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Moderne Aspekte der Herzmedizin bei multimorbiden Patienten

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Einleitung:

Das Bevölkerungsdurchschnittsalter vor allem in den industriellen Ländern nimmt stetig zu. In Deutschland ist die Gesellschaftsgestaltung maßgeblich vom demografischen Wandel beeinflusst. Derzeit sind 17,5 Millionen der Bevölkerung in Deutschland über 65 Jahre alt und diese Zahl wird in den nächsten 50 Jahren kontinuierlich und überproportional ansteigen (1). Biologisch ist Altern die Folge metabolischer Prozesse, die auch bei der Entstehung einer Reihe von Erkrankungen, wie Diabetes mellitus, Fettstoffwechselstörung und Bluthochdruck ursächlich sind. Diese bestimmen wiederum die Ätiologie schwerwiegender kardiovaskulärer Erkrankungen. Demzufolge ist davon auszugehen, dass das Alter ein Risikofaktor für Morbidität und Mortalität besonders nach einer kardialen Intervention oder Operationen im Allgemeinen ist. Dabei spielt die Schwere und die Anzahl der Komorbidität für die perioperative und Langzeitprognose dieser Hochrisikopatienten eine wesentliche Rolle.

Multimorbidität liegt vor, wenn ein Patient gleichzeitig unter zwei oder mehreren chronischen Erkrankungen leidet. Eine Erkrankung gilt als chronisch, sobald der Krankheitsverlauf einen längeren Zeitraum, über ein Jahr, überschreitet, eine fortlaufende medizinische Behandlung erfordert und zu einer Einschränkung der täglichen Aktivitäten führt (2). Die auf diese Weise definierte Multimorbidität identifiziert jedoch eine Population, die recht heterogen ist. Dies liegt zum Teil daran, dass die Anzahl, Vielfalt und Ausprägungen der Krankheiten typischerweise mit dem Alter zunehmen. Multimorbidität betrifft mehr als zwei Drittel der älteren Bevölkerung und insbesondere die Mehrheit der Patienten mit chronischer Herzkreislauferkrankung. Diese Komplexität stellt das Versorgungsmanagement vor zahlreiche Herausforderungen. Zum einen erschwert sie die Entscheidungsfindung der in den Behandlungsprozess involvierten Mediziner und die Arbeit der bereits überlasteten Pflege. Zum anderen stellt sie eine immense Belastung für den Patienten selbst und sein soziales Umfeld dar.

Generell liegt die Inzidenz der kardiovaskulären und auch chronischen Erkrankungen, wie linksventrikuläre Dysfunktion, Diabetes mellitus, chronisch obstruktive Lungenerkrankung, Nierenfunktionsstörung und periphere arterielle Erkrankung bei der über 70-jährigen Bevölkerung bei 70 % (3). Durch den demografischen Wandel steigt nicht nur der Anteil der älteren Population, sondern auch die Inzidenz

kardiovaskulärer Erkrankungen sowie notwendiger Interventionen und Operationen überproportional an. Die Altersstruktur der kardiochirurgischen Patienten in Deutschland hat sich dementsprechend seit 1990 deutlich verschoben. Während der Patientenanteil der Altersgruppe der 40- bis unter 70-Jährigen in den folgenden Jahrzehnten sank, stieg der Patientenanteil der Gruppe der 70- bis unter 90-Jährigen von 13,4 % auf 40,9 % rapide an (4). Trotz dieser Altersverschiebung gelang es, durch an diese Entwicklung angepasste interventionelle und chirurgische Konzepte (5), einen Anstieg der Letalität zu vermeiden und die Lebensqualität der älteren Patienten zu verbessern (6).

Die offene Frage nach dem Einfluss des biologischen Alters auf das operative Risiko unabhängig von der Art der Operation oder Intervention bleibt. Es gilt zu berücksichtigen, dass das Vorhandensein mehrerer chronischer Erkrankungen erheblich die Komplexität des Patientenmanagements erhöht und daher einen Paradigmenwechsel der traditionellen Versorgungsansätze erfordert. In diesem Zusammenhang ist für die Risikostratifizierung im Rahmen einer Intervention oder Operation eine frühzeitige Identifizierung systemischer und kardiovaskulärer Komorbiditäten für die Auswahl der Behandlungsmethode und die Optimierung des Behandlungsprozesses bei älteren Patienten entscheidend. Die Vielfalt der chirurgischen und interventionellen Therapiekonzepte erlauben momentan eine individuelle maßgeschneiderte Behandlung.

Die Herzchirurgie ist ein junges Fach. Der erste erfolgreiche Verschluss des Vorhofseptumdefekts wurde in Minnesota im Jahr 1952 durchgeführt. John Gibbons Oxygenator erlaubte mehr operative Komplexität am offenen Herzen. Zudem war das Jahr 1967 für die Herzchirurgie wegweisend. Nachdem René Favaloro die erste erfolgreiche Bypass-Operation durchgeführt hatte, gelang Christian Bernhard in Südafrika die erste Herztransplantation. Seither hat sich die Herzchirurgie stetig weiterentwickelt. Im Vordergrund stand dabei die Optimierung der Herz-Lungen-Maschine (HLM) und die Myokardprotektion, um Operationen am stillstehenden Herzen mit einem minimalen Risiko durchführen zu können. Sie war die Voraussetzung für die Entwicklung einer Reihe an Operationstechniken: der Bypass-Chirurgie, der Klappen-Chirurgie, der Chirurgie der Herzinsuffizienz, der Rhythmuschirurgie und der Chirurgie der Aorta.

Die Innovation der extrakorporalen Zirkulation als Derivate der Herz-Lungen-Maschine setzte sich in der Einführung der temporären und permanenten kardiopulmonalen Unterstützungssysteme fort. Derartige Systeme sind mittlerweile ein wesentlicher Bestandteil der Therapie des kardialen und/oder pulmonalen Versagens (7). Innovative Oxygeneratoren ohne Plasmaleckage, beschichtete Schlauchsysteme und Pumpen mit sehr hoher Hämokompatibilität erlauben mittlerweile einen komplikationsarmen, langfristigen temporären Einsatz bei komplexen multimorbiden Patienten.

Extrakorporale Membranoxygenierung (ECMO):

Die extrakorporale Membranoxygenierung (ECMO) ist im Wesentlichen eine modifizierte HLM, die den Gasaustausch und die Perfusion für eine längere Unterstützung bei Patienten mit schwerem aber möglicherweise reversiblem Atem- oder Herzversagen sichert. Beide Systeme setzen das fließende Blut Gas mit hohem pO2 und niedrigem pCO2 aus, was zu einem Gasaustausch über Konzentrationsgradienten führt. Dennoch gibt es gravierende Unterschiede. Die traditionelle HLM ermöglicht einen zeitlich stark limitierten Einsatz im Rahmen von einigen wenigen Stunden, da die hier erfolgende direkte Exposition des Blutes mit dem Gas im Oxygenator über einen längeren Zeitraum zur Denaturierung der Plasmaproteine und Hämolyse führt. Im Gegensatz dazu verfügt der Membranoxygenator der ECMO zwischen Blut und Gas über eine semipermeable Membran, die den direkten Kontakt zwischen Blut und Gas verhindert und somit den Einsatz über eine längere Zeitspanne ermöglicht. Des Weiteren entfällt bei der ECMO das venöse Reservoir als das thrombogenste Glied des Systems. Demzufolge ist die Antikoagulationstherapie bei der ECMO deutlich moderater. Ein weiterer wesentlicher Unterschied besteht in der Kanülierung, die beim ECMO extrathorakal durch zugängliche periphere Gefäße minimalinvasiv durchgeführt wird.

Generell unterscheidet man je nach Indikation zwei ECMO Systeme. Das ursprüngliche System ist die veno-venöse (VV) ECMO, die bei ausgeprägter respiratorischer Insuffizienz Anwendung findet und deren erfolgsversprechende Indikation durch randomisierte Studien bestätigt ist (8). Dabei wird das Blut präkardial durch Ein-/Ausflusskanüle im venösen System oxygeniert und decarboxyliert. Im Vergleich zum veno-arteriellen (VA) ECMO besteht die Stärke des Systems in der

geringeren Invasivität der Implantation, da nur periphere venöse Gefäße als Zugang dienen und der pulsatile Kreislauf durch die präkardiale Oxygenierung und die intakte Perfusion des kleinen Kreislaufes aufrechterhalten wird. Das Vorhandensein eines präkardialen Shunts zwischen beiden Kanülen, der die Effizienz der Oxygenierung beeinträchtigt, sowie die fehlende kardiale Unterstützung, limitieren generell die Effizienz der VV-ECMO.

Das Acute Respiratory Distress Syndrome (ARDS) ist die klassische Indikation der VV-ECMO. Das polyätiologische Syndrom manifestiert sich klinisch durch eine fortgeschrittene schwere respiratorische Insuffizienz, bei der die Mortalität bei bis zu 60% liegt (9). Generell hat der Einsatz der VV-ECMO beim ARDS keinen direkten kurativen Effekt. Die pulmonal unabhängige Sicherung der Oxygenierung und Decarboxylierung erlaubt eine lungenschonende Beatmung durch das Deeskalieren der Beatmungsinvasivität, was einen dramatischen strukturellen und funktionellen Einfluss auf die Lunge hat.

Die Zahl der Patienten, die eine ECMO erhalten, hat seit Beginn der 1970er Jahre, insbesondere im letzten Jahrzehnt, erheblich zugenommen (10). In diesem Zusammenhang wurde das Indikationsspektrum erweitert. Zusätzlich zur VV-ECMO, stieg der Einsatz der VA-ECMO (ECLS) bei Patienten mit primärem kardialem Versagen. Das Verstehen der Ätiologie und Kausalität der Grunderkrankungen, das Vorhandensein vielversprechender Therapieoptionen als auch die technische Entwicklung v.a. der Pumpen und Oxygenatoren haben maßgeblich zur steigenden Akzeptanz des Verfahrens beigetragen (11).

Aufgrund der Komplexität der intensiv medizinischen Behandlung der ECMO-Patienten sollte sie im Idealfall auf spezialisierte Zentren beschränkt werden, die die beste personelle und technische Expertise vorweisen (12). Da multimorbide kritisch erkrankte Patienten mit akutem Lungenversagen jedoch aufgrund einer kardio-pulmonalen Instabilität häufig nicht transportfähig sind, wird die ECMO-Implantation zur Sicherung der Transportfähigkeit zu den spezialisierten Zentren auch direkt vor Ort notwendig (13).

Generell ist der Einsatz der extrakorporalen Zirkulation durch massiven Fremd-körperkontakt und die fehlende Pulsalität nicht physiologisch und hat einen negativen Einfluss auf die Organfunktion durch u.a. pathologische metabolische Prozesse und induzierte Inflammation (14). Solche Effekte haben v.a. auf die multimorbiden älteren

Herzpatienten einen gravierend negativen Effekt. Daher sollte der Einsatz der HLM und ihrer Derivate, wenn möglich, zugunsten der wenig invasiven Maßnahmen, wie der Intervention, vermieden werden.

Interventionelle Aortenklappentherapie (TAVI):

In der letzten Dekade zeichnete sich eine klare Tendenz, die Invasivität der chirurgischen Eingriffe zu reduzieren, indem die Zugänge der Prozeduren oder der Einsatz der HLM minimiert wurden. Alterung mit entsprechender wachsender Komorbidität der Patienten ist ein entscheidender Stimulus dieser Tendenz. Im Fokus dieser Entwicklung steht vorwiegend die Behandlung der Aortenklappen.

Die Aortenklappenstenose ist die häufigste Herzklappenerkrankung in der westlichen Welt und hat nach Auftreten der ersten Symptome eine ungünstige Prognose (15). In den ersten 2 Jahren nach Auftreten der Symptome liegt die Letalität unbehandelt bei 50 % (16). Bei einer adäquaten Patientenselektion bietet der klassische chirurgische Aortenklappenersatz (SAVR) eine sichere und vielversprechende Therapie. Nichtsdestotrotz eignen sich mindestens 30 % der Patienten mit einer schweren symptomatischen Aortenklappenstenose aufgrund der Multimorbidität nicht für die chirurgische Therapie (17). Für diese Patientenkohorte wurde 2002 die Transkatheter-Aortenklappenimplantation (TAVI) eingeführt (18, 19). Hierbei wird die stenotische Aortenklappe kathetergestützt interventionell funktionell ersetzt. Das Vermeiden der chirurgischen Invasivität als auch der HLM zeigt v.a. bei den multimorbiden Patienten einen positiven Effekt (20). Der ursprünglich transseptal antegrad durchgeführte Zugang wurde aufgrund der Komplexität des Zugangs durch die transseptale Punktion, die Passage durch die Mitralklappe und den damit verbundenen Risiken zugunsten des transfemoralen (TF) retrograden Zugangs aufgegeben. Dennoch traten auch bei dieser Therapie spezifische unerwünschte Nebeneffekte, wie Schlaganfälle, Prothesendeslokation, paravalvuläre Leckage, Rhythmusstörungen und vor allem Komplikationen an den Implantationszugängen auf, die die Vorteile der Therapie relativiert haben.

Generell unterscheidet man zwischen zwei Konzepten der implantierbaren interventionellen Prothesen. Die aktiven Prothesen bestehen aus einem Nitinol-Gerüst, welches sich durch Wärme aktiv ausdehnt und die native Klappe verdrängt. Die passiven Prothesen benötigen ein Hilfsmittel in Form von aufblasbaren Ballons oder eine injizierbare, schnell aushärtende Kunststofflösung, die die native Klappe

verdrängt und der Prothese ihre endgültige Form verleiht. Dabei ist zwischen Prothesen mit Metallgerüst und metallfreien Prothesen in der Konzeption zu unterscheiden. Alle Konzepte waren in der Initiierungsphase der Therapie Gegenstand der Evaluierung, da bis zum Zeitpunkt der Untersuchungen weder Klarheit über die Praktikabilität noch Ergebnisse der unterschiedlichen Prothesenimplantate und deren Haltbarkeit vorlagen.

Nichtdestotrotz sind Form und Material der Prothesen entscheidend bei der Prävalenz der paravalvulären Leckage, die sich als starker unabhängiger Prädiktor für die Mortalität erweist (21). Die Ursachen für die Entstehung der paravalvulären Leckagen sind multifaktoriell, wobei für die Inzidenz, die Größe und Lokalisation des anulären und subanulären Kalkes sowie die Anpassungsfähigkeit der Prothesen entscheidend sind. Das Vorhandensein einer paravalvulären Leckage führt zu einer akuten vermehrten Volumenbelastung des linken Ventrikels, der durch die bis dahin vorhandene Aortenklappenstenose keine ausreichende Compliance besitzt. Daher manifestiert sich eine permanente Drucküberlastung des linken Ventrikels, die klinisch und prognostisch relevant ist. Bereits eine moderate neuauftretende postinterventionelle Leckage kann die kurz- und mittelfristige Mortalität deutlich erhöhen (22).

Die Direct Flow Medical®-Prothese (DFM, Direct Flow Medical, Santa Rosa, CA) besteht aus einem metallfreien Hochdruck-Schlauchsystem als Gerüst und erlaubt dementsprechend die präzise Repositionierung und bei Bedarf die komplette Extraktion der Prothese. Das Vorhandensein eines steuerbaren, repositionierbaren und flexiblen Gerüstes erlaubt eine präzise Prothesenimplantation, effizientere Abdichtung des verkalkten subvalvulären Apparates und geringere Inzidenz der paravalvulären Leckage (23). Das metallfreie Konzept der Prothese bietet die maximale Flexibilität und Anpassungsfähigkeit zuungunsten der Radialkraft. In Kombination mit asymmetrischer, starker Verkalkung der nativen Klappe ist der transvalvuläre Gradient im Vergleich erhöht (24).

Neben den unterschiedlichen Protheseneigenschaften hat auch die Implantations-prozedur einen direkten Einfluss auf Lebensqualität und Überleben der Patienten. Im Vordergrund der Implantationsprozedur stand der Zugangsweg und die damit vergesellschafteten Komplikationen (25). Prinzipiell muss zwischen dem transapikalen (TA) antegraden Weg und dem endovaskulären retrograden Weg unterschieden

werden. Der Fokus der Hersteller lag beim Prothesenkonzept primär auf dem endovaskulären Implantationsweg, vertreten durch die iliofemoralen Gefäße. Die ersten Generationen der Implantationssysteme erforderten bezüglich Gefäßkaliber, Kalzifikationsgrad und Verlaufsform der iliofemoralen Gefäße gewisse Voraussetzungen, die bei 30% der Patienten nicht erfüllt wurden (26). Trotz der Weiterentwicklung der Systeme und Reduktion des Durchmessers auf 18 French bleibt die Rate der Patienten, für die der femorale Zugang ungeeignet ist, bei 15 % (27). Daher wurden parallel zum TF-Zugang alternative Implantationswege evaluiert, zu denen der linksventrikuläre Apex, die Aorta ascendens und die Arterie carotis zählen (28).

Der transapikale (TA) Zugang hat sich initial als Alternativzugang etabliert (29). Dennoch kommt er bei alten und multimorbiden Patienten mit schwerer apikaler Hypertrophie oder Aneurysma sowie im Falle von Re-Operationen an seine Grenze. Die Komplikationsraten- und Formen, wie die Entstehung eines apikalen Aneurysmas, eines ventrikulären Septumdefektes, einer Verletzung des subvalvulären Apparats der Mitralklappe und chronischer postoperativer Brustschmerzen werden in der Literatur hinreichend beschrieben (30). Ein zusätzlich limitierender Faktor dieses Zuganges im Vergleich zur Wahl endovaskulärer Zugangswege stellt die Tatsache dar, dass in diesem Fall nur eine Prothesenform dafür geeignet ist.

Um die oben genannten Komplikationen der TA-Zugang bei den multimorbiden Patienten zu vermeiden und gleichzeitig einen alternativen Zugangsweg für alle Prothesenformate zu etablieren, wurde der transaortale (TAo) Zugang eingeführt. In der Herzchirurgie gehört der Umgang mit der Aorta ascendens zur Routine, da die konventionellen Ersatzoperationen der Aortenklappe via obere Mini-Sternotomie oder rechte Thorakotomie erfolgen könnten. Die gleichen Zugangswege eignen sich für TAVI. Daher hat sich dieser Alternativzugang in unserer Abteilung schnell etabliert und wurde sehr früh im TAVI Entscheidungsprozess implementiert (31, 32). Da die Datenlage zu Erfahrungen mit dieser Zugangsart in Kombination mit den unterschiedlichen Prothesenkonzepten zum damaligen Zeitpunkt noch sehr dürftig ausfiel, wählten wir dieses Verfahren zum Gegenstand unserer Untersuchungen.

Fragestellung:

Alle Publikationen setzen sich mit dem Stellenwert innovativer Therapiekonzepte zur kardiopulmonalen Versorgung multimorbider Patienten auseinander.

Extrakorporale Membranoxygenierung (ECMO):

Bei den beiden ECMO-Publikationen handelt es sich um eine multimorbide Patientenkohorte mit terminalem kardiopulmonalem Versagen, getriggert durch eine fortgeschrittene therapierefraktäre respiratorische Insuffizienz und ein eigen konzipiertes ECMO-System, das vor Ort in den peripheren Zentren eingebaut werden kann, um die Transportfähigkeit in ein primäres Versorgungszentrum abzusichern. Dabei wurden die Praktikabilität und Sicherheit des eigen zusammengesetzten ECMO-Systems und seine Effizienz zur Versorgung der nicht transportfähigen multimorbiden ADRS-Patienten über einen Zeitraum von vier Jahren retrospektiv untersucht. In diesem Zusammenhang wurde ferner geprüft, inwieweit das Geschlecht als Prädiktor für die Risikostratifizierung von Relevanz ist.

Interventionelle Aortenklappentherapie (TAVI):

Der Fokus der drei Publikationen zum Thema des interventionellen Aortenklappenersatzes lag auf den Optimierungsmöglichkeiten der Implantationsprozedur und deren Auswirkung auf den multimorbiden Patienten. Die schwerwiegenden Komplikationen der peripheren Zugangswege im Rahmen der Implantation wirkten sich vor allem bei der fragilen alten Patientenpopulation lebensbedrohlich aus. Das Etablieren eines neuen endovaskulären Zugangsweges für die unterschiedlichen Prothesenkonzepte sowie deren Einfluss auf die Implantationsprozedur und das Überleben der Patienten war Gegenstand zweier Publikationen. Aus diesem Grund fassten wir unsere ersten institutionellen Erfahrungen mit TAo TAVI unter Verwendung einer selbstexpandierenden und metallfreien Aortenbioprothese zusammen. Wir konzentrierten uns bei unserer Analyse auf die Betrachtung der Gesamtergebnisse, der prozeduralen Lernkurve und der mittelfristigen Follow-up-Ergebnisse.

Aufgrund der Tatsache, dass auch die Inzidenz der paravalvulären Leckagen und der hohen transvalvulären Gradienten nach Implantation einen gravierenden Einfluss auf die Lebensqualität und das Überleben der multimorbiden Patienten hat, wurde in einer

Publikation eine Implantationstechnik weltweit zum ersten Mal beschrieben, die die Entfaltung und Implantation der metallfreien Prothese trotz starker asymmetrischer Verkalkung ermöglicht.

Diskussion

Extrakorporale Membranoxygenierung (ECMO):

Nach unserer Erfahrung ist die ECMO-Unterstützung eine wertvolle therapeutische Option bei schwerem Lungenversagen. Ihr Einsatz sichert die Transportfähigkeit zwischen den Krankenhäusern (33, 34). Unterschiedliche miniaturisierte ECMO-Systeme konnten die Effizienz dieser Therapie bei kardiopulmonalen dekompensierten Patienten bestätigen (35, 36). Dementsprechend hat sich das Konzept der extrakorporalen Oxygenierung und Perfusion zu einem vielversprechenden Instrument bei der Behandlung von Patienten mit akutem kardiorespiratorischem Versagen entwickelt. Klinische Studien haben bereits die Effizienz der ECMO / ECLS-Systeme bei bestimmten Indikationen unter gewissen Voraussetzungen bewiesen. Beim ARDS konnten sowohl die CESAR- als auch die H1N1 Influenza Studie den positiven Effekt der ECMO-Therapie bestätigen (12, 37). Ebenso wurde der Stellenwert der ECLS Systeme beim akuten kardiogenen Schock bezüglich des Überlebensvorteils durch eine Metaanalyse bestätigt (38, 39). Trotz der Möglichkeit der Miniaturisierung und der Weiterentwicklung des Systems bleiben sie Teil eines höchst komplexen Therapiekonzeptes multimorbider fragiler Patienten. Daher ist sie spezialisierten Zentren vorbehalten (12, 33). Bei der CESAR-Studie starben zudem bereits drei Patienten vor und weitere zwei während des Transfers. Die Autoren postulieren die Initiierung der ECMO-Therapie als mögliche Ursache (37) und erachten grundsätzlich ein funktionsübergreifendes Expertenteam bereits zu Beginn des Einsatzes für erforderlich (34). Am Universitätsklinikum Halle wurde 2014 das Hallesche EcLs Programm (HELP) zur Vor-Ort-Versorgung nicht transportfähiger ARDS Patienten durch ein interdisziplinäres Team gegründet. Zur Verfügung standen einige Unterstützungssysteme, die bereits in single-center Studien untersucht wurden (38). Basierend auf unseren Erfahrungen und der Lernkurve mit dem ECMO-System haben wir in Kooperation mit dem Unternehmen Eurosets GmbH ein eigenes modulares System entwickelt, bei dem die einzelnen Komponenten unabhängig voneinander ausgetauscht werden können. Im Fokus stand dabei vordergründig die

Flexibilität im individuellen Zusammenstellen des Systems, so dass u.a. Pumpen und Oxygeneratoren unabhängig vom Hersteller frei miteinander kombinierbar sind. Dieses Konzept kommt sowohl Low-Volume- als auch High-Volume-Zentren zugute, da die vorhandenen Systeme effizient eingesetzt werden können. Ferner wurde die Hämokompatibilität des Systems durch die Oberflächenbeschichtung mit Phosphorycholin sichergestellt (40, 41), so dass die systemische Antikoagulation bei erhöhter Blutungsneigung oder das Vorhandensein von Heparin-induzierter Thrombozytopenie II (HIT II) auf ein Minimum reduziert werden. Unter kontinuierlicher Heparingabe lag die partielle Thromboplastinzeit im Durchschnitt bei 45 Sekunden. Eine Umstellung der Antikoagulation auf Argatroban erfolgte bei Vorhandensein einer HIT II. Die Inzidenz der Blutungen und thromboembolischen Komplikationen der behandelten ECMO-Patienten war vergleichbar mit denen bereits publizierter Studien (42). Bezüglich der Effizienz der Oxygenierung und Decarboxylierung zeigte das eigens konzipierte System verglichen mit anderen Konzepten hervorragende Eigenschaften (34, 43). So war es möglich, die Beatmungsintensität in Übereinstimmung mit den Therapierichtlinien unmittelbar vor Ort zu deeskalieren und eine lungenschonende Beatmung während der Rekonvaleszenzphase zu etablieren. Insgesamt entsprach die Rate der erfolgreich vom ECMO entwöhnten Patienten, den bereits veröffentlichen Daten (12, 44). Beim Vergleich der in dieser Studie erhobenen Daten war der Schweregrad der Patientenerkrankung mit denen bereits publizierter Studien anhand der SOFA- und Murray-Scores vergleichbar (34, 43). Insbesondere der Schweregrad der kardiopulmonalen Dysfunktion entsprach der Literatur, was sich im PaO2 / FiO2-Verhältnis, der Hyperkapnie, der Beatmungszeit vor ECMO, dem mittleren arteriellen Blutdruck und der Katecholamintherapie widerspiegelte (43, 45). In Anbetracht der erhobenen Daten ähneln sich nicht nur die Patientenkohorte, sondern auch die Implementierungszeiträume und Herangehensweisen mit denen in der Literatur Beschriebenen, was die Vergleichbarkeit des eigen konzipierten Systems hinsichtlich der Performanz möglich macht (33, 46).

Die Komplexität des gesamten Setups erfordert angemessene Algorithmen für eine effiziente Patientenauswahl und Risikostratifizierung (47). Ein Hauptkriterium solcher Algorithmen ist das Geschlecht des Patienten. Für die temporären Unterstützungssysteme wie ECMO/ECLS gibt es bis dato hinsichtlich der Rolle des Geschlechts zur Risikostratifizierung keine Daten, obwohl für langfristige kardiale Unterstützungssysteme (LVAD) bereits geschlechtsspezifische Hinweise als prädiktive Parameter zur

Pumpenthrombose und Mortalität zuungunsten der Frauen ausfielen (48). Eine kürzlich durchgeführte Metaanalyse konnte zeigen, dass Komplikationen wie zerebrovaskuläre Ereignisse und Rechtsherzinsuffizienz nach der LVAD-Implantation bei Frauen signifikant häufiger auftreten als bei Männern (49). Cifkova et al beschreibt verschiedene geschlechtsspezifische Unterschiede im Zusammenhang mit Herz-Kreislauf-Erkrankungen (50). In Übereinstimmung mit diesen Daten zeigen unsere Ergebnisse der transportierten ECMO/ECLS Patienten ein signifikant schlechteres Überleben der Frauen, obwohl die Zahl der reanimierten männlichen Patienten vor den Implantationen höher ausfiel und sich beide Gruppen in den Ausgangswerten nicht signifikant unterschieden. Grundsätzlich ist die Gesamtüberlebensrate von 50 % mit der anderer ECO/ECLS Studien vergleichbar. Der Grund der geschlechtsspezifischen Unterschiede kann generell nicht durch retrospektive Studien evaluiert werden. Dafür bedarf es einer weiteren Grundlagenforschung. Da geschlechtsspezifische Unterschiede aber auch in der Aortenchirurgie eine Rolle spielen, schlagen einige Autoren im Vorfeld hormonelle oder genetische Untersuchung vor, um eine effiziente Diskriminierung der Patienten zu gewährleisten (51). Obwohl die zugrundeliegenden Ursachen noch untersucht werden müssen, liefern unsere aktuellen Daten wichtige Belege für die Einbeziehung des Geschlechts in Algorithmen der Risikostratifizierung.

Interventionelle Aortenklappentherapie (TAVI):

In der Einführungsphase der TAVI-Therapie beschränkte sich die Indikation auf multimorbide, nicht operable Patienten. Zu diesem Zeitpunkt wurden die Evaluierungsstudien zum Stellenwert der Therapie initiiert. Die Daten und das Feedback der Anwender bildeten für die Hersteller die Grundlage zur Weiterentwicklung der Implantationssysteme und Prothesenkonzepte. In dieser Frühphase der TAVI-Therapie entstanden die Studien dieser Arbeit, die sich ebenfalls mit Zugangswegen und Prothesenkonzepten der TAVI-Therapie auseinandersetzten. Angelehnt an der PARTNER-1 Studie (52) haben wir die Beobachtungen für unsere Lernkurve auf eine Anzahl von 30 Patienten festgelegt.

Das große Kaliber der Implantationssysteme der ersten Generation in Kombination mit der Fragilität multimorbider Patienten in der Initiierungsphase führte häufig zu lebensbedrohlichen Blutungskomplikationen der iliofemoralen Gefäße mit schwer-wiegenden Folgen für die gesamte Prognose (53). Um die Therapie unabhängig von der Qualität der peripheren Arterien zu gewährleisten, war das Etablieren alternativer

Zugänge notwendig. Zu diesem frühen Zeitpunkt haben wir uns für den TAo-Zugang aus den folgenden Gründen entschieden. Der Zugangsweg über (Sternotomie/Thorakotomie) und der Umgang mit der Aorta asc. sind Bestandteil der täglichen Routine eines jeden praktizierenden Herzchirurgen. Sowohl der Prothesentyp als auch der Durchmesser der Implantationssysteme spielen bei diesem Zugang keine wesentliche Rolle. Zudem bietet dieser Zugang im Vergleich ein Alleinstellungsmerkmal, da bei vollständiger Sternotomie eine simultane Bypass Operation am schlagenden Herz durchgeführt werden kann. Derartige Operationen verliefen in unserer Kohorte an 5 Patienten komplikationslos, was uns in der Wahl dieses Konzeptes bestätigte.

Der TAo-Zugang kann entweder über eine rechtsseitige Mini-Thorakotomie oder über eine Mini-J-Sternotomie erfolgen. Beide Zugänge haben ihre spezifischen Vorteile. Für eine Thorakotomie spricht eine vorhandene horizontale Aorta und die Existenz retrosternaler offener Bypässe bei Reoperationen (54). Die Mini-J-Sternotomie verursacht theoretisch weniger Schmerzen als eine Thorakotomie. Darüber hinaus werden die Pleuren im Normalfall nicht eröffnet, was einen positiven Einfluss auf die postprocedurale Atemfunktion hat. Im Vergleich mit bereits publizierten Studien (54, 55) favorisierten wir den sternalen Zugang, da die Wand der Aorta auch am Übergang zum Truncus brachiocephalicus häufig qualitativ besser als die poststenotisch dilatierte dünnwandige Aorta ascendens ist. In einer durchgeführten Metaanalyse haben Amrane et al gezeigt, dass trotz limitierter Erfahrung mit unterschiedlichen thorakalen Zugangswegen und implantierten Systemen, die Datenlage homogen war (55). Die bereits vorhandene chirurgische Routine des Zuganges erklärt ebenfalls unsere durchschnittliche vaskuläre Komplikationsrate von 3%. Bei beiden PARTNER-Studien (A und B) lag die Komplikationsrate der peripheren Gefäßzugänge hingegen bei 10 %, was sich ebenfalls direkt auf die Kurzzeitmortalität auswirkte (56), (26).

In unseren Ergebnissen konnten wir zeigen, dass die chirurgische Lernkurve des TAo-Zuganges trotz geringerer Patientenanzahl flach ist. Die einzigen Parameter, die sich im Verlauf signifikant verbesserten, waren der Verbrauch an Kontrastmitteln und die Reduktion der Strahlenexposition. Durch die Perpendikularität und die Nähe zur nativen Klappe erlaubt der TAo-Zugang eine kontrollierte präzisere Positionierung der Prothese, die zu einer geringen Rate an schwereren paravalvulären Leckagen (durchschnittlich 7,5 %) führt (54). Der Prozedurerfolg lag bei beiden Gruppen bei über 90 %. Die Implantation einer zweiten Prothese war bei 9 % der Patienten notwendig, wobei sich zwischen beiden Kohorten keine signifikanten Unterschiede herausstellten.

Für die Indikation einer zweiten Prothese in unserer Kohorte war das Vorhandensein einer mittel- bis hochgradigen paravalvulären Leckage ursächlich, die auf diese Weise bei allen Patienten erfolgreich beseitigt werden konnte.

Dementsprechend wurde kein Patient der Kohorte mit mittlerer und hochgradiger paravalvulärer Leckage entlassen.

Die 30-Tage-VARC (Valve Academic Research Consortium) Sicherheits- und Effektivitäts-Endpunkte (57) als Maßstab der Implantationsqualität wurden in der Initiierungsphase nur bei 50 % der veröffentlichten Studien berücksichtigt und schwankten zwischen 9 bis 31 % mit einem gepoolten geschätzten Wert von 16,7% (58). Unser errechneter Wert lag bei 35 %, was auf den ersten Blick hoch erscheint. Interessanterweise fällt dieser Wert beim gleichen Risikoprofil der beiden Gruppen in der Frühphase geringer aus. Die meisten der nach unserer Erfahrung gemeldeten frühen Sicherheitsereignisse nach VARC-Kriterien (VARC 3a) sind als schwere Blutungen eingestuft. In den meisten dieser Fälle kam es während der Prozedur tatsächlich zu einer Abnahme des Hämoglobins um mindestens 3 g / dl. Dies war hauptsächlich das Ergebnis einer extremen perioperativen Hämodilution, die in Folge eine Bluttransfusion erforderte. Nur ein Patient musste aufgrund chirurgischer Blutungen revidiert werden.

Die 30-Tage-Mortalität der TAo TAVI lag bei einer Metaanalyse gepoolt bei 9,9% (58). Unsere errechneten Daten seit Beginn unserer Erfahrungen mit diesem Zugang bestätigten dieses Bild. Im alternativen endovaskulären Zugangsarm der CoreValve US Pivotal-Studie dokumentierten Reardon et al eine einjährige Gesamtmortalität von 36% für TAVI-Patienten (59). Die einjährige Gesamtmortalität fiel in der TF-Kohorte derselben Studie sichtlich geringer aus und lag bei 26% (60). In einer Serie von 100 TAo TAVI-Patienten, die mit einer ballonexpandierbaren Prothese behandelt wurden, dokumentierten Petzina et al eine Langzeitmortalität von 38% (61). Daten aus dem britischen TAVI-Register legen nahe, dass transapikales und TAo-TAVI mit ähnlichen Überlebensraten assoziiert sind, die beide signifikant schlechter als diejenigen, die bei TF-Zugang beobachtet wurden, ausfielen (62).

In Bezug auf die 1-Jahres-Mortalität der eigenen TAo-Kohorte gab es keine signifikanten Unterschiede zwischen beiden Phasen (Lernphase 24,1% gegenüber der späteren Phase 28,9%; P = 0,6). Sie sind vergleichbar mit denen anderer TAo-Erfahrungen, auch wenn sie geringfügig höher als die internationaler TF TAVI

Register, die mit derselben selbstexpandierbaren Prothese der ersten Generation durchgeführt wurden, ausfallen (63, 64).

In der ADVANCE-Studie dokumentierten Linke et al eine 12-Monats-Gesamtmortalität von 17,9% (64). In ähnlicher Weise veröffentlichten Barbanti et al eine einjährige Gesamtmortalität von 21% im Clinical Service Project (63).

Tatsächlich beobachteten wir, dass mehr als die Hälfte unserer Todesfälle auf nicht kardiovaskuläre Gründe zurückzuführen waren. In diesem Zusammenhang entspricht unsere einjährige kardiovaskuläre Mortalität von 13,2% eher den im ADVANCE (11,7%) und im Clinical Service Project (10%) veröffentlichen Daten (63, 64).

Aufgrund der oben genannten Ergebnisse und der erworbenen Expertise der Abteilung wurden wir vom Hersteller der gleichnamigen metallfreien Prothese Direct Flow Medical® beauftragt, den TAo-Zugang für die Prothese als alternativen Zugang zu evaluieren. Diese Arbeit war die Basis für die Zulassung eines alternativen Zuganges für die Prothese.

Für die weltweit erste Implantation wurden nach Rücksprache mit dem Hersteller Modifikationen der Prozedur vorgenommen, die eine reibungslose Implantation und das Wiederfangen der Prothese trotz des kurzen Abstandes zwischen der Schleuse und der nativen Klappe gewährleisten. Verglichen mit den ersten Erfahrungen zur TF-Implantation der Direct Flow Prothese in der DISCOVER-Studie, bei der die Inzidenz der Gefäßkomplikationen bei 2,7% lag, waren während unserer Studie zur TAo-Implantation keine relevanten Gefäßkomplikationen zu verzeichnen (65). Nach den VARC-2 Kriterien traten bei der Mehrheit der Patienten keine (67%) und wenn dann nur geringgradige (33%) paravalvuläre Leckagen auf. Diese Eigenschaft war ein Spezifikum der Prothese, da sich das metallfreie Gerüst der Prothesen an die subvalvulären Unebenheiten der nativen Klappen anpasste (66). Gleichzeitig wurde eine geringere Radialkraft der Prothese in Kauf genommen, auch wenn dies bei einer asymmetrisch starken Verkalkung zu höheren transvalvulären Gradienten (>15 mmHg) führte, da das Kalk die Prothese in ihrer Entfaltung hinderte (67). Mit der Intraprocedural Dilatation (IDIL) Technik entwickelten wir weltweit die erste Prozedur zur Optimierung der Protheseninflation durch Steigerung der Radialkraft mittels eines intravalvulären valvuloplasty Ballons. Im Gegensatz zur post-interventionellen Ballonvalvuloplastie der metallhaltigen Prothesen ist die IDIL-Technik ein optionaler, aber integraler Bestandteil der Implantation, falls die Prothese nicht zur optimalen

Entfaltung kommt. Bei allen Patienten gelang es dadurch, den transvalvulären Gradienten zu normalisieren und die Inflationsform der Prothese zu optimieren. Die potenziellen Risiken der IDIL-Technik hängen dabei mit der Tatsache zusammen, dass der Gefäßzugang für die Diagnostik von 5 bis 6 Fr auf 11 bis 12 Fr steigt. In diesem Zusammenhang traten bei unseren Patienten keine vaskulären Komplikationen auf. Zudem zeigte die 30-tägige Echokardiographie-Nachuntersuchung keine negativen Auswirkungen der IDIL-Technik auf die Prothesenfunktion.

Zusammenfassung

In den dieser kumulativen Habilitationsschrift zugrunde liegenden Arbeiten wurden mehrere Aspekte der klinischen Versorgung von multimorbiden Patienten mit kardiopulmonalen Dysfunktionen untersucht. Zunächst zeigten die retrospektiven Studien, dass mit dem eigens konzipierten temporären Unterstützungssystem die Implantation und der Transport der multimorbiden Patienten mit kardiopulmonalem Versagen effizient und sicher sind, sofern ein erfahrenes interdisziplinäres Team zur Verfügung steht. Bezogen auf das Überleben der transportierten ECMO/ECLS Patienten wies das weibliche Geschlecht eine signifikant schlechtere Prognose auf.

Anschließend zeigten unsere retrospektiven Studien zur interventionellen Versorgung der multimorbiden Patienten mit Aortenklappenstenose, dass der TAo-Zugang ein vielversprechender und sicherer alternativer endovaskulärer Zugang ist. Neben einer technisch flachen Lernkurve zeigte er zum anderen eine signifikante Reduktion des Kontrastmittelverbrauches und der radiologischen Exposition im Verlauf. Er eignet sich nicht nur zur Implantation selbstexpandierbarer sondern auch metallfreier Prothesen. Dieser Zugangsweg bietet eine direkte und genaue Kontrolle des gesamten Implantationsverfahrens. Darüber hinaus können zusätzliche Manöver wie Neupositionierung, Extraktion und IDIL implementiert werden.

Der kardiovaskuläre Sektor der Gesundheitsversorgung wird zunehmend durch die multimorbiden Patienten im Kontext des demographischen Wandels herausgefordert. Mit unseren Daten lässt sich zusammenfassend feststellen, dass die optimale Versorgung dieser anspruchsvollen Patientengruppe innovative intersektorale individualisierte Therapiekonzepte erfordert.

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Hiermit erkläre ich die vorliegende Habilitationsschrift selbständig und ohne unerlaubte fremde Hilfe angefertigt zu haben. Ich habe keine anderen als die im Literaturverzeichnis angeführte Quellen benutzt und sämtliche Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder unveröffentlichten Schriften entnommen wurden, sowie alle Angaben, die auf mündliche Auskünfte beruhen, als solche kenntlich gemacht. Ich versichere weiterhin, dass diese Arbeit nicht vorher und auch nicht gleichzeitig bei einer anderen als der Medizinischen Fakultät der Universität Rostock zur Eröffnung eines Habilitationsverfahrens eingereicht worden ist.

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Inter-hospital transfer of ECMO-assisted patients with a portable miniaturized ECMO device: 4 years of experience

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Abstract

Objectives: Extracorporeal membrane oxygenation (ECMO) in patients with severe pulmonary failure is able to keep patients alive until organ regeneration, until shunting out for further diagnostic and therapeutic options or until transportation to specialized centers. Nonetheless, extracorporeal techniques require a high degree of expertise, so that a confinement to specialized centers is meaningful. Following from this requirement, the need for inter-hospital transfer of patients with severely compromised pulmonary function is rising.

Methods: We report about our experience with a portable ECMO system during inter-hospital air or ground transfer of patients with cardiopulmonary failure.

Results: The portable ECMO system was used for transportation to the center and in-hospital treatment in 36 patients with an average age of 53 years suffering from respiratory failure. Accordingly, the ECMO system was implanted as a veno-venous extracorporeal system. Pre-ECMO ventilation time was 5.2 (2-9) days. Twelve patients were transported to our institution by ground and 24 patients by air ambulance over a median distance of 46 km. With the assistance of the ECMO device, prompt stabilization of cardiopulmonary function could be achieved in all patients without any technical complications. Post-ECMO ventilation was 9.8 days. Weaning from the ECMO system was successful in 61% of all patients after a median device working period of 12.7 days; median ICU stay was 34 days and a survival rate of 64% of patients was achieved. Technical (8%) and device-associated bleeding (11%)/thromboembolic (8%) complication rates showed very acceptable levels.

Conclusion: Our experience demonstrates that miniaturized, portable ECMO therapy allows location-independent, out-of-center stabilization of pulmonary compromised patients with consecutive inter-hospital transfer and further in-house treatment, so that sophisticated ECMO therapy can be offered to every patient, even in hospitals with primary healthcare.

Keywords

extracorporeal membrane oxygenation; miniaturized; portable extracorporeal system; pulmonary failure; inter-hospital transport

Introduction

Despite current medical advances and implementation of state-of-the-art management guidelines,[1] pulmonary failure remains the leading cause of death in hospitalized patients, regardless of etiologies. Mortality still remains high, approaching 70% in some settings.

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Extracorporeal membrane oxygenation (ECMO) systems provide immediate and adequate systemic oxygenation.[2] However, ECMO is not a cure, it is a life support system that creates time for evaluation, diagnosis and treatment of the condition that caused heart, lung or combined failure. Its usefulness has become controversial and has been seriously questioned as, in some prospective, randomized trials, the use of ECMO versus conventional therapy did not show beneficial, but even harming effects, implying that ECMO may not impact positively on mortality.[3] Renewal of interest in ECMO therapy was due to a worldwide epidemic of H_1N_1 in 2009. Finally, the scientific proof of the beneficial effects of ECMO was furnished in the randomized controlled CESAR trial.[4] However, intensive care therapy of patients on ECMO systems today is still complex and, ideally, should be restricted to specialized centers offering more technical and personnel experience.[4-6] As a consequence of this requirement, those patients should, therefore, be transported to specialized centers.[4-6] However, critically ill patients with acute pulmonary failure are often incapable of transportation due to cardiorespiratory instability so that implantation and initiation of ECMO devices may be indicated before transport to one of these centers.[7] Although transporting patients with ECMO devices is a challenge,[6] it proved to be a budding option that increases patient safety by prompt cardiorespiratory stabilization, avoiding additional organ damage by de-escalation of breathing parameters and of catecholamine regimes.

Meanwhile, a couple of different commercially available ECMO systems have proven their effectiveness in case reports or retrospective analysis of small patient groups.[6,8,9] Regarding all the systems placed at our disposal and analyzing the advantages/improvement opportunities of all the available devices, our hospital, together with the company Eurosets, applied a modified tubing system for ECMO circuits. All utilized components are commercially available. Additionally, the tube system is so designed that the centrifugal pump and oxygenator can be interchanged and replaced by other available centrifugal pumps (e.g. Sorin Revolution 5, Thoratec Centrimag) (Figures 1-3). Furthermore, our designed device provides an arterial and venous pressure sensor and is equipped with completely heparin-free materials. Hemocompatibility was ensured by phosphorylcholine-coated surfaces. Last, but not least, our system features connectors for other emergency extracorporeal devices, such as renal replacement devices or rapid infusion systems (Figure 4).

In this manuscript, we report on our four-year experience in out-of-center ECMO implantation, consecutive inter-hospital transport and in-center therapy with our miniaturized ECMO device for patients with acute respiratory failure.

Patients and methods

Patients

From 2010 to 2013, portable ECMO devices were implanted in out-of-center hospitals in 36 adult patients followed by transfer to our institution thereafter. All patients suffered from pulmonary failure and, despite maximal conservative therapy, the patients' health conditions could not be stabilized and were life-threatening. All the patients were referred to our ECMO center from external hospitals via emergency telephone contact in the framework of our "Hallesches EcLs Program" (HELP). According to a standard procedure protocol, all relevant patient data were collected and indications as well as decision-making for ECMO therapy were set by a specialized medical team, according to actual guidelines.[1,6,8-12] Inclusion and exclusion criteria are listed in Table 1. After the patient was considered suitable for out-of-center ECMO implantation, the referring hospital was asked to optimize coagulation status, according to well accepted guidelines for puncturing central vessels.[13]

As the transport of critically ill patients is an interdisciplinary task, the team consisted of a cardiac anesthetist, a cardiac surgeon and a clinical perfusionist, who were all available 24 hours 7 days a week. Transport of the team and patient was carried out by a rescue helicopter, type Eurocopter EC145 (Christoph Sachsen-Anhalt, HSD Luftrettung gemeinnützige GmbH, Filderstadt, Germany) or by specially equipped mobile intensive care vehicles, featuring a generator supplying sufficient emergency power for the ECMO device.

Device

Normally, the Eurosets Universal ECMO Set Halle tube system was applied. The ECMO circuit consists exclusively of commercially available components. By default, a Thoratec Centrimag centrifugal pump was used, emphasizing that other designated pump heads (e.g. Sorin Revolution 5) could be used. (Figures 1-3) For each centrifugal pump, the corresponding console was used. This option makes the ECMO circuit independent from possible supply inconveniences by companies and warrants that the ECMO system can be connected with the newly developed, advanced oxygenator and centrifugal pumps. As a standard, the Eurosets Alone ECMO Adult oxygenator was used. Due to the phosphorylcholine-coated surface of the commissioned extracorporeal tube system (Eurosets Universal ECMO Set Halle), systemic anticoagulation kept to a minimum. The system has a priming volume

Table 1. Inclusion and exclusion criteria for ECMO implantation in adult patients with severe pulmonary failure at the University of Halle (Saale). Adapted from Refs 1,10.

Inclusion criteria	Exclusion criteria
- Life-threatening hypoxemic pulmonary failure (PaO_2/FiO_2 <65 mmHg, P_{peak} >35 cmH_2, PEEP >10 cmH_2O) for at least 2 h	- Cardiogenic shock (relative)
- Gas exchange strongly limited (P_{peak} >32 cmH_2O, FiO_2 > 0.9, tidal volume >6 ml/kg BW) despite optimizing of all conservative therapeutic strategies for at least 12-24 h (Murray score >2.5)	- Liver cirrhosis >Child B (relative)
- Uncompensated hypercapnia with acidosis (pH <7.15) despite the best accepted standard of care for management with a ventilator	- Terminal lung disease with no chance of a prompt transplantation
- Bronchopleural fistula	- Irreversible multi-organ failure - Evidence of irreversible brain damage or untreatable metastatic cancer - High-pressure ventilation (P_{peak} >30 cmH_2O) for >10 days - Any condition that precludes the use of anticoagulation therapy - Septic shock with dubious focus - Irrepressible bleeding - Limited vessel access

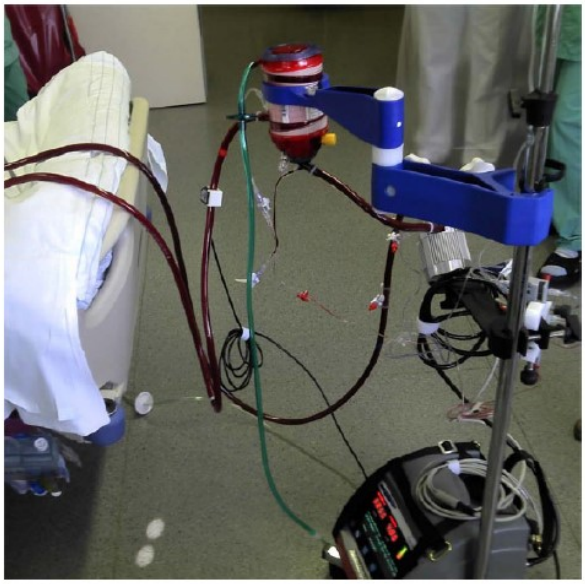

Figure 1. ECMO circuit using a Thoratec Centrimag centrifugal pump, a Eurosets Alone ECMO Adult oxygenator and a Eurosets Universal ECMO Set Halle.

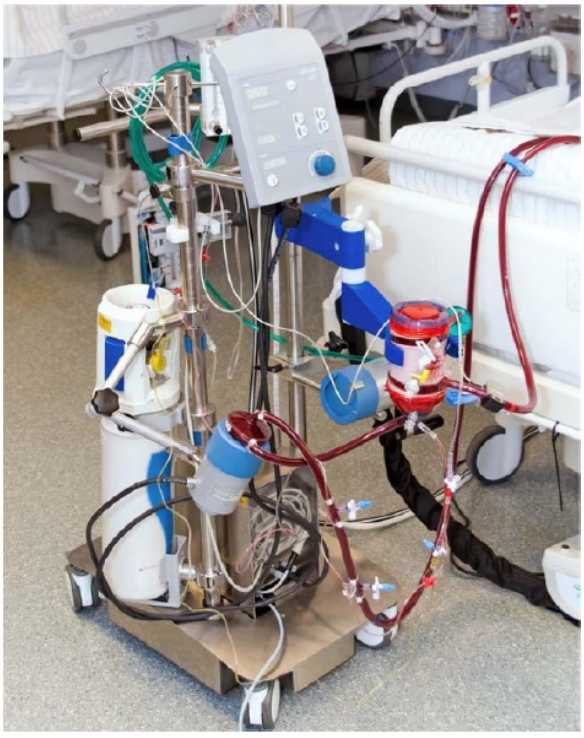

Figure 2. ECMO circuit using a Sorin Revolution 5, a Eurosets Alone ECMO Adult oxygenator and a Eurosets Universal ECMO Set Halle.

of 500 ml and features connectors for other emergency extracorporeal devices, such as renal replacement devices or rapid infusion systems for advanced in-center intensive care treatment during further courses of therapy. (Figure 4) During transportation of the patient, the ECMO oxygenator and head pump are safely fixed to the patient`s stretcher via a special metal bracket and the control module is firmly secured via accredited strap systems. A five-liter oxygen bottle

Figure 3. ECMO circuit during ground transportation with a strap system, using a Sorin Revolution 5.

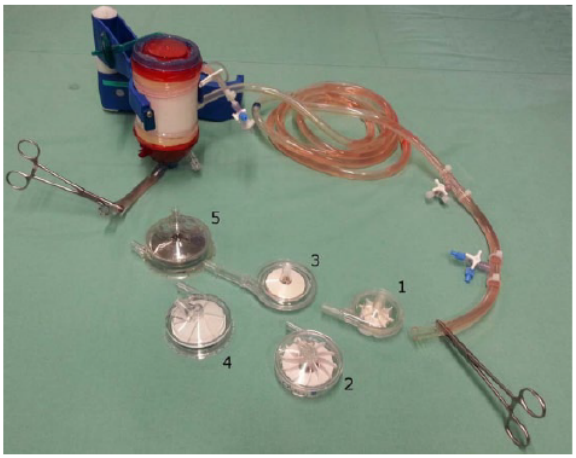

Figure 4. Composition of the Eurosets Universal ECMO Set Halle with all centrifugal pump heads available at our hospital and the Eurosets Alone ECMO Adult oxygenator; 1: Thoratec® Centrimag® Blood Pump; 2: Sorin Revolution™ Centrifugal Pump; 3: Maquet Rotaflow Centrifugal Pump; 4: Medtronic Affinity™ Centrifugal Pump; 5: Medtronic BPX-80 Bio-Pump®.

provides the required oxygen supply during transportation.

Cannula

In all patients, a 24 French cannula was used for blood drainage in the right femoral vein, whereupon restitution of the oxygenated blood was carried out by the same 24 French cannula in the left femoral vein (except one patient – left internal jugular vein due to impossibility of bi-femoral cannula placement).

Patient care

After onset at the requested hospital, the team re-evaluated and confirmed the evidence for implanting the ECMO system (Table 1). The decision was based on the actual laboratory results, on respiratory findings and on actual echocardiography to evaluate left- and right-ventricular function.[1,6,10,11]. Reaching a consensus, all concerned medical departments were interviewed to verify the evidence and to suspend any contraindication (Table 1). If possible, approval of the patient or family members was obtained. Vascular access was achieved using an ultrasound-guided Seldinger technique, verifying the correct position of the guidewire via echocardiography. A 24-French cannula was used for inflow in the right femoral vein with the tip placed in the inferior vena cava, crossing right atrium and, for blood drainage, a venous 24-French cannula was placed in the left femoral vein with tip in the femoral vein crossing to the inferior vena cava. After connection of the ECMO system, brief stabilization followed with improvements in hemodynamics and oxygenation. After cardiopulmonary stabilization, actual blood gas analyses were performed pre- and post-oxygenator and from the patient`s arterial line to adapt and optimize the ventilator support and echocardiography was carried out to verify the position of the cannula tip and, especially, to evaluate right ventricular function.

Results

During 2010 to 2013, 36 patients were directly admitted to the HELP with out-of-center in-loco implantation of the ECMO device due to severe respiratory failure. The clinical course consisted of rapid in-hospital deterioration with early ICU admission for ventilator support. Diagnoses leading at the forefront of severe respiratory failure are listed in Table 2. The Murray score was used to evaluate respiratory failure severity and the sequential organ failure assessment (SOFA) score to quantify total organ failure severity before ECMO implantation (Table 2). In three patients, cardiopulmonary resuscitation had to be performed due to non-cardiac reasons prior to ECMO implantation (Table 2).

Pre-ECMO ventilation, oxygenation and hemodynamic parameters, as well as lactate levels and catecholamine therapy, are shown in Table 3, demonstrating a strongly compromised oxygenation ratio with hypercapnia despite high peak pressure ventilation being wholly contradictory with lung-protective ventilation (Table 3).

Post-ECMO ventilation, oxygenation and hemodynamic values and catecholamine levels are reproduced on Table 4, indicating a stabilized oxygenation ratio, normocapnic conditions under de-escalated ventila-

Table 2. Demographic data of patients provided with an ECMO device out-of-center.

	Number or Median (Min-Max)
Number of patients	36
Age	53 (16–74)
Gender	23 x male 13 x female
BMI (kg/m²)	28.9 (19.4–51.4)
Days in hospital before ECMO	8.8 (5–14)
Ventilation before ECMO (days)	5 (2–9)
Resuscitation before ECMO	3
SOFA score	14.9 (9–21)
Murray score	3.1 (1.5–3.8)

BMI: body mass index; ECMO: extracorporeal membrane oxygenation; SOFA: sequential organ failure assessment.

tion and normalized mean arterial pressure with reduced catecholamine support compared to pre-ECMO (Table 4). Additionally, gas flow and oxygen concentration, as well as the revolutions per minute of the centrifugal pump (rpm) producing the non-pulsatile blood flow are specified.

Out-of-center ECMO implementation and airborne or ground transportation was performed without any system-related complications. The time on scene was 38 minutes and the transport distance from the referring hospital to our center covered 46 kilometers (Table 5).

In-house treatment with the 36 ECMO devices was maintained for 13 days. After explantation of the ECMO device, in 61% of all cases, the patients had to be ventilated for another 9.78 days before weaning was possible. Taken together, the median stay on ICU was 34 days and survival was 64% (Table 6).

During the entire study phase, the ECMO oxygenator had to be changed due to clotting in 3 cases after a mean time of 8 days of treatment. In no case did the centrifugal pump have to be replaced. Even with these technical disruptions, the patient`s safety was never compromised. Thromboembolic and bleeding events during the ECMO therapy occurred in 3 and 4 cases, respectively (Table 7).

Discussion

In our experience, ECMO support is a valuable therapeutic option for severe pulmonary failure. The use of portable systems allows the urgent rescue of patients from referring hospitals and safe inter-hospital transport.[6,8,9] Different miniaturized ECMO devices have been previously shown to be efficient and safe in a large sample of adults with severe respiratory failure.[6,8,9,14,15]

Table 3. Patient characteristics before ECMO implantation.

Pre-ECMO	Mean ± SD or Median (Min-Max)
PaO_2 / FiO_2 (mmHg)	85 (59–140)
$PaCO_2$ (mmHg)	79 (55–95)
Lactate (mg/dL)	4.9 (0.6–17)
Mean arterial blood pressure (mmHg)	55.8 ± 7.7
Norepinephrine (µg/kg/min)	0.9 (0.2–2)
Ppeak (mmHg)	35 (31–40)

ECMO: extracorporeal membrane oxygenation; Ppeak: peak ventilation pressure; $PaCO_2$: partial arterial carbon dioxide pressure; PaO_2: partial arterial oxygen pressure; FiO_2: oxygen concentration; SD: standard deviation.

Table 4. Patient characteristics after ECMO implantation and ECMO device data.

Post-ECMO	Mean ± SD or Median (Min-Max)
PaO_2 / FiO_2 (mmHg)	185.1 (81.6–258.0)
$PaCO_2$ (mmHg)	38 (25–58)
Mean arterial blood pressure (mmHg)	83.4 ± 18.3
Norepinephrine (µg/kg/min)	0.39 (0.04–1.32)
Ppeak (mmHg)	26 (21–32)
Gas flow ECLS (l/min)	5 (2–10)
FiO_2 Ventilation (%)	68 (30–100)
FiO_2 ECMO (%)	82 (60–100)
Centrifugal pump drive (rpm)	3665 (2300–7400)
Blood flow (L/min)	4.2 (2.3–9)

ECMO: extracorporeal membrane oxygenation; Ppeak: peak ventilation pressure; $PaCO_2$: partial arterial carbon dioxide pressure; PaO_2: partial arterial oxygen pressure; FiO_2: oxygen concentration; SD: standard deviation.
All values were detected ~1hour after onset at the ECMO center.

Table 5. Transport characteristics and results of ECMO inter-hospital transfer.

	Median (Min-Max) or Number
Implementation time (min)	38 (18–68)
Kind of transport	24 airborne transportation 12 ground transportation
Transport distance (km)	45.5 (3.5–115)
Complications during transport	0

ECMO: extracorporeal membrane oxygenation; Min: minutes; Implementation time: interval between patient`s bedding for ECMO support and start of ECMO.

Adapted to evolving engineering improvements and recent scientific findings, ECMO has become an auspicious device in the treatment of patients with acute cardiorespiratory failure. Veno-venous ECMO

Table 6. Follow-up data of patients with ECMO during in-center treatment.

	Number or Median (Min-Max)
Days on ECMO	12.7 (1.0–25.0)
Days on ventilator post-ECMO	9.8 (0–69)
Weaning (%)	61.0
Days on Respirator	34 (1–103)
Days in hospital	35.4 (1–103)
Survival (%)	63.9

ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation.

Table 7. Technical, thromboembolic and bleeding complications (n) of patients treated with ECMO devices out-of-center during the whole study period.

Thromboembolic events	
Myocardial infarction	1
Pulmonary embolism	1
Limb ischemia	0
Apoplexia	1
Technical	
Change oxygenator	3
Change centrifugal pump	0
Severe cannula dislocation	0
ECMO arrest	0
Bleeding	
Intracranial bleeding	1
ECMO-associated bleeding	3

ECMO: extracorporeal membrane oxygenation.

as a therapeutic option for severe respiratory failure has attracted growing acceptability in recent years.[4,6] Additionally, indications for the implementation of these systems also seems to be in flux because veno-venous ECLS is deemed to be a promising device to accomplish and guarantee lung protective or ultra-protective ventilation in addition to mere emergency therapy for refractory hypoxemia, hypercapnia and acidosis.[6,10,12]

However, the prevalent practice of ECMO should not imply that its application is extraneous and without potentially life-threatening complications, particularly when performed out-of-center.[6,7] In addition, subsequent intensive care treatment of patients on ECMO systems requires a lot of experience and fully-fledged teams. Therefore, as requested by several studies and reviews, the ECMO procedure should be restricted to specialized centers.[4-6,9] As the severity of the underlying disease is dynamic and can be aggravated with rapid progression over time in patients with cardiorespiratory failure, transportation of these patients to specialized centers is often risky and sometimes impossible.[6,8] Even within the distinguished CESAR trial, three patients died before they could be transferred and two died in the course of transit, so the authors propose the initiation of ECMO therapy at the referring hospital as a favorable answer.[4] Despite its complexity, transporting patients on ECMO is described to be accomplishable and safe, if conducted by a cross-functional expert-team.[6,8,9] In our institution, the Hallesches EcLs Program (HELP) was established, composed of the availability of a skilled team and an adequate means of conveyance 24 hours 7 days a week. This procedure is in accordance with other ECMO centers.[6,8,9,16,17] In addition to trained personnel, an extracorporeal device specially designed and adopted for the needs of inter-hospital transportation is, likewise, essential. A couple of device options are on the market, which have already been tested in single-center analyses for inter-hospital transfer.[6,8,9,16,17] However, during our own use of these systems in previous times, a couple of improvement opportunities, problems or refinements occurred to us, so that our institution, together with Eurosets, applied a modified tube system for ECMO circuits that is so designed that the centrifugal pump and oxygenator can be interchanged and replaced by other available centrifugal pumps. Especially in institutions with restricted amounts of centrifugal pumps or in departments with a great rate of different extracorporeal devices, as well as a consequent high amount of maintenance and repair, this option grants the ECMO team a great degree of freedom for the procurement and availability of ECMO devices in-house and out-of-center as well as enabling a high degree of capacity utilization of these expensive devices. Furthermore, the usage of any disposable oxygenator or pump-head application of the ECMO system is independent of possible supply problems from companies and guarantees, thus, the ECMO system can be used with all redeveloped, cutting-edged oxygenators or centrifugal pumps. The minimal technical complication rate, which is at least as low as reports from the literature, confirmed the efficacy and ease of application.[12] The median transportation time of 22 minutes could be easily covered by the battery-driven power supply of the centrifugal pump. However, because of patient safety concerns during transportion, the power cord of the ECMO system has to be connected to the vehicle`s power system to spare the internal battery. Furthermore, in accord with other devices, our tube system also provides an arterial and venous pressure sensor.[8,9] The online pressure monitoring of the venous line proved to be quite advantageous for assessing the patient`s volume status. Online pressure monitoring of the arterial line reassures the correctness of the tube position.

As the incidence of heparin-induced thrombocytopenia type II (HIT-II) has been increasing in the last

few years,[18] as extracorporeal assist devices per se are an independent risk factor for HIT-II[19] and as critically ill patients with impaired coagulation status and decreased thrombocytes quantifying a HIT-II diagnosis cannot be completely excluded, we decided to routinely use heparin-free materials for our device. Therefore, patients with the diagnosis or being under a cloud of HIT-II could be treated with our ECMO system. Hemocompatibility was ensured by phosphorycholine-coated surfaces which have already been scientifically proven in the literature[20,21] and, therefore, systemic anticoagulation also could be reduced to a minimum. Last, but not least, our system is routinely featured with connectors for other devices, such as extracorporeal renal replacement therapy or emergency infusion systems, for optimal advanced in-house intensive care treatment during further courses of therapy.

Due to the very specialized procedure, the inhomogeneity of patient demographic data, the illness severity, the disease entity, the variable approaches of different ECMO teams in specialized centers and due to the inconsistent indicators for ECMO implantation, the literature only provides a couple of single center experiences with small patient numbers. Comparing our data with the experience of these studies, illness severity demonstrated by the SOFA and Murray scores was comparable.[8,17] Also, the severity code of cardiac and pulmonary organ dysfunction is in accordance with the literature, reflected by the PaO_2/FiO_2 ratio, hypercapnia, ventilation time before ECMO, mean arterial blood pressure and catecholamine therapy.[8,17,22] Taking these data into consideration, our patients seem to be a representative control sample drawn from the population of pulmonary compromised patients. Astonishingly, apart from different collocation, approach and expertise of the teams described in the literature, the implementation time in our study was comparable to the literature, certifying the same simple adaptability of our device in comparison to the other systems.[6,9] Complication rates during transport and during in-house treatment were at least as low as recorded in previous papers. This emphasizes the safety and absolute reliability of our self-designed ECMO device.[17] In the literature, a technical complication rate, including oxygenator change, of up to 27% of all patients is described.[10] Cannulation was mostly performed (97%) in a bi-femoral fashion in our patient cohort due to it producing reduced recirculation phenomena, resulting from non-contiguous blood streams, due to the possibility of generating very high blood flows up to 7 L/min and due to the simplified positioning and anchoring of the cannula and the ECMO device resulting in a prevention of cannula dislocation during transport. Of course, constrictions in mobilization grades during weaning and the higher potential risk of thrombus formation, especially at the position of tube interference, are possible disadvantages of bi-femoral cannulation. Exploring the effects of the heparin-free, phosphorycholine-coated extracorporeal surface of our device, we investigated the incidence of thromboembolic as well as bleeding episodes in ECMO-treated patients during the whole course of disease and detected comparable values to previous ECMO studies, confirming the safety of our system;[23] as the incidence of leg ischemia was numbered in the literature between 3.7-37.5%, the frequency of venous thrombosis was estimated at 10%, the incidence of stroke between 3.9-9,7% and the incidence of ECMO-related bleeding between 14.8-63.7%.[10,12,23]

During implantation, no further anticoagulation was administered and, during continuance of ECMO therapy, low-dose anticoagulation (either with unfractionated heparin or, in the case of HIT-II, with argatroban) was performed, seeking a target activated partial thromboplastin time of 40-45 seconds.[8] As a result of the better biocompatibility of modern systems, the intensiveness of systemic anticoagulation treatment can be reduced, resulting in decreased fatal bleeding complications.[10]

Concerning the efficacy in regard to oxygenation and CO_2 removal, our ECMO therapy showed excellent performance and stacked fully equivalent up against the other ECMO centers.[8,17] As a consequence, the invasive degree of mechanical ventilation could immediately be reduced permanently in all the described cases so that lung-protective ventilation could be performed according to the generally accepted guidelines. In this study, weaning from ECMO and consequent outcome showed data that were comparable with other studies from well-established ECMO centers.[5,10]

Taken together, miniaturized, portable ECMO therapy allows location-independent, out-of-center stabilization of pulmonary compromised patients with consequent inter-hospital transfer and further in-house treatment, so that sophisticated ECMO therapy can be offered to every patient, even in hospitals with primary healthcare.

Declaration of conflicting interest

The authors have no conflicts of interest to declare.

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Arbeit 2:

Gender-Dependent Clinical Outcome and Other Predictors of In-Hospital Mortality Following Out-Of-Center Extracorporeal Membrane Oxygenation and Extracorporeal Life Support: A Single Center Experience

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Gender-Dependent Clinical Outcome and Other Predictors of In-Hospital Mortality Following Out-Of-Center Extracorporeal Membrane Oxygenation and Extracorporeal Life Support: A Single Center Experience

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ABSTRACT

Background: Out-of-center extracorporeal membrane oxygenation (ECMO) and extracorporeal life support (ECLS) implantation for the treatment of acute cardiorespiratory failure with subsequent transport to a tertiary care center has been introduced successfully into the medical practice. However, due to the very specific and resource intensive nature of this therapeutic concept, it seems important to generate algorithms for adequate patient selection. The aim of our study was to analyze the impact of patients' gender on early clinical outcome in this specific therapeutic scenario.

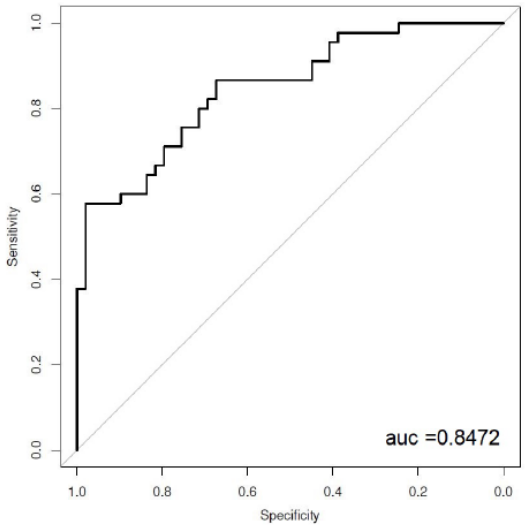
Methods: Ninety-seven consecutive patients treated by out-of-center ECMO/ECLS implantation and subsequent transport and treatment in our tertiary care cardiovascular center within the Hallesche Extracorporeal Life Support Program (HELP) retrospectively were analyzed, regarding the impact of patients' gender on early clinical outcome.

Results: Mechanical circulatory support successfully was weaned in two-thirds of the male patients. This result was achieved in only one-third of the female patients (59.4% in male vs. 33.3% in female, P = .0267). Overall survival significantly was higher in the male group (62.5% in male versus 30.3% in female, P = .0052). In uni- and multivariate logistic regression analysis, female gender was an independent predictor of in-hospital mortality (uni: OR:3.833, CI:1.597-9.745, P = .0034; multi: OR:3.477, CI:1.146-11.494, P = .0322). Worse outcome also was associated with following independent predictors, age, SOFA score, lactate and ventilation time pre-ECMO/ECLS implantation.

Conclusion: The current study demonstrates a worse early survival for women, following emergent out-of-center ECMO/ECLS implantation and subsequent transport and treatment in our tertiary care cardiovascular center. Gender should be included in patient selection algorithms while basic research approaches are needed to better understand the mechanisms underlying these gender-specific outcome disparities.

INTRODUCTION

Acute cardiorespiratory failure remains a life-threatening complication. Especially in critically-ill patients, immediate mechanical circulatory support often is the only therapeutic option to avoid permanent end-organ damage and consequent fatal outcome [Chen 2008; Sayer 2012]. However, the immediate



ROC-analysis of multivariate regression model of in-hospital mortality. AUC = area under the curve.

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Table 1. Baseline parameters prior ECMO/ECLS implantation

Parameter	Overall	Male	Female	P	
Patient number (n)	97	64 (65.98%)	33 (34.02%)		
Type of support (vv, va)	72vv 25va	46 vv (63.89%) 18 va (72.00 %)	26 vv (36.11%) 7 va (28.00%)		
Age (years)	55.0 (45.0 – 64.0)	53.5 (44.8 – 61.0)	59.0 (46.0 – 70.0)	.1620	n.s.
Height (cm)	175.0 (166.0 – 180.0)	179.5 (175.0 – 184.0)	165.0 (165.0 – 168.0)	< .00001	***
Weight (kg)	85.0 (75.0 – 102.5)	90.0 (75.0 – 110.0)	80.0 (75.0 – 90.0)	.1761	n.s.
BMI (kg/m²)	28.2 (24.8 – 33.1)	27.8 (24.6 – 33.1)	29.0 (25.7 – 32.7)	.3934	n.s.
Hospital stay prior support (days)	5.0 (2.0 – 9.0)	5.0 (2.0 – 9.0)	7.0 (3.0 – 11.0)	.2494	n.s.
Ventilation time prior support (days)	2.0 (1.0 – 5.0)	2.0 (1.0 – 5.3)	3.0 (1.0 – 5.0)	.4302	n.s.
CPR prior support (n)	19 (19.6%)	16 (25.0%)	3 (9.1%)	.1095	n.s.
SOFA score (pts.)	14.0 (12.0 – 16.0)	14.0 (12.0 – 16.0)	14.0 (12.0 – 16.3)	.9291	n.s.
Murray score (pts.)	3.0 (2.5 – 3.5)	3.0 (2.3 – 3.3)	3.3 (2.8 – 3.5)	.0096	**
APACHE II score (pts.)	28.0 (25.75 – 32.0)	28.5 (25.0 – 31.0)	28.0 (26.8 – 32.0)	.6442	n.s.

APACHE II: Acute Physiology And Chronic Health Evaluation II; BMI: body mass index; CPR: cardio-pulmonary resuscitation; SOFA: Sequential Organ Failure Assessment; va: veno-arterial; vv: veno-venous; n.s.: non-significant. *$P < .05$ **$P < .01$ ***$P < .001$; All data are presented as n (%) or median (IQR)

Table 2. Respiratory, hemodynamic and laboratory data prior to ECMO/ECLS implantation

Parameter	Overall	Male	Female	P	
PaO2/FiO2 (mmHg)	81.53 (70.00 – 110.00)	81.50 (70.23- 110.00)	81.53 (70.00 – 102.50)	.9752	n.s.
PaCO2 (mmHg)	69.00 (46.19 – 82.00)	68.00 (45.33 – 79.25)	72.00 (46.46 – 85.50)	.1929	n.s.
Mean arterial pressure (mmHg)	64.00 (57.00 – 76.00)	64.00 (56.75 – 75.25)	63.00 (58.00 – 77.00)	.5027	n.s.
Noradrenalin (µg/kg/min)	0.45 (0.19 – 0.83)	0.40 (0.15 – 0.83)	0.50 (0.20 – 0.85)	.6209	n.s.
Peak inspiratory pressure (mmHg)	32.00 (28.25 – 36.00)	32.00 (26.50 – 35.00)	35.00 (29.50 – 36.00)	.1356	n.s.
Lactate (mg/dl)	3.40 (1.38 – 6.71)	2.72 (1.30 – 6.13)	4.58 (1.50 – 8.45)	.1068	n.s.
pH	7.38 (7.23 – 7.46)	7.35 (7.23 – 7.46)	7.40 (7.24 – 7.50)	.4122	n.s.
Creatinine (µmol/l)	158.00 (97.00 – 235.00)	157.50 (90.50 – 244.50)	161.00 (110.00 – 224.00)	.7929	n.s.
INR	1.35 (1.14 – 1.63)	1.35 (1.13 – 1.55)	1.35 (1.19 – 1.69)	.5783	n.s.

INR: international normalized ratio; n.s.: non-significant; All data are presented as n (%) or median (IQR)

availability of both extracorporeal membrane oxygenation systems (ECMO, VV-ECMO) for the treatment of respiratory failure and extracorporeal life support systems (ECLS, VA-ECMO) for the treatment of cardiac failure is limited to specialized tertiary care centers, since the use requires multidisciplinary expertise and infrastructure [Beckmann 2011; Philipp 2011; Sayer 2012; Thiagarajan 2009]. As the critical patient's status often prohibits transport to such tertiary care centers, the concept of out-of-center ECMO/ECLS implantation successfully has been introduced into the clinical practice, based on recent advances in mobile mechanical circulatory support technology.

This concept includes the implementation of a specialized and mobile multidisciplinary team on permanent standby for emergent implantation of a ECMO/ECLS system in a remote hospital followed by patient transport to the tertiary care center for subsequent management, thereby increasing the patient's chance of survival [Raspé 2015; Rückert 2017].

However, despite recent advances of this approach toward establishing mobile ECMO/ECLS networks on a regional scale, there still is a lack of adequate patient selection criteria as well as systematic evaluation of early outcome parameters.

In the current retrospective study, we investigated the impact of patients' gender on the early outcome following out-of-center ECMO/ECLS implantation and subsequent transport and therapy to our tertiary care center.

Table 3. Indication/diagnosis leading to ECMO/ECLS implantation

Indication/diagnosis	N
ARDS	73 (75.26%)
Pulmonary infection	36
Aspiration	10
Sepsis	7
Other reasons	10
Unknown	10
Cardiogenic shock	24 (24.74%)
Myocardial infarction	14
Dilated cardiomyopathy	5
Pulmonary embolism	4
Postoperative cardiomyopathy	1

PATIENTS AND METHODS

Study design and period: The Hallesche Extracorporeal Life Support Program (HELP) for the treatment of acute respiratory and/or cardiac failure has been introduced in 2009.

We report here 97 consecutive patients treated by ECMO/ECLS implantation in a remote hospital by our mobile ECMO/ECLS team, since the start of the program in 2009 until 2015. After the implantation and initial hemodynamic stabilization, all patients were transferred to our center for subsequent diagnostic and therapy. In the analyzed cohort, 72 patients required ECMO for primary respiratory failure; 25 patients were treated by ECLS for primary cardiac failure.

Data prospectively were collected and retrospectively analyzed. Patients and/or their legal representatives signed consent to treatment and to the collection of their clinical information for possible future data analysis. The study was approved by our institutional review board. (Ethical Committee of Medical School Martin-Luther-University, Halle-Wittenberg, Germany, working-number 2015-122).

ECMO/ECLS team and logistics: The referring outside hospital contacts our center (Mitteldeutsches Herzzentrum, Halle, Germany) by phone via a central hotline. Relevant medical data (patient demographics, hemodynamic and ventilation parameters, and organ and laboratory values) were transferred via an online platform. A multidisciplinary team on 24/7 standby, consisting of a cardiac surgeon and anesthetist, evaluate the available medical data with our standard protocol. In parallel, the ECMO/ECLS system and required materials are prepared by a perfusion technician on-call. Once the patient has been accepted for treatment, the whole team immediately is dispatched to the referring hospital, where ECMO/ECLS support is instituted as fast as possible.

ECMO/ECLS implantation: Both systems (ECMO and ECLS) are based on a custom-made system named HELPer©. The system consists of a centrifugal pump (Centrimag©, St. Jude Medical Thoratec or Revolution 5©, LivaNova) and a membrane oxygenator (Alone ECMO Oxygenator Adult©, Eurosets). The system is primed with 500ml of 0.9% sodium chloride solution. During transport oxygen supply is secured via a 5l oxygen bottle.

Venous cannulation is performed in a percutaneous fashion in all cases via the femoral vein, utilizing a 70cm 24-French cannula (Duraflow, Edwards Lifesciences). In case of ECMO support, the second venous cannula is placed via the contralateral femoral vein, thereby placing the outflow cannula in the right atrium and the inflow cannula at the transition of the inferior vena cava and the iliac vein so to avoid blood recirculation. In one patient, percutaneous placement of a second femoral cannula was not feasible so a jugular vein was used for placement of the outflow cannula. The position of the outflow cannula within the right atrium is verified by transthoracic echocardiography and immediately corrected, if necessary.

In the case of ECLS system, a 23cm 17-French arterial cannula (HLS, Maquet) is placed in a percutaneous fashion in the femoral artery. In addition, all ECLS patients receive another 9 French arterial cannula (Super arrow flex, Arrow) to facilitate antegrade leg perfusion. If there is enough time during implementation of the ECLS system, this cannulation is performed after separate puncture of the femoral artery, otherwise leg perfusion would be monitored through INVOS™ Somatic Oximetry Adult Sensors (Medtronic). If necessary, additional cannula is placed during ICU stay.

After commencing mechanical circulatory support, stabilization of the hemodynamics and adequate oxygenation, the patient is prepared for transport. Because of the severe hemodynamic or pulmonary situation, the patients were intubated and sedated for transport. (median APACHE-II-Score of 28, first quartile: 25.75, third quartile: 32.00).

During transport, heart rate, invasive arterial blood pressure, and peripheral oxygen saturation continuously are monitored. Peripheral oxygenation and blood pressure are invasively measured at the right forearm in the arteria radialis in order to estimate effective coronary and cerebral perfusion. Mean arterial blood pressure over 60 mmHg and peripheral oxygen saturation over 90% are the goals of treatment.

For more information about methods and material, please consult previously published articles of this study [Raspé 2015; Rückert 2017].

Statistical methods: Two groups were identified, according to gender. Due to the non-normally distributed data, Mann-Whitney-U-Test was used for the comparison of quantitative variables between the male and female groups. The tests were two-tailed, and *P*-values of $< .05$ were considered statistically significant. Categorical variables were compared using chi-square test and Fischer-exact test whenever required. Uni- and multivariate linear regression analysis was used to verify gender and other parameters as independent predictors of mortality. Regression modelling estimates are presented as the mean (95% confidence intervals).

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Table 4. Respiratory, hemodynamic, laboratory data post ECMO/ECLS implantation and clinical outcome following ECMO/ECLS implantation

Parameter	Overall	Male	Female	P	
PaO2 / FiO2 (mmHg)	142.29 (101.95 – 247.51)	158.17 (104.57 – 261.28)	129.25 (97.91 – 201.14)	.3450	n.s.
PaCO2 (mmHg)	37.31 (32.00 – 41.00)	37.86 (32.75 – 42.06)	35.91 (32.00 – 38.27)	.1818	n.s.
Mean arterial pressure (mmHg)	80.50 (70.50 – 91.50)	81.00 (70.50 – 89.25)	79.00 (69.75 – 96.50)	.8057	n.s.
Noradrenalin (µg/kg/min)	0.14 (0.04 – 0.40)	0.13 (0.04 – 0.31)	0.16 (0.06 – 0.50)	.4909	n.s.
Peak inspiratory pressure (mmHg)	26.50 (24.00 – 30.00)	26.00 (23.00 – 29.00)	28.00 (26.00 – 30.00)	.0079	**
Gas flow ECMO (l/min)	5.00 (4.00 – 6.00)	4.50 (3.75 – 6.50)	5.00 (4.00 – 5.25)	.7348	n.s.
FiO2 ventilator (%)	73.00 (56.00 – 90.00)	71.00 (53.50 – 90.50)	75.00 (59.50 – 90.00)	.6989	n.s.
FiO2 ECMO (%)	90.00 (80.00 – 100.00)	100.00 (80.00 – 100.00)	80.00 (77.50 -100.00)	.0594	n.s.
rpm ECMO	3400.00 (2937.75 – 3900.00)	3325.00 (2805.50 – 3887.50)	3500.00 (3175.00 – 4050.00)	.1128	n.s.
Blood flow (l/min)	4.20 (3.67 – 4.92)	4.20 (3.62 – 5.00)	4.10 (3.73 – 4.69)	.9397	n.s.
Creatinine (µmol/l)	73.00 (46.00 – 128.75)	80.00 (50.00 – 141.75)	63.00 (37.50 – 102.25)	.2122	n.s.
Overall therapy time (days)	22.00 (10.00 – 45.00)	26.50 (14.00 – 45.25)	19.00 (7.00 – 35.00)	.1344	n.s.
Ventilation time (hours)	429.00 (165.00 – 671.00)	430.50 (167.00 – 671.50)	341.00 (168.00 – 604.00)	.6169	n.s.
Weaning (N, %)	49 (50.52%)	38 (59.38%)	11 (33.33%)	.0267	*
ICU time (days)	22.00 (10.00 – 45.00)	26.50 (13.00 – 45.25)	19.00 (7.00 – 35.00)	.1374	n.s.
Overall survival (N, %)	50 (51.55%)	40 (62.50%)	10 (30.30%)	.0052	**
Time on ECMO/ECLS (days)	11.00 (7.00 – 17.00)	11.00 (8.00 – 18.00)	12.00 (6.00 – 17.00)	.8878	n.s.

ICU: intensive care unit; rpm: rounds per minute; n.s.: non-significant; All data are presented as n (%) or median (IQR).
*$P < .05$ **$P < .01$ ***$P < .001$

RESULTS

ECMO/ECLS implantation and baseline data: A total 97 patients were treated with an emergent ECMO/ECLS implantation in an outside hospital. ECMO/ECLS implantation was uneventful in all cases. Of the patients, 72 were treated with an ECMO system, due to respiratory failure; 25 patients received an ECLS system, due to acute cardiac failure. There were 64 male patients and 33 female patients.

There only were only two significant differences between the two gender groups, regarding the baseline medical data (Table 1). Female patients had a smaller body size ($P < .00001$) and a higher Murray-Score before ECMO/ECLS was implanted ($P = .0096$). The pre-implantation hemodynamic and respiratory data immediately before ECMO positioning also were similar in the two groups (Table 2).

The most frequent diagnoses leading to ECMO/ECLS implantation are listed in Table 3. Pulmonary infection was the main cause for implantation of ECMO, while acute myocardial infarction (with or without cardiopulmonary resuscitation) was leading cause for implantation of ECLS (Table 3). Post-implant hemodynamics, oxygenation, and organ function: In both groups, ECMO/ECLS implantation resulted in an optimized oxygenation and hemodynamic status. Optimized oxygenation resulted in higher PaO2/FiO2 ratio in both groups, whereas hemodynamic stabilization resulted in higher mean arterial pressures and reduced doses of noradrenalin. Consequently, re-compensation of organ function was achieved in both groups, represented by a significant drop of serum creatinine compared with pre-implantation values (Table 4).

After 72 hours of ECMO/ECLS therapy, significant higher values of PaO2/FiO2 and mean arterial pressure ($P < .001$, $P < .001$) and significant lower values of Ppeak, Norepinephrine and PaCO2 ($P < .001$, $P = .013$, $P < .001$, respectively) were achieved.

The main functional parameters of the ECMO/ECLS systems, such as blood flow, rates per minute and Oxygenator FiO2 did not significantly differ between the two groups (Table 4). Only peak inspiratory pressure after 72 hours of ECMO/ECLS significantly differs between male and female patients ($P = .0079$).

Clinical outcome: Duration of the ICU stay, respirator times and mechanical circulatory support times did not significantly differ between the two groups. However, there was a significant difference, regarding the percentage of patients successfully weaned from the ECMO/ECLS system and likewise regarding the overall survival. While mechanical circulatory support successfully was weaned in two-thirds of the male patients, this result was achieved in only one-third of the female patients (59.4% in male versus 33.3% in female,

Table 5. Thromboembolic and bleeding complications (N) during the study period, consumption of blood products and renal replacement therapy

Complications	N (%)	Median (IQR)
Thromboembolic events	9	
Myocardial infarction	(0.00%)	
Pulmonary embolism	(3.09%)	
Arm ischaemia	(1.03%)	
Limb ischaemia	(5.15%)	
Apoplexy	(0.00%)	
Bleeding events	(0.00%)	
Intracranial bleeding	(10.31%)	
Device site bleeding	(30.93%)	
Technical complications		
Change oxygenator	30x in 22 patients (22.68%)	
Change centrifugal pump	(5.15%)	
Dislocation of canula, stillstand of ECMO/ECLS, transport complications	(0.00%)	
Blood products		
Red cell concentrate	10.31% without any transfusion	12.00 (5.00 – 23.00)
Fresh frozen plasma	41.24% without any transfusion	4.00 (0.00 – 16.00)
Platelet concentrate	44.33% without any transfusion	1.00 (0.00 – 4.00)
Renal replacement therapy		
Dialysis before treatment	(6.19%)	
Dialysis in hospital	(54.46%)	
Time of dialysis (h)		18.70 (0.00 – 102.00)
Chronic dialysis	(4.12%)	

All data are presented as N (%) or Median (IQR)

P = .0267). Similarly, overall survival significantly was higher in the male group (62.5% in male versus 30.3% in female, P = .0052) (Table 4). Complications, transfusion management and renal replacement therapy during the whole hospital stay are shown in Table 5.

To identify predictors of in-hospital mortality, a univariate logistic regression analysis was performed (gender, age, pre-ECMO/ECLS hospital and ventilation days, SOFA score, APACHE II score, Murray score, PaO2/FiO2, PaCO2, lactate, pH, PEEP, INR, dialysis, cancer disease). With the significant factors of univariate logistic regression, we performed a multivariate logistic regression analysis and were able to identify female gender, age, pre-ECMO/ECLS ventilation days, SOFA score and lactate as independent predictors for in-hospital mortality (Table 6). In multivariate analysis, female gender was the strongest independent predictor of in-hospital mortality. (Odds ratio 3.477, 95% confidence interval 1.146 –11.494, P = .032 for multivariate regression).

To test the created model, we also performed a ROC-analysis (receiver operating characteristic). The area under the curve was 0.8472 (Figure).

DISCUSSION

Recent clinical evidence underlining the general efficacy of ECMO/ECLS systems in specific acute clinical settings has further supported the implementation of concepts for out-of-center ECMO/ECLS implantation [Raspé 2015; Rückert 2017].

For example, both the results from the CESAR trial [Peek 2010] as well the reported results among patients with severe H1N1 influenza [Noah 2011] have supported the different ECMO systems as a major therapeutic option in acute respiratory distress syndrome. In case of acute cardiac failure, a recent meta-analysis reported not only improved neurologic outcome and survival in patients treated with ECLS [Khorsandi 2017; Sheu 2010], but also a significant advantage compared with treatment with an intra-aortic balloon pump [Ouweneel 2016].

Due to technical improvements resulting in high compactness of both systems, out-of-center implantation increasingly is feasible in all of the described clinical settings and allows for early onset of the organ support and coverage of the patient transport back to tertiary care centers [Philipp 2011]. Due to the given complexity of this acute therapeutic setting,

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Table 6. Multivariate logistic regression analysis of in-hospital mortality

Factor	Odds Ratio	95%-CI	P	
Female gender	3.477	1.146 – 11.494	.0322	*
Age	1.067	1.021 – 1.122	.0077	**
Ventilation pre ECMO/ECLS (day)	1.162	1.023 – 1.351	.0322	*
SOFA Score (point)	1.207	1.019 – 1.453	.0358	*
Lactate (mmol/l)	1.161	1.015 – 1.356	.0419	*
Cancer disease pre ECMO/ECLS	3.854	1.058 – 16.792	.0509	n.s.

ECLS: Extracorporeal Life Support, ECMO: Extracorporeal Membrane Oxygenation, SOFA: Sequential Organ Failure Assessment score; n.s.: non-significant.
*$P < .05$ **$P < .01$ ***$P < .001$

prospective and randomized data, regarding the early survival and clinical outcome following out-of-center ECMO/ECLS implantation, is relatively rare. Current evidence consists mainly of retrospective analyses reporting a 30-day survival of around 30% in most studies.

However, with the required logistic for out-of-center ECMO/ECLS implantation set up in and around several tertiary care centers, it seems important to generate adequate algorithms for patient selection and/or risk stratification for this very specific and resource intensive therapeutic concept [Combes 2017]. One main criterion in such algorithms is the patient's gender.

The impact of the patient's gender on early survival, following out-of-center ECMO/ECLS implantation, has not conclusively been analyzed so far, although such data already exists for the setting of long-term mechanical circulatory support. For example, results from the EUROMACS registry report relevant gender differences, regarding outcomes after isolated LVAD implantation with the survival of women on isolated LVAD support described as significantly worse compared with men [Magnussen 2018]. In fact, women and men differed in perioperative hemodynamics, adverse events, and mortality after VAD implantation. A gender-dependent association of pump thrombosis with mortality was seen [Magnussen 2018].

Equivalently, a recent meta-analysis suggests women are at greater risk of significant complications, such as cerebrovascular events and right heart failure, after LVAD implantation [Blumer 2018]. Cifkova et. al described various gender-differences in the context of cardiovascular diseases [Cifkova 2019].

In line with these findings, our results following out-of-center ECMO/ECLS implantation and transport to our tertiary care center by our institutional team demonstrate a significantly worse survival for women, despite a lower incidence of pre-implant CPR in female patients, indicating an even more critical pre-implant status of analyzed male patients. Other baseline characteristics prior ECMO/ECLS implantation did not differ significantly between the two groups and an overall early survival of 50% was comparable to other reports analyzing out-of-center ECMO/ECLS implantation.

The reason for this outcome discrepancy between men and women obviously cannot be answered conclusively in a retrospective study like ours; it will require basic research approaches.

For example, authors investigating gender differences in outcomes after aortic aneurysm surgery suggest investigation of hormonal or molecular explanations for the sex differences in aortic disease [Makrygiannis 2014].

However, although underlying reasons remain to be examined, our current data provide important evidence, regarding the inclusion of patient's gender in algorithms integrating patient selection criteria for out-of-center ECMO/ECLS implantations.

Nevertheless, it must be noted that our results were obtained in only one ECMO/ECLS-center and patients' heterogeneity could influence different results of our study.

In conclusion, in this single center retrospective study, we have demonstrated according to other groups that emergent out-of-center ECMO/ECLS implantation is a feasible therapeutic option for the treatment of acute respiratory and/or cardiac failure when performed by specialized interdisciplinary teams out of a tertiary care center providing dedicated pre- and post-implant logistics. We found significantly worse early survival for women following emergent out-of-center ECMO/ECLS implantation and subsequent transport and treatment in our tertiary care cardiovascular center. Further research is needed to better understand the mechanisms underlying these gender-specific outcome disparities.

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Arbeit 3:

Transaortic Transcatheter Aortic Valve Implantation: Learning Curve, Perioperative, and Midterm Follow-Up Results of a Single Center

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Transaortic Transcatheter Aortic Valve Implantation: Learning Curve, Perioperative, and Midterm Follow-Up Results of a Single Center

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ABSTRACT

Background: We present our initial institutional experience with transaortic (TAo) transcatheter aortic valve implantation (TAVI) using a self-expanding aortic bioprosthesis.

Methods: A total of 106 patients underwent TAo TAVI with Medtronic CoreValve through a small partial upper sternotomy. We focus our analysis on the overall perioperative results, procedural learning curve (first 30 patients), and midterm follow-up outcomes.

Results: VARC-2 device success was achieved in 95 patients (89%), and there were no intraoperative deaths. Nine patients (8.4%) required a second valve and conversion to standard surgery was required in 2 patients (1.8%). The final aortic insufficiency was grade 0 in 65 patients (62%) and grade 1 in 39 (37%). Although patients treated in the TAo TAVI learning phase required a significantly longer radiation time and contrast agent use, device success (93.4% versus 88.2%; $P = .7$) and prostheses hemodynamics were similar. All-cause mortality at 30 days was 12% (13/106). At a median follow-up of 392 days (IQR: 216-494 days) estimated overall 1-year survival was 72%. No significant differences were reported in terms of 30-day and 1-year observed mortality, and estimated 1-year survival in the learning and later phase of TAo TAVI.

Conclusion: TAo TAVI can be performed safely even in the very early phase of the learning curve. Although satisfactory results can be achieved from the beginning, a significant reduction in contrast agent use and radiological exposure are expected as the technique is mastered. Good hemodynamics have been documented and should be further improved with modifications achieved in the TAVI self-expandable valves technology.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been proposed and popularized to treat symptomatic severe aortic stenosis (AVS) in selected patients at increased risk for conventional aortic valve replacement (AVR) on cardiopulmonary bypass (CPB) [Leon 2010; Smith 2011; Popma 2014]. TAVI with a transfemoral (TF) first approach has been used in most treating centers and should be the advocated strategy for the majority of referred patients. Although the ventricular trans-apical route is the one so far mainly used when TF-TAVI is not feasible, alternative accesses have been adopted in the clinical practice to limit the surgical invasiveness. In this context, the transaxillary, transcarotid, and transaortic (TAo) approaches have all been proposed as valid alternatives to TF TAVI [Thourani 2015a].

The cumulative experience with the TAo approach for TAVI using both self-expanding and balloon expandable prosthesis has shown encouraging results regarding feasibility, safety, and overall outcomes [Amrane 2017; Thourani 2015b; Bapat 2016; Bruschi 2015; Reardon 2014; Fröhlich 2015]. Clinical data in single-center everyday practices are still limited, as well as information concerning the learning curve of TAo and its follow-up outcomes.

For this reason, in the present manuscript, we summarize our initial institutional experience with TAo TAVI using a self-expanding aortic bioprosthesis. We focus our analysis on the overall results, procedural learning curve, and midterm follow-up outcomes.

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METHODS

Patients and Procedures

All patients were treated at the University Heart Center Halle/Saale, Germany, for symptomatic severe AVS from September 2012 through August 2014. Patients underwent TAVI with the Medtronic CoreValve self-expanding prosthesis (Medtronic, Minneapolis, MN, USA) using TAo access. All procedures were performed by the same senior surgeon (HB) or under his strict supervision.

The standard screening process included transthoracic and/or transoesophageal echocardiography (TTE/TEE), coronary angiography, and ECG gated multidetector computed tomography (MDCT) of the aortic valve, entire aorta, and iliofemoral vessels. The screening was aimed at defining the anatomy and geometry of the aortic unit and excluding

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Table 1. Preprocedural Data

	Overall (n = 106)	TAo Learning Phase (n = 30)	TAo Later Phase (n = 76)	P
Age, y	80.3 ± 6.2	79.4 ± 7.3	80.3 ± 5.4	.5
Log EuroSCORE	16.4 (IQR: 10.1-26.1)	17.3 (IQR: 8.4-22.6)	16.2 (IQR: 10.2-27.2)	.4
STS score	6.0 (IQR: 3.6-9.2)	7.3 (IQR: 3.6-10.7)	6.6 (IQR: 3.5-12.9)	.2
BMI, kg/m²	27.2 ± 4.5	28.4 ± 4.3	26.8 ± 4.4	.09
LVEF %	51.2 ± 14.3	47.7 ± 16.5	52.5 ± 13.0	.1
TEE aortic EOA, cm²	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	.2
Mean TransAo gradient, mmHg	41.0 (IQR: 30.0-49.2)	39.0 (IQR: 29.0-45.5)	42.0 (IQR: 31.2-52.2)	.6
Annulus diameter at CT	25.8 ± 9.9	25.5 ± 10.0	25.9 ± 9.9	.8

STS indicates Society of Thoracic Surgeons; BMI, body mass index; LVEF, left ventricular ejection fraction; TEE Aortic EOA, transesophageal echocardiography aortic effective orifice area; CT, computed tomography.

the presence of significant atherosclerotic disease of the ascending aorta.

In the present series, TAo TAVI was the chosen approach independently by the quality of the femoro-iliac vasculature. The decision for the access type was discussed and finalized by a dedicated multidisciplinary heart team, including the cardiologist and heart surgeon.

As for institutional policy, TAo TAVI is performed under general anesthesia, endotracheal intubation, and mechanical ventilation. A temporary pacemaker is placed in the right ventricle through the femoral vein to perform rapid ventricular pacing whenever required and as a back-up to treat complete atrioventricular block after TAVI.

Most of the surgical aspects of the TAo TAVI have been already clarified in the previous literature.

A partial upper sternotomy is the favored incision in our practice for the majority of patients. This incision is the one that most resembles the standard approach used for surgical AVR. After spreading the sternal edges with a minithoracotomy retractor, the aorta is identified, and digital palpation is used to confirm the absence of atherosclerotic plaques.

At this stage, an ascending aorta aortography is performed with a graduated pigtail to define the exact position of the entry site in relation to the aortic annulus. In fact, having the CoreValve a total stent length of 5.5 cm, the aortic entry site should be located at least at 6 cm from the aortic annulus. After opening the upper third of the pericardium, the pericardial edges are suspended, and two aortic purse-string sutures are placed at the aortic entry site.

The remaining parts of the procedure, including aortic cannulation, aortic balloon valvuloplasty, and TAVI are performed as previously described [Amrane 2017; Thourani 2015b; Bapat 2016; Bruschi 2015; Reardon 2014; Fröhlich 2015].

Data Collection and Statistical Analysis

All patients gave signed informed consent for treatment and use of their data for scientific research purposes. The study was approved by the local research committee, and no ethical committee evaluation was required, as the procedures and additional treatments described in the study are part of our clinical standard of practice.

After treatment and discharge, patients underwent a telephone based follow-up. Data were collected prospectively and analyzed retrospectively. Data are presented as rates for categorical variables and mean with standard deviation (normally distributed variables) or median with 75% interquartile ranges (IQR) (not normally distributed variables) for continuous variables. Variables normality has been tested by means of Wilk-Shapiro test.

To identify the possible impact of learning curve upon outcomes, two groups were identified. The first 30 TAo TAVI patients were considered as learning curve patients, in accordance with previously published evidence on patients undergoing transapical TAVI [Suri 2016].

Differences between the two groups were tested by means of unpaired Student t test, Mann-Whitney test, Person chi-square test, and Fischer exact test whenever appropriate.

Moreover, the effect of the learning curve was assessed by the time effectivity of the procedure focusing on operating time, contrast medium use, and fluoroscopy time. Changes during the study period were correlated with the consecutive number of the procedure (Spearman rank test). Linear regression was used to quantify the trends over time. Finally, Kaplan-Meier curves for survival were built, and estimated rates were reported for the overall cohort. Moreover, equality of survival distribution between patients belonging to the learning and later treatment phases was tested (Mantel-Cox, Breslow, Tarone-Ware).

The statistical calculations were run using the SPSS 11.0 software (SPSS for Windows, Chicago, SPSS).

RESULTS

Patients

A total of 106 patients underwent TAo TAVI with Medtronic CoreValve. The demographic and baseline

Table 2. Periprocedural Data

	Overall (n = 106)	TAo Learning Phase (n = 30)	TAo Later Phase (n = 76)	P
Valve 26 mm, n (%)	54 (51)	10 (33)	44 (58)	.04
Valve 29 mm, n (%)	41 (39)	19 (63)	22 (29)	
Valve 31 mm, n (%)	11 (10)	1 (3)	10 (13)	
Second valve implanted, n (%)	9 (8)	3 (10)	6 (8)	.8
Implantation time, min	111.3 ± 43.7	112.8 ± 27.3	111.0 ± 48.2	.8
Contrast agent, mL	120.6 ± 56.2	171.4 ± 46.2	99.3 ± 45.1	<.0005
Fluoroscopy time, min	14.2 ± 8.1	20.7 ± 9.4	11.8 ± 5.4	<.0005
VARC-2 device success, n (%)	95 (89)	28 (93)	67 (88)	.7
Mean Trans-Ao gradient, mmHg*	4.3 ± 2.4	5.0 ± 2.1	4.0 ± 2.5	.06
Final AI 0, n (%)*	65 (62)	22 (73)	43 (58)	.4
Final AI I, n (%)*	39 (37)	8 (27)	31 (42)	

*Two patients converted to standard aortic valve replacement are excluded.
VARC indicates Valve Academic Research Consortium; AI, aortic insufficiency.

clinical characteristics are summarized in Table 1. Although the cohort had a highly comorbid profile, as demonstrated by the high median logistic EuroSCORE of 16.4% and median Society of the Thoracic Surgeons predicted risk of mortality score (STS-PROM) of 6.0%, severe peripheral vascular disease (PVD) limiting a possible TF access was present in only 36 patients (34%).

Moreover, Table 1 shows no significant difference in the demographic and baseline surgical risk profile of the learning curve (first 30 TAo TAVI patients) and later phase TAo TAVI patients (76 patients).

Perioperative Outcomes

Procedural characteristics and composite endpoints according to Valve Academic Research Consortium (VARC) are presented in Table 2. VARC-2 device success was achieved in 95 patients (89%), and there were no intraoperative deaths. Partial upper sternotomy was performed in 100 patients (94%) and minithoracotomy in one patient (1%). Five patients (5%) underwent concomitant off-pump CABG and TAo TAVI through a full sternotomy.

All patients underwent an aortic balloon valvuloplasty with a non-compliant balloon before TAVI.

Nine patients (8.4%) required a second valve: 3 (10%) in the early phase and 6 (7.8%) in the later phase ($P = .7$) of the TAo experience. A second prosthesis of the same size (5 patients) or a larger size (4 patients) was used to treat persistent moderate to severe paravalvular leak. No valve migrations were reported.

Conversion to standard AVR was required in 2 patients (1.8%), in one patient to treat the consequences of acute coronary occlusion and in one patient to manage persistent severe aortic regurgitation. Both conversions occurred in the later phase of TAo experience.

Post-dilatation due to more than moderate aortic regurgitation was necessary in 8 patients (7.5%). Excluding the two patients undergoing conversion to surgical AVR on CPB, the final AI at TEE was grade 0 in 65 patients (62%) and grade 1 in 39 (37%).

Although patients treated in the TAo TAVI learning curve phase required a significantly longer radiation time and contrast agent use, device success (93.4% versus 88.2%; $P = .7$) and prostheses hemodynamics were similar in the two groups (Table 2).

Using Spearman test, there was no significant correlation between TAo TAVI overall implantation time and experience ($P = .2$). Fluoroscopy time and contrast agent amount decreased significantly during the study period (rho = -0.5, $P < .0001$ and rho = -0.7, $P < .0001$ respectively). At linear regression per every treated patient, there was a significant 7.5 seconds reduction in fluoroscopy time (B = -7.5, CI: -10.1/-5.0; $P < .0001$) and a decrease of 1.2 mL in used contrast agent (B = -1.2, CI: -1.4/-0.9; $P < .0001$).

Clinical Outcomes

Table 3 summarizes 30-day morbidity and mortality.

The incidence of access site (major vascular) complications was 3.7% (4/106 patients), and no aortic dissection was observed. Life-threatening bleeding occurred in 13% of patients (n = 14), whereas the median amount of transfused packed red blood cells was 1.0 (IQR: 0-2 units). Acute kidney injury developed in 20 patients (19%), though stage 2 and 3 injury was present in 7 (6.6%) and 2 (1.8%) patients. Myocardial infarction occurred periprocedurally in one case (1%) due to occlusion of the left coronary ostium by plaque shift (conversion to surgical AVR). One patient (1%) suffered from a major cerebral stroke. New pacemaker implantation was required in 29 cases (27%).

In synthesis, the 30-day VARC-2 early safety endpoint was reached overall in 35% (37/106) of the TAo patients, more specifically in 7 of the learning phase (23.3%) and 30 (39.5%) of the late

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Table 3. 30-day Morbidity and Mortality

	Overall (n =106)	TAo Learning Phase (n = 30)	TAo Later Phase (n = 76)	P
VARC early safety, 30-days, n (%)	37 (35)	7 (23)	30 (39)	.1
All-cause mortality, n (%)	13 (12)	2 (7)	11 (14)	.5
Acute kidney injury, stage 2 or 3, n (%)	9 (8)	3 (10)	6 (8)	.7
Major vascular complication, n (%)	4 (4)	0 (0)	4 (5)	.5
Life-threatening bleeding, n (%)	14 (13)	1 (3)	13 (17)	.08
Revision for bleeding, n (%)	1 (1)	0 (0)	1 (1)	1.0
Transfusion, unit RBC, n (%)	1 (IQR: 0-2)	1 (IQR: 0-2)	1 (IQR: 0-2)	.8
Myocardial infarction, n (%)	1 (1)	0 (0)	1 (1)	1.0
Stroke, n (%)	1 (1)	1 (3)	0 (0)	.2
Permanent pacemaker implantation, n (%)	29 (27)	10 (33)	19 (25)	.3

VARC indicates Valve Academic Research Consortium; PRBC, red blood cells.

phase (P = .1). All-cause mortality at 30 days was 12% (13/106) (TAo learning phase 7% versus TAo later phase 14%; P = .5).

Specific complications rates were similar in the learning and later phase of TAo TAVIs.

Follow-Up Outcomes

All surviving patients were discharged either to a rehabilitation center or home. One-year cardiovascular-related rehospitalization was observed in 10 patients (9.4%). No patient required additional intervention on the aortic valve at midterm follow-up. Overall mortality at one year was 27% (29/106) and cardio-vascular related death occurred in 14 patients (13.2%). At a median follow-up of 392 days (IQR: 216-494 days) estimated overall 1-year survival was 72%.

No significant differences in terms of 1-year observed mortality (learning phase 24.1% vs later phase 28.9%; P = .6) and 1-year estimated survival (learning phase 76% versus later phase 71%; P = .5) were reported between the learning and later phase TAo TAVI patients (Figure).

DISCUSSION

The present study represents possibly one of the largest single-center experiences with TAo TAVI and gives some new insights in terms of learning curve and midterm outcomes of this underused approach.

These patients were treated in a very early TAVI phase when the real benefits and feasibility of a mainly TF approach were not yet clear. At that time TAo TAVI was considered as a possible and reasonable approach independently by the quality of the femoro-iliac vasculature. In the present report severe PVD was present in only 34% of the patients and most of the treated patients could have been managed also using a TF approach.

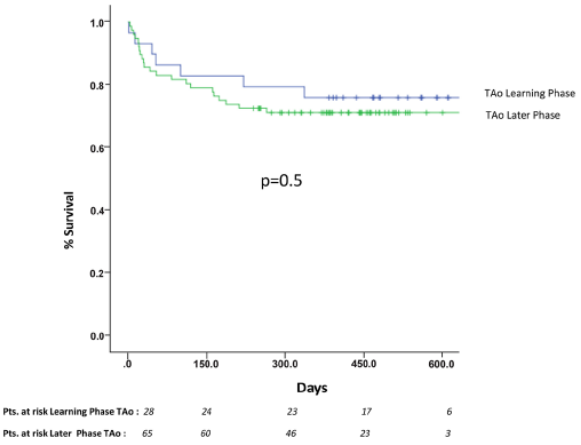
TAVI operators are nowadays aware that the TF approach is the gold standard. In fact, there are a limited number of TAVI candidates that, at least with the present technology, cannot be treated using the TF approach. Consequently, treating physicians have few opportunities to master alternative surgical approaches for TAVI.

While satisfactory results have been shown when using alternative approaches for TAVI, a learning curve should be expected before steady-state results can be achieved. In this context, the TAo route may represent the most familiar and easily learnable approach for the majority of surgeons for two main reasons: type of incision (sternotomy) and type of vascular access (ascending aorta cannulation) are part of the daily routine of every practicing cardiac surgeon. To further simplify the procedure, in our experience we have mainly adopted an upper partial sternotomy to guarantee for optimal distance between sheath entry point and native aortic valve annulus. Using this incision, the aorta immediately proximal to the brachiocephalic trunk can be reached. At this level, the aortic wall quality is often better than that observed in the more proximal post-stenotic and dilated ascending aorta site.

In a recent meta-analysis Amrane et al [Amrane 2017] showed that the reporting of TAo TAVI remains quite limited with not even 2000 cases documented in the existing literature. Although no specific investigation concerning the learning curve of TAo TAVI has been so far conducted, results seem to be homogenous independently by center experience (ranging from 13 to 94 patients for single-center studies), used surgical incision (partial mid-sternotomy or small-thoracotomy), and adopted TAVI prosthesis (self-expandable or balloon expandable) [Amrane 2017].

Although the majority of published TAo experiences have not reported results according to VARC criteria, the average device success rate of 91% and 30-day early safety rate of 16% are encouraging and comparable to those achieved with the TF approach [Amrane 2017].

This could be due to the fact that, as already emphasized, cannulation of the ascending aorta is mastered by every practicing cardiac surgeon and direct exposure of the vessel



Follow-up survival curves in patients undergoing TAo TAVI.

facilitates immediate and agile management of local complications. As a result, the vascular complication rate of TAo TAVI is 3% on average [Amrane 2017]. This satisfactory result has been achieved even in the earlier phases of TAo TAVI while adopting first generation TAVI prostheses that were loaded on higher profile sheaths. In the same context, both PARTNER trials (A and B) have reported a vascular complication rate of TF-TAVI over 10% with a direct relationship between short-term mortality and vascular complications [Leon 2010; Smith 2011].

Precise prosthesis positioning within the selected landing zone is one of the prerogatives to achieve adequate valve hemodynamics during TAVI. The vicinity between the ascending aorta entry point and the native aortic annulus guarantees for a controlled and timely prosthesis positioning that results in a low rate of residual severe paravalvular leak (6.7% on average) [Amrane 2017]. These results have to be interpreted in light of the fact that most of the reported TAo experiences (like the one herein presented) have included mainly patients treated with first-generation TAVI prosthesis where features of optimized valve sealing and prosthesis resheathability/repositionability were not yet available.

As confirmed in our findings the TAo TAVI learning curve is not steep and, after a contained number of patients, radiation exposure and contrast agent use are significantly reduced, and continue to decrease as operator experience increases.

We tested a learning curve cut-off of 30 patients that was already proposed in a sub-group analysis of the PARTNER-I trans-apical TAVI patients [Suri 2016]. It is noteworthy that none of the patients treated in the earlier phase of our experience required conversion to standard AVR and/or cardiopulmonary bypass support. Moreover, since the beginning of the TAo experience, device success was over 90%. Whenever necessary, implantation of a second valve occurred in 10% of the patients that were treated in the early phase. Implantation of a second valve was mainly adopted to manage severe residual paravalvular leak after final complete release of a first generation self-expandable and non-re-sheathable TAVI prosthesis. This may have led to a rate of second valve implantation higher than expected. Finally, none of the patients presented here experienced residual paravalvular regurgitation greater than mild at discharge. These results are expected to be further optimized since the recent introduction of fully repositionable and resheathable self-expandable TAVI devices that can also be implanted through the TAo route.

As already noted, the 30-day VARC early safety of TAo TAVI has seldom been reported (in only 50% of the existing studies) and has been ranging between 9% and 31% with a pooled estimated value of 16.7% [Amrane 2017]. Our proposed value of 35% within our global experience may seem in this context very high. Interestingly, at parity of patients risk profile, 30-day adverse events were less common in the early phase of the TAo experience. In any case, most of the early safety events reported in our experience have been categorized as major bleeding according to VARC criteria (BARC 3a). In most of these cases, in fact, there was a decrease in hemoglobin of at least 3 gr/dL during the procedure. This was mainly the result of extreme perioperative hemodilution. Blood transfusion rate was contained, and only one patient required revision for surgical bleeding.

In hospital 30-day mortality of TAo TAVI is within the ranges observed with the TF approach. Amrane et al calculated in their meta-analysis a pooled value of 9.9% [Amrane 2017]. Our reported 30-day mortality rate is in line with the values proposed in the literature, and it has remained contained since the beginning of our experience with TAo TAVI.

Follow-up outcomes after TAo TAVI have seldom been investigated. In the alternative access arm of the CoreValve US Pivotal Trial, Reardon et al documented a 36% one-year overall mortality rate for TAVI patients treated using either the trans-subclavian or TAo approach [Reardon 2014]. This value is slightly higher than the 26% all-cause one-year mortality rate observed in the TF cohort of the same trial [Popma 2014]. In a series of 100 TAo TAVI patients treated with an expandable balloon prosthesis, Petzina et al documented long-term mortality of 38% [Petzina 2017]. A 30.3% one-year mortality rate has been documented in a US multicenter experience with TAo TAVI using a balloon expandable device [Thourani 2015; Thourani 2015b].

Data from the UK TAVI registry suggest transapical and TAo TAVI to be associated with similar survivals that are both significantly worse than those observed with the TF and trans-subclavian routes [Fröhlich 2015].

Our 27% one-year all-cause mortality is comparable to those proposed in other TAo experiences, but it is slightly higher than those documented in real-world registries of TF TAVI with the same first generation self-expandable prosthesis [Linke 2014; Barbante 2015].

In the ADVANCE study, Linke et al documented a 12-month overall mortality rate of 17.9% [Linke 2014]. Similarly, Barbanti et al published a 21% one-year overall mortality in the Clinical Service Project [Barbanti 2015].

In reality, we observed that more than half of our follow-up deaths occurred for non-cardiovascular reasons. In this context, our one-year cardiovascular mortality of 13.2% is more in line

with the values proposed in the ADVANCE (11.7%) and Clinical Service Project (10%) [Linke 2014; Barbante 2015].

In any case, when we strictly focus upon the impact of the learning curve in TAo TAVI, we clearly see that even midterm survival is not influenced by the learning curve. In fact, estimated one-year survival remains similar in the early and later phase patients treated with TAo TAVI.

Conclusion

As the boundaries of TF TAVI are expanding, operators have a limited possibility to master alternative approaches for TAVI. In this context the TAo approach presents some characteristics that could make it more suitable to the standard cardiac surgery practice, whenever required.

We confirm that TAo TAVI can be performed safely even in the very early phase of the learning curve. Although satisfactory results can be achieved from the beginning, a significant reduction in contrast agent use and radiological exposure are expected as the technique is mastered with the increasing in experience. Good hemodynamic performances of the implanted TAVI prostheses have been documented and should be further improved with the recent modifications achieved in the TAVI self-expandable valves technology. Midterm follow-up outcomes are encouraging and in line with those observed when using the TF approach.

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Arbeit 4:

Direct aortic access for transcatheter aortic valve replacement with a fully repositionable and retrievable nonmetallic valve system

EVOLVING TECHNOLOGY: CARDIAC

Direct aortic access for transcatheter aortic valve replacement with a fully repositionable and retrievable nonmetallic valve system

Hasan Bushnaq, MD,[a] Dietrich Metz, MD,[a] Asen Petrov, MD,[a] Stefan Frantz, MD,[b] Ulrich Hofmann, MD,[b] Christoph Raspé, MD,[c] and Hendrik Treede, MD[a]

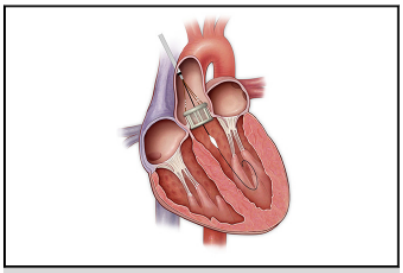
ABSTRACT

Objective: The standard procedure of transcatheter aortic valve implantation involves transfemoral access. Nevertheless, the use of this access route is limited by the vessel diameter, calcification, and tortuosity, making a subgroup of patients ineligible for peripheral access. We report the first use of direct aortic transcatheter aortic valve implantation with the Direct Flow Medical valve (Direct Flow Medical, Inc, Santa Rosa, Calif) in 15 patients at the Halle-Wittenberg University.

Methods: Between January 2014 and May 2015, 55 patients with severe aortic valve disease underwent transcatheter aortic valve implantation with the Direct Flow Medical valve at the Halle-Wittenberg University. Subgroups of 15 patients were treated using direct aortic access because of small vessel diameter, excessive calcification, or extreme tortuosity of the iliofemoral vessels.

Results: The mean patient age was 79.1 ± 6.72 years, and 10 patients (66%) were male. The mean logistic European System for Cardiac Operative Risk Evaluation was 23.4% ± 16.9%, and the mean Society of Thoracic Surgeons score was 7.8% ± 6.8%. Access related to redo-sternotomy during transcatheter aortic valve implantation was required in 4 patients (27%). Valve retrieval was performed in 2 patients (13%). There was no conversion to surgical aortic valve replacement and no incidence of major stroke. The postimplant mean gradient was 9.3 ± 2.5 mm Hg. No patient had moderate or severe paravalvular leakage. All patients survived the first 30 days.

Conclusions: Direct aortic access seems to be a feasible and safe endovascular alternative for implantation of the Direct Flow Medical valve. This access provides direct and accurate control of the entire implantation procedure. (J Thorac Cardiovasc Surg 2016;152:1611-5)



DFM valve implantation via the ascending aorta.

Central Message

DA access is feasible for implantation, repositioning, and retrieval of the DFM valve (Direct Flow Medical, Inc, Santa Rosa, Calif).

Perspective

In this study, we demonstrated that implantation of the DFM valve (Direct Flow Medical, Inc, Santa Rosa, Calif) via DA access is feasible and safe. Moreover, additional maneuvers could be performed during this access, which enables expansion of the prosthesis selection for this surgical approach.

See Editorial Commentary page 1616.

Despite major improvements in conventional surgical aortic valve replacement (SAVR), there remains a large patient population with a high operative risk.[1,2] Transcatheter aortic valve implantation (TAVI) has emerged as a less-invasive alternative to SAVR for extreme- and high-risk surgical patients.[3-5] TAVI can be performed through a variety of access sites,[6] and the transfemoral (TF) approach is the most widely used procedure.[7] However, this access is limited by the access vessel diameter, calcification, and tortuosity, making a subgroup of patients ineligible for TF TAVI. Alternative access routes, such as the direct aortic (DA), subclavian, and transapical access routes, have been established as viable alternatives for the treatment of these patients.[8-10]

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Abbreviations and Acronyms
DA = direct aortic
DFM = Direct Flow Medical
IDIL = intraprocedural dilatation
PVL = paravalvular leakage
SAVR = surgical aortic valve replacement
TAVI = transcatheter aortic valve implantation
TF = transfemoral

The Direct Flow Medical (DFM) valve (Direct Flow Medical, Inc, Santa Rosa, Calif) is a unique nonmetallic bovine aortic bioprosthesis. The inflatable and deflatable Dacron polyester frame enables precise positioning, complete repositioning, and full retrievability. Device success and early safety results have been reported in patients treated transfemorally.[11] We report the first experience of DA TAVI with the DFM valve in 15 patients treated at the Halle-Wittenberg University.

MATERIALS AND METHODS

Patients and Procedure

From January 2014 to May 2015, a total of 55 patients with severe aortic valve disease underwent TAVI with the DFM valve at the Halle-Wittenberg University according to recent recommendations.[12] All patients signed an informed consent form. The standard screening process includes transthoracic or transesophageal echocardiography, coronary angiography, and multidetector computed tomography of the aortic valve, entire aorta, and iliofemoral vessels. The multidetector computed tomography data were analyzed using 3mensio SDK Express software (3mensio Medical Imaging BV, Bilthoven, The Netherlands). The vessel and annular calcification were assessed, and the perimeter, area, and mean diameter of the aortic valve annulus were measured. On the basis of this evaluation, 40 patients were treated through the TF access. The remaining 15 patients were treated using the DA access because of poor peripheral vascular access as a result of a small vessel diameter, excessive calcification, or extreme tortuosity of the iliofemoral vessels or abdominal aorta. At that time, the DA access was the preferred alternative procedure. A dedicated multidisciplinary heart team consisting of a cardiologist, cardiac surgeon, perfusionist, and cardio-anesthesiologist discussed the access decision.

Direct Aortic Access Implants Description

All procedures were performed in a hybrid operating room under general anesthesia. DA access and valve deploy were performed according to standard techniques, as described by Reardon and colleagues.[10]

However, our protocol demanded procedural modifications: After marking the aortic annulus by a 5F pigtail catheter positioned in the noncoronary cusp, DynaCT (Artis Zee; Siemens Healthcare Solutions, Erlangen, Germany) of the aortic root was performed. An upper J-mini-sternotomy or a 5-cm incision in the second intercostal space facilitated aortic access. With increasing experience, mini-sternotomy was favored. A mini-retractor exposed the ascending aorta for placement of 2 purse-string sutures at least 6 cm above the aortic valve. A 7F catheter was inserted. Under fluoroscopic guidance, a Terumo wire was advanced through the aortic valve and exchanged for a curved Amplatz super stiff guidewire (Boston Scientific, Natick, Mass). An 18F introducer was placed in the ascending aorta and fixed by a modified arm. A TRUE Dilatation Balloon (BARD, Tempe, Ariz) was used for valvuloplasty under rapid pacing. Overlay 3-dimensional fluoroscopy based on DynaCT and transesophageal

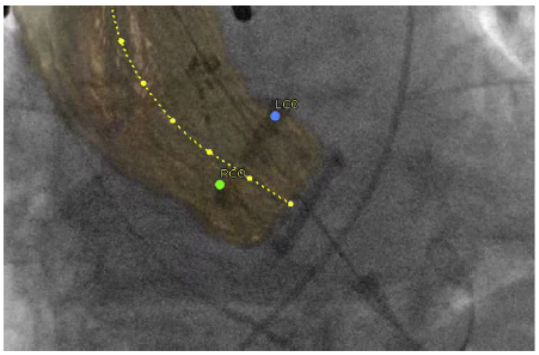

FIGURE 1. Three-dimensional reconstruction of the aortic root in overlap mode on live fluoroscopy.

echocardiography guided the positioning of the DFM prosthesis (Figure 1). After native-valve passage, the DFM was pressurized in the left ventricle. Subsequently, the valve was pulled into the annulus and positioned using the 3 control wires (Figure 2). If the valve was accidentally pulled through the native valve into the ascending aorta, the retrieval basket extracted the device. Angiography confirmed the positioning of the final valve, the coronary artery patency, and the degree of residual AR before exchanging the contrast with the polymer. After polymer exchange, the valve positioning wires were detached, and the introducer was removed. Chest closure was performed in the standard manner. The patients were extubated in the operating room if possible.

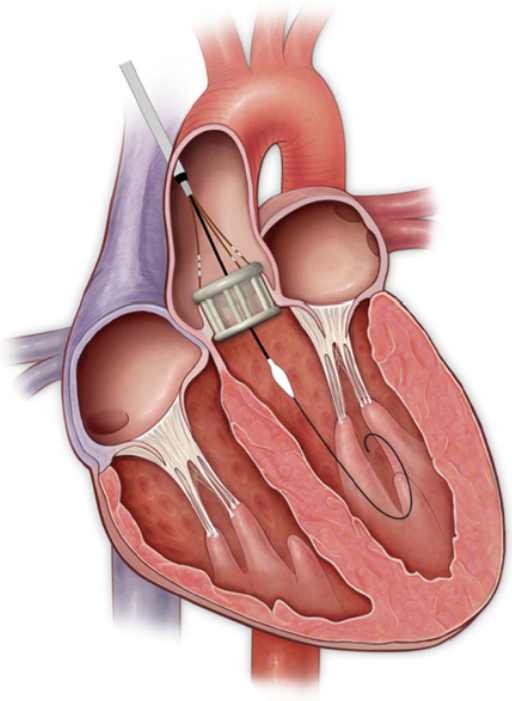

FIGURE 2. DFM (Direct Flow Medical, Inc, Santa Rosa, Calif) valve implantation via the ascending aorta.

RESULTS

Patients

The demographic and baseline clinical characteristics of the 15 patients who underwent DA TAVI with the DFM valve for severe aortic valve stenosis are summarized in Table 1. The mean patient age was 79 years (range, 60-87), and 66% were male. Twelve patients (80%) had coronary artery disease with a history of percutaneous coronary intervention (12, 80%) or coronary artery bypass grafting (4, 27%); these cases also represent access-related redo-sternotomy. Patients presented with several comorbidities, as reflected by the high mean logistic European System for Cardiac Operative Risk Evaluation of 23.4 and the Society of Thoracic Surgeons score, which indicates the risk of mortality, of 7.8.

TABLE 1. Baseline characteristics

	Mean ± SD or no. (%)
Patient No.	15
Age (y)	79.1 ± 6.72
Male gender	10 (66)
Log euroSCORE	23.4 ± 16.9
STS-PROM	7.8 ± 6.8
BMI kg/m^2	28.6 ± 5.03
NYHA class >II	13 (87)
Hypertension	4 (93)
Diabetes	5 (33)
Chronic renal failure Stage ≥3	11 (73)
Peripheral artery disease	9 (60)
Coronary artery disease	12 (80)
Prior PCI	12 (80)
Prior CABG	4 (27)
Atrial fibrillation	7 (47)
Prior pacemaker implantation	1 (7)
Prior stroke	2 (13)
Left ventricular ejection fraction	48.5 ± 13.1
Preoperative hemoglobin level (g/dL)	11.8 ± 1.7
Transaortic mean gradient (mm Hg)	48.9 ± 26.5
Aortic regurgitation (≥2)	2 (13)
Mitral regurgitation (≥2)	1 (6)

SD, Standard deviation; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *STS*, Society of Thoracic Surgeons; *PROM*, Predicted Risk of Mortality; *BMI*, body mass index; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.

Perioperative Outcomes

The procedural characteristics are presented in Table 2. There were no intraoperative deaths. A partial sternotomy was performed in 14 patients (93%), and a mini-thoracotomy was performed in 1 patient (7%). There was no conversion to SAVR. Valve retrieval was necessary in 2 patients (13%) because of accidental pull-through of the valve into the ascending aorta. The valve was retrieved uneventfully using a particular retrieval technique adapted for the DA setting. DA access allows the use of a larger introducer, simplifying the retrieval procedure. Given the short distance available, only half of the retrieval basket was released to successfully capture the valve for retrieval. Intraprocedural dilatation (IDIL) was performed in 2 patients to optimize valve expansion and reduce the transvalvular pressure gradient. In total, the mean transvalvular gradient measured invasively immediately after implantation was 9.3 ± 2.5 mm Hg, and the mean echo gradient before discharge was 11.9 ± 4.5 mm Hg. As assessed by periprocedural transesophageal echocardiography, 10 patients (67%) had no paravalvular leakage (PVL), and 5 patients (33%) had mild PVL. No patient had moderate or severe PVL. The procedure time (skin to skin) was 125 ± 28 minutes. Eleven patients (73%) were extubated immediately after the procedure in the operating room. Procedural success, as defined by the Valve Academic Research Consortium 2,[13] was accomplished in 100% of the patients (n = 15).

Clinical Outcomes

No major vascular complications occurred during this preliminary experience. Life-threatening bleeding, defined as the transfusion of at least 4 packed red blood cells related to the access and after the implantation procedure, was absent. During the intensive care unit stay, 2 patients received more than 3 units of blood for known preoperative cardiac-related pneumonia that was not caused by the implantation or the access method. Both patients were dialyzed after the procedure. No renal failure occurred in the other patients. The mean amount of packed red blood cells given was 1.9 ± 1.7 units. New pacemaker implantations were required in 2 cases (14%) because of complete atrioventricular block and persistent bradycardia. No major stroke occurred, as detailed in Table 3. All patients survived the first 30 days and were discharged to rehabilitation or home with an improved New York Heart Association functional class and functional capacity.

DISCUSSION

For TAVI, choosing the optimal access route remains critical for success and patient safety. Because of its minimally invasive and completely percutaneous nature, and aided by the availability of vascular closure systems and a limited learning curve, TF access is the first choice for TAVI procedures. However, access vessel calcification, diameter, and tortuosity may not allow TF access, requiring viable alternatives in select patients. Indeed, peripheral vascular complications, when they occur, have a negative impact on clinical outcomes in this highly fragile patient population.[14] The unidirectional orientation of the DFM valve limits the retrograde endovascular access. In this study, we investigated the DA access route as a full-fledged alternative to the TF access route.

TABLE 2. Procedural characteristics

	Mean ± SD or no. (%)
Patient No.	15
Valve size (mm)	
25	9 (60)
27	4 (27)
29	2 (13)
Procedure time from cut to suture (min)	125 ± 28
Contrast agent (mL)	97.4 ± 36.6
Fluoroscopy time (min)	16.9 ± 6.7
Mean transaortic gradient (mm Hg)	9.3 ± 2.5
Moderate and severe paravalvular regurgitation	0 (0)
VARC device success	15 (100)
Retrieval and second valve implantation	2 (13)
Conversion to SAVR	0 (0)
Patients extubated in OR	11 (73)
Intraoperative mortality	0 (0)

SD, Standard deviation; *VARC*, Valve Academic Research Consortium; *SAVR*, surgical aortic valve replacement; *OR*, operating room.

Apart from the standardized TF approach, DA access required technical modifications. To achieve the world's first DA DFM valve implantation, we modified the manufacturer's provided technique. This modification allowed uneventful and successful deployment and retrieval of the valve, despite a shortened distance between the introducer and the native valve in the DA setting (Figure 3).

The implementation of additional maneuvers via the DA access, such as IDIL, was performed in 2 patients. This new technique was used if the residual intraoperative postimplantation transaortic pressure gradient remained more than 15 mm Hg, if there was an incomplete expansion of the prosthesis, or if a noncircular upper ring indicated inadequate capture of the native leaflet.

In contrast to postimplant dilatation, IDIL is part of the implantation procedure. Through the secondary access, the same valvuloplasty balloon was placed inside the DFM prosthesis.

TABLE 3. Clinical outcomes

	Mean ± SD or no. (%)
Major vascular complication	0 (0)
Life-threatening bleeding	0 (0)
Transfusion (units PRBC)	1.9 ± 1.7
Myocardial infarction	0 (0)
Clinical evidence of stroke	0 (0)
ICU stay (d) (median, IQR)	2 (1-7)
Permanent pacemaker implantation	2 (13)
Reintervention	0 (0)
Acute kidney injury - Stage >3	2 (13)
Hospital stay (d)	15 ± 9.1
All-cause mortality at 30 d	0
Mean echo gradient before discharge (mm Hg)	11.9 ± 4.5

SD, Standard deviation; *PRBC*, packed red blood cell; *ICU*, intensive care unit; *IQR*, interquartile range.

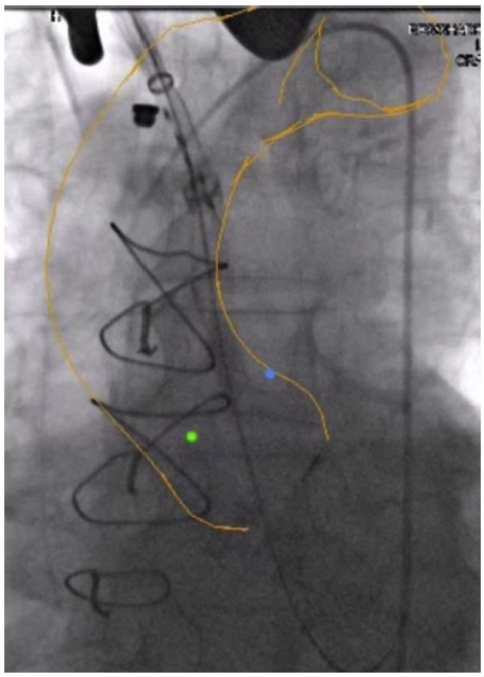

FIGURE 3. Valve retrieval via DA access. The basket, as part of the retrieval process, covers both the valve and the nose.

Under rapid pacing and during slow inflation of the balloon, the upper ring of the DFM prosthesis was deflated. After reaching maximum expansion of the balloon, under this protection, the upper ring was reinflated in its final position; the balloon was then deflated, and rapid pacing was terminated.

By using the described protocol, no relevant vascular complications occurred in this series of patients who were treated via DA access. Our results compare favorably with a 2.7% incidence reported from an initial TF experience with the DFM device in the DISCOVER study.[11]

Freedom from aortic regurgitation according to the Valve Academic Research Consortium 2 criteria was evident in the majority of patients (67%) without any moderate or severe regurgitation.

DA access still serves as an important endovascular alternative TAVI route; data provided by the Sapien group, published by Thourani and colleagues,[15] and the CoreValve group, published by Reardon and colleagues,[10] indicate the relevance of DA TAVI. In this context, the results obtained from our small cohort of DFM cases even surpassed the excellent results obtained in the previously published Sapien and CoreValve studies.

CONCLUSIONS

DA access appears to be a promising and safe alternative endovascular route for DFM implantation. This access route

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provides direct and accurate control of the entire implantation procedure. Furthermore, it allows the implementation of additional maneuvers, such as repositioning, retrieval, and IDIL.

Conflict of Interest Statement

H.B. is Proctor for Direct Flow Medical, Inc. All other authors have nothing to disclose with regard to commercial support.

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Key Words: direct aortic access, transcatheter aortic valve implantation, aortic valve stenosis, direct flow valve

Arbeit 5:

A new technique to implant a transcatheter inflatable, fully repositionable prosthesis in aortic stenosis with severe asymmetric calcification

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NEW IDEAS – ADULT CARDIAC

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A new technique to implant a transcatheter inflatable, fully repositionable prosthesis in aortic stenosis with severe asymmetric calcification†

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Abstract

OBJECTIVES: In contrast to stented transcatheter aortic valves, the Direct Flow Medical (DFM) valve is a stentless bovine aortic bioprosthesis mounted in a non-metallic inflatable frame. Hence, severe asymmetric annular calcification may result in residually elevated transaortic pressure gradients after DFM implantation. We present a novel intraprocedural dilatation (IDIL) technique for successful implantation of the DFM valve in the presence of complex annular calcification.

METHODS: Between January 2014 and May 2015, 55 patients underwent DFM valve-based transcatheter aortic valve implantation at our institution. Of these, 5 patients required an IDIL technique due to a residual intraoperative transaortic pressure mean gradient above 15 mmHg. The mean patient age was 73 ± 8.2 years; the mean logistic EuroSCORE was 24.5 ± 8.2% and the mean Society of Thoracic Surgeons score was 6.3 ± 4.3%.

RESULTS: The IDIL technique immediately attenuated transvalvular mean pressure gradients from 20 ± 2 mmHg to 6 ± 1 mmHg. The results remained stable during the 30-day observation period at 10 ± 3 mmHg. Minimal paravalvular aortic regurgitation (trace) was detected in 2 patients. No in-hospital deaths were observed.

CONCLUSIONS: The IDIL technique facilitates safe DFM valve implantation in patients with complex asymmetric annular calcification without adverse side effects on valve structure or performance in short-term follow-up.

Keywords: Aortic valve stenosis • Paravalvular leack • Transcatheter aortic valve implantation • Valvuloplasty

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become an accepted treatment for aortic valve stenosis in high-risk patients [1–3]. In contrast to conventional TAVI valve prostheses that are supported by a metal framework, the Direct Flow Medical (DFM) valve (Direct Flow Medical, Santa Rosa, CA, USA) consists of an inflatable Dacron-polyester double-ring design, containing non-compliant angioplasty balloon technology [4]. A cylindrical bridge connects the upper (aortic) and lower (ventricular) balloon rings. Hollow positioning wires independently pressurize the cylinders. Upon pressurization, the lateral struts connecting the 2 rings exert a radial opening force via the cylindrical part. Complete valve expansion results, with the lateral struts perpendicular to the 2 rings (Fig. 1C).

In standard metal-stented valves, severe asymmetric calcification hinders complete expansion of the valve frame and thus comes with an increased risk for paravalvular regurgitation [5, 6]. In this scenario, the flexibility of the DFM prosthesis allows improved adaptation of the lower ring to the native valve, reducing the incidence of paravalvular leak (PVL) [7].

However, extreme calcification may resist the opening force exerted by pressurization of the DFM prosthesis (Video 1) and results in residual transaortic pressure gradients. To overcome the increased transaortic gradients, we established a new intraprocedural dilatation (IDIL) technique.

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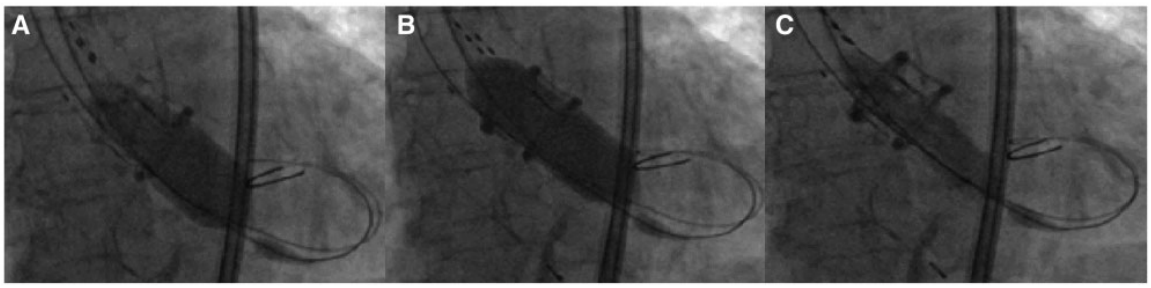
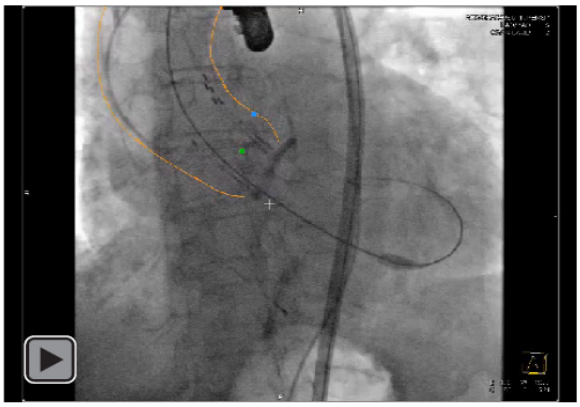


Figure 1: The 3 steps of the intraprocedural dilatation technique. (**A**) Deflation of DFM upper ring during balloon inflation; (**B**) DFM inflation while the balloon is maximally expanded; (**C**) balloon deflation. DFM: Direct Flow Medical.



Video 1: Incomplete expansion of the Direct Flow Medical cylindrical bridge, resulting in elevated transvalvular pressure gradients.

MATERIALS AND METHODS

Patient characteristics

Between January 2014 and May 2015, 55 patients underwent DFM implantation. Table 1 presents preoperative patient characteristics. Of those, 5 patients required IDIL. Preoperative imaging included coronary angiography, echocardiography and computed tomography. A dedicated software (3mensio Medical Imaging, B.V., Bilthoven, Netherland) analysed the data for native valve calcification, iliofemoral vessels and valve diameter. A multidisciplinary heart team selected the valve size and access route.

Implant supported by intraprocedural dilatation

Indications for the IDIL technique included a postimplantation transaortic pressure gradient above 15 mmHg, incomplete valve expansion or a non-circular upper ring suggestive of inadequate capture of the native leaflet. We performed the IDIL technique after 2 failed valve-repositioning attempts.

In contrast to post-dilatation of conventional TAVI valves, performed after implantation of a valve prosthesis, the IDIL technique constitutes an optional step within the primary implant procedure. Therefore, additional vascular access is mandatory to advance the valvuloplasty balloon. The diagnostic access sheath placed in the contralateral femoral artery is exchanged with a 12-Fr interventional access sheath. The lower ring of the DFM prosthesis is pulled into the optimal position. A valvuloplasty balloon is placed via a stiff guidewire inside the DFM prosthesis (Video 2). The same balloon used for the original valvuloplasty was chosen for prosthesis dilatation. Under rapid pacing and slow balloon inflation, the DFM upper ring is deflated (Fig. 1A). After reaching the maximum expansion of the balloon, the upper ring is reinflated in its final position (Fig. 1B). Under this protection, the angioplasty balloon is deflated, and rapid pacing is terminated (Fig. 1C).

After the balloon is withdrawn, a pigtail catheter replaces the stiff guidewire to determine the transvalvular pressure gradient. The procedures were completed according to standard implant techniques [4, 7].

Table 1: Demographics and baseline characteristics of the patient cohort

Baseline characteristics	Mean ± SD or *n* (%)
Number of patients	5
Age (years)	73 ± 8.2
Male gender	2 (40)
Logistic EuroSCORE	24.5 ± 8.2
STS predicted risk of mortality	6.3 ± 4.3
BMI (kg/m^2)	30 ± 5
NYHA Class >II	5 (100)
Hypertension	5 (100)
Diabetes	5 (100)
Chronic renal failure ≥Stage 3	1 (20)
Peripheral artery disease	2 (40)
Coronary artery disease	2 (40)
Prior PCI	1 (20)
Prior CABG	1 (20)
Atrial fibrillation	3 (60)
Prior pacemaker implantation	0
Prior stroke	0
Left ventricular ejection fraction	35 ± 16
Preoperative haemoglobin level (g/dl)	12.7 ± 2
Transaortic mean gradient (mmHg)	46 ± 25.3
Aortic regurgitation (≥2)	1 (20)
Mitral regurgitation (≥2)	3 (60)

BMI: body mass index; CABG: coronary artery bypass grafting; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons.

RESULTS

Patients

Five patients were treated using the IDIL technique. Three patients underwent valve implantation and the IDIL technique

valve expansion. To avoid a detrimental impact on valve integrity, we used the same balloon size as was used for the initial valvuloplasty for intraprosthetic balloon inflations with valvuloplasty balloons at least 2 mm smaller than the DFM. Using this strategy, the IDIL technique did not impair valve functions in any patient.

Our study demonstrated an improvement in the transvalvular gradient using the IDIL technique with valve function remaining stable throughout the observation period. As our confidence in the IDIL technique has increased, both procedure times and the use of contrast agent have decreased.

The potential risks of the IDIL technique are related to the fact that the diagnostic access site has to be increased from 5–6 Fr to 11–12 Fr to perform the valvuloplasty. By applying the IDIL technique, the benefit of reducing the residual transaortic pressure gradient has to be weighed against the risk of vascular complications. However, no vascular complications or detrimental impacts to prosthesis function have been observed.

The small number of patients clearly limits the impact of this report. However, our data suggest that the IDIL technique provides an intraprocedural option, optimizing configuration and performance of the DFM prosthesis in complex annular configurations. The IDIL technique should only be performed as a last resort before retrieving the prosthesis. We restrict the indication for this technique to an intraprocedural, unacceptably elevated gradient (>20 mmHg), despite unsuccessful attempts to optimize valve positioning. Native aortic valve asymmetric calcification challenges the implantation and positioning of transcatheter aortic valve prostheses. The IDIL technique-supported implantation is a new technique, allowing the deployment of the DFM under conditions that ensure transvalvular gradient reduction. The 30-day echocardiography follow-up revealed no negative impact of the IDIL technique, indicating good DFM function.

Conflict of interest: Hasan Bushnaq is proctor for Direct Flow Medical. The other authors have nothing to disclose.

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