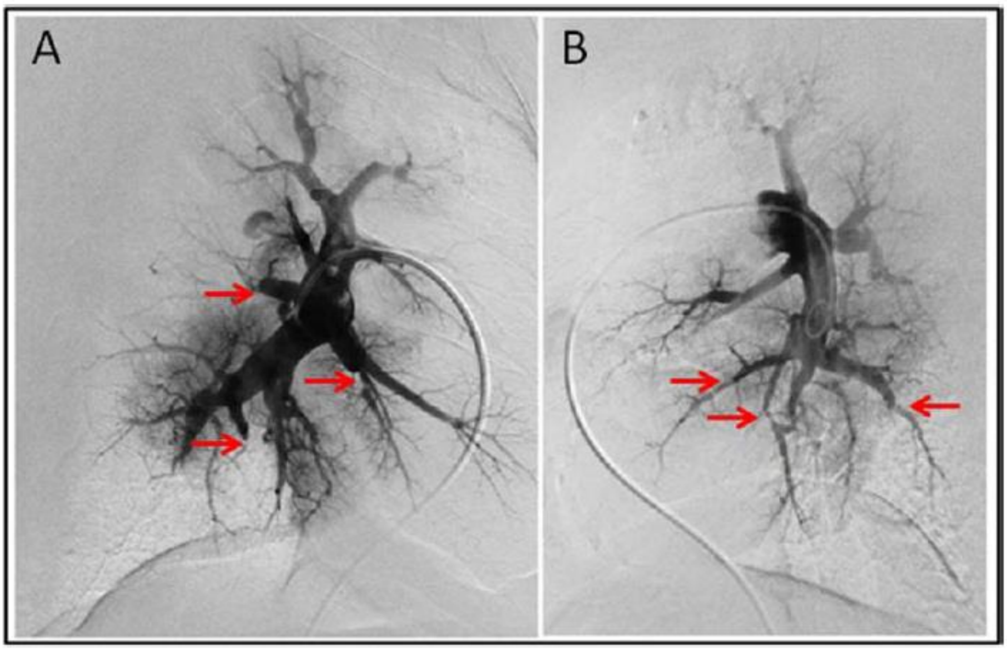


Abbildung 21: Präinterventionelle Pulmonalisangiographie (laterale Projektion) bei Patient 3. A) rechte Pulmonalarterie mit chirurgisch erreichbaren Obstruktionen (Pfeile); B) linke Seite mit sehr distal lokalisierten Läsionen (Pfeile).

Während der Aufwärmphase nach Beendigung der PEA wurde dann die BPA (Abbildung 28) der linken Seite durchgeführt. Diese Phase benötigt zumeist 1 bis 1½ Stunden, welche ein ausreichendes Zeitintervall für die Angioplastie bietet und bei allen drei Patienten ausreichte. Hierzu werden in den Truncus pulmonalis zwei Tabaksbeutelnähte gelegt und dann eine 6-F-Schleuse (Terumo) in die linke PA eingebracht. Darüber wird ein Führungskatheter (Multipurpose, Medtronic) in die linke PA eingebracht und in die betroffenen Segmentarterien unter Durchleuchtung intubiert. Unter reduziertem Fluss des kardiopulmonalen Bypasses und inspiratorischem Halt des Ventilators erfolgt die An-

Abbildung 22: Endarteriektomiertes Gewebe aus der rechten Pulmonalarterie.

gioplastie. Dazu werden Führungskatheter und Drähte über die stenosierten Bereiche vorgeschoben und daran anschließend werden mit Ballonkathetern multiple Dilatationen durchgeführt (Emerge, 2,0/20 mm, 4,0/20 mm und 5,0/20 mm; Boston Scientific).

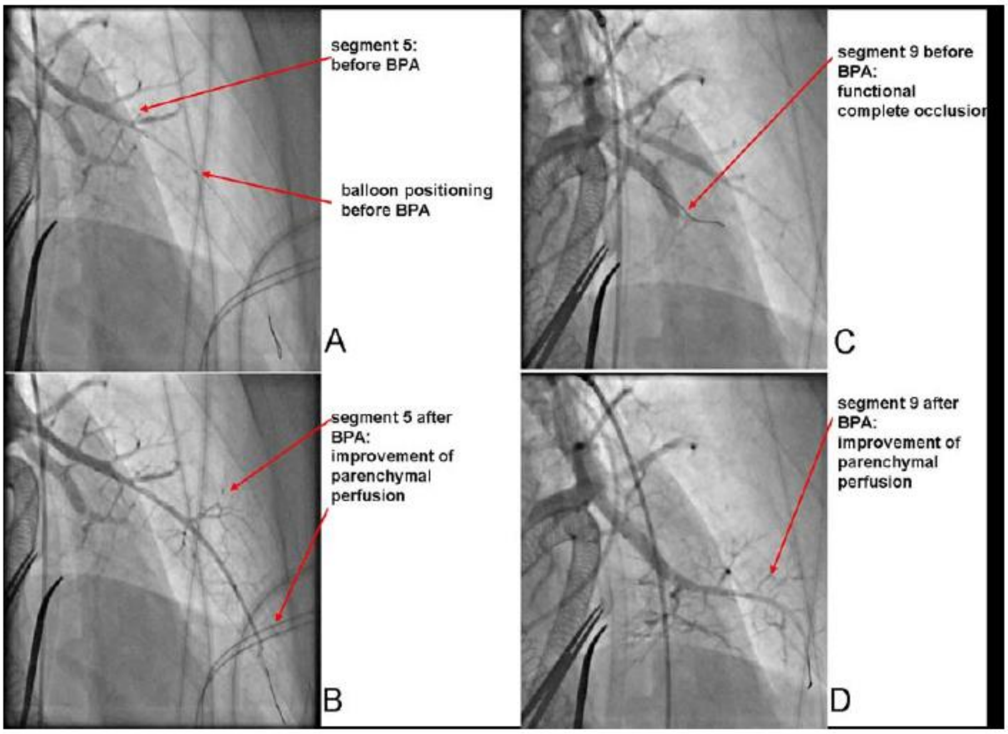


Abbildung 23: A-D) periinterventionelle Pulmonalisangiographie während der pulmonalen Ballonangioplastie der linken Lunge von Patient 2

Am Morgen (7 Uhr) des 1. postoperativen Tages wurde vor der Entfernung des PA-Katheters die pulmonale Hämodynamik kontrolliert. Eine mittlere PVR-Reduktion von 842 dyn·s·cm^{-5} wurde hierbei gemessen (Tabelle 22). Alle drei Patienten konnten am ersten postoperativen Tag extubiert werden. Für alle drei Patienten wurden im Verlauf mittels Röntgen-Thorax Zeichen für ein Reperfusionsödem gesehen und zwei Patienten mussten für mindestens 2 Tage non-invasiv beatmet werden. Zusätzlich entwickelten zwei Patienten ein intermittierendes tachykardes Vorhofflimmern, welches medikamentös behandelt wurde.

Tabelle 24: Pulmonale Hämodynamik und WHO-Funktionsklasse aller Patienten

	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 = pulmonalarterieller Druck; PVR = pulmonalvaskulärer Widerstand; WHO = Weltgesundheitsorganisation
[a] Hämodynamische Variablen wurden in der initialen Phase der Operation („pre“) und am 1. postoperativen Tag („post“) erfasst, mit Angabe der Differenz im PVR (Δ-PVR). Die WHO-Funktionsklasse wurde präoperativ („pre“) und einige Monate postoperativ („post“) erfasst.

Die Abklärung der Operabilität ist die Hauptaufgabe bei der Evaluation von CTEPH-Patienten. Die Verteilung der Obstruktionen und die eingeschränkte RV-Funktion sind von besonderer

Bedeutung [150]. Die perioperative Letalität wird hierbei bestimmt von einem hohen präoperativen PVR oder einem postoperativen PVR > 500 dyn·s·cm^{-5} [15, 49].

Von den 220 Patienten, die 2014 in unserem Zentrum evaluiert wurden, wurden 152 als operabel eingestuft. Acht Patienten wurden aufgrund distaler Obstruktionen und schlechter pulmonaler Hämodynamik als mögliche Kandidaten für einen Hybrideingriff klassifiziert. Hiervon wurden fünf Patienten komplett mittels PEA operiert und lediglich bei drei Patienten kam zusätzlich die BPA zur Anwendung.

6.9.1 Schlussfolgerung

Der Hybrideingriff aus PEA und BPA ist für selektionierte hoch-risiko Patienten eine neue und nützliche Behandlungsoption im gesamten chirurgischen und interventionellen Behandlungsspektrum eines erfahrenen CTEPH-Zentrums. Zentrales und somit chirurgisch erreichbares thromboembolisches Material kann wie üblich durch eine PEA entfernt werden, wohingegen die distalen, nicht zu erreichenden Läsionen mittels BPA während der Operation dilatiert werden, um die endoluminalen bindegewebigen Webs aufzureißen und in die Gefäßwand zu drücken. Gefäße, die unzureichend chirurgisch endarteriektomiert wurden, sollten hierbei nicht durch eine BPA behandelt werden, da dort ein hohes Blutungsrisiko durch Verletzungen durch den Führungsdraht gegeben ist. Für diese komplexe Behandlung ist ein erfahrenes multidisziplinäres Team unabdingbar.

7 Zusammenfassung

Die chronisch thromboembolische pulmonale Hypertonie (CTEPH) ist eine Form der pulmonalen Hypertonie, für die in den letzten Jahren neben der pulmonalen Endarteriektomie (PEA) die gezielte medikamentöse Therapie und die pulmonale Ballonangioplastie als zusätzliche Behandlungsoptionen hinzugekommen sind. Mit dieser Arbeit werden die Entwicklungen in der Diagnostik und Therapie thematisiert und in den Kontext der Etablierung des CTEPH-Zentrums am Campus Kerckhoff der Justus-Liebig-Universität an der Kerckhoff-Klinik gestellt (Abbildung 24).

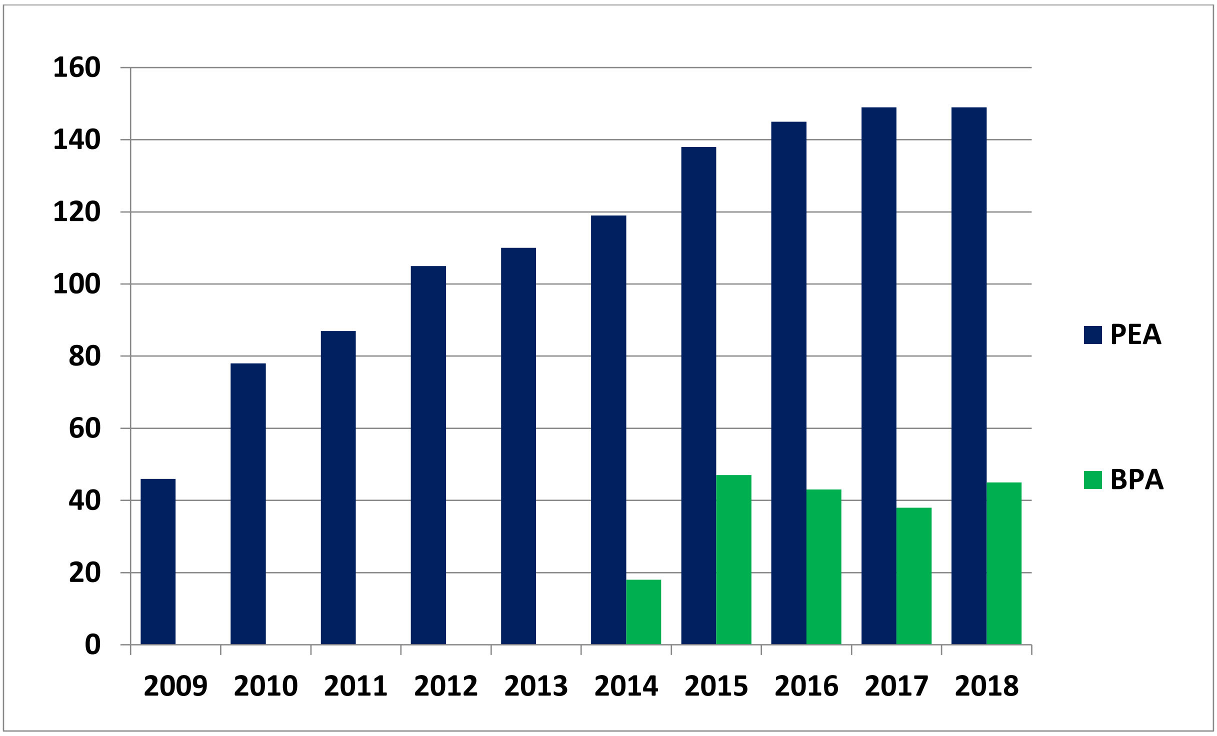


Abbildung 24: Entwicklung der jährlichen Patientenzahlen bzgl. der pulmonalen Endarteriektomie (PEA) und der Ballonangioplastie (BPA) an der Kerckhoff-Klinik

Es besteht nach wie vor Uneinigkeit bezüglich der Inzidenz der CTEPH in Deutschland sowie weltweit und die Spanne der Patienten, die nach überstandener Lungenembolie eine CTEPH entwickeln sollen, reicht von 0,5 bis 10%. Für Deutschland wurde eine prospektive Datenerhebung der drei CTEPH/PEA-Zentren initiiert, die die Evaluation der Patienten hinsichtlich einer PEA durchführen. Ergänzt wurde dies mit den Daten aus dem COMPERA-Register, um auch jene Patienten zu erfassen, die nicht in einem der vorgenannten Zentren vorstellig wurden. Als Ergebnis wurde eine Inzidenz von 5,7 pro 1 Mio. Erwachsene ermittelt, so dass pro Jahr in Deutschland mindestens 350 bis 400 neuerkrankte CTEPH-Patienten pro Jahr zu erwarten sind.

In der Diagnostik der PH und somit der CTEPH ist der Rechtsherzkatheter (RHK) der Goldstandard, um zum einen die Diagnose zu stellen und zum anderen den weiteren Therapieerfolg zu dokumentieren. Bislang bestehen die Hauptdaten des RHK aus Ruhemessungen, da die Definition der PH ausschließlich auf Ruhewerten beruht. Betrachtet man jedoch die Anamnese der Patienten, so wird schnell ersichtlich, dass am Anfang der Erkrankung die belastungsbedingten Einschränkungen (z.B. Belastungsdyspnoe) ganz im Vordergrund stehen. Aus diesem Grund werden seit mehreren Jahren die RHK-Untersuchungen an der Kerckhoff-Klinik sowohl in Ruhe, als auch unter Belastung (Fahrrad-Ergometrie) durchgeführt. In einer ersten Studie an insgesamt 16 Patienten, für die prä- und postoperative Belastungs-RHK aus unserer Klinik vorlagen, wurden die Veränderungen der Hämodynamik ca. 1 Jahr nach der PEA mit den präoperativen Werten verglichen. Neben dem zu erwartenden Abfall der Ruhewerte bzgl. MPAP, SPAP, DPAP und PVR bzw. der Steigerung des HZV, zeigten sich unter Belastung deutliche Änderungen bei den Steigungen der unterschiedlichen Druck-Fluss-Beziehungen, wobei vor allem der diastolische pulmonale Gradient den stärksten Abfall in der Steigung aufwies. Diese Ergebnisse legen nahe, dass durch die Belastungsuntersuchungen die linksventrikuläre Komponente (d.h. postkapilläre Komponente) der PH demaskiert wird, die für einen gewissen Anteil der residualen bzw. rekurrenten PH verantwortlich gemacht werden muss.

Noch größere Bedeutung hat der Belastungs-RHK für jene Gruppe von Patienten, die nach der gültigen Definition keine pulmonale Hypertonie aufweisen, da deren gemessene Mitteldrücke in Ruhe noch unter 25 mmHg liegen. Diese Patienten zeigen die gleichen morphologischen Obstruktionen wie CTEPH-Patienten und haben zum Teil eine erhebliche Belastungseinschränkung und man subsummiert sie unter dem Begriff der chronisch thromboembolischen Erkrankung. Unter Belastung zeigen CTED-Patienten im RHK einen überschießenden Anstieg des MPAP, der mit einem inadäquaten HZV-Anstieg korreliert. Da es derzeit in den Leitlinien keine gültige Definition für die pulmonale Hypertonie unter Belastung gibt, aber viele Kliniker auf diesem Feld weiter forschen, hat sich eine Arbeitsdefinition für die Belastungs-PH etabliert, die für Patienten mit einem Ruhe-MPAP unter 25 mmHg unter Belastung einen MPAP > 30 mmHg und einen totalen pulmonalen Widerstand > 3,0 WU bei einem erreichten HZV von unter 10 l/min fordern. Ebenso sollte die Steigung der MPAP/HZV-Beziehung bei einem Wert > 3,0 WU liegen. In einer Arbeit zu diesem Patientenkollektiv der CTED konnten wir bei 12 Patienten für die Belastungshämodynamik im Vergleich vor und ein Jahr nach einer PEA eine signifikante Abnahme der Widerstandswerte unter Belastung nachweisen, die sich für den TPR im Mittel auf 2,7 WU und für die MPAP/HZV-Steigung auf 2,3 WU reduzierten. Diese Ergebnisse unterstützen das Konzept der Belastungs-PH und somit sollten für diese Patienten RHK-Untersuchungen unter Belastung ebenfalls zum Standard werden.

Die unmittelbaren Auswirkungen der PEA auf die rechtsventrikuläre Funktion wurden mittels Kombination volumetrischer Daten aus der kardialen MRT sowie aus Daten des Routine-RHK untersucht. Es konnten Surrogatmarker der rechtsventrikulären Nachlast ($E_{a\text{-}pulm}$) und der rechtsventrikulären Kontraktilität ($E_{es\text{-}RV}$) abgeleitet werden, die zeigen, dass CTEPH-Patienten ein massives Uncoupling zwischen Nachlast und RV-Kontraktilität aufweisen. Bereits wenige Tage nach erfolgreicher PEA verbesserte sich aufgrund der Nachlastsenkung das Coupling wieder in Richtung einer Normalisierung dieser Werte.

Bezüglich des therapeutischen Vorgehens bei der CTEPH wurden wesentliche Neuerungen initiiert, um die perioperativen Komplikations- und Letalitätsraten zu minimieren. In einer prospektiven randomisierten verblindeten kontrollierten Studie wurde die Auswirkung der frühzeitigen Gabe einer niedrigdosierten Heparingabe vor Einschwemmung des PA-Katheters untersucht. Hierbei ließ sich sowohl eine signifikante Reduktion der Thrombenanzahl als auch ihrer Größe dokumentieren. Somit werden alle Patienten vor Anlage des PAK heparinisiert und der Katheter postoperativ wieder früh entfernt.

Eine der schwerwiegendsten Komplikationen während der PEA ist die massive endobronchiale Hämorrhagie, welche das Entwöhnen von der extrakorporalen Zirkulation verhindert und per se mit einer hohen Letalität einhergeht. Wir konnten zeigen, dass durch die Etablierung einer kurzen venoarteriellen ECMO-Unterstützung (49 ± 13 min) mit gleichzeitiger Protamingabe die endobronchiale Blutung gestoppt werden kann. Dadurch gelang es, die Patienten anschließend noch im Operationssaal von diesem ECMO-System wieder zu entwöhnen. Die Patientenletalität konnte durch dieses neue Konzept deutlich gesenkt werden.

Letztendlich konnten wir die Wichtigkeit und Bedeutung der Entwicklung von CTEPH-Zentren darlegen, um sowohl durch multidisziplinäre diagnostische als auch therapeutische Ansätze die PEA als ein sicheres Verfahren auch für die Behandlung von schwer kranken und älteren Patienten anbieten zu können. Es zeigte sich, dass die Prognose nicht durch die Baseline-Charakteristika, Komorbiditäten sowie die präoperative Hämodynamik der Patienten, sondern im Wesentlichen durch intraoperative Komplikationen bestimmt wird. Umso wichtiger ist es, diese Komplikationen effektiv therapieren zu können, um die Gesamtletalität von CTEPH-Patienten weiter zu minimieren. In der nachfolgenden Abbildung 25 wird die Entwicklung der Anzahl der PEA-Operationen der Letalität der normalen PEA-Operationen an der Kerckhoff-Klinik gegenübergestellt, welche sich für unser Zentrum in einem Bereich von 2% bis 3% stabilisiert hat und vergleichbar ist mit den weltweit drei weiteren großen Zentren mit mehr als 100 Operationen pro Jahr.

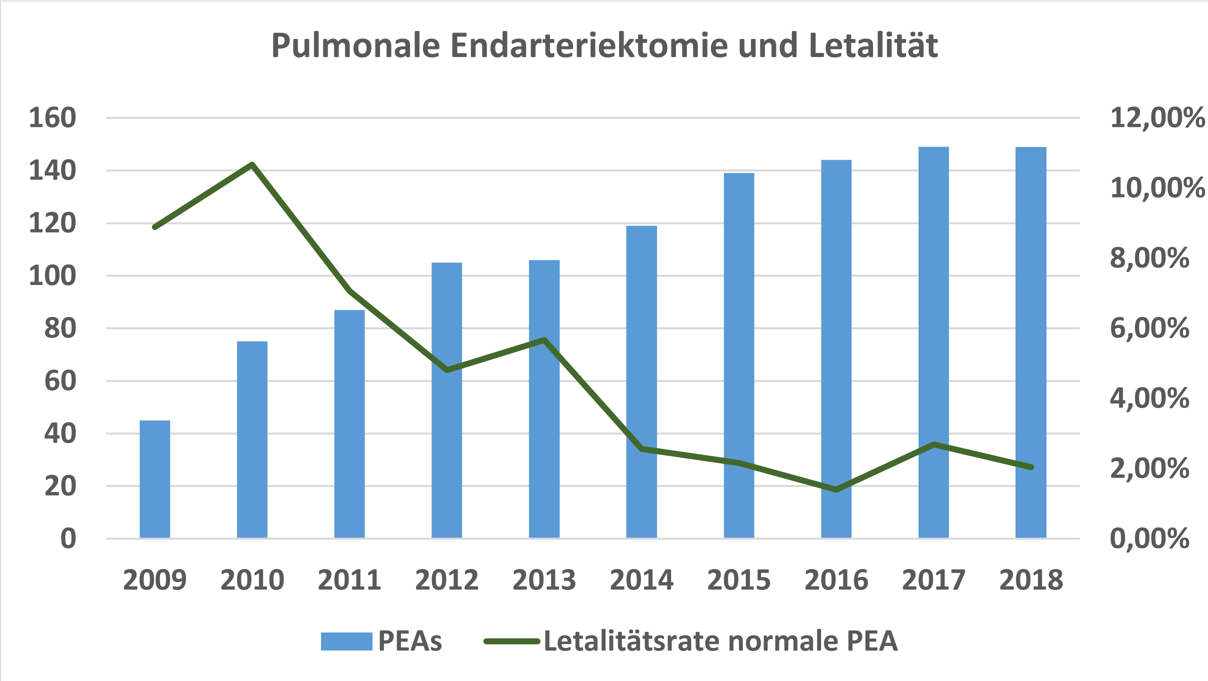


Abbildung 25: Anzahl der pulmonalen Endarteriektomien (PEA) pro Jahr und die Entwicklung der Letalitätsrate

Für Patienten mit inoperabler CTEPH haben wir in unserem Zentrum ebenfalls 2014 das Verfahren der pulmonalen Ballonangioplastie eingeführt, um inoperablen Patienten eine weitere Therapieoption anbieten zu können. Wir haben in einer Arbeit das Konzept der initialen medikamentösen Therapie gefolgt von der BPA und somit den Therapiealgorithmus eines hochvolumigen deutschen CTEPH-Zentrums dargelegt. Es konnte gezeigt werden, dass diese Kombinationstherapie die physische Belastbarkeit und die pulmonale Hämodynamik positiv beeinflusst und das Therapiespektrum für inoperable Patienten effektiv erweitert.

Die Einführung der BPA hat auch die Behandlung von Hochrisikopatienten mit nur eingeschränkter Operabilität erweitert. In unserem Zentrum wurden erstmalig die PEA und die BPA als sogenanntes Hybridverfahren angewandt. Durch die Möglichkeiten eines Hybrid-Operationssaals, der durch einen hochauflösenden C-Durchleuchtungsbogen gekennzeichnet ist, können während einer Operation sowohl die PEA als auch die BPA simultan durchgeführt werden.

Somit kann sowohl durch die Maximierung der reperfundierten Lungenareale durch Operation als auch durch die interventionelle BPA das perioperative Risiko für diese hochselektionierten Patienten zusätzlich reduziert werden.

8 Abstract

Chronic thromboembolic pulmonary hypertension can be curatively treated by pulmonary endarterectomy. Recently, the treatment was complemented by targeted medical therapy and balloon pulmonary angioplasty. This paper summarises the diagnostic and therapeutic advances and puts these into context with the development of the CTEPH centre at Kerckhoff-Clinic (Campus Kerckhoff of the Justus-Liebig-University).

The incidence of CTEPH in Germany is still unknown, and worldwide the speculations range between 0.5 to 10% of patients after acute embolism. A prospective registry was started in Germany by the three major CTEPH/PEA centres to collect all incident CTEPH patients of one year and was amended by the COMPERA registry to identify those patients who were not treated by these centres. The annual incidence of CTEPH in Germany was estimated at 5.7 per million adults, expecting 350 to 400 new patients with CTEPH per year.

Right heart catheterisation (RHC) is the gold standard method to assess pulmonary haemodynamics in PH and CTEPH and is necessary to document the success of treatment. The majority of data arise from measurements at rest and the current definition of PH relies on these measurements. Taking a look at the history of patients, however, we must acknowledge that at the beginning of the disease their symptoms arise from physical exertion (e.g. exertional dyspnoea). Therefore, we have been performing RHC for many years also during exercise. In one study we identified 16 patients with pre- and postoperative exercise RHC and we examined changes in pulmonary haemodynamics one year after pulmonary endarterectomy compared to preoperative values. Besides improvements of the resting values we could display marked decreases in different slopes of pressure/flow-relations, which was most impressive for the diastolic pressure gradient. These results unmask a left ventricular component of exercise pulmonary hypertension that contribute to postoperative residual or recurrent PH.

Exercise RHC is almost more important for patients with chronic thromboembolic disease (CTED) because at rest they do not fulfil the criteria of PH (i.e. MPAP < 25 mmHg). During exercise CTED patients show an overwhelming increase in MPAP that is accompanied by an impaired increase in cardiac output (CO). These patients surpass an MPAP of 30 mmHg. The total pulmonary resistance (TPR) is > 3.0 WU and the slope of the MPAP/CO relation is also > 3.0 WU. In a further study, we could demonstrate a significant decrease in MPAP and PVR during rest and exercise after pulmonary endarterectomy with a mean TPR of 2.7 WU and a

mean slope of the MPAP/CO relation of 2.3 WU. These results support the concept of exercise PH.

We were able to derive surrogate markers of right ventricular ($E_{es\text{-}RV}$) and pulmonary arterial elastance ($E_{a\text{-}pulm}$) by combining data from the RHC with volumetric data from standard CINE cardiac magnetic resonance (CMR). Both parameters were elevated before PEA with overwhelming increase of $E_{a\text{-}pulm}$ resulting in severe uncoupling between right ventricular contractility and pulmonary vascular load. A few days after surgery ventriculo-arterial coupling was restored resulting in an immediate reverse remodeling of the right ventricle and its ejection fraction and volumes.

Several improvements in the treatment of CTEPH patients were implemented in our clinic to reduce complication rates and mortality. A randomised double-blinded study examined the effect of early low-dose heparin application prior to pulmonary artery catheter insertion. We found a significant reduction in number and in weight of thrombi on the catheter tip. So, we changed our protocol in terms of early heparin application and early postoperative catheter removal.

A feared complication of PEA is endobronchial bleeding which precludes weaning from cardiopulmonary bypass. By intraoperative switching to a short-term venoarterial ECMO support that allows for application of protamin we could demonstrate to control this devastating complication and could wean all patients from extracorporeal circulation in the operation theatre. This new concept decreased mortality significantly.

Furthermore, we highlighted the importance of establishing a centre for CTEPH where patients are diagnosed and treated in a multidisciplinary setting offering pulmonary endarterectomy as a safe surgical treatment even for old and very sick patients. Displaying the prognostic relevance of intraoperative complications which were much more important than baseline characteristics and comorbidities underscores a reliable complication management to further minimise mortality of patients with CTEPH. We could stabilise our mortality rate in a range between 2 to 3% and this is comparable with the other 3 major centres worldwide which perform more than 100 PEA operations per year.

Besides surgery, since 2014 we have been treating inoperable CTEPH patients since 2014 by targeted medical treatment and balloon pulmonary angioplasty. In our concept, we start with drug treatment which is then followed by BPA. We were able to demonstrate the beneficial

effects of this combined treatment in terms of improved haemodynamics measured by right heart catheterisation and physical capacity.

The introduction of BPA also offered new treatment possibilities for high-risk CTEPH patients with marginal operability. Our centre performed the first hybrid treatments of CTEPH patients where PEA and BPA were conducted simultaneously to maximise lung reperfusion and to minimise the perioperative risk of these highly selected patients.

9 Abkürzungsverzeichnis

BMI	=	Body-Mass-Index
BPA	=	Pulmonale Ballonangioplastie
CAMPHOR	=	Cambridge Pulmonary Hypertension Outcome Review
CI	=	Herzindex (cardiac index)
CMR	=	Kardiale Magnetresonanztomographie
CO	=	Herzzeitvolumen (cardiac output)
COMPERA	=	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
C_{Pa}	=	Pulmonalarterielle Compliance
CTED	=	Chronisch thromboembolische Erkrankung
CTEPH	=	Chronisch thromboembolische pulmonale Hypertonie
DPAP	=	Diastolischer pulmonalarterieller Druck
DPG	=	Diastolischer pulmonaler Gradient
DSA	=	Digitale Subtraktionsangiographie
$E_{a\text{-}pulm(\_i)}$	=	Pulmonalarterielle Elastance (indiziert)
$E_{es\text{-}RV(\_i)}$	=	Endsystolische rechtsventrikuläre Elastance (indiziert)
EF	=	Ejektionsfraktion
ESV	=	Endsystolisches Volumen
ECMO	=	Extrakorporale Membranoxygenierung
EKZ	=	Extrakorporale Zirkulation
FC	=	Funktionsklasse
HR	=	Herzfrequenz
HZV	=	Herzzeitvolumen
IAPH	=	Idiopathische pulmonalarterielle Hypertonie
IQR	=	Interquartile Range
Mio	=	Million
MPAP	=	Mittlerer pulmonalarterieller Druck
NOAK	=	nicht-Vitamin-K-abhängige orale Antikoagulation
NT-proBNP	=	N-terminales pro B-Typ natriuretisches Peptid
OR	=	Chancenverhältnis (Odds Ratio)
PAH	=	Pulmonalarterielle Hypertonie

PAK	=	Pulmonalarterieller Katheter
PAWP	=	Pulmonalarterieller Wedge-Druck (pressure)
PEA	=	Pulmonale Endarteriektomie
PH	=	Pulmonale Hypertonie
PH_{ex}	=	Pulmonale Belastungshypertonie
PVR	=	Pulmonalvaskulärer Widerstand
RA	=	Rechtes Atrium
RAP	=	Rechtsatrialer Druck
RHK	=	Rechtsherzkatheter
RHK_{ex}	=	Belastungs-Rechtsherzkatheter
RV	=	Rechter Ventrikel
RVESP	=	Rechtsventrikulärer endsystolischer Druck
SD	=	Standardabweichung (Standard Deviation)
SPAP	=	Systolischer pulmonalarterieller Druck
S_vO_2	=	Gemischtvenöse Sauerstoffsättigung
SV	=	Schlagvolumen
TAPSE	=	Systolische Exkursion der Ebene des Trikuspidalklappenanulus (tricuspid annular plane systolic excursion)
TPG	=	Transpulmonaler Gradient
TPR	=	Totaler peripherer Widerstand
Va	=	Venoarteriell
$V'E/V'CO_2$	=	Ventilatorisches Äquivalent für CO_2
Vv	=	Veno-venös
WHO-FC	=	World Health Organization – Funktionsklasse (functional class)
WSPH	=	World Symposium on Pulmonary Hypertension
WU	=	Wood Units / Wood-Einheiten
6MGT	=	6-Minuten-Gehtest

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12 Zugrundeliegende Publikationen

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ORIGINAL PAPER

Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany

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Abstract

Background The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) is unknown. Previous studies from the United Kingdom and Spain have reported incidence rates of 1.75 and 0.9 per million, respectively. These figures, however, may underestimate the true incidence of CTEPH.

Methods We prospectively enrolled patients newly diagnosed with CTEPH within 2016 in Germany. Data were obtained from the three German referral centers and from the German branch of COMPERA, a European pulmonary hypertension registry. The CTEPH incidence was calculated based on German population data, and patient characteristics and treatment patterns were described.

Results A total of 392 patients were newly diagnosed with CTEPH within 2016 in Germany, yielding an incidence of 5.7 new cases per million adults. The (mean ± standard deviation) age was 63.5 ± 15.0 years; males and females were equally affected; 76.3% of the patients had a history of venous thromboembolism. A total of 197 (50.3%) patients underwent pulmonary endarterectomy. Almost all non-operated patients received targeted drug therapy, and 49 patients (25.1% of the non-operated patients) were treated with balloon pulmonary angioplasty.

Conclusion The incidence of CTEPH in Germany 2016 was 5.7 per million adults and thus higher than previously reported from other countries. Half of the patients were operated while the remaining patients received medical or interventional therapies.

Clinical trials registration http://www.clinicaltrials.gov NCT02660463 and NCT01347216.

Keywords Chronic thromboembolic pulmonary hypertension · Incidence · Epidemiology · Pulmonary endarterectomy · Balloon pulmonary angioplasty

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined by an elevated mean pulmonary artery pressure at rest caused by persistent obstruction of pulmonary arteries despite therapeutic anticoagulation for at least 3 months following pulmonary embolism [1, 2]. Among the various forms of pulmonary hypertension (PH), CTEPH has some unique features including the availability of a variety of treatment options. The majority of patients with CTEPH

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can be effectively treated, and often cured, by pulmonary endarterectomy (PEA) [3–6]. For patients who are not candidates for surgery, medical and interventional therapies are available [7–11].

The epidemiology of CTEPH is largely unknown. The annual incidence of acute pulmonary embolism ranges from 750 to 2700 per million adults [12–14]. Several studies on the risk of developing CTEPH in survivors of acute pulmonary embolism came up with figures ranging from 1 to 9% [15–18]. A recent meta-analysis of the available data suggested that the incidence of CTEPH in survivors of acute pulmonary embolism is about 3% [19]. Based on these numbers, the expected incidence of CTEPH would be 22.5 to 81 per million adults. In contrast, the reported numbers of patients with an established diagnosis of CTEPH are substantially smaller. Two nationwide registries have assessed the incidence of CTEPH: In the United Kingdom, the CTEPH incidence was 1.75 per million population [20]; in Spain, it was 0.9 per million adults [21].

In the present study, we prospectively assessed the incidence and characteristics of CTEPH in 2016 in Germany.

Methods and patients

We designed a prospective registry to obtain data from the three German CTEPH referral centers (Kerckhoff Heart and Lung Center, Bad Nauheim, Hannover Medical School and Saarland University Medical Center, Homburg) and from Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), a European-based PH registry which includes adult patients with all forms for PH who receive targeted medical therapy. COMPERA is the official German PH registry and has broad participation from German PH centres [22]. We extracted from the COMPERA database all German patients who had been newly diagnosed in 2016 with CTEPH but who had not been referred to one of the three above-mentioned centers, thereby avoiding double counting. Data were collected at the baseline visit and included demographics, haemodynamics, functional class, diagnostic tools and treatment strategies.

For the present analysis, we included adult patients $\geq$ 18 years of age with a newly established CTEPH diagnosis between 1 January and 31 December 2016. The diagnostic criteria were in accordance with the current European Guidelines on Pulmonary Hypertension [23]. Patients referred from other countries were not eligible. Although the study included exclusively patients who received their first diagnosis of CTEPH within 2016, the database was locked only on 30 June 2017, to allow for a brief follow-up period focussing on treatment decisions and outcomes of patients who underwent surgery.

The study was approved by the institutional review boards of the participating centers and has been registered under the clinical trials.gov identifier NCT02660463. All patients provided written informed consent.

Statistical analysis

The data were captured on Excel spreadsheets in the participating centers and were merged with data exported from COMPERA. All descriptive analyses were done with SPSS v25 and no formal statistical analyses were performed.

Results

In 2016, a total of 392 patients were newly diagnosed with CTEPH in Germany. Bad Nauheim contributed $N=234$ (59.7%) patients, Homburg $N=69$ (17.6%), Hannover $N=57$ (14.5%) and COMPERA $N=32$ (8.2%). Given the 68.6 million adults living in Germany in 2016 (http://www.destatis.de, website accessed 18 October 2017), the calculated CTEPH incidence was 5.7 per million adults.

The patients' characteristics are shown in Table 1. The mean age was 63.5 years and the female-to-male ratio was equal. The mean age of the COMPERA patients was 71 years and thus about 8 years higher than the age of the patients referred to the CTEPH centers. Most of the patients

Table 1 Patients characteristics at time of diagnosis in 392 patients with newly diagnosed chronic thromboembolic pulmonary hypertension

	$n=392$
Age (years), $N=392$	63.5 ± 15.0
Female/male (%), $N=392$	50.8/49.2
Body mass index (kg/m^2); $N=389$	28.1 ± 6.5
6 min walk distance, $N=156$	326 ± 121
WHO functional class, $N=305$	I, 1 (0.3%)
	II, 76 (24.9%)
	III, 182 (59.7%)
	IV, 46 (15.1%)
RAP (mmHg), $N=306$	9 ± 45
PAPm (mmHg), $N=374$	43 ± 10
PAWP (mmHg), N = 357	11 ± 4
CO (l/min), $N=315$	4.6 ± 1.4
CI (l/min/m^2), $N=345$	2.5 ± 1.9
PVR (dyn s cm^{-5}), $N=345$	652 ± 396
SvO_2 (%), $N=235$	64 ± 8

RA right atrial pressure, *PAPm* mean pulmonary artery pressure, *PAWP* pulmonary arterial wedge pressure, *CO* cardiac output, *CI* Cardiac Index, *PVR* pulmonary vascular resistance, SvO_2 mixed venous oxygen saturation presented with moderately or severely impaired exercise capacity at the time of diagnosis.

76.3% of the patients had a history of venous thromboembolism and 150 (38.3%) had at least one predisposing factor, most commonly thrombophilia (8.2%), malignancy (5.6%), antiphospholipid antibodies (4.6%), cardiac pacemakers (2.6%) and splenectomy (1.5%).

The diagnostic assessment included ventilation–perfusion scintigraphy in 93.8% of the patients. Computed tomography angiography and pulmonary angiography were performed in 88% and 76% of the patients, respectively.

Anticoagulants were used in all patients, predominantly direct oral anticoagulants (51%) and vitamin K antagonists (46.2%). A small proportion of patients (2.8%) received low molecular weight heparins. Inferior vena cava filters were inserted in three (0.8%) patients.

Treatment pathways are shown in Fig. 1. A total of 197 (50.3%) patients underwent PEA surgery; 148 (75.1%) in Bad Nauheim, 30 (15.2%) in Homburg and 19 (9.6%) in Hannover. The overall perioperative mortality rate was 5/197 (2.5%). The perioperative mortality rates for the individual centers were 4/148 (2.7%) in Bad Nauheim, 0 (0%) in Homburg and 1/19 (5.3%) in Hannover.

PH targeted therapies were used in 36/197 (18.3%) patients who were later operated and in 184/195 (94.4%) of the non-operated patients. Reasons for withholding drug therapy in non-operated patients were primary BPA ($n=4$), malignancy ($n=1$), advanced left heart disease ($n=1$), or were unknown ($n=5$). Riociguat was the drug used predominantly as initial treatment (81.1% of the patients who received medical therapy), followed by phosphodiesterase 5 (PDE5) inhibitors (15.5%) and endothelin receptor antagonists (ERA; 3.4%).

Forty-nine patients underwent balloon pulmonary angioplasty (BPA). This represented 12.5% of the entire patient population and 25.1 of the non-operated patients. There were no deaths associated with BPA in these patients.

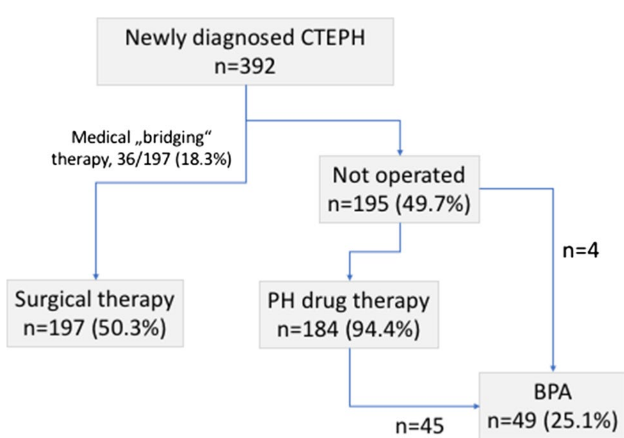

Fig. 1 Treatment patterns in 392 patients with newly diagnosed chronic thromboembolic pulmonary hypertension (CTEPH). *PH* pulmonary hypertension, *BPA* balloon pulmonary angioplasty

Discussion

According to our data, 392 patients were newly diagnosed with CTEPH in 2016, resulting in a CTEPH incidence of 5.7 per million adults in Germany. This figure is considerably larger than the previously reported estimates of 1.75 per million and 0.9 per million from the United Kingdom and Spain, respectively [20, 21]. On the other hand, our numbers closely mirror those observed in France where approximately 300 patients are newly diagnosed with CTEPH each year [24], resulting in a rough estimate of the CTEPH incidence in France of 5–6 per million adults.

Although higher than previously reported, these figures are lower than one would expect if 3% of survivor of acute pulmonary embolism develop CTEPH as it has been suggested recently by Ende-Verhaar and co-workers [19]. Approximately, 56,000 patients are admitted each year to German hospitals for treatment of acute pulmonary embolism (http://www.destatis.de, assessed 8 November 2017), and approximately 80% of these patients (i.e., about 45,000 patients) are expected to be alive after 1 year [25]. If 3% of these patients were to develop CTEPH, we should have identified at least 1400 patients with newly diagnosed CTEPH. In fact, the numbers should have been even higher (i.e., approximately 1750 patients) as 25% of the CTEPH patients in our series had no history of venous thromboembolism. It is likely that these assumptions overestimate the incidence of CTEPH. Given the similar numbers of patients newly diagnosed with CTEPH in Germany and France, two countries with a well-developed health care system, it is possible that the risk of developing CTEPH after acute pulmonary embolism may be lower than previously reported, presumably at about 1%, although underestimation due to missing cases cannot be ruled out (see below).

In terms of age, sex, predisposing factors, baseline 6 min walking distance, functional class and haemodynamics, our patients were largely comparable to those reported previously from a European CTEPH registry [26]. The same was true for the proportion of patients with previous venous thromboembolism, which was approximately 75% in both series [26]. Still, some differences were observed. In the European CTEPH registry, vena cava filters were used in 12.4% of the patients [26], whereas only 0.3% of the patients in the present series received a vena cava filter. This may reflect regional differences but perhaps also a global decline in the use of vena cava filters for both acute pulmonary embolism [27] and CTEPH. Our data also suggest that direct oral anticoagulants are increasingly used in patients with CTEPH. To the best of our knowledge, this is the first large

CTEPH series where these drugs were used more frequently than vitamin K antagonists. There is still a lack of data on the use of direct oral anticoagulants in patients with CTEPH. The same is basically true for the vitamin K antagonists, except that these compounds have been used for decades in this patient population.

In the above-mentioned European CTEPH registry [26], 56.8% of the patients underwent surgery, which was slightly higher than the 50.3% of the patients who underwent surgery in our series. However, some patients in our series were still undecided or under continued assessment for surgery when the database was closed. It is unlikely that the availability of BPA in Germany had a relevant impact on the numbers of surgical procedures as the participating centers offer BPA exclusively to non-operable patients [28]. The perioperative mortality rate after PEA of 2.5% was comparable to previous reports from other centers [5, 6].

Drug therapy targeting PH was used in less than 20% of patients who eventually underwent PEA surgery. This came as surprise as previous reports have been suggesting an increasing use of PH medications in patients with operable disease (20% in 2005 and 37% in 2007, respectively) [29]. We assume that the relatively infrequent use of PH drugs in operable patients in our series was due to the fact that the vast majority of patients had been referred to a CTEPH center for diagnostic work-up and that the time span between referral and admission was usually short, i.e., less than 4 weeks, in all three centers (data not shown). This, together with relatively short waiting times for surgery may have obviated the need for bridging therapies.

Our study has limitations, in particular that full datasets were not available from all patients and that we could include only patients who were referred to a CTEPH center or enrolled into COMPERA. We were unable to capture patients who were never referred to one of the participating centers. Thus, we cannot exclude the possibility that we have missed some cases and we cannot provide reasonable estimates on how many patients this might have been. Still, in countries like Germany with an advanced health care system and nationwide PH centres, there should not be many patients diagnosed with CTEPH who are not referred for further work-up and treatment. On the other hand, recent data from the US have shown that many patients with PH are not treated at specialized centres and that the diagnostic work-up of these patients is often incomplete [30]. This includes a low rate of ventilation–perfusion scanning, which remains the most sensitive tool to detect CTEPH [31]. Despite the lack of comparable data from Germany, it is likely that we face similar issues. Hence, our numbers reflect the most conservative estimate of the CTEPH incidence in Germany, and the true incidence may be even higher. Finally, we wish to emphasize that the reported treatments represent a snapshot of how the patients under study were managed in the centres. These data do not confer any recommendation regarding the best possible therapy for patients with newly diagnosed CTEPH.

In summary, the incidence of patients with an established CTEPH diagnosis in Germany was 5.7 per million adults in 2016. Although these numbers reflect a conservative estimate, they indicate that the incidence of CTEPH is higher than previously reported. Roughly half the patients underwent PEA surgery, whereas the remaining patients required targeted drug therapy and, occasionally, interventional treatment.

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Compliance with ethical standards

Conflict of interest T. Kramm has received speaker fees from Actelion, Bayer and GSK. H. Wilkens has received speaker fees and honoraria for consultation from Actelion, Bayer, Boehringer-Ingelheim, GSK, MSD, Pfizer and Roche. J. Fuge has nothing to disclose. HJ Schäfers has received speaker fees from Bayer. S. Guth has received speaker fees from Actelion, Bayer, GSK and Pfizer. CB Wiedenroth has received speaker fees or consultant honoraria from Actelion, Bayer AG, BTG, MSD and Pfizer. B. Weingard has received speaker fees and consultation honoraria from Bayer. D. Huscher has received author and consultation honoraria from Actelion. D. Pittrow has received speaker fees or honoraria for consultations from Actelion, AstraZeneca, Aspen, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Shield and Pfizer. M.M. Hoeper has received speaker fees and honoraria for consultations from Actelion, Bayer, Gilead, GSK, MSD and Pfizer. S. Cebotari has nothing to disclose. E. Mayer has received speaker and consulting fees from Actelion, Bayer, GSK, and Pfizer. KM Olsson has received speaker fees and honoraria for consultations from Actelion, Bayer, GSK, Pfizer and United Therapeutics.

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Pulmonary Hemodynamic Response to Exercise in Chronic Thromboembolic Pulmonary Hypertension before and after Pulmonary Endarterectomy

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Key Words
Chronic thromboembolic pulmonary hypertension · Pulmonary endarterectomy · Exercise · Right heart catheterization

Abstract
Background: Pulmonary endarterectomy (PEA) is the treatment of choice in surgically accessible chronic thromboembolic pulmonary hypertension (CTEPH). An important predictor of outcome is postsurgical residual pulmonary hypertension. ***Objective:*** We aimed to use the hemodynamic response during exercise before PEA as a measurement for the hemodynamic outcome 1 year after PEA. ***Methods:*** Between January 2011 and December 2013, 299 patients underwent PEA in our center. A total of 16 patients who were assessed by means of invasive hemodynamic measurements during exercise both at baseline and 1 year after PEA were retrospectively analyzed. ***Results:*** Pre-PEA mean pulmonary arterial pressure (mPAP) increased during exercise from 35.8 ± 7.6 to 53.8 ± 5.1 mm Hg, diastolic pulmonary arterial pressure (dPAP) from 21.5 ± 5.6 to 30.3 ± 9.6 mm Hg, cardiac output (CO) from 4.4 ± 0.8 to 6.5 ± 1.9 l/min and diastolic pulmonary gradient (DPG) from 14.6 ± 4.9 to 20.7 ± 12.7 mm Hg. Post-PEA mPAP increased from 23.7 ± 6.6 at rest to 43.2 ± 7.1 mm Hg, while CO increased to a higher extent from 5.1 ± 0.9 to 8.4 ± 1.9 l/min. There were significant correlations between pre-PEA DPG/CO and dPAP/CO slopes with the pulmonary vascular resistance (Spearman r = 0.578, p = 0.019, and r = 0.547, p = 0.028) and mPAP at rest after PEA (Spearman r = 0.581, p = 0.018, and r = 0.546, p = 0.028). ***Conclusions:*** In CTEPH, the presurgical dynamic DPG/CO and dPAP/CO slopes during submaximal exercise are associated with the hemodynamic outcome 1 year after PEA.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by unresolved pulmonary vascular obstruction following acute pulmonary embolism. Untreated, the disease may progress towards increased pulmonary pressures, progressive right ventricular load and finally

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failure [1, 2]. Initially, an increase in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) is caused predominantly by the mechanical obstruction of the proximal pulmonary arteries; the further progression of the disease is mainly thought to be induced by secondary small-vessel arteriopathy in the nonobstructed, hyperperfused areas [1, 2]. The right ventricle (RV) adapts to the increased afterload either by hypertrophy or maladaptive dilatation [3], while the patient outcome is mostly determined by the response of the RV to strain [4, 5]. Pulmonary endarterectomy (PEA) has proven to substantially enhance pulmonary hemodynamics, exercise capacity [6–9] and survival [10]. However, predicting those patients with favorable long-term results remains challenging. Residual pulmonary hypertension (PH) after surgery has been identified as the main determinant for long-term outcome in terms of survival [11] or functional capacity [12]. Preoperative predictors of early postoperative outcome in terms of decreased PVR 48 h after PEA are mPAP [13], serum creatinine level, the number of involved segments, PVR and gender [14]. Parameters for risk stratification for PEA include preoperative forced expiratory volume in 1 s and cardiac index (CI) as well as preoperative arterial oxygenation [13]. However, predictors for long-term hemodynamic response are less well defined. In most cases, the residual PH after PEA results from a combination of concomitant small-vessel disease, incomplete removal of obstructions and a varying degree of right ventricular recovery after surgery [15]. Thus, the optimal characterization of the contribution of large- and small-vessel disease in CTEPH is important regarding the indication and outcome after PEA [16]. Along these lines, the echocardiographic parameter 'notch ratio', which describes the pulmonary arterial blood flow pattern, was shown to predict residual PH 3 months after PEA [17], whereas resting hemodynamic parameters before PEA did not correlate with hemodynamic parameters after PEA [18]. In idiopathic pulmonary arterial hypertension (PAH), recently published data indicate a superiority of exercise pulmonary measurements as prognostic factors [19]. Moreover, in a small cohort of CTEPH patients with persistent dyspnea after PEA but normal pulmonary hemodynamics at rest, the diminished pulmonary arterial compliance (Cpa) during exercise was a strong predictor of limited functional capacity [20]. Furthermore, Blumberg et al. [21] showed that in a heterogeneous group of PAH and inoperable CTEPH patients the relationship of mPAP to cardiac output (CO) during exercise served as a predictor of survival. In healthy volunteers, exercise leads to an increased CO and mean left atrial pressure, each of which results in a slightly increased mPAP with a flat slope of mPAP/CO between 0.5 and 3.0 mm Hg/l/min [22]. In contrast, PAH was characterized by a reduced CO at rest with inadequate response to exercise and a steep mPAP/CO slope [22–24].

We thus hypothesized that exercise hemodynamics with assessment of pressure/flow slopes in surgically accessible CTEPH patients may determine hemodynamic improvements after PEA.

Methods

Patients

We retrospectively we evaluated 299 consecutive patients diagnosed with CTEPH, referred to the Department of Thoracic Surgery, Kerckhoff Clinic, Bad Nauheim, Germany. Between January 2011 and December 2013, 299 PEA were performed. In 114 of these patients, right heart catheterization (RHC) before PEA was performed in-house, and 62 patients returned for the 1-year post-PEA follow-up undergoing RHC (fig. 1). According to internal safety standards, only patients with compensated right heart function with an mPAP <50 mm Hg and a CI >1.5 l/min/m^2 at rest were selected for exercise RHC. We here describe the results of 16 patients who underwent exercise RHC in the Kerckhoff Clinic before and 1 year after PEA under the same conditions by the same investigator; complete data were available from all patients. Residual PH 1 year after PEA was defined by an mPAP >25 mm Hg and PVR >240 dyne · s/cm^5 at rest [12].

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the Ethics Committee of the Faculty of Medicine at the University of Giessen (approval No. 67/14).

All CTEPH patients were diagnosed according to current guidelines [25]. Operability assessment was done by a multidisciplinary board consisting of PEA surgeons, radiologists and pulmonary physicians. All patients performed a 6-min walk test, cardiopulmonary exercise testing, echocardiography and measurement of N-terminal pro-brain natriuretic peptide levels (NT-proBNP). At inclusion, all patients received oral anticoagulants for at least 3 months. Exclusion criteria for the study were defined by concomitant left-sided heart disease. All patients included underwent PEA according to the protocol of the Kerckhoff Clinic [26]. The CTEPH type was classified by the surgical specimen as reported previously [27].

Right Heart Catheterization

All included patients underwent RHC by insertion of a Swan-Ganz catheter under local anesthesia. Pressure values at rest were continuously assessed [systolic pulmonary arterial pressure (sPAP); diastolic pulmonary arterial pressure (dPAP); mPAP; right atrial pressure, and pulmonary arterial wedge pressure (PAWP)], while the CO was measured by the thermodilution technique, averaging 3 of 5 output determinations. Baseline parameters were assessed 30 min after insertion of the catheter. PVR and CI were calculated as described previously [PVR = (mPAP – PAWP)/CO; CI = (CO/body surface area)] [25]. Exercise was performed on a cycle ergometer in supine position with a constant external workload of 25, 50 or 75 W. The workload was judged by the operator clinically and according to the workload achieved

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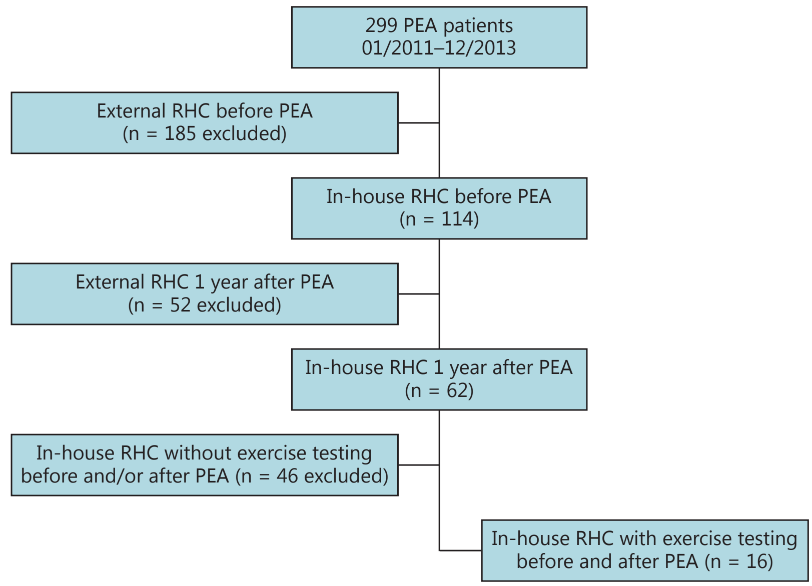

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Fig. 1. Flowchart of the patient selection.

during cardiopulmonary exercise testing, to allow the patient to exercise in a steady-state condition for at least 8 min, as reported previously [21, 28]. The anterior axillary line served as the zero reference in all supine measurements [28]. During constant workload, 3 min after the start of exercise, the measurements of exercise hemodynamic parameters were performed, with a total duration of approximately 5–7 min [19]. Pulmonary pressures were averaged over several respiratory cycles during the constant workload under exercise [29]. Mixed venous oxygen saturation (SvO_2) was obtained via blood gas analysis at rest and at the end of exercise. The following hemodynamic parameters were calculated: transpulmonary gradient (TPG) = mPAP – PAWP, diastolic pulmonary gradient (DPG) = dPAP – PAWP, and the slopes of hemodynamic parameters related to CO as described previously (mPAP/CO, PVR/CO, sPAP/CO, dPAP/CO, PAWP/CO, SvO_2/CO, TPG/CO and DPG/CO) [22, 30]. Adjustment of these pressure-flow curves can be done with a mathematical model, but in recent studies, the slopes were best described by a linear approximation [22, 30].

Cardiopulmonary Exercise Testing

All patients performed a symptom-limited incremental cardiopulmonary exercise testing (Masterscreen®, Carefusion®) 1 day before RHC according to current recommendations using a ramp protocol with an incremental rate of 5–15 W/min judged by the operator [31]. Patients were seated in semi-supine position, wearing a face mask until the end of exercise. The latter was terminated when the predefined endpoints were reached [31] or at any time the patient felt he/she was unable to continue due to symptoms.

The 6-Min Walk Test

The 6-min walk test was performed according to current recommendations and recorded as the distance covered in meters (6MWD) [32]. All patients were instructed to walk at their own pace along a 30-meter corridor while standard phrases as stated in the American Thoracic Society protocol were communicated [32].

Echocardiography

Right heart echocardiography was performed according to current recommendations with the assessment of pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) [33].

Statistical Analysis

Data are expressed as means ± SD or means ± SEM. Parameters before PEA and 1 year after PEA were compared with the paired t test for normally distributed parameters or the Wilcoxon signed-rank test for nonnormally distributed parameters. The two-tailed t test or Mann-Whitney U test was used to test for differences between residual and nonresidual PH. Spearman's rank correlation test was used to determine whether hemodynamic slopes before PEA were associated with parameters after PEA. $p < 0.05$ was considered statistically significant for comparison between groups. Statistical analysis was performed using SPSS, version 21.0 (IBM, Armonk, N.Y., USA).

Results

Pre-PEA Patient Characteristics and Pulmonary Hemodynamics at Rest

A total of 16 patients with a mean age of 60.8 ± 14.8 years and a mean BMI of 24.7 ± 4.6 were included. At baseline, 12 patients (71%) were in WHO functional class III and 1 patient was receiving specific PAH therapy as

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Table 1. Baseline characteristics

	Before PEA	One year after PEA
Patients, n	16	
Male/female	10/6	
Age, years	60.8±14.8	61.9±14.4
BMI	24.7±4.6	25.9±5.2**
WHO functional class, n (%)		
I	–	4 (23)
II	3 (18)	12 (71)
III	12 (71)	1 (6)
IV	2 (11)	–
NT-proBNP, pg/ml	1,419.8±1,093.1	413.7±369.7**
Peak VO_2, $ml \cdot kg^{-1} \cdot min^{-1}$	13.6±5.9	17.9±4.6**
TAPSE, mm	17.7±5.5	18.8±3
PASP, mm Hg	81.7±19.8	43.4±8.7#
6MWD, m	345.6±117.5	485.6±105.9#
Targeted PAH therapy, n (%)	1 (6)	–
Phosphodiesterase type 5 inhibitors, n (%)	1 (6)	–
Therapy naive, n (%)	15 (94)	–
Jamieson type, n (%)		–
I	2 (13)	
II	9 (56)	
III	5 (31)	

Values represent mean ± SD unless indicated otherwise. # $p < 0.001$ (Wilcoxon signed-rank test), ** $p < 0.01$ (* = paired t test) versus baseline. VO_2 = Oxygen uptake; BMI = body mass index.

shown in table 1. Increased NT-proBNP levels were noticed while the exercise capacity was substantially reduced. Right heart echocardiography showed a decreased TAPSE and an elevated PASP (table 1).

Pre-PEA patients exhibited a precapillary PH with an elevated mPAP, TPG, DPG and PVR, a normal PAWP and an impaired CO, while the SvO_2 was reduced (table 2).

Pulmonary Hemodynamic Profile during Exercise before PEA

During exercise, the heart rate significantly increased while SpO_2 and SvO_2 decreased. The pulmonary hemodynamic profile showed an increase in mPAP from 35.8 ± 7.6 to 53.8 ± 5.1 mm Hg, while the CO increased only slightly from 4.4 ± 0.8 to 6.5 ± 1.9 l/min, resulting in a steep mPAP/CO slope of 13.3 ± 10.8 mm Hg/l/min (fig. 2a). In parallel, sPAP, dPAP, PAWP, right atrial pressure, TPG and DPG increased significantly during exercise, while the change in PVR during exercise was minimal. The relationship between CO and the hemodynamic parameters is displayed in table 3. Steep slopes of sPAP/CO, dPAP/CO, PVR/CO, DPG/CO, PAWP/CO and TPG/CO were observed (table 3; fig. 2).

One Year after PEA

One year after PEA, patients presented with a slightly higher BMI and mostly in WHO functional class I (23%) and II (71%), respectively. Significant improvements in the exercise capacity (6MWD, peak VO_2), PASP and reduction of NT-proBNP levels were evident in comparison with pre-PEA values (table 1).

mPAP, sPAP, dPAP and TPG after PEA were lower during rest and exercise with concomitant improvement of CO and SvO_2 (table 2), while the absolute changes during exercise were not significantly different in comparison to pre-PEA (table 3). In contrast, the CO during exercise increased after PEA to a significantly higher extent than pre-PEA (table 3). Therefore, the post-PEA slopes of sPAP/CO, mPAP/CO and TPG/CO were flattened compared to before PEA (fig. 2). However, the slopes of dPAP/CO, PAWP/CO, PVR/CO, SvO_2/CO and DPG/CO were not significantly different (table 3; fig. 2).

A residual PH was observed in 7 patients, while significantly impaired pulmonary hemodynamics at rest and during exercise in comparison with nonresidual PH were observed. Numerically, albeit not significant, the slopes of mPAP/CO, dPAP/CO and TPG/CO showed a less steep pattern in nonresidual PH (table 4).

Association of Pre-PEA Hemodynamics with Hemodynamic Outcome One Year after PEA

With the exception of TPG, resting pressure values before PEA were not significantly associated with hemodynamics after PEA (table 5).

The dPAP/CO and DPG/CO slopes before PEA were significantly associated with PVR at rest after PEA and mPAP at rest after PEA, while mPAP/CO, sPAP/CO and TPG/CO failed to correlate with parameters after PEA (table 5; fig. 3).

Additionally, mPAP/CO was significantly associated with NT-proBNP after PEA (Spearman $r = 0.59$, $p = 0.03$), and sPAP/CO was correlated with 6MWD after PEA (Spearman $r = -0.7$, $p = 0.02$).

Discussion

In the current study, we could show for the first time that the hemodynamic response to exercise before PEA is associated with hemodynamic outcome after PEA. The

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Table 2. Hemodynamic parameters at rest and during exercise

	Before PEA		One year after PEA	
	rest	exercise	rest	exercise
sPAP, mm Hg	64.5±13.3	94.2±8.5#	39±10.8*	70.9±15.5*, #
mPAP, mm Hg	35.8±7.6	53.8±5.1#	23.7±6.6*	43.2±7.1*, #
dPAP, mm Hg	21.5±5.6	30.3±9.6#	14.1±6.4*	23.7±5.4**, #
RA, mm Hg	5.9±2.1	13±3.4#	5.8±2.8	14.7±4.6#
PAWP, mm Hg	7.3±2.9	11.8±4.8#	10.4±3.6***	19.1±6.1**, #
TPG, mm Hg	28.9±6.8	44.3±8.8#	13.3±6.9*	24.1±7.9*, #
DPG, mm Hg	14.6±4.9	20.7±12.7†	3.6±6.9††	4.6±6.8
PVR, dyne·s/cm^5	522.6±151.2	529.8±161.5	213±117.3*	246.2±113.6*
CO, l/min	4.4±0.8	6.5±1.9#	5.1±0.9***	8.4±1.9*, #
CI, l/min/m^2	2.4±0.5	3.5±1.2#	2.6±0.5	4.7±1.9**, #
SvO_2, %	66.6±6.2	41.7±14.2#	72.8±5.4*	39.5±5.9#
HR, beats/min	74±15	96±15#	75.7±10.6	104.3±15.7***, #
SpO_2, %	93.9±3.1	88.5±4.8#	96.1±2.5***	92.3±3.1***, ##
Workload, W	–	32±16.4	–	44±20.2†††

Values represent mean ± SD. * p < 0.001, ** p < 0.01, *** p < 0.05 versus before PEA, # p < 0.001, ## p < 0.01 versus rest (*,# = paired t test), † p < 0.01 versus rest, †† p < 0.001, ††† p < 0.01 versus before PEA († = Wilcoxon signed-rank test). RA = Right atrium; HR = heart rate; SpO_2 = blood oxygen saturation.

Table 3. Hemodynamic parameters in absolute change (Δ) from rest to exercise and related to CO (l/min)

	Before PEA		One year after PEA	
	Δ	slope (CO)	Δ	slope (CO)
sPAP, mm Hg	29.7±12.1	19.9±12.6	31.9±8.7	12.5±8.8***
mPAP, mm Hg	18.1±7	13.3±10.8	19.4±4.6	6.4±2.6†††
dPAP, mm Hg	8.8±8	7.7±13.2	9.6±4.9	3.4±2.5
PAWP, mm Hg	5.1±4.9	4.4±5.1	8.7±4.6***	3.5±2.7
RA, mm Hg	7.1±2.9	5.9±6.3	9±3.6***	5.8±4.5
PVR, dyne·s/cm^5	26.1±66.2	16.4±122.3	25.8±62.5	11.5±36.7
SvO_2, %	–27.9±14.3	–23.4±20.6	–33.4±5.9	–25.1±17.5
TPG, mm Hg	15.4±9.5	19.7±20.6	10.8±5.5	6.6±4.9***
DPG, mm Hg	6.1±11	5.1±14.3	0.9±5.4	0.6±3.4
CO, l/min	2.1±1.7	–	3.3±1.5***	–

Values represent mean ± SD. *** p < 0.05 versus before PEA (paired t test); ††† p < 0.01 versus before PEA (Wilcoxon signed-rank test). RA = Right atrium.

novel findings of the present study show that exercise-dependent pressure-flow relationships before PEA were improved 1 year after PEA, indicating an enhanced capacity of the pulmonary vascular system after PEA, and that they were better correlated to the hemodynamic outcome 1 year after PEA than baseline resting hemodynamic parameters. To the best of our knowledge, this is the first study that evaluated submaximal exercise hemodynamic parameters in a selected cohort of CTEPH patients and demonstrated their impact on the hemodynamic outcome after PEA.

The investigated study population was comprised of patients diagnosed with surgically accessible CTEPH (PH group 4 according to the WHO classification) and severe-

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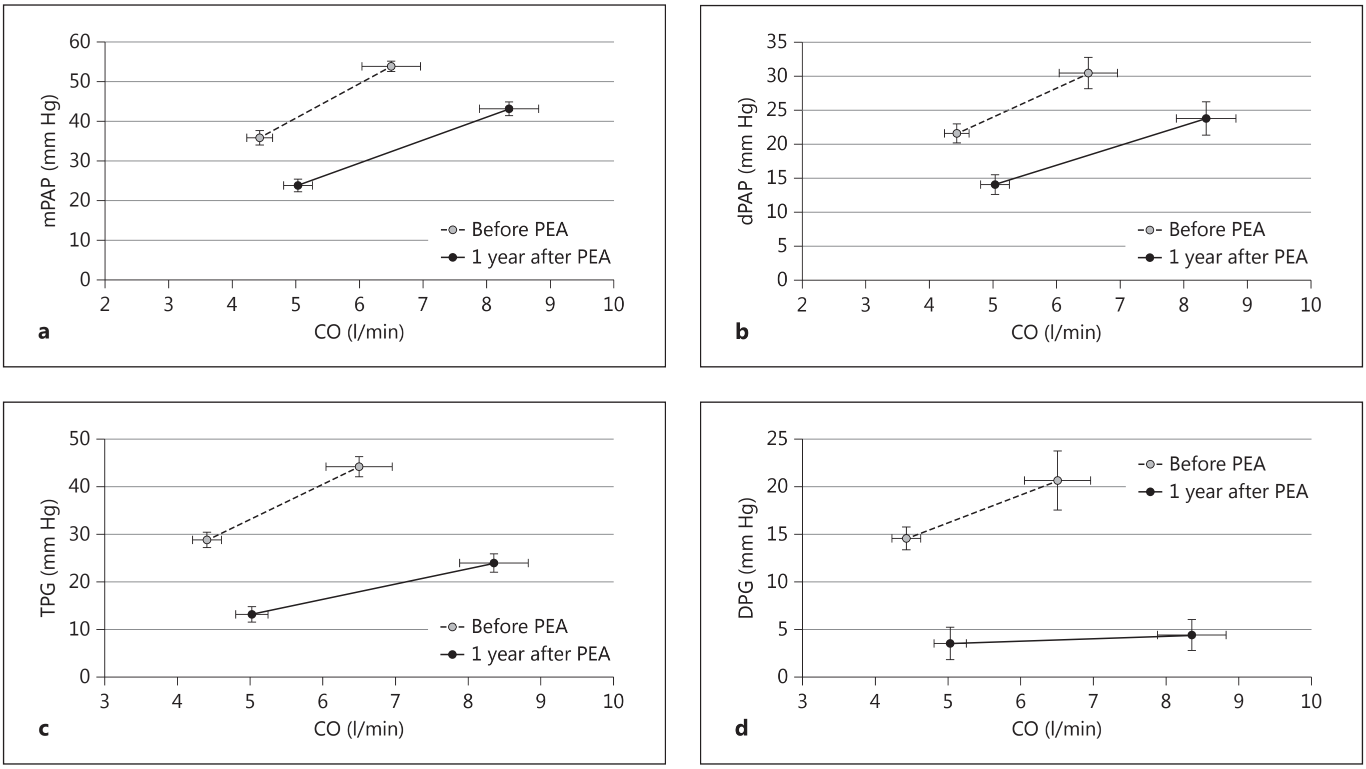

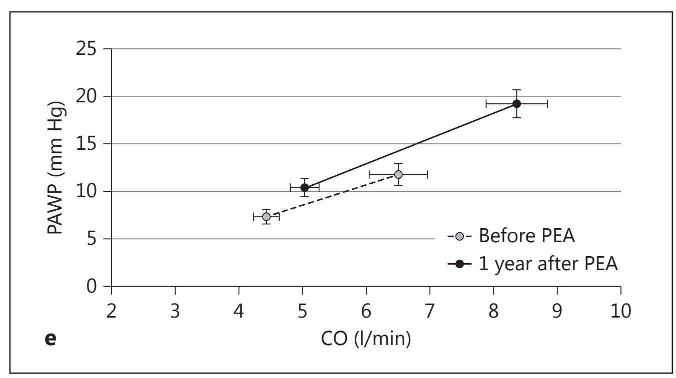

Fig. 2. Linear pressure-flow relationships before and after PEA during constant exercise. **a** mPAP/CO slope. **b** dPAP/CO slope. **c** TPG/CO slope. **d** DPG/CO slope. **e** PAWP/CO slope. Values represent mean ± SEM.

ly impaired exercise capacity characterized by low 6MWD, low peak VO_2, and mostly being in WHO functional class III. In comparison to previous studies, our patient group showed a similar hemodynamic profile at rest characterized by an impairment of the RV function as well as high PVR and pressures before PEA [6, 34–37]. As expected, the mPAP, PVR and CO at rest after PEA in our study improved significantly; however, 7 patients exhibited residual PH in our selected cohort. Our findings are in accordance with previously published data showing substantial improvement of the pulmonary hemodynamics 1 year after PEA. However, the individual outcome differed and approximately 10–24% of patients remain symptomatic after PEA [9, 38] and up to 35% presented with residual PH [12, 36, 39].

For example, cardiac magnetic resonance imaging studies under strain indicated that in CTEPH, exercise was limited by an RV impairment and increased PVR, which failed to be reversible after PEA in some patients [40]. Taking into account that PEA is a surgery with considerable risk, patients that most likely benefit from the surgery in the long term have to be selected carefully. Persistence or recurrence of PH is regarded as main prognostic factor for long-term survival [11] or functional capacity [12]. Several mechanisms such as incomplete removal of obstructions and irreversible small-vessel arteriopathy

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Table 4. Parameters according to residual PH after 1 year

	Nonresidual PH (n = 9, 56%)		Residual PH (n = 7, 44%)	
	rest	exercise	rest	exercise
mPAP, mm Hg	18.7±2.6*	30.3±3.1*	30.3±3.1	49.6±4.5
dPAP, mm Hg	9.6±3.3*	20.2±3.6*	19.9±4.1	28.1±3.9
PAWP, mm Hg	9.7±3.7	19.3±6.9	11.4±3.4	18.9±5.2
TPG, mm Hg	9±4.1*	18.9±6.2*	18.8±6	30.7±3.4
DPG, mm Hg	2.5±2.8	3.0±4.7###	7.8±4.1	8.4±6.5
PVR, dyne•s/cm^5	130.6±50.3#	161.1±35.2*	319±88.1	365.4±56.7
CO, l/min	5.3±0.9	9.1±1.9	4.6±0.8	7.4±1.5
HR, beats/min	76±11	105±15	75±10	103±17
mPAP/CO, mm Hg/l/min	5.8±2.5		7.2±2.7	
dPAP/CO, mm Hg/l/min	3.2±1.7		3.7±3.3	
TPG/CO, mm Hg/l/min	4.8±3.8		9.1±5.4	
DPG/CO, mm Hg/l/min	0.6±2.5		0.5±4.6	
NT-proBNP, pg/ml	159.1±122.5##		753.2±303.9	
6MWD, m	511±111.1		454±94	
Jamieson type, n (%)				
I	2 (22)			
II	5 (56)		4 (57)	
III	2 (22)		3 (43)	

Values represent mean ± SD unless otherwise indicated. * p < 0.001; ## p < 0.01; ** p < 0.01; ### p < 0.05; *** p < 0.05 versus residual PH (* = two-tailed t test, # = Mann-Whitney U test).

Table 5. Correlations between hemodynamic parameters before PEA with PVR and mPAP at rest 1 year after PEA using Spearman's rank correlation test

Parameters before PEA	PVR at rest (dyne•s/cm^5) one year after PEA		mPAP at rest (mm Hg) one year after PEA	
	r	p value	r	p value
mPAP rest (mm Hg)	0.29	0.28	0.48	0.055
sPAP rest (mm Hg)	0.3	0.25	0.51	0.045
dPAP rest (mm Hg)	0.22	0.42	0.32	0.22
CO rest (l/min)	–0.4	0.11	–0.15	0.57
CI rest (l/min/m^2)	–0.14	0.62	0.05	0.85
TPG rest (mm Hg)	**0.49**	**0.057**	**0.57**	**0.02**
DPG rest (mm Hg)	0.38	0.14	0.36	0.18
PVR at rest (dyne•s/cm^5)	**0.41**	**0.13**	0.44	0.9
mPAP/CO (mm Hg/l/min)	0.39	0.14	0.29	0.27
sPAP/CO (mm Hg/l/min)	0.22	0.41	0.25	0.35
dPAP/CO (mm Hg/l/min)	**0.547**	**0.028**	**0.546**	**0.029**
TPG/CO (mm Hg/l/min)	0.3	0.25	0.31	0.25
DPG/CO (mm Hg/l/min)	**0.578**	**0.019**	**0.581**	**0.018**

Figures in bold are highlighting significant values (p < 0.05).

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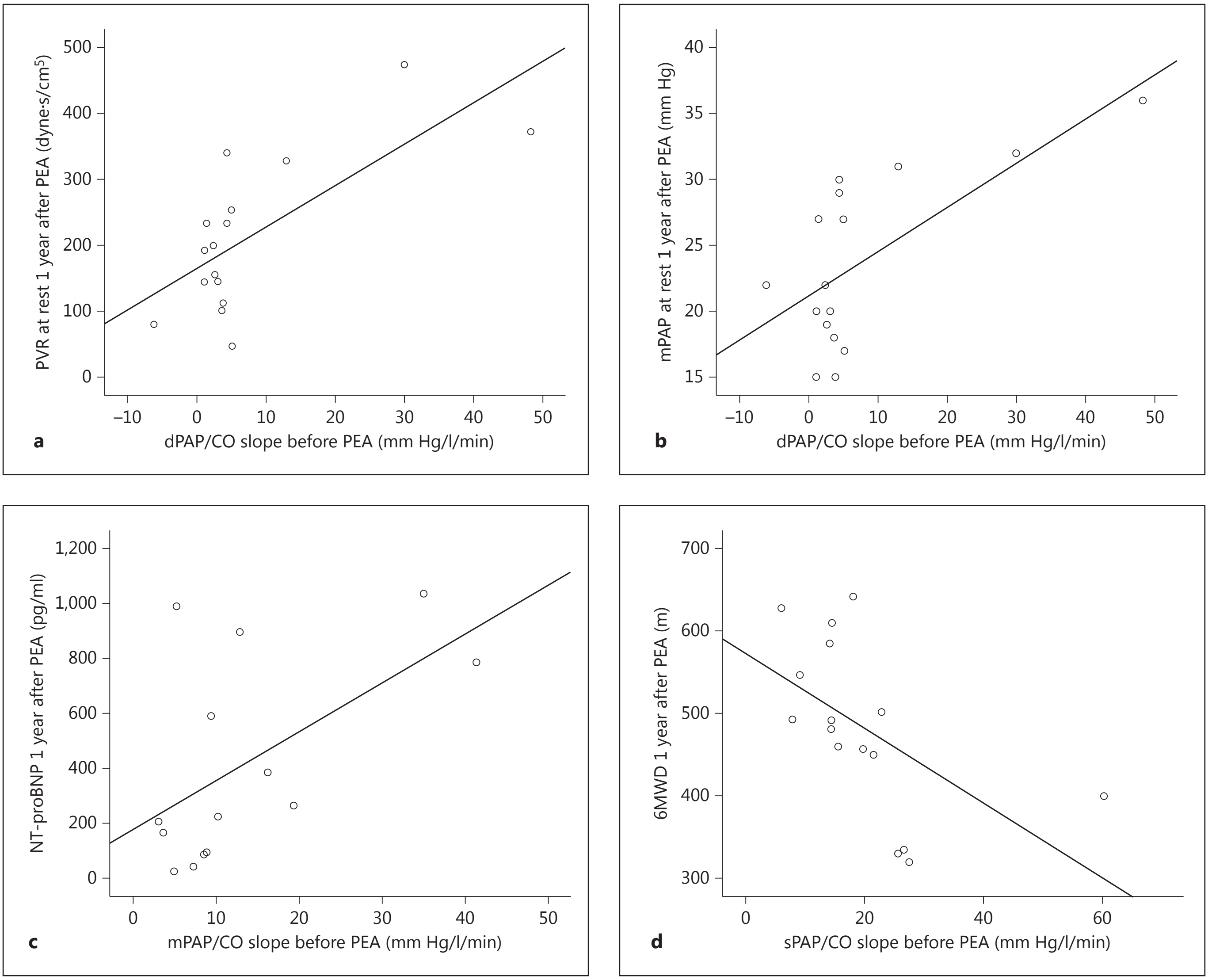

Fig. 3. Associations between the dPAP/CO slope before PEA and PVR at rest after PEA (**a**), between the dPAP/CO slope before PEA and mPAP at rest after PEA (**b**), between the mPAP/CO slope before PEA and NT-proBNP after PEA (**c**), and between the sPAP/CO slope before PEA and 6MWD after PEA (**d**).

with persistent high afterload of the RV are contributing to altered pulmonary hemodynamics after PEA [20]. It has been postulated that the outcome of PEA depends on the relationship of small-vessel arteriopathy contributing to CTEPH and the capacity of the small vessels to dilate [16]. In this regard, one can speculate that the relationship between PVR and Cpa was reduced in CTEPH before PEA in our cohort and partly remained impaired after PEA, probably due to persistent structural changes of distal vessels after the removal of proximal obstructions [15].

Physiologically, the pulmonary vessels are a high-flow, low-resistance system, which results in flat mPAP/CO slopes during exercise [22]. The extent of small-vessel arteriopathy and the limited potential to vasodilate and/or recruit previously nonperfused vascular areas during increased CO may be reflected by steep pressure-flow slopes, as was shown in heterogeneous groups of PAH patients [22–24]. Thus, hemodynamic measurements that may detect the extent of small-vessel disease may improve the prediction of outcome after PEA.

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Moreover, current data suggested that exercise measurements might be stronger predictors of outcome than resting pulmonary hemodynamics in PAH [19, 21, 41, 42]. In a recent study, it has been shown that Cpa during exercise correlated with peak VO_2 in surgically treated CTEPH patients and was a strong predictor of limited exercise capacity after PEA [20].

Our study is in line with these findings, demonstrating improvements of hemodynamic parameters after PEA at rest, as well as a flattened slope of pressure-flow curves during exercise, indicating an increased capacity of the pulmonary vasculature for a higher cardiac output. Furthermore, the flattening of pressure-flow slopes after PEA was numerically even more enhanced in nonresidual PH. Particularly, the slopes of DPG/CO and dPAP/CO decreased and were significantly associated with the hemodynamic outcome after PEA as well as the sPAP/CO slope with 6MWD and mPAP/CO with NT-proBNP. In this context, the diastolic parameters may correlate better with the hemodynamic outcome than sPAP/CO, mPAP/CO and TPG/CO as they are less influenced by the CO and overall fluid load. Recently, the RV contractile reserve in PH has been defined by the ability of the RV to eject a large stroke volume despite high pressures and served as a prognostic factor [43], while Cpa was defined as the ratio of stroke volume to pulse pressure also with prognostic significance in CTEPH [2, 20]. The flattening of pressure-flow slopes after PEA are reflecting both, an enhanced Cpa and RV contractile reserve after PEA. However, a further discrimination of Cpa and RV contractile reserve by hemodynamic slopes cannot be drawn from our data as both are reflected by an increase in CO. However, the DPG is probably less sensitive to changes in Cpa [44], and therefore, the flattened DPG/CO and dPAP/CO slopes are probably more indicative of an enhanced RV contractile reserve after PEA.

In a different study, the DPG was strongly associated with pulmonary vascular remodeling in left-sided heart disease [45] and, therefore, our findings may indicate a substantial increase in pulmonary vascular compliance in our patients, while the resting DPG after PEA was almost reaching a normal range. Along these lines, in patients with chronic left heart failure, the response of mPAP, TPG and PVR to exercise was better related to outcome than resting hemodynamic measurements [46, 47], underlining that the compensatory capacity of the right ventricular pulmonary vascular system is influencing disease progression.

Interestingly, the PAWP/CO slope in our cohort before and after PEA was comparable to previously published data from patients with left ventricular systolic dysfunction (3.9 mm Hg/l/min) [47]. Moreover, PAWP was increasing during exercise after PEA, which can be interpreted both as a physiological response to the increased CO but partially also as a response unmasking previously unknown left ventricular diastolic dysfunction. With the latter in mind, it is interesting to observe PAWP values >20 mm Hg throughout exercise in elderly subjects [23, 48]. Nevertheless, we conclude that our patients mainly exhibited precapillary PH as (1) the steep TPG/CO slope of our patients before PEA was reflecting a disproportionate increase in mPAP during exercise and (2) mean DPG at baseline was >5 mm Hg indicating a predominantly precapillary PH [44].

As reported previously, the surgical CTEPH type is significantly associated with the frequency of PH after PEA [18, 27]. We did not observe significant differences in hemodynamic slopes or in the frequency of PH after PEA with regard to the Jamieson type, while the study group consisted mainly of Jamieson type II/III patients. Our study did not include systematic postsurgical imaging with angiography to assess the quantification and differentiation of the proportion of postsurgical perfusion impairment due to nonremovable material and/or secondary microvascular disease. However, our finding that presurgical slopes are correlated with the degree of postsurgical residual PH possibly reflects the combination of the above. A larger sample size with the inclusion of Jamieson types I and IV are warranted. However, one can speculate that patients with Jamieson type IV 1 year after PEA will provide steeper hemodynamic slopes in case of concomitant PH after PEA due to enhanced small-vessel pulmonary arteriopathy and impaired Cpa.

Limitations of the study are the small sample size and retrospective analysis of the selected patient population in a single-center study; furthermore, the pathophysiological findings of our study remain to be elucidated in larger prospective trials potentially combined with postprocedural angiographies for the quantification of residual perfusion impairments. Additionally, the sample size limited the statistical analysis; a multivariate regression analysis was not performed. As we are a national referral center, baseline RHC was often performed in the referring hospital, and therefore, these patients could not be included in our analysis. The 1-year follow-up visit was also not mandatory in our center. The investigator who performed the RHC was not blinded to the patient's data and the rate of residual PH after PEA was slightly higher than reported in the literature; therefore, a selection bias is possible.

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In conclusion, this is the first study to evaluate the pulmonary hemodynamic profile during submaximal exercise in CTEPH. Our preliminary results indicate that in CTEPH the pulmonary response to exercise before PEA was more closely related to the hemodynamic outcome 1 year after PEA than to measurements at rest. The flattening of pressure-flow slopes after PEA reflects the enhanced capacity of the right ventricular pulmonary vascular system in response to increased CO. For the evaluation of pressure-flow slopes as an independent predictor of outcome after PEA, future studies in larger patient groups are warranted.

Financial Disclosure and Conflicts of Interest

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

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Exercise right heart catheterisation before and after pulmonary endarterectomy in patients with chronic thromboembolic disease

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ABSTRACT Symptomatic patients with chronic thromboembolic disease (CTED) without pulmonary hypertension often show an excessive increase in mean pulmonary arterial pressure (MPAP) during exercise.

We report on the impact of pulmonary endarterectomy (PEA) on pulmonary haemodynamics in a prospective series of 32 consecutive CTED patients who underwent PEA. All patients had a comprehensive diagnostic work-up including right heart catheterisation at baseline and 12 months after PEA. Furthermore, in 12 patients exercise right heart catheterisation was performed before and after PEA.

After PEA, MPAP was lower at rest (20±3 *versus* 17±3 mmHg; p=0.008) and during maximal exercise (39±8 *versus* 31±6 mmHg; p=0.016). The mean total pulmonary resistance (TPR) decreased from 3.6±0.8 Wood Units (WU) pre-operatively to 2.7±0.7 WU 1 year after PEA (p=0.004) and the mean slope of the MPAP/cardiac output (CO) relationship decreased from 3.6±1.0 to 2.3±0.8 WU (p=0.002). Peak oxygen uptake increased from 1.2±0.4 to 1.5±0.3 $L \cdot min^{-1}$ (p=0.014) and ventilatory equivalents of carbon dioxide decreased from 39±2 to 30±2 (p=0.002). There was a significant improvement in quality of life assessed by the Cambridge Pulmonary Hypertension Outcome Review questionnaire.

In CTED patients, PEA resulted in haemodynamic and clinical improvements. The means of TPR and MPAP/CO slopes decreased to <3.0 WU.

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Introduction

Pulmonary endarterectomy (PEA) is the gold standard treatment option for patients with chronic thromboembolic pulmonary hypertension (CTEPH) [1]. In CTEPH patients, fibrotic transformation of pulmonary artery clots associated with secondary microvasculopathy leads to an increase in pulmonary vascular resistance (PVR) [2–4]. Patients with chronic thromboembolic obstructions without pulmonary hypertension (mean pulmonary arterial pressure (MPAP) at rest <25 mmHg) are diagnosed with chronic thromboembolic disease (CTED) [5, 6]. These patients have symptoms like dyspnoea upon exertion or fatigue that hamper their daily activities and diminish their quality of life. CTED patients show the same exercise limitations and symptoms as World Health Organization (WHO) Functional Class II or III CTEPH patients as described by Donahoe *et al.* [7]. These symptoms are in line with an inadequate response in pulmonary haemodynamics during exercise [8–10]. Successful PEA has been reported in a limited number of patients with CTED without mortality [9, 10]. The rationale for PEA in operable CTED patients is improvement of their quality of life by improving symptoms and exercise tolerance as reported by Taboada *et al.* [9] and van Kan *et al.* [10]. In addition, with early treatment, potential long-term complications like the development of secondary small-vessel vasculopathy and right heart failure can be avoided [1, 7, 11]. Recently, a report of a multicentre registry of inoperable CTED patients was published that showed improvements in physical capacity and PVR after balloon pulmonary angioplasty, but no exercise data were reported [12].

There is an ongoing discussion about the definition of exercise pulmonary hypertension, which is not reflected by current guidelines [5, 13–15]. Kovacs *et al.* [16] describe exercise pulmonary hypertension as the presence of resting MPAP <25 mmHg and MPAP >30 mmHg during exercise with total pulmonary resistance (TPR) >3 Wood Units (WU). In CTED patients the MPAP/cardiac output (CO) slope during exercise is steeper than in healthy subjects [10, 16]. Naeije *et al.* [15] and Lewis *et al.* [13] have proposed that TPR and MPAP/CO slopes should not exceed 3.0 WU during maximal supine exercise in healthy subjects. The clinical challenge in terms of diagnosis and treatment of exercise pulmonary hypertension was recently summarised [14]. The impairment in circulatory adaptation in CTED patients is also manifested in an increase in dead space ventilation, reduced oxygen pulse and decreased peak oxygen uptake during cardiopulmonary exercise testing (CPET) [10].

Our group reported data on exercise haemodynamics obtained in CTEPH patients before and 1 year after PEA that showed improvement in MPAP/CO slopes after PEA [17]. In CTED patients, PEA has been shown to improve the quality of life (Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) scores) [9] and reduces MPAP at rest [10]; however, data from exercise right heart catheterisation (RHC) before and after PEA are lacking. We hypothesise that PEA in CTED patients may lead to a decline in TPR and MPAP/CO slopes to ⩽3.0 WU because microvasculopathy probably does not contribute significantly to haemodynamic impairment in this population. Therefore, the aim of the study was to examine parameters of exercise RHC before and after PEA, with a focus on changes in TPR and MPAP/CO slopes.

Patients and methods

Patients

For this observational study patients with CTED (MPAP <25 mmHg) at baseline RHC who underwent PEA between January 1, 2010 and March 31, 2016 were selected from our prospective institutional database. Operability assessment was carried out by a multidisciplinary team consisting of PEA surgeons, (interventional) radiologists, cardiologists and pulmonary physicians. Patients underwent a 6-min walk test, CPET, echocardiography and measurement of N-terminal pro-brain natriuretic peptide levels. Health-related quality of life was measured using the CAMPHOR questionnaire [18]. All patients included underwent PEA according to our institutional protocol [11]. The collection of data was approved by the institutional ethics committee and conducted in keeping with the Declaration of Helsinki (approval AZ 199/15). All patients gave written informed consent.

Right heart catheterisation

RHC was accomplished by insertion of a Swan–Ganz catheter *via* the jugular vein under local anaesthesia. Pressure values at rest were assessed continuously and CO was measured by the thermodilution technique, averaging three out of five output determinations. Baseline parameters were assessed 30 min after insertion of the catheter. PVR and cardiac index (CI) were calculated as described previously [19]. Exercise was performed on a cycle ergometer in the supine position with a constant external workload of 25, 50 or 75 W [20].

The zero reference level for the pressure transducer was placed at the mid-thoracic level in the supine position. During exercise, all pulmonary pressures were averaged over several respiratory cycles, which is thought to be the most reasonable compromise to compensate for respiratory fluctuations, especially under maximal exercise [19, 21]. The following haemodynamic parameters were calculated as the main outcome measures: TPG=MPAP−PAWP, DPG=DPAP−PAWP, the slope of the MPAP/CO relationship [13] and C_{pa}=(CO/heart rate)/(SPAP−DPAP), where TPG is the transpulmonary gradient, PAWP is the pulmonary arterial wedge pressure, DPG is the diastolic pulmonary gradient, C_{pa} is the pulmonary arterial compliance and SPAP is the systolic pulmonary arterial pressure. Exercise pulmonary hypertension was defined by the presence of resting MPAP <25 mmHg and MPAP >30 mmHg at peak exercise while TPR >3.0 WU as proposed by the European Respiratory Society Task Force [16].

Cardiopulmonary exercise testing

Patients underwent symptom-limited incremental CPET (MasterScreen, CareFusion; BD, Heidelberg, Germany) according to current recommendations using a ramp protocol with an incremental rate of 5–15 W·min^{-1} as judged by the operator [22].

The 6-min walk test

The 6-min walk test was performed according to current guideline recommendations and results were recorded as the distance covered in metres [23].

Surgical technique

PEA was performed using the standard technique [24]. Briefly, a median sternotomy was performed and during cardiopulmonary bypass patients were gradually cooled to a core temperature of 20°C for safe circulatory arrest [25, 26], which was limited to intervals of 20 min.

Statistical analysis

Continuous variables were tested for adherence to a normal distribution by the D'Agostino–Pearson normality test for normal data and are expressed as mean with standard deviation or as median (interquartile range). Univariate comparisons between patients were performed using the Chi-squared test or Fisher's exact test, where appropriate, for dichotomous variables; the t-test or Mann–Whitney U-test was applied for continuous variables. Statistical tests were two-sided; differences where $p<0.05$ were considered significant. Prism version 7.03 for Windows (GraphPad, La Jolla, CA, USA) was used for the data and statistical analyses.

Results

Baseline characteristics

From January 2010 to March 2016, 664 consecutive symptomatic patients with chronic thromboembolic vascular obstructions underwent PEA surgery at our institution. The in-hospital mortality rate was 3.6% (24 patients). Within the entire cohort, 32 patients were diagnosed with CTED (defined as MPAP <25 mmHg at rest). All CTED patients survived the perioperative period.

Results of pre-operative and 1-year post-operative exercise RHC in 12 CTED patients

Patient characteristics and baseline noninvasive measurements

The study flowchart is depicted in figure 1. Baseline characteristics of the 12 CTED patients (median (IQR) age 34 (28–60) years, 50% females) who underwent exercise RHC are presented in table 1. Results of pulmonary function tests were normal. Eight patients were in WHO Functional Class II and four patients were in WHO Functional Class III. Patients were not on pulmonary hypertension-targeted medication. Nine patients had no perioperative complications. Two patients had minor complications (one urinary tract infection and one atrial fibrillation), and one patient with re-do surgery developed post-operative seizures with suspicion of hypoxic brain damage and needed tracheostomy. Fortunately, this patient had a complete recovery.

Surgical specimens

All patients had a significant burden of bilateral thromboembolic disease. The endarterectomy specimens as per Jamieson classification were classified as type 1 or 2 disease for the majority of patients (n=8). Specimens from two patients were classified as type 3 disease and for two patients these data were not available.

Exercise RHC before and 1 year after PEA

Exercise RHC data before PEA and 1 year after PEA are depicted in figure 2. Before PEA the slope of the MPAP/CO relationship was >3.0 WU in nine patients (range 1.7–4.9 WU) and TPR was also >3.0 WU in nine patients who had MPAP >30 mmHg. In one patient TPR was 3.0 WU but MPAP only 29 mmHg. At 1 year after PEA, only three patients still fulfilled the criteria of exercise pulmonary hypertension with

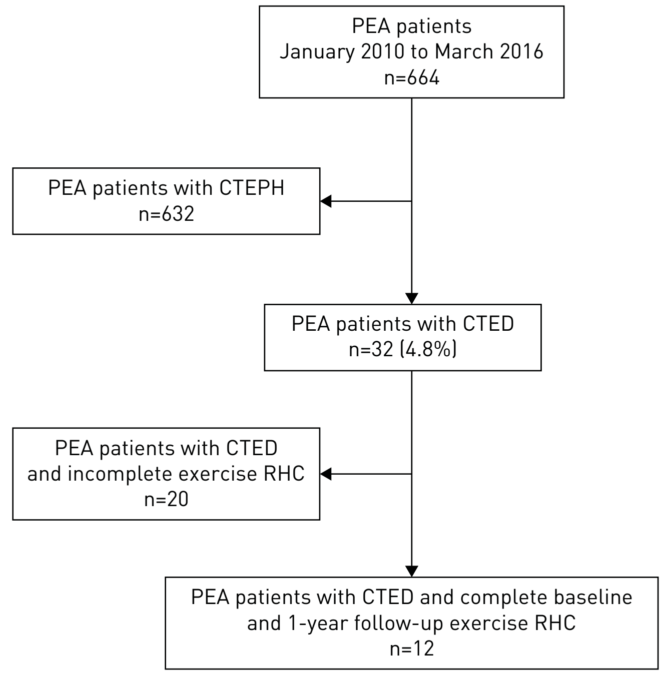


FIGURE 1 Flowchart of patient selection. PEA: pulmonary endarterectomy; CTEPH: chronic thromboembolic pulmonary hypertension; CTED: chronic thromboembolic disease; RHC: right heart catheterisation.

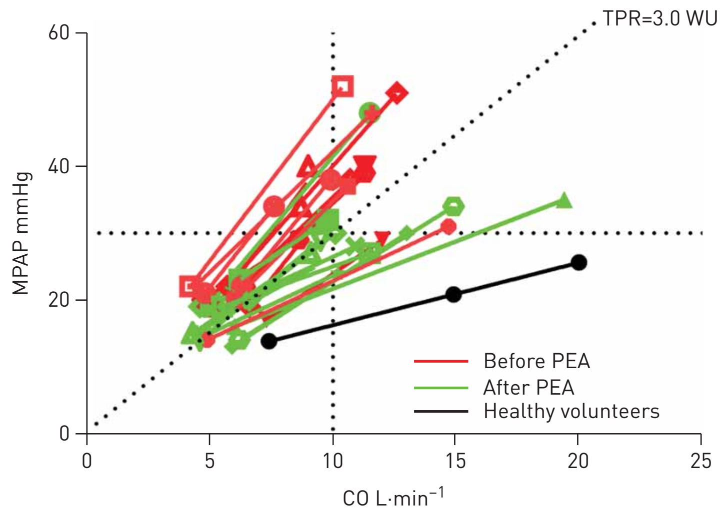
MPAP >30 mmHg and TPR >3.0 WU. However, after PEA the MPAP/CO slope was <3.0 WU in 11 patients and increased in one patient from 3.5 to 4.3 WU. In this patient an excessive rise in PAWP to 25 mmHg was observed, indicating left ventricular diastolic dysfunction. Figure 3 shows the individual changes in TPR and MPAP/CO slope before and after PEA. The mean TPR (3.6±0.8 to 2.7±0.7 WU; p=0.0040) and mean MPAP/CO slope (3.6±1.0 to 2.3±0.8 WU; p=0.0024) decreased after PEA. Patients with values >3.0 WU showed a more pronounced decrease, whereas patients with slope values <3.0 WU showed only a minor decrease.

Haemodynamic responses before and after PEA are summarised in table 2. MPAP at rest showed a reduction from 20±3 to 17±3 mmHg (p=0.006). Further decreases were observed for SPAP, TPG, PVR and TPR. PAWP showed an increase from 8±3 to 11±4 mmHg (p=0.02). During exercise RHC pulmonary haemodynamics improved after PEA, whereas CO and CI did not change. Exercise TPG decreased after

TABLE 1 Baseline characteristics of the 12 chronic thromboembolic disease patients with exercise right heart catheterisation who underwent pulmonary endarterectomy

Baseline characteristics	
Age years	34 (24–60)
Sex	
Male	6
Female	6
Height cm	175±7
Weight kg	81±17
BMI kg·m^{-2}	26.6±4.9
Pulmonary function	
FVC L	3.9±0.8
FVC % pred	91±11
FEV_1 L	3.1±0.8
FEV_1 % pred	83±11
FEV_1/FVC %	78±6
T_{LCO} % pred	72±18
NT-proBNP ng·L^{-1}	68 (25–147)

Data are presented as median (interquartile range), n or mean±SD. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; T_{LCO}: transfer factor of the lung for carbon monoxide; NT-proBNP: N-terminal pro-brain natriuretic peptide.



Before PEA WU	After PEA WU
3.7	1.4
4.8	2.5
1.8	1.7
3.6	1.7
4.4	1.3
4.6	2.5
4.2	2.9
4.6	2.6
3.5	2.3
2.3	2.0
3.5	4.3
2.5	2.4

FIGURE 2 Mean pulmonary arterial pressure (MPAP)/cardiac output (CO) relationship of 12 patients with exercise right heart catheterisation before and 1 year after pulmonary endarterectomy (PEA). TPR: total pulmonary resistance; WU: Wood Units. The values of the individual slopes are given in the table. The black line shows the mean slope (0.94 WU) of healthy volunteers from Kovacs *et al.* [27].

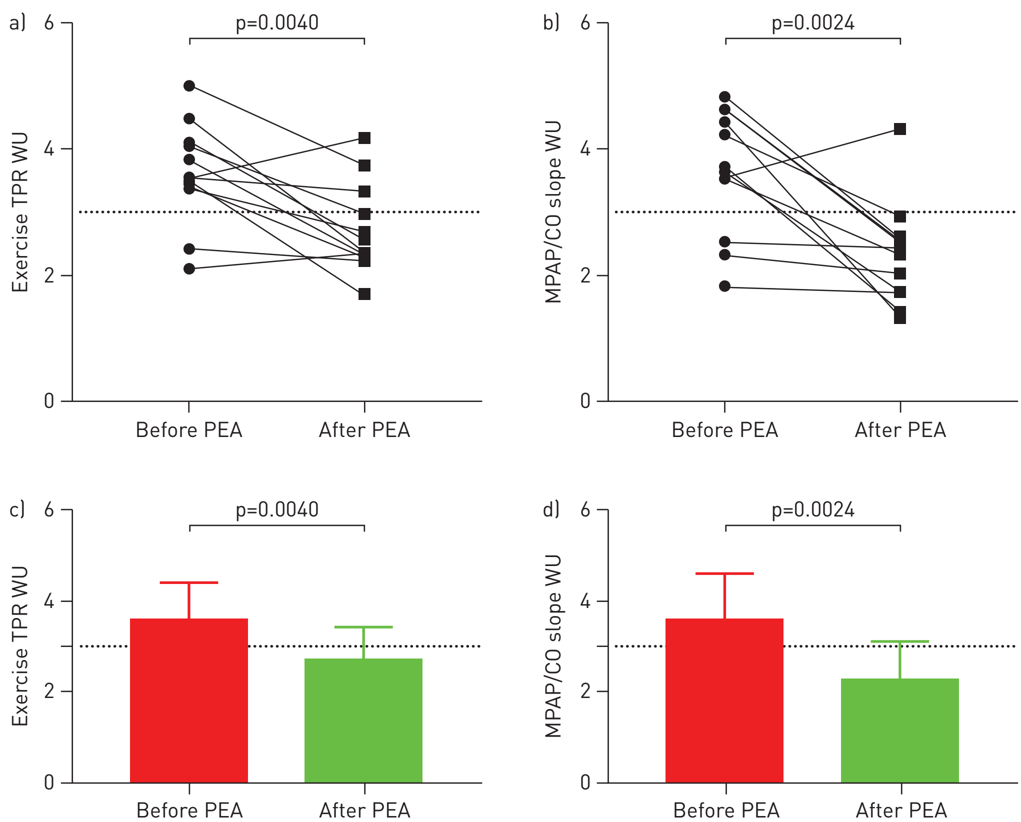


FIGURE 3 a, b) Individual and c, d) mean±SD changes in a, c) total pulmonary resistance TPR during exercise and b, d) slopes of the mean pulmonary arterial pressure (MPAP)/cardiac output (CO) relationship of 12 patients with exercise right heart catheterisation before and 1 year after pulmonary endarterectomy (PEA). WU: Wood Units. The dotted line depicts 3.0 WU, which is the upper limit of normal proposed by Naeije *et al.* [15].

TABLE 2 Right heart catheterisation parameters before and 1 year after pulmonary endarterectomy (PEA)

	Before PEA	After PEA	p-value#
Rest			
SPAP mmHg	33±7	29±5	0.04
MPAP mmHg	20±3	17±3	0.006
DPAP mmHg	10±3	9±4	0.4
PAWP mmHg	8±3	11±4	0.02
RAP mmHg	4.3±2.4	6.5±3.0	0.1
TPG mmHg	12±4	7±4	0.004
PVR WU	2.1±0.9	1.5±0.5	0.01
CO $L \cdot min^{-1}$	5.6±1.0	5.6±0.7	0.9
CI $L \cdot min^{-1} \cdot m^{-2}$	2.7±0.3	2.9±0.5	0.39
C_{pa} $mL \cdot mmHg^{-1}$	3.9±1.6	4.0±1.0	0.86
SV $mL \cdot min^{-1}$	70±15	77±12	0.72
Heart rate $beats \cdot min^{-1}$	72±9	73±7	0.77
Maximal exercise			
SPAP mmHg	62±15	51±14	0.04
MPAP mmHg	39±8	31±6	0.02
DPAP mmHg	19±5	16±5	0.05
PAWP mmHg	11±5	11±4	>0.9
TPG mmHg	26±8	18±6	<0.0001
PVR WU	2.7±1.1	1.8±1.0	0.001
CO $L \cdot min^{-1}$	10.9±1.8	11.6±3.0	0.52
Exercise pulmonary hypertension	9	3	0.04
CI $L \cdot min^{-1} \cdot m^{-2}$	5.4±1.6	6.2±1.8	0.17
C_{pa} $mL \cdot mmHg^{-1}$	2.6±1.1	3.6±0.8	0.03
SV $mL \cdot min^{-1}$	102±14	113±29	0.4
Heart rate $beats \cdot min^{-1}$	106±23	106±9	>0.9

Data presented as mean±SD or n, unless otherwise stated. SPAP: systolic pulmonary arterial pressure; MPAP: mean pulmonary arterial pressure; DPAP: diastolic pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; RAP: right atrial pressure; TPG: transpulmonary pressure gradient; PVR: pulmonary vascular resistance; WU: Wood Units; CO: cardiac output; CI: cardiac index; C_{pa}: pulmonary arterial compliance; SV: stroke volume. #: p<0.05 considered significant.

1 year for all patients. Interestingly, during exercise the mean C_{pa} increased from 2.6±1.1 $mL \cdot mmHg^{-1}$ before PEA to 3.6±0.8 $mL \cdot mmHg^{-1}$ (p=0.03) after PEA.

Noninvasive CPET and quality of life

CPET parameters and CAMPHOR score outcomes were improved after PEA, as presented in table 3. At 1 year after PEA patients had higher maximal workload, peak oxygen uptake (V'_{O_2}) and peak oxygen pulse compared with baseline values. The ventilatory equivalents of carbon dioxide (minute ventilation (V'_E)/V'_{CO_2}) at peak exercise decreased without a change in maximal ventilation. In addition, the V'_E/V'_{CO_2} slope was lower after PEA. PEA improved symptoms in all patients, and all patients returned to WHO Functional Class I and II during the first year after PEA (table 3). The mean values of WHO Functional Class decreased from 2.3±0.5 to 1.4±0.5 (p<0.001) (figure 4). We observed improvements in the total CAMPHOR score and in all three domains (*i.e.* symptoms, activity and quality of life).

Discussion

The optimal treatment for CTED patients is still a matter of debate [9, 10]. After pulmonary embolism there is a continuum of symptoms, ranging from patients with "only" detectable perfusion defects (~30–50%) [28, 29] to very ill patients with severe CTEPH [6, 30–32]. The rationale for offering PEA is that the pathophysiology leading to exercise limitation in CTED is comparable to that in CTEPH. Nevertheless, there are no data available on invasive pre- and post-operative exercise pulmonary haemodynamics. Therefore, the aim of the present study was to determine parameters of exercise RHC before and after PEA, with a focus on changes in TPR and MPAP/CO slopes.

The main findings of the study are: 1) CTED patients showed a decrease in MPAP and exercise TPR 1 year after PEA, 2) the means of TPR and MPAP/CO slopes decreased to <3.0 WU, which is proposed as

TABLE 3 Noninvasive chronic thromboembolic disease parameters, Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) scores and 6-min walk distance (6MWD) before and 1 year after pulmonary endarterectomy (PEA)

	Before PEA	After PEA	p-value[#]
Functional parameters			
Maximal workload W	109±31	131±42	0.01
V'_{O_2} peak $L \cdot min^{-1}$	1.24±0.36	1.54±0.26	0.01
V'_{O_2} peak % pred	64±16	81±22	0.02
Maximal heart rate $beats \cdot min^{-1}$	142±23	133±30	0.13
V'_E/V'_{CO_2} at peak	39±2	30±2	0.002
V'_E/V'_{CO_2} slope	38±3	30±4	0.006
Peak oxygen pulse $mL \cdot beat^{-1}$	10±2	12±3	0.02
CAMPHOR scores			
Total score	23 (14–33)	6 (2–4)	<0.001
Symptoms	8 (4–12.5)	2 (1–3)	0.001
Activity	8 (4–9.5)	3 (0.5–6)	0.001
Quality of life	7 (3.5–12)	2 (0.5–3)	0.002
6MWD m	437±105	498±64	0.2

Data presented as mean±SD or median (interquartile range), unless otherwise stated. V'_{O_2}: oxygen uptake; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production. #: p<0.05 considered significant.

the upper limit of normal under exercise, and 3) patients showed improved ventilatory efficiency, increased exercise tolerance and improved quality of life.

Recent studies on CTED by TABOADA *et al.* [9] and by VAN KAN *et al.* [10] reported the beneficial effect of PEA on CPET parameters, WHO Functional Class, CAMPHOR scores and symptoms. There was a significant improvement in the total score of the CAMPHOR questionnaire from 40 at baseline to 11 at 6 months and this improvement was sustained at 1 year [9, 10]. MPAP was reduced from 21 mmHg at baseline to 18 mmHg 6 months after PEA and PVR decreased from 164 to 128 $dyn \cdot s \cdot cm^{-5}$. VAN KAN *et al.* [10] reported further that 1 year after PEA the oxygen pulse had increased, whereas both peak heart rate and the heart rate response during exercise had decreased. In addition, V'_E/V'_{CO_2} both at the anaerobic threshold and at peak exercise had decreased, without a concomitant change in maximal ventilation [10]. However, exercise RHC evaluations before and after PEA were not reported in these two publications on CTED.

We were able to demonstrate similar improvements in these values (table 3) as well as improvements in exercise pulmonary haemodynamics (table 2) after PEA measured by RHC. Therefore, exercise RHC in CTED patients seems to provide a further diagnostic option in terms of possible treatment decisions.

Furthermore, we found a significant decrease in PVR at rest and during exercise after surgery. In addition, pulmonary arterial compliance, which is considered as an independent predictor of exercise capacity in CTEPH patients, was also improved 1 year after PEA [33]. Along these lines, CLAESSEN *et al.* [34]

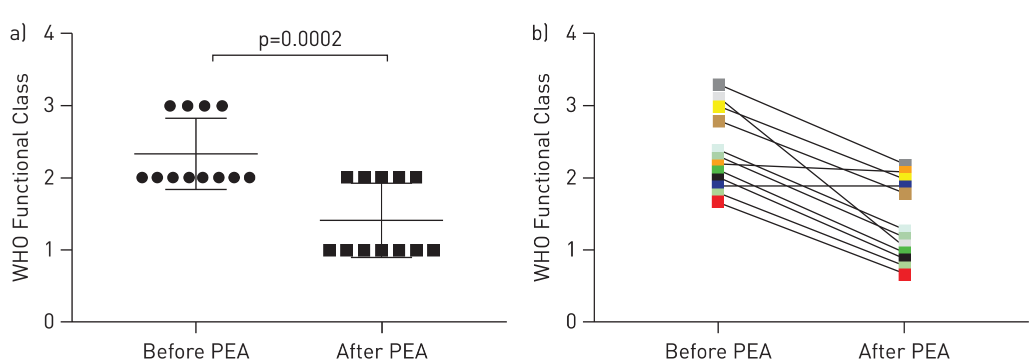


FIGURE 4 Changes in World Health Organization (WHO) Functional Class of 12 patients before and 1 year after pulmonary endarterectomy (PEA). a) Scattered dot plot of the distribution of WHO Functional Class showing mean±SD before and after PEA. b) Individual changes in WHO Functional Class before and after PEA.

emphasised that the MPAP/CO slope and C_{pa} are sensitive measures of resistive and pulsatile pulmonary vascular function.

These findings highlight the importance of exercise RHC in the diagnosis and treatment of patients with CTED [13, 15, 16].

Definition of exercise pulmonary hypertension

CTED patients do not fulfil the definition of pulmonary hypertension. Nevertheless, exercise-based examinations reveal their impaired ability to sufficiently increase their oxygen supply.

From recent data and reflections [9, 13–15, 20], a reasonable definition of exercise pulmonary hypertension should contain TPR values or MPAP/CO slopes >3.0 WU. Thus, for MPAP >30 mmHg, CO should be <10 $L \cdot min^{-1}$. However, there are still several potential confounders (*e.g.* influence of age, workload, distribution of obstructions and training) that may have an influence. In our study, nine out of 12 patients fulfilled the aforementioned criteria, as they had a TPR and MPAP/CO slope >3.0 WU before surgery, and five patients even had slopes >4.0 WU (figure 2). The mean TPR as well as the mean slope (figure 3) were 3.6 WU, which lies above the proposed upper limit of normal. Interestingly, in all patients but one the slope decreased to <3.0 WU after PEA, whereas TPR was >3.0 WU in three patients. Thus, the mean TPR was reduced to 2.7 WU and using the proposed criteria, nine patients had no "exercise pulmonary hypertension" 1 year after surgery. The mean slope 1 year after surgery was significantly reduced to 2.3 WU and 11 patients had a slope <3.0 WU 1 year after surgery.

Cardiopulmonary exercise tests

In CTEPH, as in pulmonary arterial hypertension, ZHAI *et al.* [35] demonstrated that the ventilatory efficiency is impaired and highlighted that for CTEPH there was no correlation to the functional classes; however, no CTED patients were included in their report. DONAHOE *et al.* [7] demonstrated increased ventilatory equivalents for carbon dioxide at anaerobic threshold and peak exercise similar to the results for our patients, but no post-operative data exist. One case report of CTED described improvements in right ventricular performance and ventilatory efficiency following PEA, but no exercise RHC data were mentioned [36]. Recently, it was shown by HELD *et al.* [37] that CPET is a valuable diagnostic tool for the detection of CTED/CTEPH in patients with suspected pulmonary hypertension but normal echocardiography, and that individual CPET parameters can help to distinguish between CTEPH patients and controls. Our results of CPET (table 3) are in line with the improved haemodynamic response obtained from exercise RHC. At 1 year after PEA, patients significantly increased their maximal workload, peak oxygen uptake and peak oxygen pulse. VAN KAN *et al.* [10] also reported CPET data from CTED patients but did not observe significant differences before and after PEA. However, they stated that V'_E/V'_{CO_2} at peak and at the anaerobic threshold as well as the V'_E/V'_{CO_2} slope significantly decreased 1 year after PEA. We observed the same significant decreases in ventilatory equivalents and V'_E/V'_{CO_2} slopes after PEA, which were restored to normal or at least near-normal values.

This improvement in quality of life and exercise tolerance is further demonstrated in marked decreases in scores in all CAMPHOR subcategories. However, since the long-term survival of CTED patients might be excellent without PEA, the indication for surgery in these patients must be assessed individually, and must take into account their expectations and acceptance of risk [38].

Relevance of exercise RHC

Our data confirm the clinical relevance of the assessment of pulmonary haemodynamics during exercise and are in line with the new concept of exercise pulmonary hypertension. There was an improvement in haemodynamics after PEA and there was no excessive rise in MPAP during exercise except for one patient with a high PAWP.

Since our data show that 1 year after surgery the means of TPR and MPAP/CO slopes decreased to <3.0 WU within CTED patients, the new definition of exercise pulmonary hypertension seems meaningful and should be applied. Recently, KOVACS *et al.* [20] reported exercise data from a study including 141 patients of whom 32 had borderline PAP elevation (MPAP 21–24 mmHg). The reasons for applying RHC were exertional dyspnoea that could not be explained by heart or lung disease, or suspected pulmonary hypertension due to pulmonary hypertension-associated diseases such as collagen vascular disease or myelodysplastic syndrome. KOVACS *et al.* [20] showed that during exercise, the MPAP/CO slope in patients with borderline pulmonary hypertension was significantly steeper (5.2 WU) than in patients with resting MPAP <21 mmHg (3.2 WU). This was accompanied by a higher mortality in the borderline group. DONAHOE *et al.* [7] reported one of 22 CTED patients with progression to CTEPH requiring lung transplantation, suggesting a realistic risk of worsening. However, larger studies providing evidence for the prognostic relevance of exercise pulmonary hypertension in CTED are needed.

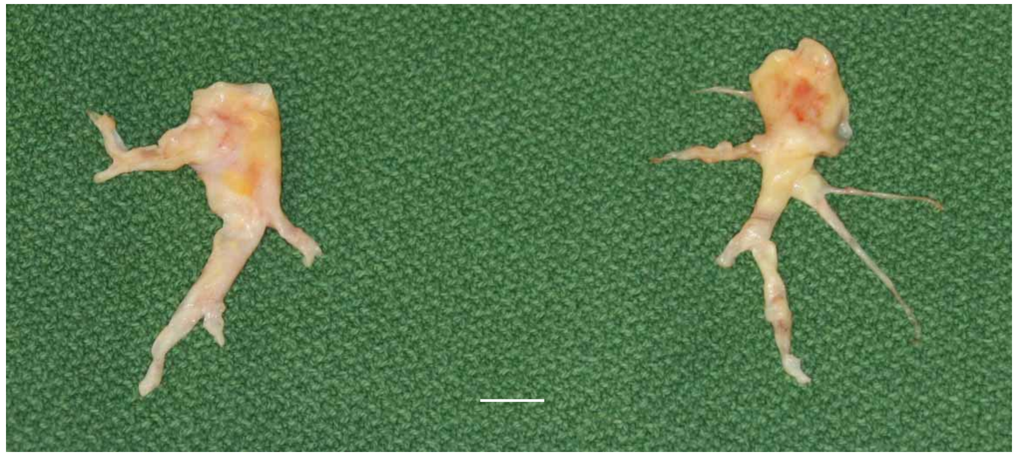


FIGURE 5 Pulmonary endarterectomy specimens of a patient with chronic thromboembolic disease. Scale bar: 1 cm.

Limitations

There are several limitations of the present study. The number of patients included was low, there was no comparative cohort of patients with CTED who were treated conservatively and RHC was performed at only two time-points. A major concern that should also be noted is the fact that we offer a complex operation to patients who experience symptoms only during exercise. Even when PEA is performed at an expert centre [1, 32], there remains a considerable perioperative risk and it is debatable whether surgery should be offered to these patients. However, given their significant symptoms in the context of an abnormal haemodynamic response during exercise, we offered surgery because these patients complain about their unacceptable quality of life. The post-operative course was uneventful in all patients but one, who developed seizures in the early post-operative phase after re-do surgery. Fortunately, the patient completely recovered after a prolonged hospital stay. However, all patients who had complained about their daily physical shortcomings showed significantly improved physiological responses upon exercise after PEA, which translated to a better or normalised quality of life. Therefore, in carefully selected patients with symptomatic CTED, treatment by PEA appears to be a reasonable option, but should only be performed at expert centres (figure 5) [39].

Conclusions

Patients with CTED showed an excessive rise in MPAP and steep slopes of the MPAP/CO relationship during exercise RHC in combination with poor performance in CPET. The mean values of TPR and MPAP/CO slopes were >3.0 WU, but after successful PEA surgery the haemodynamic response improved significantly, and the means of TPR and MPAP/CO slopes were 2.7 and 2.3 WU, respectively, which is clearly below the proposed upper limit of normal. These results were accompanied by better exercise tolerance and quality of life.

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Right ventricular adaptation to pulmonary pressure load in patients with chronic thromboembolic pulmonary hypertension before and after successful pulmonary endarterectomy - a cardiovascular magnetic resonance study

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Abstract

Background: The aim of the study was to characterize RV adaptation to varying loading conditions in patients with chronic thromboembolic hypertension (CTEPH) before and after pulmonary endarterectomy (PEA). Nearly 4% of patients with pulmonary embolism develop CTEPH. PEA offers a cure with excellent outcome. By use of cardiovascular magnetic resonance (CMR) combined with hemodynamic measurements pulmonary arterial elastance ($E_{a\text{-}pulm\_i}$), end-systolic right ventricular elastance ($E_{es\text{-}RV\_i}$) and ventriculo-arterial coupling ($E_{a\text{-}pulm\_i}/E_{es\text{-}RV\_i}$) can be studied before and after PEA.

Methods: Sixty-five patients (mean age 41 ± 12 years, 28 female) underwent CMR pre- and post-PEA. Ejection fraction (EF), end-diastolic (EDV_i), end-systolic (ESV_i), and stroke (SV_i) volumes were indexed for body surface area. $E_{a\text{-}pulm\_i}$ was calculated as pulmonary artery mean pressure (mPAP)/SV_i, and $E_{es\text{-}RV\_i}$ as mPAP/ESV_i.

Results: mPAP decreased from 47 ± 12 to 25 ± 9 mmHg, p =0.0001. $E_{a\text{-}pulm\_i}$ was increased before PEA and normalized afterwards (2.8 ± 2.1 vs. 0.85 ± 0.4 mmHg/ml/m^2, p =0.0001). $E_{es\text{-}RV\_i}$ was depressed before and after PEA (0.72 ± 0.27 vs. 0.66 ± 0.3 mmHg/ml/m^2, p =0.13). EF improved from 25 ± 12% to 46 ± 10%, p =0.0001, because ventriculo-arterial coupling was restored (4.2 ± 3 vs. 1.4 ± 0.6, p =0.0001). EDV_i and ESVi mproved significantly (EDV_i 92 ± 32 to 72 ± 23 ml, p =0.0001; ESV_i 69 ± 31 to 41 ± 18 ml, p =0.0001).

Conclusion: RV function is largely determined by afterload and returns to normal once afterload is normalized. This is paralleled by a significant improvement of CMR indices of right ventricular remodelling.

Keywords: Cardiovascular magnetic resonance, Chronic thromboembolic pulmonary hypertension, Pulmonary endarterectomy

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is an important and frequent cause of pulmonary hypertension. The WHO has therefore acknowledged it as an independent entity in the renewed Dana Point Classification [1]. Estimates of its incidence after acute pulmonary embolism vary between 0.5 and 3.8% [2-4]. Detailed epidemiologic data are available from the UK, where dedicated pulmonary hypertension centers are monitored by the National Audit of Pulmonary Hypertenion (NAPH). Per year and per one million population 124 patients were seen, of which 19.2 percent were classified as having CTEPH, in the past annual surveillance period 143 patients underwent pulmonary endarterectomy (PEA) [5]. CTEPH is the only form of pulmonary hypertension that offers a potential cure PEA with excellent long-term results [6,7].

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The changes found in the pulmonary vasculature in CTEPH are a consequence of incomplete thrombus resolution, remodelling of the thrombus, and neoangiogenesis [8]. In later stages of the disease vascular remodelling extends beyond the central vessels and also involves the vascular bed not primarily affected by thrombemboli. At this stage the histopathology of the vasculature resembles that found in idiopathic pulmonary arterial hypertension [9]. Consequently, mean pulmonary arterial pressure (mPAP) and resistance (PVR) rise and are typically on the order of 49 ± 19 mmHg and 1,015 ± 454 dyn*sec*cm^{-5}, respectively, in a surgically treated cohort [6]. This in turn leads to hemodynamic changes and remodelling of the right ventricle (RV). End-systolic and end-diastolic volumes increase while the ejection fraction deteriorates. Furthermore, diastolic properties of both ventricles are affected as diastolic pressures of the RV increase and a leftward shift of the septal wall ensues [10].

Deterioration of RV function can be readily assessed by cardiovascular magnetic resonance (CMR), which has emerged as the gold standard for evaluating RV function as it allows full coverage of the complex geometry of the RV [11-14]. This decline in RV function is preceded by a rise in RV afterload. In the early stages of the disease contractile properties of the RV compensate for this increase in afterload. Once the compensation is insufficient, RV function will quickly decrease.

For a more in-depth understanding of this process it is important to consider arterial load and ventricular performance independently as well as their coupling. $E_{a\text{-}pulm,,}$ the effective pulmonary artery elastance, is a well-validated measure of arterial load; $E_{es\text{-}RV}$ characterizes the effective right ventricular elastance and is a measure of contractiliy. Their ratio $E_{es\text{-}RV}/E_{a\text{-}pulm}$ describes ventriculo-arterial coupling, which should have a value close to 1.0 in order to achieve sufficient energy transfer from the RV to the pulmonary vasculature [15-19].

Traditionally, these parameters have been derived from conductance catheter measurements or simultaneously acquired CMR volumetric and right heart catheter (RHC) data [17]. Both methods are time-consuming, require specialized catheters, and are hence not suitable for clinical routine. Therefore, approximation methods have been proposed that are either completely non-invasive or combine CMR measurements and routine RHC measurements registered outside the MR suite [15,20-22].

In this study of 65 patients who underwent PEA for CTEPH, we combined cine-cardiac CMR data and hemodynamic data available from routine right heart catheterization to study RV adaption to pressure overload and reverse remodelling of the RV before and after surgery.

Although we are not aware of any study directly comparing CMR to Echo with respect to their accuracy of reflecting right ventricular remodelling in terms of volumes and mass, we are convinced that CMR is superior to Echo in this setting. While there are well validated echocardiographic indices of right ventricular function (TEI index, TAPSE etc.) volumetric evaluation of the RV is difficult with echo. Geometric assumptions on which left ventricular volumetric quantification is based, are not valid for the triangular shaped RV. In that respect CMR evaluation of the RV yields additional information not available from echo. D'Armini *et al.* report longitudinal data from CTEPH patients, which show reduced RV volumes after PEA, which are sustained after 12 month. The hemodynamic improvement, they found was paralleled by improved RV volumes and function. However the authors did not link hemodynamic data and CMR measurements.

CTEPH is an excellent setting to study these changes as it behaves like an on/off phenomenon of PH before and after surgery and is therefore the only entity of pulmonary hypertension, that allows to study potential reversal of CMR and hemodynamic indices of RV remodelling.

In this paper we try to establish a link between remodelling and the possible physiological bases for the volumetric changes observed by combining hemodynamic data and CMR indices.

Methods

Patients and ethics

We retrospectivley defined a two year period during which we screened all 159 patients who were referred to and underwent PEA.

Of these Sixty-five consecutive patients completed CMR as part of their perioperative routine workup and were enrolled in this study.

Indication for CMR was at the discretion of both the attending thoracic surgeon and cardiologist and was based on the need for further evaluation of right ventricular function.

Contraindications for CMR and exclusion criteria were renal failure with a glomerular filtration rate below 30 ml/min/1.73 m^2, incompatible metallic implants, known intolerance to gadolinium, and claustrophobia or the unability to lie supine for the duration of the protocol because of dyspnea.

The primary diagnosis of CTEPH was based on right heart catheter measurements, perfusion/ventilation scintigraphy and pulmonary angiography findings. All patients gave written informed consent. The study was approved by the ethics committee of the University of Gießen, Germany.

Hemodynamic background and formulas

Elastance describes the change in pressure for a given change in volume. Hence, effective arterial elastance of the pulmonary artery can be approximated by the following formula [19,20,22]:

$$E_{a-pulm} \approx RVESP/SV \quad (1)$$

where RVESP is the end-systolic pressure of the RV and SV is the stroke volume of the RV. RVESP can be further approximated by [19]

$$RVESP \approx mPAP \quad (2)$$

where mPAP is the systolic pressure of the pulmonary artery measured by routine RHC. Thus, effective arterial elastance can be simplified as

$$E_{a-pulm} \approx mPAP/SV \quad (3)$$

$E_{a\text{-}pulm}$ is a reliable measure of the load faced by the right ventricle during systole and accounts for pulmonary vascular resistance, compliance, and impedance, and thus also includes the pulsatile components of arterial load [19,20].

Similarly, $E_{es\text{-}RV}$ characterizes the chamber elastance at end-systole and can be approximated by [19,20]

$$E_{es-RV} \approx mPAP/RVESV \quad (4)$$

where RVESV is the right ventricular end-systolic volume.

In order to provide sufficient energy transfer from the ventricle to the arterial system these properties should be equivalent. The ratio of these parameters, the ventriculo-arterial coupling, is defined as $E_{a\text{-}pulm}/E_{es\text{-}RV}$. Uncoupling describes the situation in which $E_{es\text{-}RV}$ cannot compensate the disproportionate rise of $E_{a\text{-}pulm}$, and rapid deterioration of RV function ensues [19]. $E_{a\text{-}pulm\_i}$ and $E_{es\text{-}RV\_i}$ as well as $E_{a\text{-}pulm}/E_{es\text{-}RV\_i}$ were indexed for body surface area (BSA).

Cardiac MRI (CMR)

Volumetric measurements of right ventricular function were performed in a standard fashion by cine CMR covering the RV in short-axis slices from base to apex. Typical sequence parameters were TE 1.5 ms, TR 38.8 ms, 13 segments, 1.6 × 2.2 mm in-plane resolution, flip angle 70°, bandwidth 930 Hz/px, slice thickness 8 mm, interslice gap 2 mm.

Endocardial and epicardial contours were drawn on the RV to determine end-diastolic (EDV), end-systolic (ESV) and stroke (SV) volumes as well as RV myocardial mass (RVMASS) and ejection fraction (EF) using CAAS Software (Pie Medical, Maastricht, the Netherlands). Trabeculations were excluded from the myocardium. All volumetric parameters were normalized for BSA (EDV_i, ESV_i, $RVMASS_i$, SVi). Median time between preoperative CMR and surgery was 1 day (IQR 1- 3). Median time between postoperative CMR and surgery was 12 days (IQR 11-12).

Right Heart Catheter Measurements (RHC)

RHC measurements were performed using standard Swan Ganz catheters introduced via 6 F sheaths through the internal jugular, subclavian, or femoral vein. Measurements were obtained from routine RHC procedures during the preoperative evaluation and postoperative monitoring on the intensive care unit, median time difference between RHC and CMR preoperatively was 43 days (IQR 36 - 56) and median time between postoperative RHC and postoperative CMR was 11 days (IQR 10 - 11). Patients were not under therapy with vasoactive agents during postoperative RHC measurements.

Statistics

The Shapiro-Wilk test was used to test the data for normality. Metric values are presented as means ± SD, and counts are presented as absolute frequencies and percentages. Student's t-test for paired data was used to test for significant differences between pre- and postoperative values. A chi-square test was used to compare count variables. An alpha error less than 0.05 was accepted as significant. All tests were computed using STATA11 (StataCorp, College Station, Texas, USA).

Results

Of the sixty-five consecutive patients enrolled in the study, 28 were female, the mean age was 56.7 ± 16 years, and the mean BSA was 1.96 m^2, the majority of patients was NYHA class III, 6 minute walking distance was 386 ± 116 before surgery and 399 ± 120 after surgery (Table 1). mPAP was markedly increased before PEA and significantly dropped after surgery (47 ± 12 vs. 25 ± 9 mmHg, p =0.0001). RV afterload, as represented by the effective arterial elastance $E_{a\text{-}pulm\_i}$, was pathologically increased before PEA and decreased to near normal values after PEA (2.8 ± 2.1 vs. 0.85 ± 0.4 mmHg/ml/m^2, p =0.0001).

There was a lower, but not significantly lower right ventricular elastance $E_{es\text{-}RV\_i}$ after surgery, with only marginally changed absolute values (0.72 ± 0.27 vs. 0.66 ± 0.3 mmHg/ml/m^2, p =0.13). Consequently, there was marked ventriculo-arterial uncoupling $E_{a\text{-}pulm}/E_{es\text{-}RV\_i}$ before PEA, which significantly improved to near normal values after surgery (4.2 ± 3 vs. 1.4 ± 0.6, p =0.0001) compare Figure 1.

The ejection fraction EF was severely depressed before PEA and significantly improved afterwards (25 ± 12 vs. 46 ± 10%, p =0.0001). Right ventricular volumes (EDV_i and ESV_i) significantly decreased after PEA (92 ± 32 vs. 72 ± 23 ml/m^2, p =0.0001; 69 ± 31 vs. 41 ± 18 ml/m^2, p =0.0001, respectively). Conversely, SV_i improved significantly after PEA (22 ± 10 vs. 32 ± 9 ml/m^2, p =0.0001). $RVMASS_i$ was increased before PEA and decreased significantly afterwards but was not clinically relevant (32 ± 9 vs. 30 ± 9 mg/m^2, p =0.03). Ea_pulm_i was well correlated

Table 1 patient characteristics, remodelling and hemodynamic parameters

	Before PEA	After PEA	p value
Mean age (years)	56.7 ± 16		
Female gender (%)	28(43)		
BSA (m^2)	1.96 ± 0.22		
NYHA class II(%)	7(11)		
NYHA class III(%)	48(74)		
NYHA class IV(%)	10(15)		
6 minute walking distance	386 ± 116	399 ± 120	0.48
mPAP (mmHg)	47 ± 12	25 ± 9	0.0001
PVR (dyn*sec/cm^5)	531 ± 176	331 ± 278	0.01
PCWP mmHg	8.7 ± 3.7	10.7 ± 5.7	0.19
CO (l/min)	4.7 ± 1.5	4.6 ± 1.3	0.7
EDVi (ml/m^2)	92 ± 32	72 ± 23	0.0001
ESVi (ml/m^2)	69 ± 31	41 ± 18	0.0001
SVi (ml/m^2)	22 ± 10	32 ± 9	0.0001
RVMASSi (ml/m^2)	32 ± 9	30 ± 9	0.03
EF (%)	25 ± 12	46 ± 10	0.0001
$E_{a\text{-pulm\_i}}$ (mmHg/ml/m^2)	2.8 ± 2.1	0.85 ± 0.4	0.0001
$E_{es\text{-RVi}}$ (mmHg/ml/m^2)	0.72 ± 0.27	0.66 ± 0.3	0.13
$E_{a\text{-pulm}}/E_{es\text{-RV}}$	4.2 ± 3	1.4 ± 0.6	0.0001

Hemodynamic and volumetric results before and after PEA.

with mPAP (r =0.5499, p =0.0001) preoperatively and postoperatively Ea_pulm_i vs. mPAP (r =0.584, p =0.0004) compare Figure 2.

Compare Table 1 for an overview of the results.

Discussion

In contrast to pulmonary hypertension of other etiologies, CTEPH is potentially curable. After successful PEA, pulmonary vascular hemodynamics can return to normal [6]. Previous studies have shown that the RV has the extraordinary ability to undergo reverse remodelling after PEA, despite severely depressed function before surgery [23,24]. To the best of our knowledge this is the first study that examines RV adaptation to increased RV afterload in patients with CTEPH.

In combination with routine hemodynamic data, CMR offers the possibility to independently study RV function, remodelling, afterload, and contractile properties. Using this approach, we sought to determine how the RV adapts to increased afterload and what role RV afterload plays in the reverse remodelling of the RV.

Several methods have been proposed to quantify afterload without the use of conductance catheters for the right as well as the left ventricle, some even completely non-invasively [15,16,20,22,25]. The simplified method of calculating $E_{a\text{-pulm\_i}}$ and $E_{es\text{-RV\_i}}$ from mPAP and volumetric measurements seemed most reasonable to us, as it was simple to calculate and hemodynamic data were readily available over a long period postoperatively. Also, it was found to correlate well with PVR and complex methods to quantify E_a by several authors [15,20,22]. The negligence of the pulmonary capillary wedge pressure tends to overestimate $E_{a\text{-pulm}}$, but as we performed a longitudinal study, examining the same patients before and after PEA, this seemed irrelevant.

We found markedly increased pulmonary arterial load $E_{a\text{-pulm\_i}}$ before PEA that normalized after surgery. Data on normal values for $E_{a\text{-pulm\_i}}$ and RV volumetric parameters are sparse. On the basis of a normal value for mPAP of 10 to 20 mmHg and a stroke volume index of 55 ± 9 ml[14], a normal $E_{a\text{-pulm\_i}}$ can be estimated as ≈ 0.3 mmHg/ml/m^2. Consequently, the values of arterial load that we found were almost 9-fold higher than this calculated normal limit. These values are higher than published by Sanz *et al.* [20], who found an $E_{a\text{-pulm\_i}}$ of 0.88 in a cohort of 124 PH

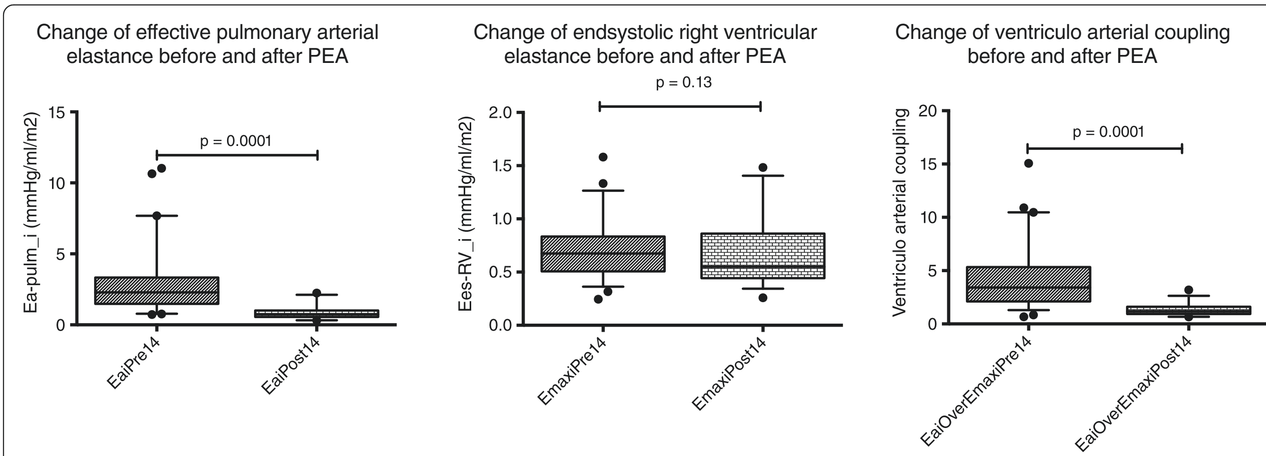

Figure 1 Change of pulmonary arterial load, RV contractile state and ventriculo-arterial coupling. Because arterial load decreases post-PEA, ventriculo-arterial coupling is restored despite a continuously depressed contractile state.

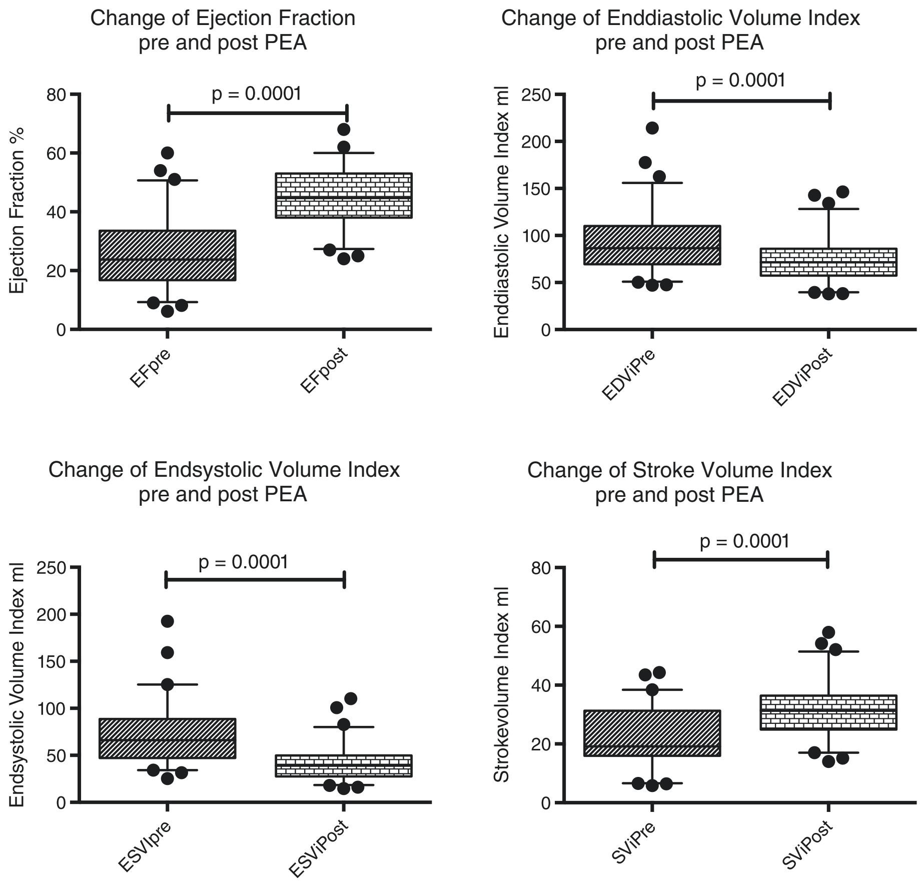

Figure 2 Change of ejection fraction and volumes. The RV shows reverse remodelling as early as 10 days post-PEA.

patients of varying etiology and a similar mPAP (42 mmHg); however, only 3 patients of this cohort had CTEPH and ejection fraction as well as stroke volumes were much lower in our cohort, hence $E_{a\text{-}pulm\_i}$ higher (RVEF 37% as compared to our 25% and 35.5 ml/m^2 as compared to our 22 ml/m^2). Kühne *et al.* reported a similar $E_{a\text{-}pulm}$ of 2.7 in a series of 6 patients with an mPAP of 56 mmHg, which was derived from simultaneously measured pressure-volume curves [17]. This value is slightly higher than that of our cohort; however, mPAP was also higher than that of our cohort by 13 mmHg. Conversely, Amin *et al.* found an $E_{a\text{-}pulm}$ (not normalized for BSA) of 0.75, which is lower than our values by the same degree, as mPAP in their study group was lower and stroke volumes were higher [22]. Thus, within the context of other published studies, our measurements seem plausible and demonstrate markedly increased RV afterload before PEA. Consequently, we also observed the typical remodelling of the RV with increased $RVMASS_i$ and greater volumes.

The contractile state of the RV was depressed before and after PEA, with a trend towards lower values after surgery and only marginally changed absolute values. It is a typical response of the heart to increase E_{es} in the face of rising afterload, which has been intensively studied in the systemic circulation. This is frequently observed in hypertensive heart disease, where E_{es} compensates for increasing loading conditions until E_a increases disproportionately and E_{es} cannot rise accordingly [26-29]. In a swine model of repetitive acute pulmonary embolism, Kerbaul *et al.* found increasing $E_{es\text{-}RV}$ in the initial period after the first embolism, which later decreased with rising afterload and reached levels below the initial value [30]. $E_{es\text{-}RV\_i}$ values reported here are in good agreement with other studies [20,31]. Surprisingly $E_{es\text{-}RV\_i}$ did not improve immediately after surgery. However, it is important to note that ESV_i decreased dramatically after PEA and that the computation of $E_{es\text{-}RV\_i}$ is based on a much smaller ESV_i. It is therefore essential to study $E_{es\text{-}RV\_i}$ in relation to $E_{a\text{-}pulm\_i}$.

The effective ventriculo-arterial coupling between pulmonary arterial vasculature and RV expressed as the ratio $E_{a\text{-}pulm\_i}/E_{es\text{-}RV\_i}$ was markedly increased before PEA, indicating severe uncoupling. However, RV afterload dropped by 70% after PEA, and thus ventriculo-arterial coupling was restored despite the fact that contractile properties were still compromised, reflecting sufficient energy transfer from the RV to the pulmonary arterial system. The most efficient energy transfer was found to be at an E_a/E_{es} ratio of 0.6 to 1.2 for the left ventricle [27,32-34]; for the RV data on normal values are sparse. Kühne *et al.* reported an E_a/E_{es} ratio of 0.52 for controls and 0.91 for PH patients (in the original work E_{es}/E_a was reported; this is the inverse) [17], Sanz *et al.* reported an $E_a/E_{es\ ratio}$ of 0.37 for controls and 1.26 for PH patients [20]. Hence, in light of data from these other publications, preoperative values of 4.2 indicate marked uncoupling of right ventricle and pulmonary artery. The postoperative value of 1.4 can probably be considered to be a significant improvement towards normal ventriculo-arterial coupling.

Essentially, PEA reverses the increased RV afterload like an on/off phenomenon in these CETPH patients. Our data show that the RV function is largely afterload dependent and that it can return to normal once normal pulmonary arterial afterload decreases and ventriculo-arterial coupling of the RV is restored. This is in good agreement with data of Kerbaul *et al.*, who showed in an animal model of pulmonary arterial embolism that levosimendan is superior to dobutamine in improving ventriculo-arterial coupling because it not only increases E_{es} (as dobutamine does) but sufficiently lowers E_a. Although contractility was more enhanced under dobutamine treatment, ventriculo-arterial coupling was better under levosimendan because afterload was nearly half the value found under dobutamine [30,35].

The $E_{a\text{-}pulm\_i}/E_{es\text{-}RV\_i}$ ratio and the ejection fraction showed a curvilinear relationship, with a steep decline of the ejection fraction in the early phase of uncoupling (compare Figure 3).

Hemodynamic changes were paralleled by reverse remodelling of RV volumes and an improvement in the ejection fraction. ESV_i decreased by 40% while RV-EF almost doubled. This has been described previously [24,36]; however, it is remarkable that the RV maintains the ability to undergo reverse remodelling despite its severely reduced function before PEA. Of note, the RV was also considerably hypertrophied, suggesting myocyte hypertrophy as well as interstitial adaptation are involved. Nevertheless, RV volumes and EF values returned to almost normal. As RV afterload and ventriculo-arterial coupling changed most substantially, these parameters seem to have the pivotal role in remodelling and reverse remodelling. The instant remodelling of the RV also suggests that we did not simply measure a short-term hemodynamic effect but a lasting restoration of ventricular and pulmonary arterial function.

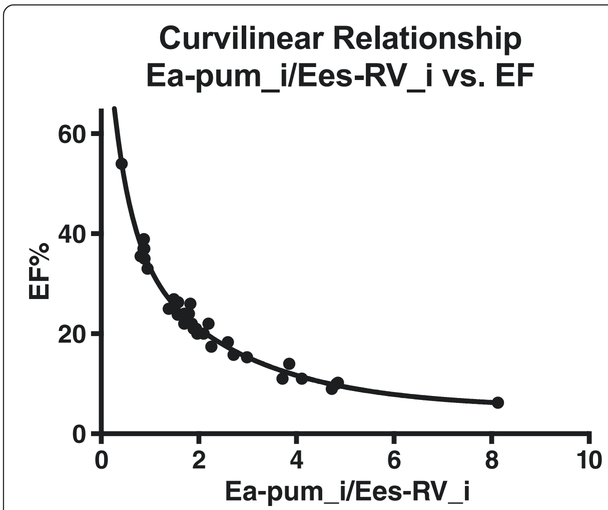

Figure 3 Curvilinear relationship between ventriculo-arterial coupling and EF. Once uncoupling between RV and pulmonary vasculature has occurred, the EF declines steeply.

Limitations

The inferences made in this study are based on surrogate markers and not on the gold standard of conductance catheters. However, these markers have been thoroughly validated in previous studies [20,22,30]. This is the largest cohort of CTEPH patients published to date and all parameters have been evaluated in a longitudinal setting, allowing conclusions from our data about the general physiology of the right ventricle.

In this paper we have looked at remodelling in terms of changed RV-volumes, mass and ejection fraction and a possible physiological basis for these changes. These findings do not allow to make inferences to histological remodelling. With the advent and further improvement of T1 Mapping techniques, we might be able to correlate our findings with interstitial remodelling in the future.

Conclusion

By combining readily available data from routine RHC measurements and CMR volumetric data in CTEPH patients, we were able to quantify RV contractile properties and pulmonary arterial afterload. We demonstrated that RV function is largely determined by afterload and returns to normal once ventriculo-arterial coupling and effective pulmonary arterial elastance are restored by PEA.

This makes CMR in combination with simple RHC measurements an ideal tool to study RV properties in the follow up of PH patients in the clinical and study setting.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
AR contributed to the design of the study, acquired and analyzed the data and drafted the manuscript. JR, WK, and JB contributed to data acquisition, design and analysis of the data and revised the manuscript. HM, HN, CL, HG, GK and CH contributed to the idea and design of the study, analysis of the data and revision of the manuscript. TK, SG and EM performed surgery and contributed to the design and idea of the study from the surgeons perspective and revised the manuscript. All authors read and approved the final manuscript.

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The effective systematic heparin pre-treatment on thrombus formation on pulmonary artery catheter tips during pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a randomized, double-blind study

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Abstract Pulmonary artery (PA) catheters are routinely used for hemodynamic management in patients with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy (PEA). Tip-associated thrombi are frequently detected and might increase the perioperative risk in these patients. The aim of the study was to investigate the effects of low-dose heparinization before the insertion of the PA catheter on thrombus formation and thrombus weight during PEA surgery. From September 2013 to February 2015, 60 CTEPH patients undergoing PEA were included in the study and randomized into two groups of 30 patients each, including a heparin group (heparin bolus (70 IU per kg body weight) administration before PA catheter insertion) and a control group (pretreatment with placebo). During the PEA procedure the distal part of the PA catheter was drawn out of the PA and thrombus presence and weight were recorded. There were no significant differences in baseline characteristics between the two groups. Twelve patients (20%) had thrombophilic disorders. In the control group, thrombi were detected in 17 patients (57%) with a median thrombus weight of 27 mg (IQR 41). In the heparin group, tip-associated thrombi were found in five patients (17%) with a median weight of 12 mg (IQR 7). There were no bleeding complications in either group. This study demonstrates a high risk of PA catheter-related thrombi in patients with CTEPH. Prophylactic administration of low-dose heparin reduces thrombus formation and thrombus weight without an increased rate of bleeding complications.

Keywords Chronic thromboembolic pulmonary hypertension · Pulmonary endarterectomy · Pulmonary artery catheter · Thrombus · Heparin

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Introduction

Central venous catheters and pulmonary artery (PA) catheters are widely used in the management of high-risk patients in the intensive care setting or during complex surgery. Catheter-associated thrombus formation is a common complication with an incidence reported as high as 12.5 to 29% [1–3]. PA catheters are used for hemodynamic management in patients with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy (PEA). CTEPH is seen as a late onset complication of pulmonary embolism. In its definition, an episode of at least 3 months of anticoagulation is mandatory for the diagnosis [4]. Coagulation disorders [5] including anti-phospholipid-syndrome [6] are frequent in this patient population. During PEA surgery, the former thrombotic material remodeled to scar tissue is dissected from the pulmonary vasculature.

In PEA surgery, a PA catheter is used for the peri- and postoperative monitoring of pulmonary hemodynamics. The catheter is usually placed into the PA before starting extracorporeal circulation and removed on the first postoperative day. During PEA, the right and left central PAs are incised; therefore, the tip of the PA catheter can be inspected.

The aim of the study was to investigate the effects of low-dose heparin administration before insertion of the PA catheter to prevent or reduce tip-associated thrombus formation and to compare the results to the standard protocol of anticoagulation during PEA surgery.

Methods

Selection of patients

From September 2013 to February 2015, 288 patients with suspected CTEPH were referred to our CTEPH center. Patients were assessed for PEA in a multidisciplinary conference by an experienced team, and a total of 179 patients underwent PEA during this period.

All patients included in the study provided written informed consent to participate in the study, and approval of the ethics board (AZ 64/13) was obtained. The investigation was performed in concordance with the principles outlined in the Declaration of Helsinki.

Standard procedure

CTEPH patients are treated with lifelong anticoagulation according to the current guidelines [4]. The local standard is to change to low-molecular weight heparins (LMWH) from vitamin K antagonists 7 days before admission or from non-vitamin K antagonist oral anticoagulants (NOACs) 5 days before admission for a PEA procedure. The last dose of LMWH is administered on the evening before surgery. All patients are treated following the local standard protocol for PEA. A full heparin dose for cardiopulmonary bypass is given with incision of the pericardium. The full heparin dose is calculated based on body weight: 400 IU per kg body weight. Patients are switched to extracorporeal circulation and are cooled to 20 °C. Both PA are incised intrapericardially. The tip of the PA catheter is removed from the pulmonary artery to simplify access for endarterectomy. The endarterectomy is performed during phases of deep hypothermic circulatory arrest. Rewarming is started after closure of the incisions, and thereafter patients are weaned from cardiopulmonary bypass [7].

Study procedures

During the study period, 60 patients were included and randomized. Exclusion criteria were previous sternotomy or cardiac surgery, known heparin-induced thrombocytopenia, and known heparin allergy. Thrombophilic disorders were documented.

Patients were randomized into two groups. The heparin-group comprised patients receiving an intravenous 5-ml low-dose heparin pretreatment (17.5% of the full dose calculated with 400 IU per kg body weight) before PA catheter placement in the pulmonary artery. The remaining 82.5% of the heparin dose was administered after incision of the pericardium. The control group received an intravenous bolus of 5 ml of NaCl 0.9% as a pretreatment and the full dose of heparin according to the current standard after incision. Patients and surgeons were blinded with regard to the pretreatment.

Partial thromboplastin time (PTT), activated clotting time (ACT), anti-factor-Xa-level (anti-Xa), antithrombin 3 (AT3), international normalized ratio (INR), and D-dimers were measured at two time points. Time point 1 (= T1) corresponds to baseline values and time point 2 (= T2) to values after the low-dose heparin or NaCl bolus was administered.

Following the local standard procedure the surgeon inspected the tip of the PA catheter (Swan-Ganz 131F7, Edwards Lifesciences, Irvine, California, USA) for the presence of thrombus (Fig. 1). Identified thrombus was wiped off the catheter tip with a sterile sponge and weighed together with the sponge (KB 3600-2N, Kern und Sohn GmbH, Balingen-Frommern, Germany). Afterwards, the sponge was weighed alone and thrombus weight was calculated.

Outcome measures

The primary endpoint was the difference in thrombus formation between the two groups. Secondary efficacy endpoints were thrombus weight and parameters of anticoagulation: ACT, PTT, anti-Xa, AT3, INR, and D-dimers.

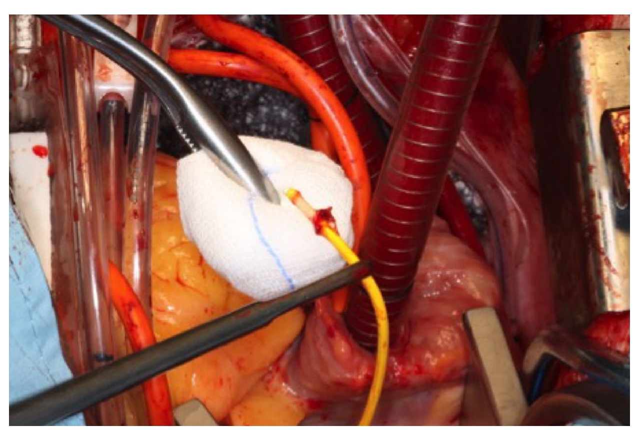

Fig. 1 Intraoperative view of fresh thrombus on the tip of the pulmonary artery catheter withdrawn from the right pulmonary artery

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for normally or non-normally distributed parameters, respectively. Between-group differences were analyzed with Student's *t* test for normally distributed parameters, the Mann–Whitney U test for non-normally distributed parameters, and Pearson's Chi square test with continuity correction for categorical parameters, with $p < 0.05$ considered to be statistically significant.

Results

Clinical characteristics of all patients (30 male, 30 female, mean age 62 years [range 19–85 years]) included in the study are shown in Table 1. Thrombophilic disorders were found in 12 patients (20%: 4 patients in control group, 8 patients in heparin group); 5 had factor V Leiden thrombophilia, 3 had protein S deficiency, 2 had anti-thrombin deficiency, one had anti-phospholipid syndrome, and one had a methylene tetrahydrofolatereductase (MTHFR) gene mutation. In one patient the final diagnosis after histopathological evaluation of the specimen was pulmonary artery sarcoma with in situ thrombosis. There were no peri-operative bleeding complications observed in either group, and there were no significant differences in transfusion rates of erythrocyte concentrates, platelet concentrates, or fresh frozen plasma. After PEA, patients were treated with heparin for 5 days. Long-term anticoagulation was then initiated with vitamin K antagonists in 31 patients (52%) and with NOACs in 29 (48%) according to individual preoperative anticoagulation.

The tip of the PA catheter was located in the right PA in 51 patients (85%). There were no significant differences in the duration of surgical procedures in the two groups: the duration from PA catheter insertion to incision of the pericardium (= D1) was 47 ± 21 min in the control group and 39 ± 16 min in the heparin group ($p = 0.097$) (Table 2). The mean duration from incision of the pericardium to inspection of the PA catheter (= D2) was 74 ± 21 min in the control group and 83 ± 25 min in the heparin group ($p = 0.154$). The mean duration from PA catheter insertion to PA catheter inspection (= D3) was 122 ± 19 min in the control group and 122 ± 31 min in the heparin group ($p = 0.945$). The mean total heparin dose was 31,860 ± 5960 IU in the control group and 33,080 ± 7280 IU in the heparin group ($p = 0.480$).

At T1, there were no significant differences in the two groups in PTT, ACT, anti-Xa, AT3, INR, and D-dimers. At T2, there was a significant difference in PTT, ACT and anti-Xa (Table 2).

In the control group thrombotic material was found on the PA catheter tip in 17 patients (56.7%) with a median thrombus weight of 27 mg (IQR 12 to 53 mg). A thrombus was found in 6 patients (20%) in the heparin group, with a median thrombus weight of 9.8 mg (IQR 4 to 16 mg). Thus, patients in the heparin group had significantly fewer thrombi ($p < 0.001$) of significantly lower weight ($p < 0.001$) compared with patients in the control group (Fig. 2).

Discussion

Central venous catheters are often used in daily clinical practice, and complications due to these catheters, especially thrombus formation and infections, are common and jeopardize patient health [1]. In particular, centrally located catheters exhibit a high risk of thrombus formation [2]. Ducatman et al. described an incidence of 29% for catheter-induced right-heart thrombi in a prospective series of 141 autopsies [3], and Gilon and colleagues demonstrated an incidence of 12.5% in a prospective study of 55 patients [2]. Right-heart thrombi increase the risk of pulmonary embolism. Torbicki et al. reported pulmonary embolism in up to 6% of patients with central venous catheters, and that the presence of right-heart thrombus coincided with an increase in the 3-month mortality from 16 to 29% [1]. The variation in incidences given in the literature is due to differences in patients' characteristics (malignant diseases, coagulopathies), different catheters, and localizations.

Table 1 Patient characteristics

	Control group[a] (n = 30)	Heparin group[a] (n = 30)	p value
Age (years)	63.7 ± 14	60.3 ± 14	0.832
Sex (female/male)	12/18	18/12	0.196
Mean PA pressure (mmHg)	42 ± 12	43 ± 10	0.543
Mean PA occlusion pressure (mmHg)	11 ± 4	11 ± 3	0.816
Cardiac output (l/min)	5.0 ± 1.2	4.6 ± 1.3	0.450
Pulmonary vascular resistance (dyn*sec/cm^5)	617 ± 323	702 ± 471	0.465
WHO functional class	2.9 ± 0.5	2.8 ± 0.6	0.351

[a]All values are shown as mean (±standard deviation) of all 30 patients in each group. *PA* pulmonary artery

Table 2 Outcome measures

	Control group[a] (n = 30)	Heparin group[a] (n = 30)	p value*
Total heparin dose (IU)	31,860 ± 5,956	33,080 ± 7,280	0.480
D1 = duration from PA catheter insertion to full heparin dose administration (min)	47 ± 21	39 ± 16	0.097
D2 = duration from full heparin dose administration to luxation of PA catheter (min)	74 ± 21	83 ± 25	0.154
D3 = duration from PA catheter insertion to luxation (min)	122 ± 19	122 ± 31	0.945
ACT at T1 (sec)	124 ± 11	129 ± 14	0.130
ACT at T2 (sec)	127 ± 13	184 ± 18	<0.001
PTT at T1 (sec)	33 ± 4	34 ± 8	0.300
PTT at T2 (sec)	31 ± 4	193 ± 18	<0.001
Anti-Xa at T1 (IE/ml)	0.29 ± 0.18	0.37 ± 0.22	0.118
Anti-Xa at T2 (IE/ml)	0.25 ± 0.17	1.52 ± 0.32	<0.001
AT3 at T1 (IE/ml)	84 ± 11	84 ± 10	0.884
AT3 at T2 (IE/ml)	81 ± 11	82 ± 9	0.677
INR at T1	1.1 ± 0.1	1.1 ± 0.1	0.785
INR at T2	1.1 ± 0.1	1.2 ± 0.1	0.002
D-dimers at T1 (mg/l)	105 (223)	87 (82)	0.156
D-dimers at T2 (mg/l)	117 (245)	95 (91)	0.075

[a]All values are mean ± standard deviation of all 30 patients in each group with the exception of the D-dimers, which are presented as median [IQR]

*p values are derived from a t-test except the D-dimers, for which a Mann–Whitney U test was applied

PA pulmonary artery, *ACT* activated clotting time, *PTT* partial thromboplastin time, *anti-Xa* anti-factor-Xa level, *AT3* antithrombin 3, *INR* international normalized ratio, *T1* baseline, *T2* after intervention (placebo/heparin)

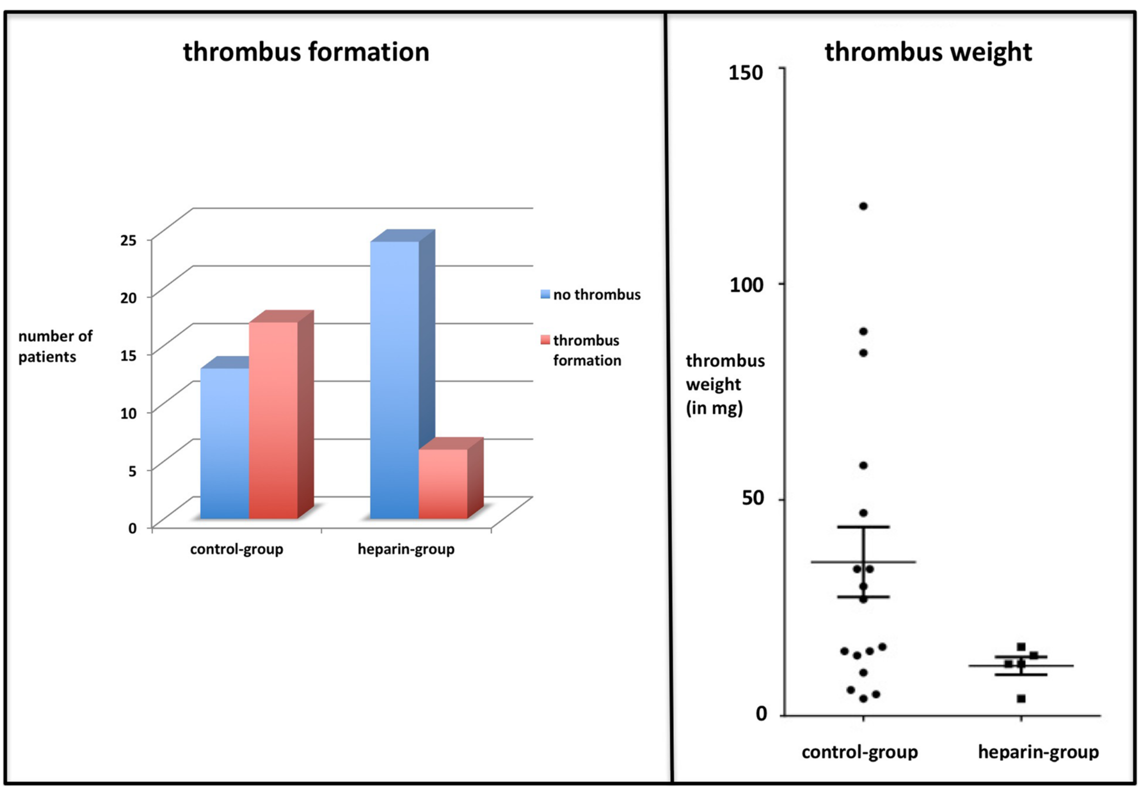

Fig. 2 Thrombus presence and weight in control and treatment groups

PA catheters are widely used to monitor hemodynamics in high-risk patients in intensive care units or during surgery. This study was designed to investigate the effects of low-dose heparinization before PA catheter placement on thrombus formation and thrombus weight in CTEPH patients undergoing PEA. The major findings of the present study are: (1) low-dose heparin pretreatment significantly decreased the number of thrombi at the PA catheter tip; (2) thrombus weight was significantly reduced in patients pretreated with low-dose heparin; (3) heparin pretreatment was not associated with peri-operative bleeding complications.

PEA surgery allows unique, in situ visualization of PA catheter tips. All patients undergoing this operation have CTEPH, a disease that is frequently associated with coagulation disorders. These thrombophilic disorders can be found in up to one-third of CTEPH patients, which is comparable to the 20% incidence in our patient cohort/study population [5]. The participants in our study cannot be directly compared with other patient populations in intensive care units; however, patients with the need for central venous or PA catheters are usually in poor clinical condition with an activated coagulation system and a higher risk of venous thromboembolism [8]. Furthermore, the insertion of a central venous catheter itself induces a hypercoagulable state [9]. In spite of this, the prophylactic use of LMWH to prevent possible catheter-associated thrombus formation is not recommended by the American Society of Clinical Oncology for central venous catheter care in patients with cancer [10].

Our data highlight a significant incidence of thrombus formation at the PA catheter tip in more than half of patients undergoing PEA despite full-dose heparinization 42 min after PA catheter placement. Low-dose heparin administration before PA catheter placement decreased the number of thrombi from 57% (group 2) to 17% (group 1) and the mean thrombus weight from 36 mg (group 2) to 10 mg (group 1). These findings contradict the results of Niers et al. who did not demonstrate a benefit of nadroparin administration for prevention of catheter-related venous thrombosis in patients undergoing chemotherapy for hematologic malignancies [11]. On the other hand, Vegting et al. showed that prophylactic anticoagulation with LMWH or vitamin K antagonists decreased catheter-related thrombosis and occlusion in children with home parenteral nutrition [12]. All published studies showing a heterogeneous patient population with children and adults with and without malignancies challenge the interpretation of the data regarding advice on anticoagulation for patients with central venous catheters. Furthermore, in none of these studies the catheter tip could be directly visualized; therefore, extrapolating previously published results to patients undergoing procedures with PA catheters is not possible.

Although bleeding complications are difficult to monitor in the complex setting of PEA surgery, there were no signs of increased blood loss and postoperative transfusions in the intervention group (group 1).

To the best of our knowledge, this is the first investigation comparing a low-dose heparin pretreatment before PA catheter placement to the standard clinical practice without pretreatment. The findings of the current study have led to a change in our local standard protocol, which now uses low-dose heparin pretreatment before PA catheter insertion for PEA surgery, and may stimulate others to re-evaluate their standard procedures. Further studies are necessary to evaluate thrombus formation in other indications for PA catheters like right heart catheter or monitoring of hemodynamics in severely ill ICU patients.

Limitations

This is a single-center randomized study with small sample size. Our analysis, however, reflects "real-world" CTEPH patients undergoing surgery, and despite the small number of patients a significant difference between groups was detected.

Compliance with ethical standards

Conflict of interest CBW has received speaker fees from Actelion, Bayer AG, BTG, MSD and Pfizer. CL having received lecture honoraria from Abbott, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer – Bristol-Myers Squibb. HG has received support and/or honoraria from Actelion, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Cilag, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, and United Therapeutics/OMT. TR and MA have nothing to declare. EM has received speaker or consulting honoraria from Actelion, Bayer, MSD, GSK, Pfizer and MSD. SG has received speaker fees from Actelion, Bayer, GSK and Pfizer.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Short-term venoarterial extracorporeal membrane oxygenation for massive endobronchial hemorrhage after pulmonary endarterectomy

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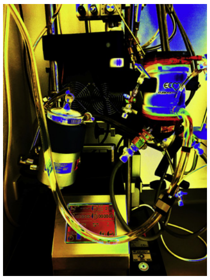
ABSTRACT

Objectives: Pulmonary endarterectomy (PEA) is the only curative treatment option for patients with chronic thromboembolic pulmonary hypertension. Massive endobronchial bleeding that precludes weaning from cardiopulmonary bypass is an often-fatal complication of PEA. The aim of this study was to determine whether short-term extracorporeal membrane oxygenation (ECMO) is a safe and feasible procedure in patients with severe endobronchial bleeding.

Methods: From January 2014 to December 2016, 396 patients (mean age 60 ± 18 years, 54.5% male) underwent PEA in our department. Patients with severe endobronchial hemorrhage at the time of weaning from cardiopulmonary bypass (CPB) were switched to a heparin-coated venoarterial ECMO circuit. After full-dose protamine administration to restore normal coagulation, weaning from ECMO was attempted in the operating room.

Results: In-hospital mortality was 2.3% (9/396 patients). Eight patients (2.0%) developed severe endobronchial bleeding classified as diffuse (n = 6) or localized (n = 2) by bronchoscopy. After reinstitution of CPB and subsequent switch to ECMO, the mean duration of ECMO support was 49 ± 13 minutes, and all 8 patients were weaned successfully from ECMO in the operating theater without further signs of endobronchial bleeding. One patient needed venovenous ECMO support for poor oxygenation 6 hours after surgery. Seven patients were discharged after a prolonged postoperative stay of 17.6 ± 4.1 days. One patient died. This new concept significantly reduced mortality compared with previous (2009-2013) ECMO support ($P = .0406$).

Conclusions: For patients with massive endobronchial bleeding after PEA, the intraoperative switch from CPB to venoarterial ECMO support with full-dose protamine administration is a new and potentially life-saving treatment concept. (J Thorac Cardiovasc Surg 2018;155:643-9)



Extracorporeal membrane oxygenation.

Central Message

Short-term venoarterial extracorporeal membrane oxygenation support is a new and feasible concept for the successful treatment of severe endobronchial bleeding in the operating theater.

Perspective

Pulmonary endarterectomy is the only curative treatment for chronic thromboembolic pulmonary hypertension. Severe endobronchial bleeding is a feared complication of pulmonary endarterectomy. Short-term venoarterial extracorporeal membrane oxygenation support was implemented successfully as a new concept for addressing this serious complication and reducing mortality. This short-term solution avoids further complications linked to longer periods of extracorporeal circulatory support.

See Editorial Commentaries pages 650 and 651.

See Editorial page 641.

Pulmonary endarterectomy (PEA) is the most successful treatment option for chronic thromboembolic pulmonary hypertension,[1-3] and with growing experience, favorable results have been reported.[4-7] The aim of surgery is a complete removal of fibrotic material from pulmonary

Scanning this QR code will take you to a supplemental video for the article.

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Abbreviations and Acronyms

CPB	= cardiopulmonary bypass
ECMO	= extracorporeal membrane oxygenation
PEA	= pulmonary endarterectomy
PVR	= pulmonary vascular resistance

artery branches, leading to an instant reduction of right ventricular afterload and improving right heart function, gas exchange, exercise capacity, and survival. A major risk factor for mortality after PEA is the degree of pulmonary vascular resistance (PVR), especially when it is greater than 1000 dynes·s·cm^{-5}.[8] Patients with predominantly distal disease (thromboembolic disease classification type III) also have a greater mortality due to a greater risk of postoperative residual pulmonary hypertension.[9]

Severe complications of PEA surgery include reperfusion injury of the lungs with poor oxygenation capability, persistent pulmonary hypertension, right ventricular failure, and endobronchial bleeding.[10] These complications early after surgery account for most of the in-hospital deaths, whereby intraoperative endobronchial bleeding is one of the most critical and fatal complications.

Extracorporeal membrane oxygenation (ECMO) is a well-established technique for providing emergency gas exchange and circulatory support for patients with respiratory and/or circulatory failure. ECMO is provided as a venovenous[11] or a venoarterial[12] system. Particularly for endobronchial bleeding complications during PEA, ECMO support is reported to be a life-saving tool that can be used for several days until bleeding stops followed by weaning from the system.[13,14] Prolonged venoarterial ECMO support, however, fosters further complications, such as thrombocytopenia, systemic embolization, and rethrombosis of the pulmonary vasculature due to the reduced pulmonary arterial flow. Therefore, to reduce these complications, short-term ECMO support is preferable.

One benefit of using ECMO systems with heparin-coated circuits instead of conventional extracorporeal circulatory support during PEA surgery is the fact that blood coagulation can be completely restored with protamine with a minimal risk of clot formation inside the oxygenator. In 2014, we changed our treatment concept for severe endobronchial bleeding to one that uses short-term venoarterial ECMO support with immediate restoration of normal coagulation. Here we report the first use of short-term venoarterial ECMO support for the treatment of severe endobronchial bleeding after PEA (Video 1).

PATIENTS AND METHODS

Patients

From January 2014 to December 2016, 396 patients underwent PEA at our center. This collective consisted of 216 men (54.5%) and 180 women (45.5%) with a mean age of 60 ± 18 years. All data were collected prospectively in a dedicated database. The data collection was approved by the institutional ethics committee and conducted in keeping with the Declaration of Helsinki. All patients provided written informed consent.

Surgical Techniques

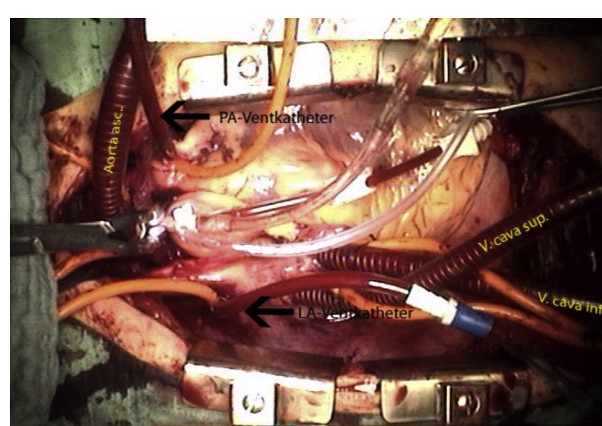
PEA was performed via the standard technique described by the San Diego group using median sternotomy with deep hypothermic circulatory arrest.[15] Bronchoscopy was performed after rewarming of the patient, who was subsequently slowly weaned from the cardiopulmonary bypass (CPB); the operation was concluded in the usual manner.

ECMO Management

The decision for venoarterial ECMO support was made immediately after severe endobronchial hemorrhage (ie, >250 mL) was confirmed by bronchoscopy. After the detection of endobronchial bleeding, the patient was returned immediately to CPB and the switch to venoarterial ECMO was planned. If localized bleeding was present, the affected bronchus was blocked by the application of fibrin glue under bronchoscopy (this occurred in 2 cases). Units of fresh-frozen plasma, platelets, and red blood cells were ordered. The patients were switched directly from CPB to venoarterial ECMO support by clamping the arterial and venous cannulas, disconnecting the CPB tubes, and connecting the tubes of the ECMO system. The flow of the venoarterial ECMO system was restored immediately to the calculated cardiac output, and, if necessary, additional volume (crystalloids and fresh-frozen plasma) was added. Under ECMO support, the patients received a full dose of protamine to restore normal blood coagulation. Positive end-expiratory pressure was increased to 15 mm Hg, and the ventilation frequency was increased to 15 to 20 breaths per minute. After a short stabilization period, the next attempt to wean the patient from the ECMO support was initiated.

The ECMO Circuit

The circuit consists of a preassembled tubing set including the oxygenator and an additional centrifugal pump head. In all cases, the ECMO ADULT oxygenator (Eurosets, Medolla, Italy) was used, and the centrifugal pump head was a Revolution 5 (Sorin S.p.A., Milan, Italy). The oxygenator has a filling volume of 225 mL and a gas exchange area of 1.81 m^2. The maximum blood flow rate is 7 L/min. The pump has a filling volume of 57 mL and can operate at up to 5 L/min blood flow. Including the tubes, the ECMO system



VIDEO 1. Presentation of the short-term extracorporeal membrane oxygenation concept including a video of pulmonary endarterectomy surgery. Video available at: http://www.jtcvsonline.org/article/S0022-5223(17)31962-1/fulltext.

TABLE 1. Hemodynamic characteristics of all patients undergoing pulmonary endarterectomy

Characteristics	
n	396
Age, y	60 ± 18
Male, n (%)	216 (54.5)
Pre-CPB sPAP, mm Hg	70 ± 23
Pre-CPB mPAP, mm Hg	45 ± 13
Pre-CPB dPAP, mm Hg	29 ± 16
Pre-CPB PVR, dynes·s·cm^{-5}	620 ± 320
Pre-CBP SVR, dynes·s·cm^{-5}	1220 ± 440
Pre-CPB CVP, mm Hg	10.9 ± 4.7
Pre-CPB CO, L·min^{-1}	4.8 ± 2.0
Jamieson type	I (34.5%), II (34.2%), III (31.3%)

Values shown are n (%) or mean ± SD. *CBP*, Cardiopulmonary bypass; *sPAP*, systolic pulmonary arterial pressure; *mPAP*, mean pulmonary arterial pressure; *dPAP*, diastolic pulmonary arterial pressure; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance; *CVP*, central venous pressure; *CO*, cardiac output.

has an overall filling volume of 600 mL. A crystalloid solution (Jonosteril; Fresenius, Bad Homburg, Germany) was used for system priming. The oxygenator and the tubes are coated with phosphorylcholine.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation. Univariate comparisons between patients were performed with a χ^2 test or Fisher exact test, where appropriate, for dichotomous variables; the Student *t* test or Mann-Whitney *U* test was applied for continuous variables. Statistical tests were 2-sided; differences in which *P* was less than .05 were considered significant. GraphPad Prism version 6.00 for Windows was used for the data and statistical analyses (GraphPad Software, La Jolla, Calif; www.graphpad.com).

RESULTS

Table 1 shows demographics, hemodynamic characteristics, and Jamieson classification of all 396 patients who underwent PEA. The mean age was 60 ± 18 years with a near-equal sex distribution of 216 men (54.5%) and 180 women (45.5%). Mean pulmonary arterial pressure was 45 ± 13 mm Hg, cardiac output 4.8 ± 2.0 L/min, PVR 620 ± 320 dynes·s·cm^{-5}, and central venous pressure 12.3 ± 4.2 mm Hg. Regarding the thromboembolic disease type, 34.5% of the patients had type I, 34.2% type II, and 31.3% type III.

In-hospital mortality of the overall cohort was 2.3% (9/396 patients). A total of 16 patients needed ECMO support after surgery (4.0%). Of those, 8 patients (2.0%) developed severe endobronchial bleeding during the first weaning attempt and required venoarterial ECMO support. The mean age of the 6 women and 2 men was 67 ± 11 years, which was slightly older than the non-ECMO patients (60 ± 16 years) (Table 1). The ECMO group had a lower cardiac output of 3.7 ± 1.1 L/min and greater PVR of 857 ± 553 dynes·s·cm^{-5}.

TABLE 2. ECMO postpulmonary endarterectomy (short-term venoarterial ECMO)

Characteristics	
n	8
Age, y	67 ± 11
Male, n (%)	2 (25)
Jamieson Classification I, n (%)	3 (38)
Jamieson Classification II, n (%)	1 (13)
Jamieson Classification III, n (%)	4 (50)
Cardiopulmonary bypass time, min	308 ± 45
Aortic crossclamp time, min	103 ± 32
Circulatory arrest time, min	38 ± 8
Lowest core temperature, °C	18.6 ± 1.2
Duration of va ECMO, min	49 ± 13
Weaned, n (%)	8 (100)
Discharged from hospital, n (%)	7 (88)
Blood products	
pRBCs, U	7.0 ± 3.2
FFP, U	7.9 ± 3.8
Platelets, U	1.7 ± 1.3

Values shown are n (%) or mean ± SD. *va ECMO*, Venoarterial extracorporeal membrane oxygenation; *pRBCs*, packed red blood cells; *FFP*, fresh-frozen plasma.

CPB time was 308 ± 45 minutes, aortic crossclamp time 103 ± 32 minutes, and total circulatory arrest time 38 ± 8 minutes. The lowest body core temperature was 18.6 ± 1.2°C.

One of these 8 patients died as the result of multiple-organ failure. The procedural characteristics of the ECMO group are given in Table 2. In all of these patients, the ECMO circuit was connected intraoperatively after severe endobronchial bleeding was confirmed by bronchoscopy. The average ECMO support time was 49 ± 13 minutes (range 20-113 minutes). All 8 patients with venoarterial ECMO were successfully weaned intraoperatively from the circuit, and 1 patient needed venovenous ECMO support for poor oxygenation 6 hours postoperatively.

All patients with venoarterial ECMO support had a significant blood transfusion requirement. The necessary support was provided with multiple units of packed red cells

TABLE 3. Complications in patients undergoing ECMO

Complication	
Atrial fibrillation	2
Pericardial tamponade	1
Temporary acute renal failure with continuous venovenous hemofiltration	1
Pneumonia	1

TABLE 4. Clinical course of patients undergoing ECMO

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y	71	54	70	81	75	75	61	50
Sex	Female	Female	Male	Female	Male	Female	Female	Female
WHO FC	III	III	III	III	III	III	III	III
Duration of ECMO support, min	29	50	70	35	20	36	25	104
Ventilator support, h	206	113	43	27	102	335	34	146
Bronchus block (fibrin glue)	X		X					X
Parenchymal lesion in CT	S8 RLL		S2 RUL, S8/S9 RLL	S5 lingula	S5 ML, S9 RLL, S1 LUL	S5 ML		S2, S5, S6
ICU, d	11	10	9	9	8	16	2	12
Hospital stay, d	22	22	16	13	15	19	26	14
pRBCs, U	8	6	7	4	9	12	2	10
FFP, U	14	6	10	3	6	12	6	4
Platelets, U	0	2	4	2	2	0	2	2
Discharged from hospital	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

WHO FC, World Health Organization functional class; *ECMO*, extracorporeal membrane oxygenation; *CT*, computed tomography; *S*, segment; *RLL*, right lower lobe; *RUL*, right upper lobe; *ML*, middle lobe; *LUL*, left upper lobe; *ICU*, intensive care unit; *pRBCs*, packed red blood cells; *FFP*, fresh-frozen plasma.

(6.8 ± 3.0), fresh-frozen plasma (8.1 ± 3.7), and platelets (1.7 ± 1.3) (Table 2). The additional complications after PEA were atrial fibrillation, pericardial tamponade (requiring reoperation), renal failure requiring continuous venovenous hemofiltration, and pneumonia (Table 3).

Details of the individual patients supported by ECMO are listed in Table 4. All patients with endobronchial bleeding were preoperatively in World Health Organization functional class III, and computed tomography scans showed in some cases parenchymal lesions that were most likely remnants of pulmonary infarctions. Table 5 shows operative and postoperative time lines. Operation time (489 ± 36 vs 416 ± 65 minutes, $P < .0001$), ventilation time (164 ± 139 vs 52 ± 76 hours, $P < .0001$), intensive care unit stay (9.4 ± 1.1 vs 3.6 ± 3.1 days, $P < .0001$), and hospital stay (15 ± 5 vs 12 ± 20 days, $P = .0102$) were significantly longer in the venoarterial ECMO group. Seven patients were discharged from the hospital. One patient who needed venovenous ECMO support for poor oxygenation died on postoperative day 12 due to multiple-organ failure. Currently, all 7 patients are alive and in functional class I (n = 3), II (n = 3), or III (n = 1) with a mean follow-up of 2.6 years. One year after surgery, these patients showed significant improvements in functional class from (3.1 ± 0.4 to 1.7 ± 0.8), in mean pulmonary arterial pressure from (45 ± 14 to 24 ± 10 mm Hg), and in PVR from (671 ± 272 to 296 ± 211 dynes·s·cm^{-5}) (Table 6).

Figure 1 depicts the survival of patients with severe endobronchial bleeding during 2 periods: (1) between 2009 and 2013 with 2 survivors and 6 nonsurvivors and (2) between 2014 and 2016 with 7 survivors and 1 nonsurvivor. In the latter period with short-term ECMO support mortality was significantly lower ($P = .0406$).

DISCUSSION

In this article, we describe our experience with the novel, short-term use of venoarterial ECMO in combination with restored coagulation to manage intraoperative endobronchial hemorrhage after PEA. To our knowledge, this is the first documentation of the reversal of anticoagulation during short-term, intraoperative ECMO support followed by successful weaning.

TABLE 5. Postoperative course in patients with and without short-term venoarterial ECMO support

Variable	Non-ECMO group (n = 388)	Short-term va ECMO group (n = 8)	*P*
Operation time, min	416 ± 65	489 ± 36	<.0001
Ventilation time, h	52 ± 76	164 ± 130	<.0001
ICU time, d	3.5 ± 3.1	9.4 ± 1.1	<.0001
Postop hospital stay, d	12 ± 20	15 ± 5	.0102

ECMO, Extracorporeal membrane oxygenation; *ICU*, intensive care unit; *postop*, postoperative.

TABLE 6. Hemodynamic changes and pre- and postoperative WHO FC in patients with short-term venoarterial ECMO

Characteristics	Preoperative	1-year postoperative	
WHO FC	3.1 ± 0.4	1.7 ± 0.8	($P = .0027$)
mPAP, mm Hg	45 ± 14	24 ± 10	($P = .0424$)
CI, L/min/m^2	2.3 ± 0.3	2.5 ± 0.2	($P = .3236$)
PVR, dynes·s·cm^{-5}	671 ± 272	296 ± 211	($P = .0242$)

Values shown are mean ± SD. *WHO FC*, World Health Organization functional class; *mPAP*, mean pulmonary arterial pressure; *CI*, cardiac index; *PVR*, pulmonary vascular resistance.

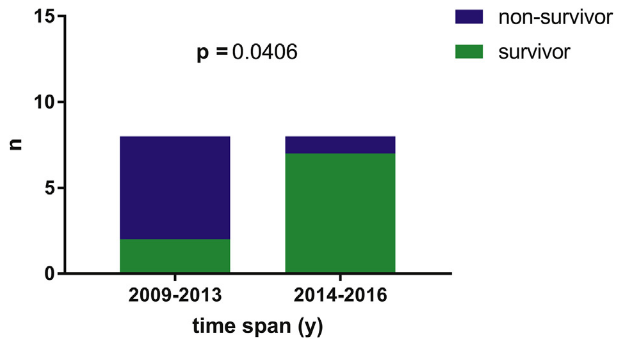


FIGURE 1. Comparison of survival between 2 different concepts of venoarterial ECMO support. Depicted are long-term ECMO support between 2009 and 2013 and short-term ECMO support between 2014 and 2016. Short-term venoarterial ECMO support resulted in a significant reduction in mortality ($P = .0406$). *Green* indicates survivor; *blue* indicates nonsurvivor.

PEA is the treatment of choice for chronic thromboembolic pulmonary hypertension. Rare but serious complications are reperfusion edema, persistent pulmonary hypertension, and endobronchial bleeding. All of these complications are potentially fatal.[5] With increasing experience and extended indications for PEA surgery, all major PEA centers (centers with more than 100 PEA procedures per year) have to deal with these complications to save the lives of their patients. In this article, we focus on massive endobronchial hemorrhage and its management.

During the PEA procedure, surgeons have the unique opportunity for early anticipation of possible airway bleeding and may treat intraoperative defects to avoid this complication. If during endarterectomy denuded vessels or only a thin layer of adventitia or perforation is detected, endobronchial bleeding must be considered. In some cases, perforated vessel layers can be repaired with fibrin glue. In particular, disruptions of a distal pulmonary artery can be detected intraoperatively using the ‘‘bubble’’ technique, as reported by Morsolini and colleagues[10]: if a pulmonary arterial branch shows bubbles during gentle ventilation of the lung, this branch should be blocked with topical application of a surgical sealant such as fibrin glue.

During rewarming of the patient to the normal core temperature, we routinely perform a bronchoscopy. If small amounts of blood are visible but there is no blood ascending from the bronchi, weaning from CPB can be carried out in the routine manner. In the majority of cases, endobronchial bleeding commences during the weaning phase due to increased pulmonary arterial pressures. It can be detected early, however, by monitoring tidal or minute volume during pressure-controlled ventilation. Decreasing values are the earliest signs of a reduced ventilatory space that might be caused by endobronchial bleeding before blood is detected in the endotracheal tube. Immediate assessment by bronchoscopy is then warranted.

In dealing with this complication the bronchoscopic diagnosis is usually clear, but it is often difficult to discern whether bleeding is localized or diffuse. Because of the spilling of blood into the entire bronchial system, blood can be aspirated from multiple locations during bronchoscopy. As evident from Table 4, however, in 2 of 8 patients we had the impression that the blood predominately came from one segmental bronchus. Consequently, we also blocked this bronchus with fibrin glue, administered with the aid of a bronchoscope. There are also descriptions of the use of endobronchial blockers or double-lumen endobronchial tubes in cases of severe endobronchial bleeding,[16] but they all have the disadvantage that the amount of blocked lung area is considerably greater compared with a blocked lung segment treated with fibrin glue.

In cases of severe and diffuse airway bleeding, a conservative approach (eg, bronchus blocking) is not sufficient to handle this complication. Increasing experience in extracorporeal support has led to 2 ECMO techniques that are currently in use: for reperfusion edema or impaired lung function of other origin, venovenous ECMO is the preferred support[11]; otherwise, if hemodynamic compromise is a factor, venoarterial ECMO support with central or peripheral cannulas is preferable.[12]

One of the first reports describing venovenous ECMO support for patients after PEA came from a group in San Diego.[11] During a period of 15 years, 1790 patients underwent PEA at this center. Twenty patients (1.1%) had to be supported with venovenous ECMO due to severe respiratory failure. Of these 20 patients, 6 survived. In this report, endobronchial hemorrhage did not play a role.[11] Another article was published 2 years later by a group in Cambridge who reported 127 consecutive patients who underwent PEA.[12] In 7 patients (5.5%), venoarterial ECMO support was required postoperatively, 5 patients were weaned successfully from the circuit, and 4 were discharged from hospital. In this report, also, endobronchial bleeding was not the reason for ECMO support.[12]

Pulmonary hemorrhage remains a rare complication after PEA (prevalence of 0.5%-2%) that has been treated historically almost entirely without ECMO support.[17,18] More recently, however, a number of case reports have been published in which the use of ECMO support is described to manage this serious complication.[13,14,16,19] The individual management of these cases was different and depended on the type of ECMO connection (venovenous or venoarterial). In some instances, the ECMO circuit was connected intraoperatively before weaning from CPB; in other patients, ECMO support was initiated after weaning from CPB. In all cases the mean duration of ECMO support was 3.5 days, ranging from 2 to 4 days. Long-term venoarterial ECMO support, however, that bypasses the lungs for several days may lead to blood stasis in the pulmonary vasculature with the hazard of rethrombosis of the freshly endarterectomized pulmonary arteries. This fatal complication had occurred in one of our patients in the previous year and led us think about an alternative approach to manage this problem.

In severe endobronchial hemorrhage, the coagulopathy must be reversed, but in this situation the patient cannot be weaned from CPB. Therefore, we decided to switch the circulatory support immediately to a venoarterial ECMO circuit, because there all components have a heparinized lining. This allows for complete restoration of the coagulation system by administering the full dose of protamine during extracorporeal perfusion, and with an increased positive end-expiratory pressure value of 15 cm H_2O we were able to wean all patients from the venoarterial ECMO support in the operating theater. The risk of clotting within the heparin-coated oxygenator is minimal, but it is important to provide pulsatile flow to the pulmonary arteries to avoid clotting in the newly endarterectomized vessels.

The reason for the 8 incidents of severe endobronchial bleeding (2%) that occurred within the 3-year study time frame at our center is not clear. The mechanism of pulmonary hemorrhage remains obscure. Surgical trauma resulting in disruption of the pulmonary arterial vessel and/or a markedly increased capillary permeability after the reperfusion of nonperfused pulmonary parenchyma, similar to ischemia–reperfusion lung injury after transplantation, are possible mechanisms. In 6 of our patients, some parenchymal lesions (possibly remnants of pulmonary infarctions) were detectable that could have conceivably served as foci of pulmonary hemorrhage (Table 4). In addition, the fact that our center treats a large number of patients with distal pulmonary vascular disease might be an explanation. Moreover, compared with other cohorts,[4] our patients are approximately 10 years older, which might lead to a greater rate of endobronchial hemorrhage. In our series, most of the patients (5 of 8) were older than 70 years of age. The fact that weaning was possible after restoration of the coagulation system suggests that the vasculobronchial connections were of small caliber. In addition, administered blood products such as fresh-frozen plasma and platelets were effective in sealing the bleeding sites. Thus far, we can only speculate on the true cause of bleeding in the individual patient and are not able to recommend different treatment options for different types of bleeding. Our concept of short-term ECMO has proven to be very effective for all patients with potentially different causes of hemorrhage.

In this case series of patients with endobronchial bleeding, the success of weaning from venoarterial ECMO support is very encouraging and demonstrates that this devastating complication is manageable in the majority of patients in the operating theater and that the operation can be concluded in the usual manner. Furthermore, this concept avoids ECMO-related long-term complications and is resource-saving.

There are some limitations to our study: (1) our small sample size of only 8 patients with endobronchial hemorrhage; and (2) the decision to use ECMO support is subjective and bronchoscopical blocking might be equally feasible in some cases. Because of the success of this approach in a life-threatening situation, however, we have made this our standard procedure.

This is not the first report to describe ECMO support for managing endobronchial bleeding,[13,14,16,19] but to our knowledge, it is the first small case series that describes the short-term management of this bleeding complication in the operating theater. In all other case reports the duration of ECMO support ranged from 2 to 4 days and ECMO support was almost always initiated after weaning from CBP.

CONCLUSIONS

Severe endobronchial bleeding is a feared complication of PEA for which different concepts of management have been reported. With our new concept of short-term venoarterial ECMO support, successful weaning from the extracorporeal support in the operating theater is feasible.

Conflicts of Interest Statement

Dr Guth: speaking fees from Actelion, Bayer, and Pfizer. Dr Ghofrani: speaking fees from Actelion, Bayer, Actelion, GSK, Pfizer, Merck, Novartis, Takeda Pharmaceuticals, Eli Lilly, Bellerophon, and Pulse Technologies. Dr Mayer: speaking and consulting fees from Actelion, Bayer, GSK, Pfizer, and MSD. Dr Wiedenroth: speaking fees from Actelion, Bayer, BTG, and MSD. Dr Richter: speaking fees from Actelion, Bayer, Mundipharma, OMT, Roche, and United Therapeutics. All other authors have nothing to disclose with regard to commercial support.

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Key Words: CTEPH, pulmonary endarterectomy, ECMO, endobronchial hemorrhage

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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 remodeling of the non-occluded, hyperperfused pulmonary

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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 man agement, and complications of patients with CTEPH who underwent PEA at a large national surgical referral center in Germany.

Methods

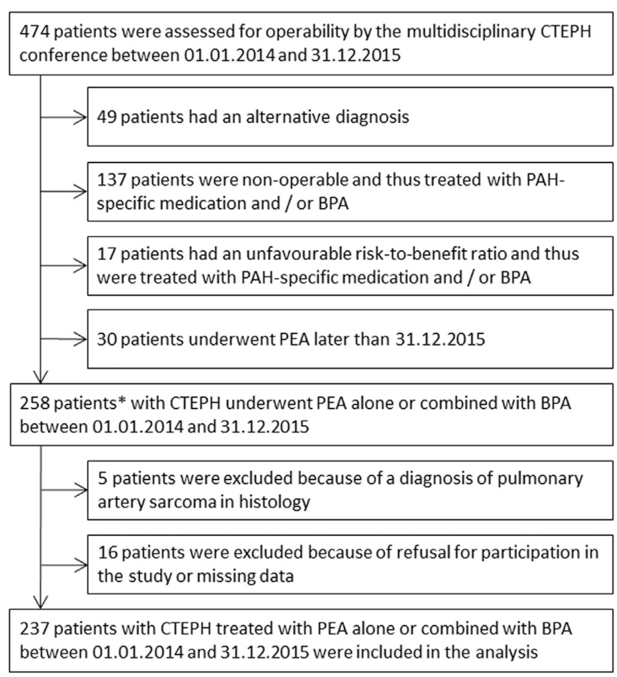
All patients admitted to the Kerckhoff Clinic, Bad Nauheim, Germany, for scheduled PEA between January 2014 and December 2015 were considered eligible for inclusion in the present prospective, non-interventional cohort study. The Kerckhoff Clinic serves as a national referral center for PEA, with >100 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 ≤20°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



*of those, 17 patients were discussed by the multidisciplinary CTEPH conference before 01.01.2014.

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

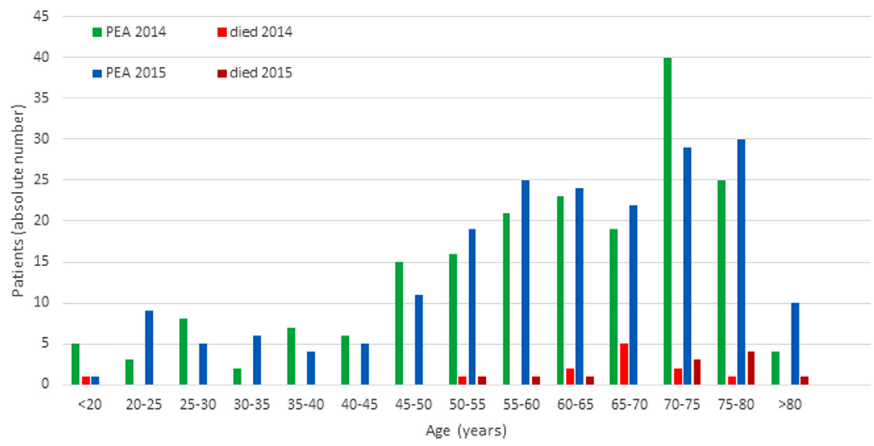


Figure 2 Absolute numbers of patients undergoing PEA (OPS number 5-381.42) and of in-hospital deaths in Germany in 2014 and 2015 as reported by the Federal Statistical Office of Germany (Statistisches Bundesamt).

(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.

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.

Echocardiographic 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.

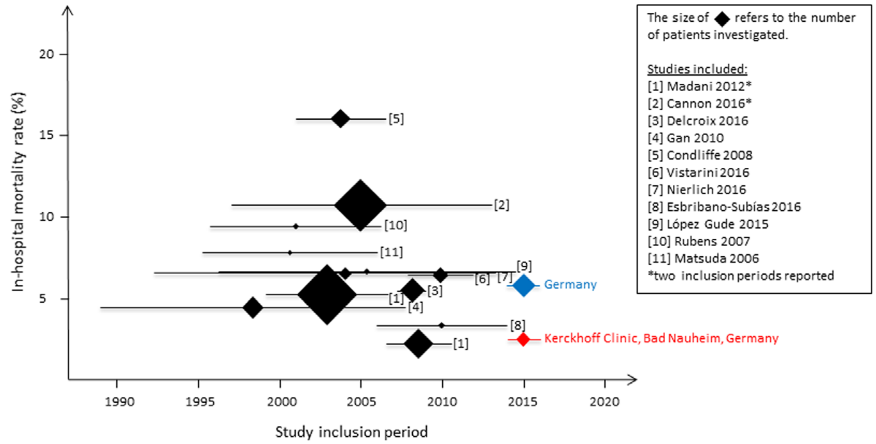


Figure 3 In-hospital mortality rates of patients with CTEPH undergoing PEA in relation to the study observation period. Only studies reporting on ≥100 patients are shown, and studies reporting on the same cohort (such as patients included in the international CTEPH registry or the UK PH registry) are 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%,

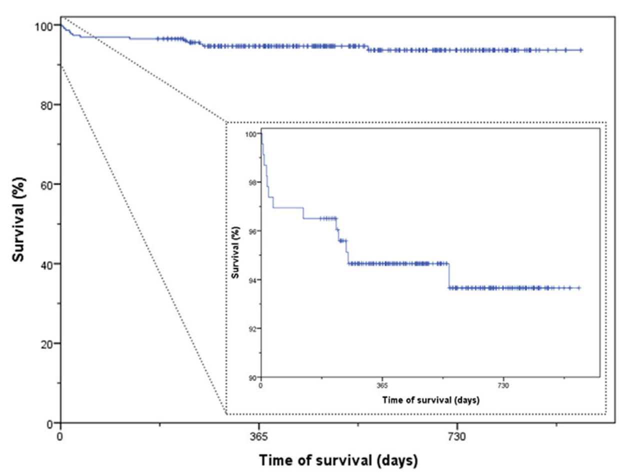


Figure 4 Probability of midterm survival of patients with CTEPH undergoing PEA.

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 multi-variable 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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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.

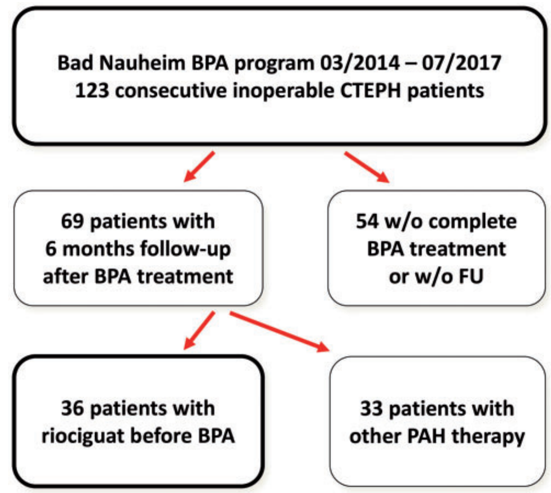

Fig. 1. Flow chart describing the balloon pulmonary angioplasty program in Bad Nauheim showing patient selection.

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,

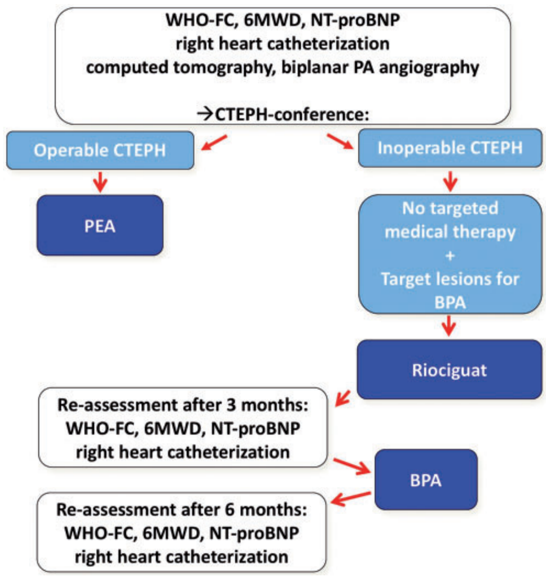

Fig. 2. Study flow chart for the 36 patients included in the study.

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;

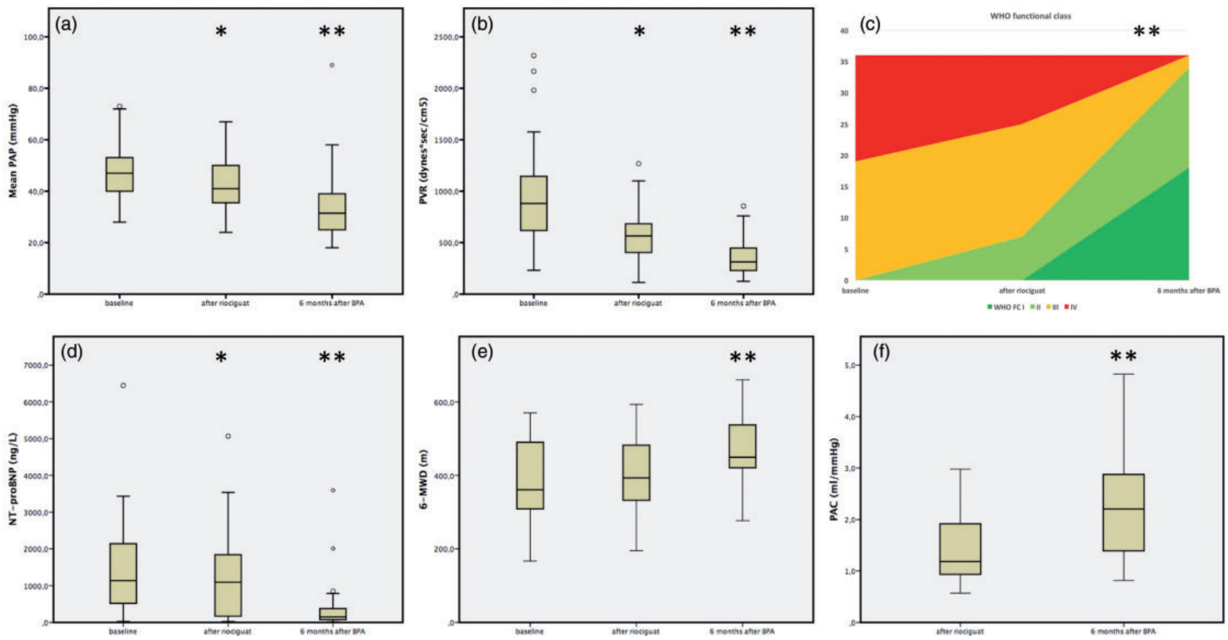

Fig. 3. Effects of riociguat and BPA on (a) mPAP, (b) PVR, (c) WHO FC given in mean values, (d) NT-proBNP, (e) 6MWD, and (f) PAC. The asterisk indicates the significance level (*$P < 0.05$; **$P < 0.001$).

$P = 0.0001$). 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.

Acknowledgments

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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.

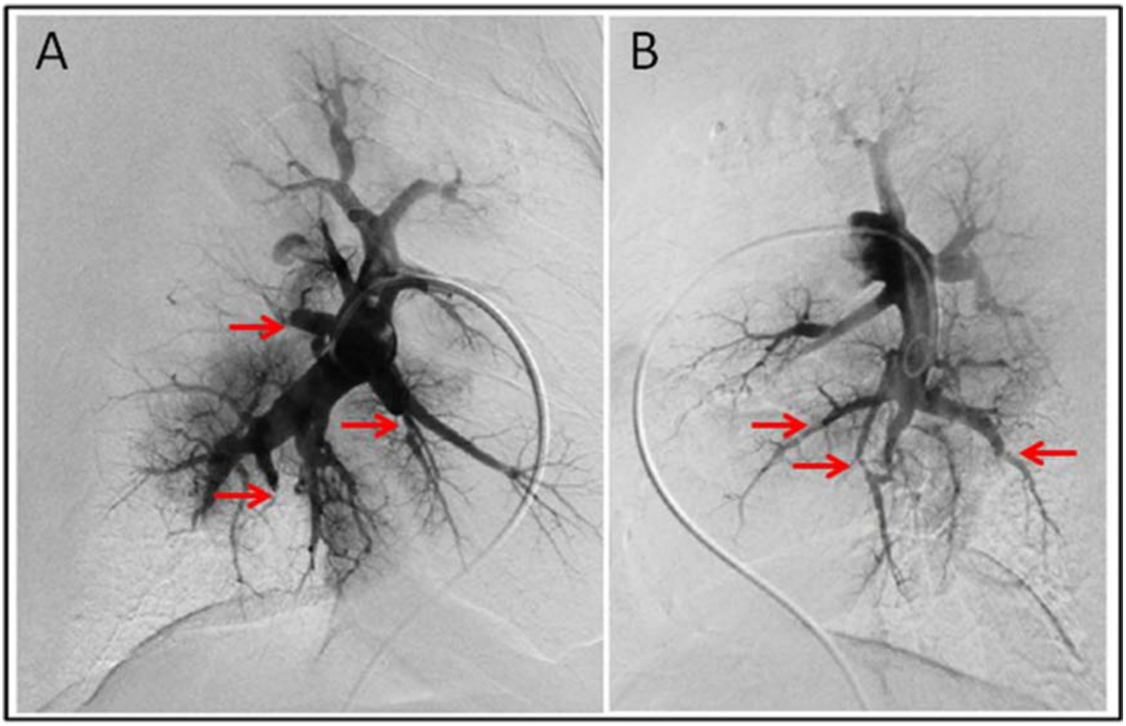

Figure 1 Pre-procedural pulmonary angiography (lateral projections) in Patient 3. (A) Right pulmonary artery with surgically removable lesions (arrows); (B) left side with very distally located lesions (arrows).

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;

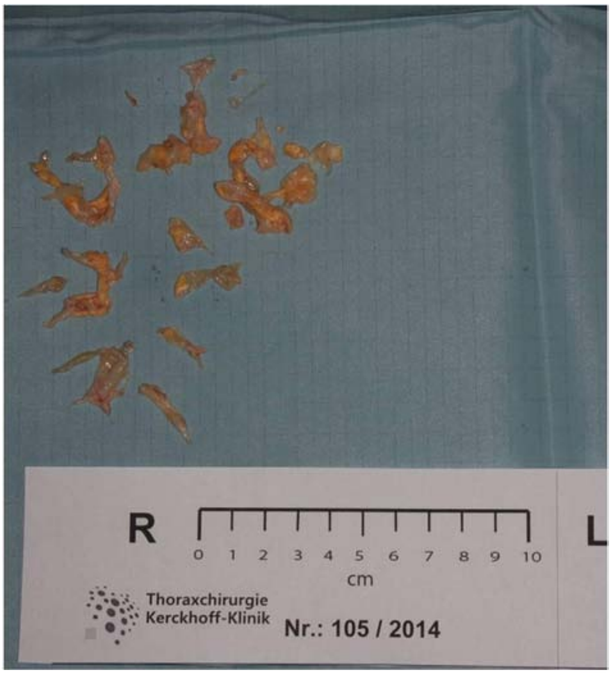

Figure 2 The surgically removed obstructing tissue from the right pulmonary artery in Patient 2.

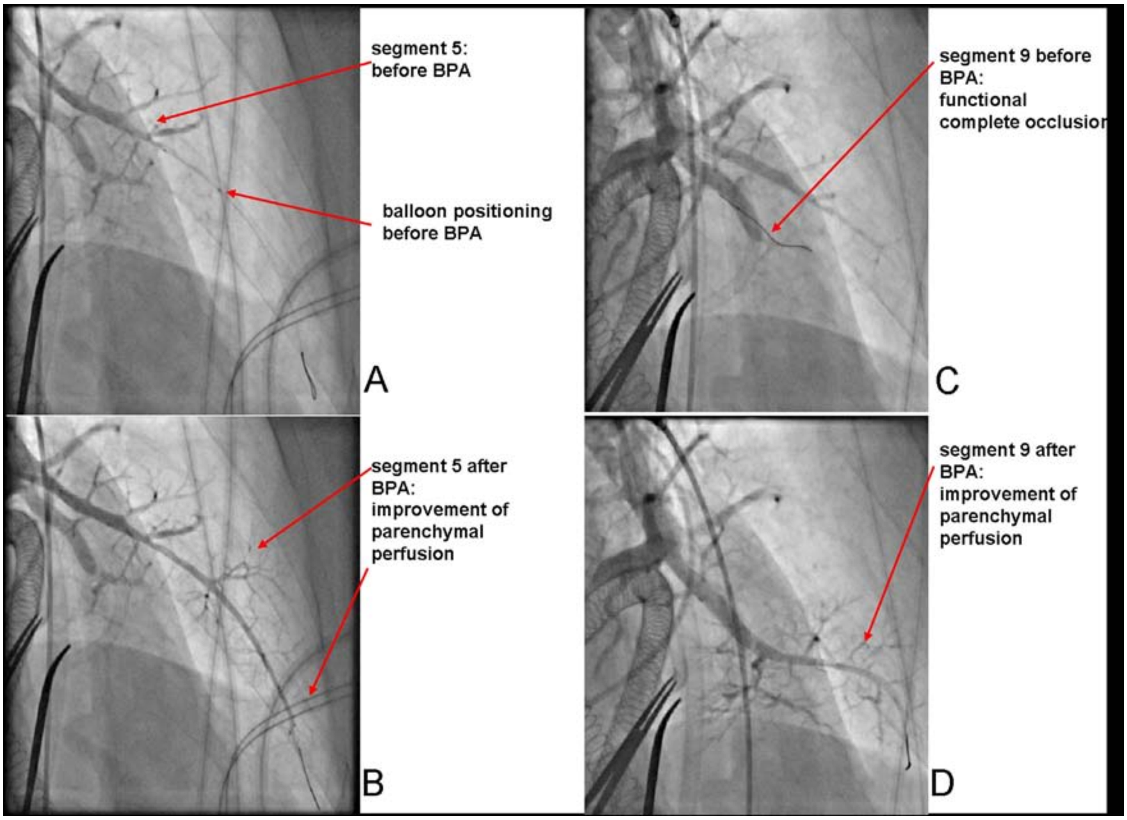

Figure 3 (A–D) Peri-procedural pulmonary angiography during balloon pulmonary angioplasty (BPA) of the left pulmonary artery in Patient 2.

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 · 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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