Aus der Klinik für Kinderkardiologie und angeborene Herzfehler am Deutschen Herzzentrum München

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Titel

Perkutane Pulmonalklappenimplantation – Erweiterung der Indikationen und hämodynamische Auswirkung

Dissertation zum Erwerb des Doktorgrades der Medizin an der Medizinischen Fakultät der Ludwig-Maximilians-Universität zu München

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Inhaltverhaltnis:

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München, 09.12.2020

Stanimir Georgiev

Abkürzungsverzeichnis:

RV – rechter Ventrikel

PA – Pulmonalarterie

RVOT – Rechtsventrikulärer Ausflusstrakt

RVEDV – MRT gemessenes rechtsventrikuläres end-diastolisches Volumen

RVOTO – RVOT Obstruktion

LV – linker Ventrikel

CT – Computertomographie

MRT – Magnetresonanztomographie

Publikationsliste:

1. Georgiev S, Tanase D, Ewert P, Meierhofer C, Hager A, Pabst von Ohain J, Eicken A. Percutaneous pulmonary valve implantation in patients with dysfunction of a „native“ right ventricular tract – mid-term results. International Journal of Cardiology 2018; 258: 31-35.
2. Tanase D, Ewert P, Georgiev S, Meierhofer C, Pabst von Ohain J, McElhinney D, Hager A, Kühn A, Eicken A. Tricuspid regurgitation does not impact right ventricular remodelling after percutaneous pulmonary valve implantation. JACC: Cardiovascular Interventions 2017; 10: 701-708.

Einleitung.

Die angeborenen Herzfehler haben eine Inzidenz von 0,6-0,9% [1]. Mit der rasanten Entwicklung sowie der Kinderkardiologie mit ihren besseren diagnostischen Methoden und interventionellen Behandlungsmaßnahmen als auch der Kinderherzchirurgie können fast alle Herzfehler heutzutage behandelt werden. Dadurch haben sich das Überleben und die Lebensqualität dieser Patienten dramatisch verbessert. Bei der Behandlung vieler Patienten wird der rechtventrikuläre Ausflusstrakt im Kindesalter chirurgisch angegangen – entweder plastisch mit Patcherweiterung oder durch die Implantation von klappentragenden oder klappenlosen RV-PA Conduits. Das sind schätzungsweise etwa 20% der Patienten mit angeborenen Herzfehlern, beispielsweise solche mit Fallot`scher Tetralogie, Pulmonalatresie mit Ventrikelseptumdefekt, Truncus arteriosus communis, Transposition der großen Gefäße nach Rastelli Operation, valvuläre Aortenstenose nach Ross Operation. Egal welche Methode für die Erweiterung des rechtsventrkulären Ausflusstraktes benutzt wird, sind mehrere weitere Reinterventionen vorprogrammiert. Das liegt einerseits an der natürlichen Degeneration aller biologischen Herzklappen. Anderseits erlauben die kleinen Dimensionen des kindlichen Thorax lediglich die Implantation kleineren Conduits, die mit dem Wachstum relativ eng werden. Nicht zuletzt bekommen viele von diesen Patienten eine Patch-Erweiterung des rechtsventrikulären Ausflusstraktes, was zu einer praktisch fehlenden Pulmonalklappenfunktion führt.

Das Gemeinsame bei den oben beschriebenen Patienten ist eine mittel-bis hochgradige Pulmonalinsuffizienz sowie restliche Pulmonalstenosen. Lange war die Meinung verbreitet, dass diese Läsionen gutartig sind und dass sie keine wesentlichen Konsequenzen für die Patienten haben. Klinische Untersuchungen haben aber gezeigt, dass die Pumonalinsuffizienz zu einer RV Erweiterung mit sekundärer Trikuspidalklappeninsuffizienz, mit Abnahme der körperlichen Belastbarkeit und mit zunehmender Neigung zu fatalen ventrikulären Arhythmien führt. Die „klassische“ Behandlung von solchen Patienten erfolgt durch die chirurgische Implantation eines neuen RV-PA Conduits mit adäquater Größe oder einer biologischen Pulmonalklappe [2].

In 2000 berichtete Phillip Boehnhoffer zum ersten Mal über die interventionelle Implantation einer biologischen Herzklappe im Menschen [3]. Er benutzte dafür eine Rinderhalsvenenklappe, die in einem covered Cheatam-Platinum Stent angenäht wurde. Der Stent mit der Klappe wurde auf einem Ballon-in-Ballon montiert und in der üblichen Weise in den RV

Ausflusstrakt eines 12-jährigen Patienten implantiert. Dieses System wurde durch die Firma Medtronic als die Melody® Klappe (Abb. 1) weiterentwickelt und ab Ende 2006 in Europa und ab 2010 in den USA zugelassen. In den nächsten Jahren wurden viele Patienten mit sehr gutem frühem und mittelfristigem Ergebnis behandelt [45678910]. Später wurde die initial für den interventionellen Aortenklappenersatz entwickelte Sapien® Klappe (Abb 2) auch für Pulmonalposition zugelassen und ähnlich gute Ergebnisse allerdings mit kürzerem Follow up wurden auch damit berichtet [1112]. Das Deutsche Herzzentrum in München war einer der Pioniere bei der Durchsetzung der neuen Methode weltweit, beginnend mit der ersten Implantation Ende 2006. Mittlerweile wurden im Deutschen Herzzentrum in München über 240 Patienten mit der Melody und der Sapien Klappe behandelt mit sehr guten langfristigen Ergebnissen. Die Zusammenfassung von diesen Ergebnissen stellt ein bereits abgeschlossenes Projekt und Objekt einer weiteren Publikation (JACC: Cardiovascular Interventions in press) des Doktoranden dar.

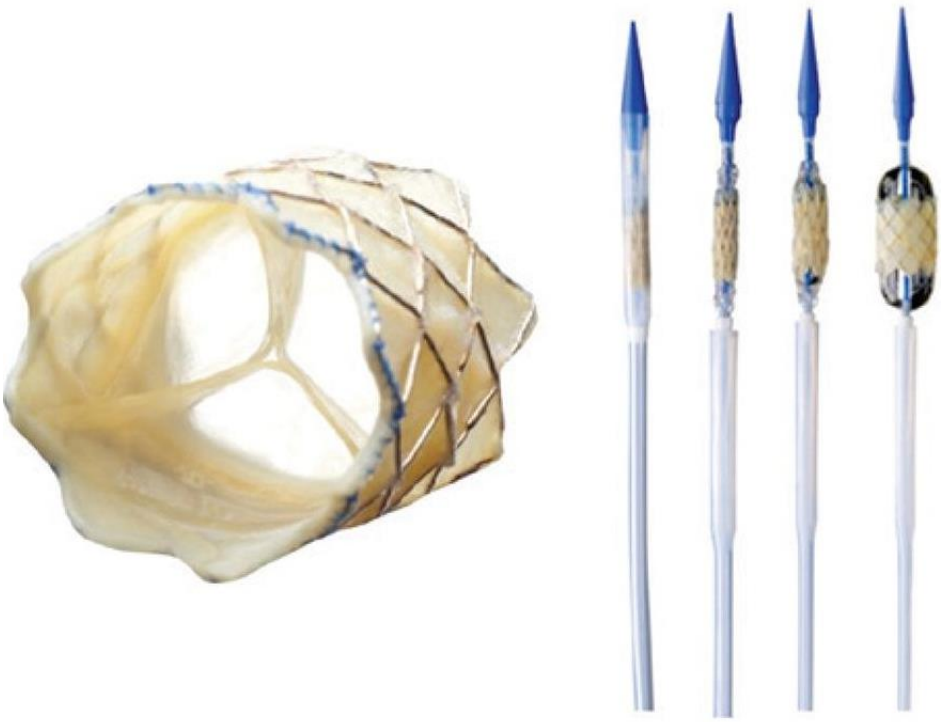

Abb. 1 A. Melody Klappe links und Implantationssystem rechts.

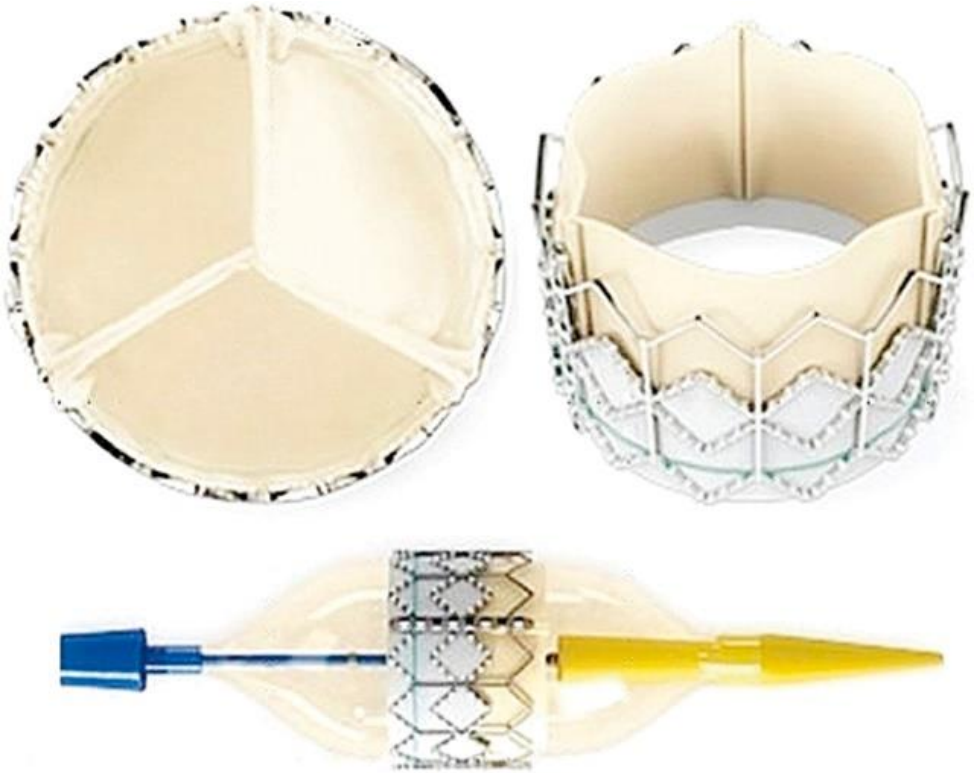

Abb 2. Sapien XT Klappe

Die Indikationen für die interventionelle Implantation einer Pulmonalklappe sind noch Objekt von Diskussionen. Die am häufigsten zitierten Studien diesbezüglich beziehen sich auf chirurgisch implantierte Klappen [131415]. Da diese Methode allerdings deutlich weniger invasiv als der klassische chirurgische Pulmonalklappenersatz ist, werden die Patienten tendenziell früher für die Intervention indiziert, noch bevor der RV die Grenze von 150ml/m2 für das indizierte enddiastolsiche Volumen erreicht hat. Die Indikationen für interventionelle Pulmonalklappenimplantation in dem Deutschen Herzzentrum München sind in Tabelle 1 angegeben.

- RVOT Obstruktion mit oder ohne Pulmonalinsuffizienz und:
  - Trikuspidalinsuffizienz mit Doppler Jet Geschwindigkeit > 3,5 m/s bei Symptomen oder reduzierter Belastbarkeit < 65% der Norm.
  - Trikuspidalinsuffizienz mit Doppler Jet Geschwindigkeit > 4,3 m/s oder RV Druck > 2/3 vom Systemdruck bei fehlenden Symptomen.
- Schwere Pulmonalinsuffizienz mit progressiver RV Dilatation mit einem indizierten RVEDV > 150ml/m2 oder mit reduzierter RV Funktion.

und:

- RV-PA Conduit oder Conduit freier RVOT mit einem passenden minimalen Durchmesser, sodass eine von den zurzeit verfügbaren Klappen implantiert werden kann (maximal 29mm).
- Körpergewicht (>20kg), das die Anlage einer großen venösen Schleuse für die Klappenimplantation ermöglicht.

Tabelle 1. Indikationen für interventionelle Pulmonalklappenimplantation in dem Deutschen Herzzentrum in München.

Offene Fragen bei der interventionellen Pulmonalklappenimplantation:

Die Entwicklung der Methode zur interventionellen Pulmonalklappenimplantation zählt ohne Zweifel zu einer der wichtigsten Erfindungen in den letzten Jahrzehnten in der Kardiologie der angeborenen Herzfehler. Dadurch können bei vielen Patienten wiederholte Operationen, die mit zunehmenden Risiken verbunden sind, vermieden werden. Allerdings gibt es noch offene Fragen, die weiteren Studien in diesem Gebiet voraussetzen. Durch die gewonnene Information könnten nicht nur diese Patienten mit besseren Ergebnissen behandelt werden. Dadurch könnten auch die Indikationen für die Intervention deutlich erweitert werden, was das operationsfreie Überleben mit gutem Lebensqualität von vielen anderen Patienten ermöglichen würde.

Eine solche offene Frage ist die Behandlung von Patienten mit den sogenannten „nativen“ oder Conduit freien RVOTs. Die Melody Klappe wurde für die Verlängerung des Lebens von

RV-PA Conduits oder von biologischen Pulmonalklappen konzipiert. Die Klappe ist in dem Inneren eines Ballon expandierbaren Stents angenäht. Damit man sie stabil verankern kann, ist eine stabile Landungszone notwendig. Diese wird durch die Implantation eines oder mehreren Ballon expandierbaren Stents in den RVOTO geschaffen. Das ist allerdings nur dann möglich, wenn eine relativ steife Engstelle im RVOT vorhanden ist. Diese Voraussetzung ist bei den Patienten mit RV-PA Conduits in den meisten Fällen erfüllt, da diese häufig verkalkt sind und damit eine steife Landungszone für die Prestents anbieten (Abb. 3).

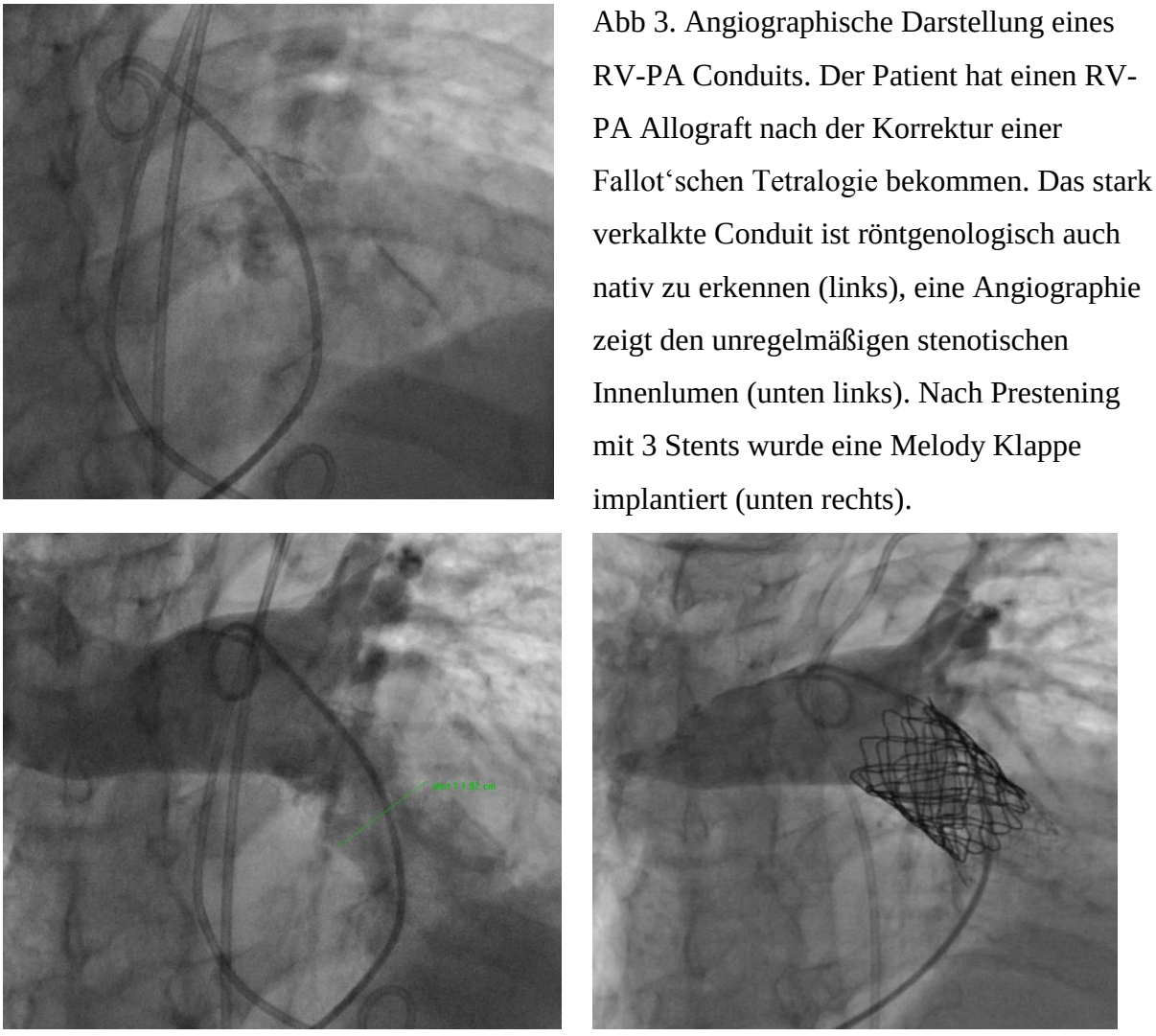

Abb 3. Angiographische Darstellung eines RV-PA Conduits. Der Patient hat einen RV-PA Allograft nach der Korrektur einer Fallot‘schen Tetralogie bekommen. Das stark verkalkte Conduit ist röntgenologisch auch nativ zu erkennen (links), eine Angiographie zeigt den unregelmäßigen stenotischen Innenlumen (unten links). Nach Prestening mit 3 Stents wurde eine Melody Klappe implantiert (unten rechts).

Zusätzlich kann die Melody Klappe auf maximal 22mm Ballon implantiert werden. Damit die Klappe stabil implantiert werden kann und damit es keinen signifikanten paravalvulären Leck gibt, ist ein RVOT vorausgesetzt, der maximal 22mm weit ist. Das macht die RVOTs mit bereits implantierten Conduits eine perfekte Landungszone für die Melody Klappe. Sie sind steif, oft sehr verkalkt und selten weiter als 22mm und da können sicher und stabil Ballon implantierbare Stents eingesetzt werden.

Allerdings nur wenige von den Patienten, die einen Pumonalklappenersatz brauchen, haben ein Conduit im RVOT. Die meisten Patienten haben eine Fallot´sche Tetralogie, die im Kindesalter korrigierend operiert worden ist. In den meisten Fällen wird bei dieser Operation kein Conduit eingesetzt, sondern die RVOT Obstruktion wird durch eine Muskelresektion und einen transvalvulären Patch erweitert. Dadurch wird die Pulmonalklappenfunktion beinträchtigt, es besteht eine freie Pulmonalinsuffizienz und im Laufe der Zeit wird die Indikation zum Pulmonalklappenersatz gestellt. Nach einigen Einschätzungen sind das über 80% der Patienten, die einen Pulmonalklappenersatz brauchen. Typischerweise haben diese Patienten zurzeit der Indikationsstellung sehr weite RVOTs, die manchmal bis 40mm und mehr im Durchmesser sein können (Abb 4).

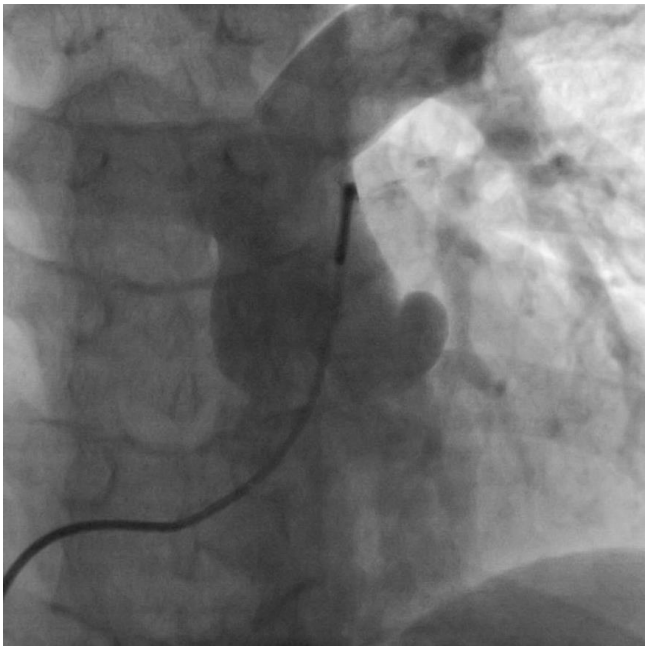

Abb 4. Angiographische Darstellung eines Conduit-freien oder „nativen“ RVOT. Der Patient hatte ursprünglich eine Fallot’schen Tetralogie, die im Kindesalter mit einem transannulärem Patch korrigiert wurde. Da der RVOT in solchen Fällen sehr erweitert und weich ist, ist die stabile Verankerung eines Ballon-implantierbaren Stents sehr schwierig oder sogar unmöglich.

Zusätzlich sind diese RVOTs sehr weich und dynamisch, sie bewegen sich mit jedem Herzzyklus, was das komplikationslose Erreichen einer stabilen Stent Position sehr problematisch macht. Das sind die Gründe, warum die klassische Indikation zum interventionellen Pulmonalklappenersatz immer ein RV-PA Conduit oder eine biologische Pulmonalklappe voraussetzt [4]. Die Erfahrung mit der Melody Klappe und die Einführung der größeren Sapien Klappe für Pulmonalposition stellte sich die Frage, ob auch Patienten mit „nativen" oder Conduit-freien RVOTs damit behandelt werden können. Der erste Bericht, der gezeigt hat, dass das möglich ist, kommt von der Gruppe aus London, wo auch der Entwickler der Melody Klappe, Phillip Bonhoeffer zu dieser Zeit tätig war[16]. Die Autoren berichten über 6 Patienten mit RVOT Dysfunktion ohne RV-PA Conduits, die erfolgreich mit gutem Ergebnis behandelt wurden. Technisch war das möglich, in dem Patienten selektiert wurden, bei denen der RVOT noch nicht sehr erweitert war und dadurch die direkte Implantation eines Stents und anschließend der Melody Klappe möglich war. Das setzte allerdings voraus, dass der RVOT nicht weiter als der Durchmesser der Melody Klappe (maximal 22mm) ist. Die Gruppe von Boudjemline, auch einer von den Entwicklern der Melody Klappe, publizierte in 2014 [17] die Ergebnisse nach interventionellem Pulmonalklappenersatz bei 34 Patienten mit „nativen" RVOTs, 16 von denen ein größeren RVOT hatten. Die Autoren haben unterschiedliche sehr komplexe interventionelle Techniken benutzt – „jailing technique", „russian doll technique", „russian jailing". In der Literatur sind weitere Publikationen von Patienten mit interventionellem Pulmonalklappenersatz bei „nativem" RVOT zu finden [1819]. Das Gemeinsame in allen Veröffentlichungen sind die sehr kleine Zahlen von Patienten. So hat die größte multizentrische Studie in den USA insgesamt nur 31 Patienten aus 5 Zentren eingeschlossen [20]. Damit ist die Behandlung von Patienten mit Conduit-freien RVOTs mit interventionellen Pulmonalklappen noch nicht etabliert und viele technische Details müssen noch geklärt werden.

Nicht nur technische Fragen sind bei dem interventionellen Pulmonalklappenersatz noch offen. Diese Methode bietet ein Model an, das die Entwicklung eines besseren Verständnisses über die Pathophysiologie der RVOT Dysfunktion und ihrer Folgen ermöglicht. Das liegt daran, dass die Pulmonalstenose, die Pulmonalinsuffizienz oder die Kombination aus beidem schnell und atraumatisch, ohne die negativen Auswirkungen der Herzlungenmaschine und der chirurgischen Ventrikulotomie, beseitigt wird. So wurde in eine Studie aus London die Auswirkung der Beseitigung der RVOT auf die RV und LV Volumina und Funktion, aber auch auf die Belastbarkeit der Patienten beschrieben [212223 24]. Offen bleibt aber, wie sollen

Patienten behandelt werden, die zusätzlich zu der RVOT Dysfunktion eine signifikante Trikuspidalklappeninsuffizienz haben. Unabhängig davon, ob es sich um eine RVOT Obstruktion, um eine Pulmonalinsuffizienz oder um eine Kombination aus Beidem handelt, führt die RVOT Dysfunktion zu einer Erweiterung des RV, dementsprechend erweitert sich der Trikuspidalklappenannulus, die Segelkoaptation wird dadurch gestört und die Trikuspidalklappe wird insuffizient. Die Trikuspidalinsuffizienz an sich führt zur weiteren Dilatation des RV und so schreitet der Prozess fort [2526]. Es ist zu erwarten, dass mit der Beseitigung der RVOT Dysfunktion durch den Pulmonalklappenimplantation die Funktion der Trikuspidalklappe sich verbessert, trotzdem wird es empfohlen, dass bei einem chirurgischen Pulmonalklappenersatz in solchen Fällen die Trikuspidalklappe plastisch angegangen wird [2728]. Werden aber solche Patienten auch mit einer interventionellen Pulmonalklappenimplantation, bei der die Trikuspidalklappe nicht angegangen werden kann, nicht gut behandelt? Würde sich die Funktion der Trikuspidalklappe alleine durch die Beseitigung der RVOT Dysfunktion verbessern? Und was noch wichtiger ist, profitieren die Patienten, die eine Trikuspidalinsuffizienz haben, von einem interventionellen Pulmonalklappenersatz genauso gut wie diese, die eine RVOT Dysfunktion mit einer erhaltenen Trikuspidalklappenfunktion noch haben? Muss die Indikation für einen Pulmonalklappenersatz in solchen Patienten anders gestellt werden?

Die Indikationen für die interventionellen Pulmonalklappenimplantation wird zurzeit anhand Daten und Empfehlungen gestellt, die aus Studien mit chirurgischem Pulmonalklappenersatz stammen. Da sich die beiden Methoden aber in ihrer Invasivität und möglichen Komplikationen, aber auch möglicherweise an der Funktion der Implantierten Klappen im Langzeit follow up unterscheiden, müssen die konkreten Indikationen für die interventionelle Pulmonalklappenimplantation präzisiert werden. Um das möglich zu machen, ist es von großer Bedeutung, Studien, die nicht nur die technischen Details, die technischen Möglichkeiten der Methode, die potenziellen Komplikationen, aber auch die physiologischen Effekte von der Prozedur beschreiben. Die Arbeiten, die in dieser Doktorarbeit eingeschlossen werden, dienen diesem Ziel – durch mehr Information über die Effektivität und die Risiken der Methode, die Indikationen für die interventionelle Pulmonalklappenimplantation auf einer Studien-basierte Grundlage zu stellen.

Zusammenfassung.

In dem Deutschen Herzzentrum München wurden zwischen Dezember 2006 und September 2018 265 Patienten mit interventionellem Pulmonalklappenersatz behandelt. Eine Langzeit Follow up Studie wird zurzeit zur Publikation eingereicht und zeigt sehr gute Ergebnisse nach dem Eingriff. Die Patienten haben ein Überleben ohne weitere Eingriffe nach 10 Jahren von 73% und bei Patienten mit Prestenting und einem postinterventionellen Gradienten unter 15 mm Hg sogar von 88%. Einen sogenannten „nativen" RVOT, oder einen RVOT ohne RV-PA Conduit hatten 26 Patienten (11%). Achtzehn von denen wurden in der Studie für die zur kumulativen Dissertation benutzten Publikation [29] inkludiert. In der Veröffentlichung werden innovativen Methoden für die „off label" Behandlung von solchen Patienten dargestellt. Nicht nur technische Aspekte werden vorgestellt, sondern auch Probleme und Indikationen für diese Methoden werden diskutiert.

Eine Voraussetzung für PPVI ist das Schaffen einer stabilen Landungszone für die Klappe. Die Landungszone wird mit Ballon implantierbaren Stents vorbereitet – sie dienen als stabile Grundlage für den Stent der perkutanen Klappe. Damit die Implantation eines Stents in ein Gefäß oder Herzstruktur überhaupt möglich ist und damit er in der gewünschten Position bleibt, ist eine relative Engstelle notwendig. Diese Engstelle muss nicht unbedingt eine hämodynamisch relevante Stenose sein, muss allerdings nicht nur eine gewisse Steifigkeit, sondern auch einen Durchmesser haben, der etwas kleiner ist als der gewünschte Stentdurchmesser. Dementsprechend ist es notwendig, dass die konkrete RVOT Morphologie des Patienten bekannt ist, nicht nur als dreidimensionale Vorstellung der Anatomie, aber auch mit Information über die Dehnbarkeit der RVOT Strukturen. Bei jedem Patienten wird vor der Intervention CT oder MRT durchgeführt, um die konkrete Anatomie darzustellen. Zusätzlich werden am Anfang der Herzkatheteruntersuchung nicht nur Angiographien mit unterschiedlichen Drehungen, sondern auch der sogenannte Ballon Test gemacht. Bei diesem Test wird ein weicher, großer Ballon mit relativ wenig Druck im RVOT aufgeblassen und seine Form radiologisch dokumentiert (Abb 5). Gleichzeitig wie vor jedem interventionellen

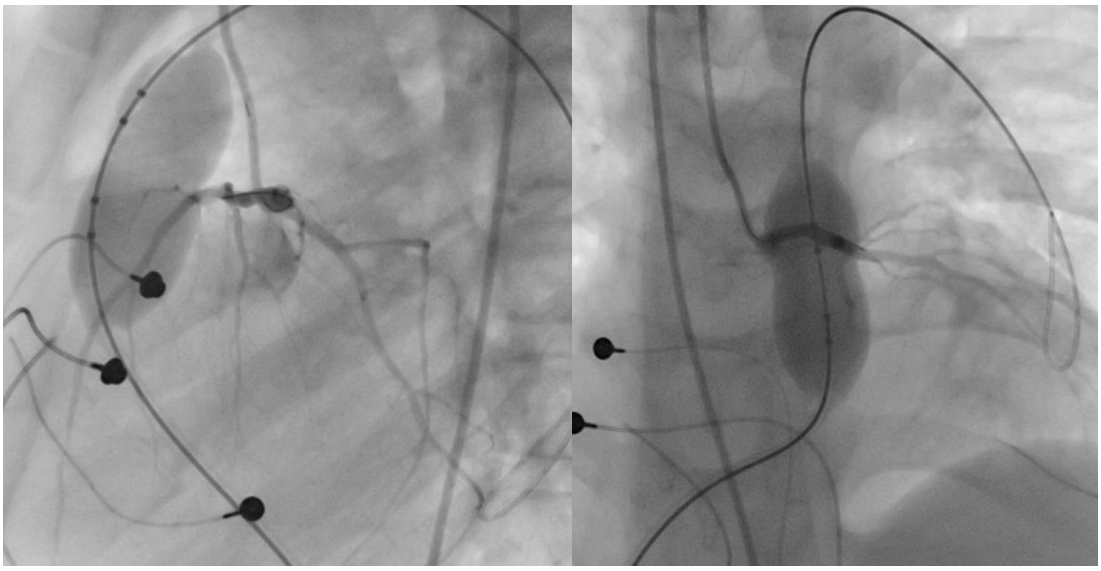

Abb.5 Ballon Test mit einem 30mm Ballon und gleichzeitiger selektiver Angiographie der linken Koronarterie in zwei Ebenen. Der Ballon zeigt eine Taille, wo ein Prestent für die Landungszone implantiert werden kann. Es gibt genügend Abstand zwischen der linken Koronararterie und dem RVOT.

Pulmonalklappenersatz werden die Koronararterien dargestellt, um die Gefahr einer Koronarkompression mit dem Stent der perkutanen Klappe auszuschließen. Dieser Test ist sehr großer Bedeutung für die weitere Planung der Prozedur. Bei dem wird nämlich eingeschätzt, wo genau eine Engstelle sich befindet, ob sie groß und steif genug für die Implantation eines Ballon-implantierbaren Stents ist. Dieser Stent dient als Verankerungsbasis („anchoring point“) für die Landungszone der perkutanen Klappe.

Unsere Patienten wurden in zwei Gruppen geteilt, abhängig davon, wo sich diese relative Enge für die Verankerung eines oder mehreren Stents für die Landungszone befindet.

Die eine Gruppe umfasst 10 Patienten, und bei denen wurde der RVOT oder der Pulmonalarterienstamm als eine Verankerungsstelle für die Stents benutzt. Bei diesen Patienten befindet sich eine Engstelle im Pulmonalarterienstamm und in diese Enge wird mindestens ein Prestent implantiert, bevor die perkutane Klappe in ihn eingesetzt wird. Die Implantionstechnik unterscheidet sich nicht wesentlich von der klassischen interventionellen Pulmonalklappenimplantation (Abb 6).

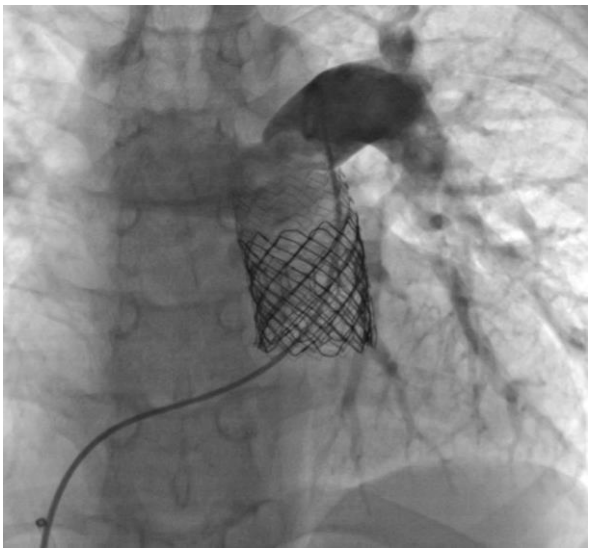

Abb. 6. Patient mit einem weiten nativen RVOT nach Korrektur einer Fallot'schen Tetralogie. Die Landungszone wurde zuerst mit einem langen Stent vorbereitet und danach wurde eine 29mm Sapien Klappe implantiert.

Die andere Gruppe besteht aus 8 Patienten, die einen weiten RVOT ohne Stenosen haben, allerdings eine Engstelle am Abgang einer der Pulmonalarterien haben. In diese Stenose wird ein kurzer Stent implantiert, der als Verankerungsstelle eines Stentkonstrukts für die Landungszone dient. Typischerweise wird der nächste Schritt mit 2-3 Monaten verschoben um eine Endothelialisierung und auf diese Weise auch Stabilität des Stents zu ermöglichen. Bei dem nächsten Herzkatheter wird dahin ein längerer Stent so implantiert, dass er in den RVOT „hängt". Dieser Stent überdeckt den kontralateralen Pulmonalarterienast. Das wird in eine Publikation als „branch PA jailing" bezeichnet [17]. Um das zu vermeiden und um bessere Adaptation des langen Stents zu dem Pulmonalarterienstammes zu ermöglichen, wird dieser Stent zu dem kontralateralen Pulmonalarterienast durch die Maschen sondiert und mit zunehmend größeren Ballons dilatiert und so wird ein freier Zugang dahin gewährleistet ist. Wenn eine Stenose am Abgang der kontralateralen Pulmonalarterie diagnostiziert wird, kann dahin noch ein langer Stent implantiert werden. So mit einem Y-Stent könnte eine komplexe Bifurkationsstenose interventionell behandelt werden (Abb. 7). In dem unteren Teil des langen Stents wird dann die perkutane Klappe implantiert und so wird die Pulmonalarterienabgangsstenose und gleichzeitig die Pulmonalinsuffizienz behandelt.

Alle in der Studie eingeschlossenen Interventionen waren erfolgreich, bis auf zwei behandelbare Komplikationen gab es keine Zwischenereignisse. Die ambulante Betreuung der Patienten zeigte gute mittelfristige Ergebnisse, die sich prinzipiell nicht von diesen der Patienten mit interventionellem Pulmonalklappenersatz in RV-PA Conduits unterscheiden. Es

gab eine bakterielle Endkarditis vier Monate nach der Implantation, was zeigt, dass Patienten mit perkutanen Pulmonalklappe in „nativen“ RVOTs von dieser Komplikation auch gefährdet sind.

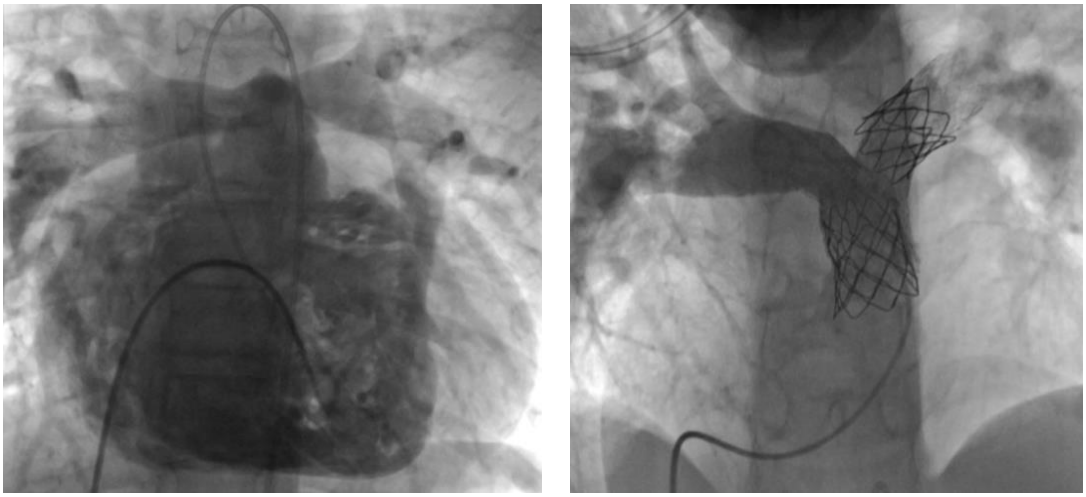

Abb 7. Patient mit hochgradiger Pumonalinsuffizienz und Abgangstenosen beider Pulmonalarterien (links) nach Korrektur einer Fallot`schen Tetralogie. Der Patient wurde mit einem Y-Stentkonstrukt behandelt, in unterem Teil davon wurde eine Melody Klappe implantiert.

Die Patientenselektion für diese Methode zur Pulmonalklappenimplantation muss außer den physiologischen, rein hämodynamischen Indikationen, die in Tabelle 1 der Einführung zusammengefasst sind, auch einige technische Aspekte berücksichtigen. Empfehlungen dafür werden in der Publikation gegeben. Der maximale Durchmesser der RVOT sollte kleiner als die größte vorhandene Klappe (zurzeit 29mm) sein. Sonst könnte auch bei einer technisch erfolgreichen interventionellen Pulmonalklappenimplantation eine bedeutsame paravalvuläre Pulmonalinsuffizienz entstehen. Zusätzlich muss es irgendwo im RVOT eine Engstelle geben, wo die Implantation eines Stents möglich ist. Nicht zuletzt haben einige von diesen Patienten ein relativ kleines perioperatives Risiko zum chirurgischen Pulmonalklappenersatz und sie sollten immer im „Heart team“, zusammen mit den Herzchirurgen besprochen werden.

Diese Studie beschreibt eine innovative „off label“ Methode zur Behandlung von Patienten mit interventionellem Pulmonalklappenersatz. Es werden vor allem technische Aspekte bei

der Prozedur aber auch das „follow up“ von diesen Patienten untersucht. Damit ist sie eine von den ersten, die sich mit diesem Thema beschäftigen. Da Patienten mit „nativen“ oder Conduit-freien RVOTs am häufigsten einen Pulmonalklappenersatz brauchen, besteht großes Interesse an den Möglichkeiten ihrer interventionellen Behandlung. Neue Klappen speziell für diese Indikation werden bereits entwickelt [3031]. Bis sie kommerziell verfügbar sind, konnte unser Behandlungsvorschlag eine wichtige Alternative sein.

Die zweite Publikation, die in Dissertation inkludiert ist[32], beschreibt die Effekte des perkutanen Pulmonalklappenersatz auf die Funktion der insuffizienten Trikuspidalklappe. Die Hypothese dieser Studie ist, dass Patienten mit RVOT Dysfunktion kombiniert mit bedeutsamer Trukuspidalklappeninsuffizienz, genauso gut profitieren von einem interventionellen Pulmonalklappenersatz, wie Patienten mit einer normal funktionierenden Trikuspidalklappe. Mit anderen Worten eine zusätzliche Intervention an der Trikupisdalklappe (was Chirurgie bedeutet) ist bei diesen Patienten nicht notwendig und sie können mit perkutanem Pulmonalklappenersatz behandelt werden.

Für diese Studie wurden alle 22 Patienten, die im Deutschen Herzzentrum München einen interventionellen Pulmonalklappenersatz bekommen haben und zusätzlich zu der RVOT Dysfunktion eine bedeutsame Trikuspidalklappeninsuffizienz hatten, identifiziert und eingeschlossen. Wichtig ist, dass bei allen Patienten die Trikuspidalklappe initial eine normale Funktion hatte. Eine retrospektive Evaluierung der echokardiographischen Untersuchungen in den letzten Jahren zeigte, dass die Trikuspidalklappeninsuffizienz sich langsam mit der Zeit im Rahmen der RV Dysfunktion entwickelte. Für jeden von diesen Patienten wurde ein Patient mit vergleichbaren Charakteristiken, aber ohne bedeutsame Trikuspidalklappeninsuffizienz ausgewählt. So wurden passende Kontrollpaare („matched control pairs“) gebildet, dessen Behandlungsergebnisse in der Studie verglichen wurden. In den meisten Trikuspidalinsuffizienz Patienten (83%) führte der perkutane Pulmonalklappenersatz zu einer Verbesserung der Funktion der Trikuspidalklappe, die nach einem im Median 6,5 Jahren Follow up stabil blieb. Interessanterweise verbesserte sich bei einem Patienten die Trikuspidalklappeninsuffizienz mit dem Pulmonalklappenersatz und verschlechterte sich später parallel zu einer zunehmenden Stenose der Melody Klappe. Nur 3 Patienten hatten keine Verbesserung des Trikuspidalklappeninsuffizienz-Grades. (Abb 8).

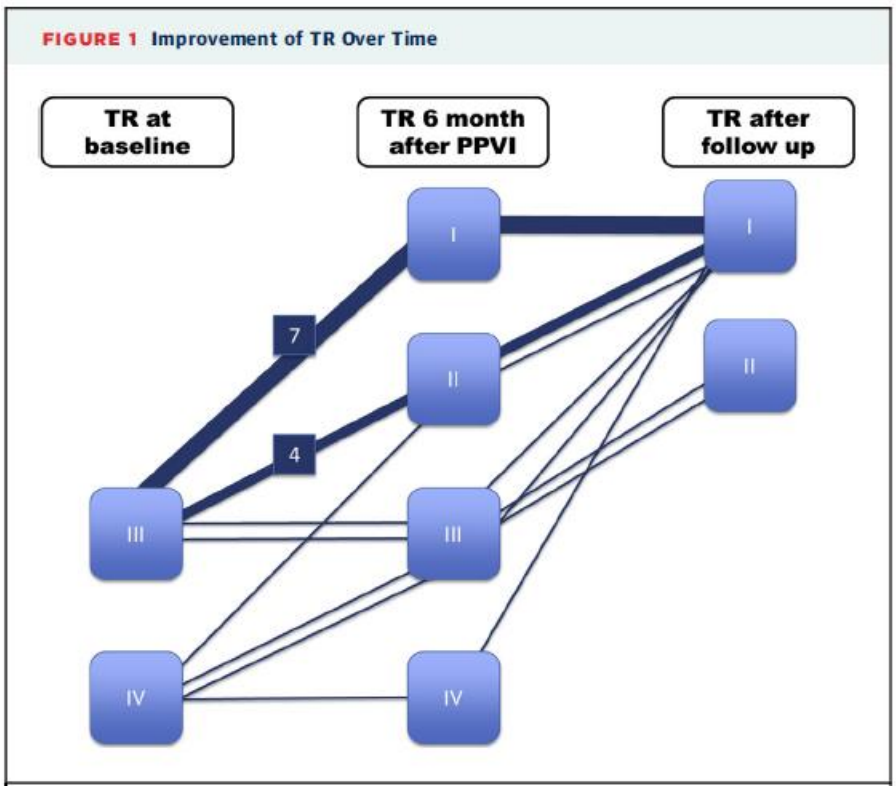

Abb 8. Veränderung des Trikuspidalklappeninsuffizienz-Grades mit PPVI und am Follow up.

Der perkutane Pulmonalklappenersatz führt bekanntermaßen zu einer Reduktion der RV Dilatation [2233]. Der Vergleich beider Gruppen in unserer Studie zeigte, dass das unabhängig von dem Vorhandensein einer Trikuspidalinsuffizienz passiert. Die RV Dilatation bildete sich mit dem interventionellen Pulmonalklappenersatz in beiden Gruppen zurück und das Ausmaß der Reduktion des end-diastolischen Volumens in den Patienten mit und ohne Trikuspidalklappeninsuffizienz war vergleichbar (Abb 9).

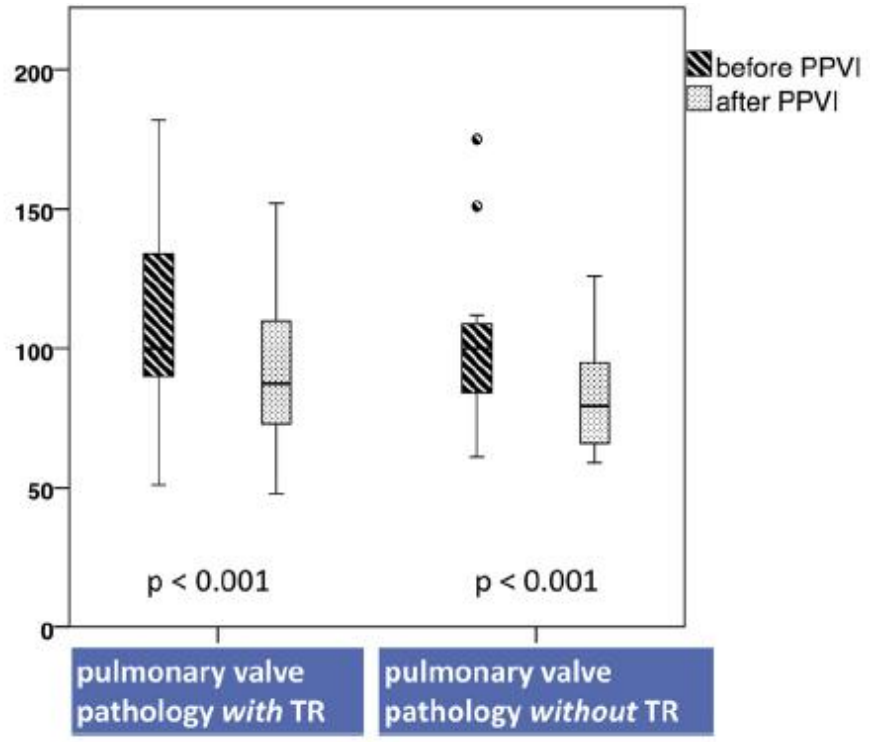

Abb. 9. Das indizierte enddiastolische RV Volumen verringerte sich mit dem interventionellen Pulmonalklappenersatz (PPVI) unabhängig von dem Vorhandensein einer TI vor der Intervention.

Was der Veränderung der körperlichen Belastung angeht, gab es auch keine signifikanten Unterschiede zwischen den Gruppen. Sowie die maximale Sauerstoffaufnahme als auch die maximale Belastung hat sich in beiden Gruppen nach dem Pulmonalklappenersatz verbessert und ähnlich wie bei den RV Volumina gab es keinen Unterschied in dem Ausmaß der Verbesserung zwischen den Patienten mit und ohne Trikuspidalklappeninsuffizienz (Abb 10).

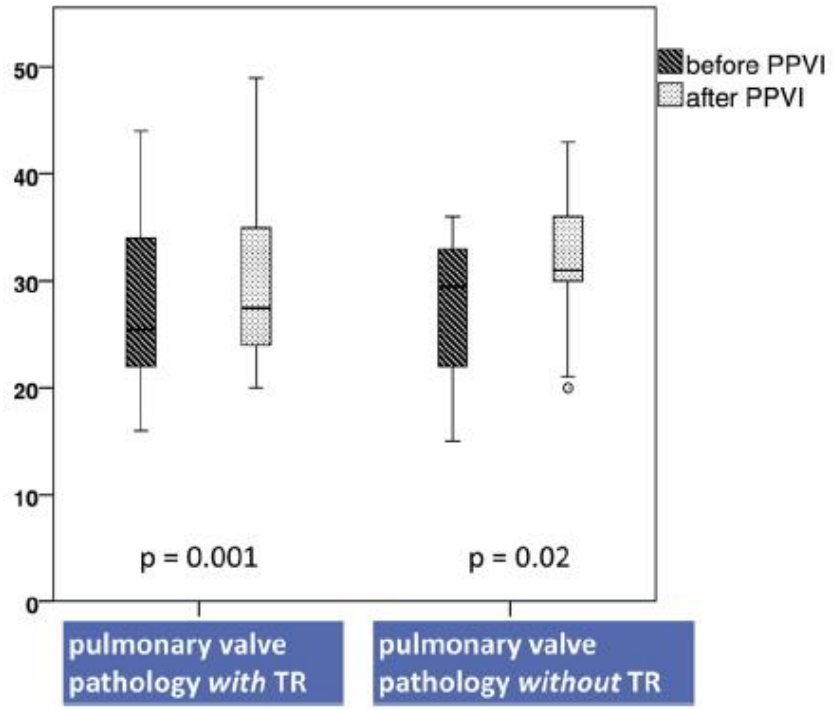

Abb. 10. Veränderung der maximalen Sauerstoffaufnahme mit PPVI in Patienten mit und ohne Trikuspidalinsuffizienz. Der perkutane Pulmonalklappenersatz führt zu einer Verbesserung der körperlichen Belastbarkeit unabhängig von dem Vorhandensein einer Trikuspidalklappeninsuffizienz.

Diese Studie hat zwei wichtige Aspekte.

Einerseits werden pathophysiologische Effekte der RVOT Dysfunktion und der PPVI erleuchtet. Eine RVOT Dysfunktion, unabhängig davon ob Pulmonalstenose -Insuffizienz oder beides, kann mit der Zeit zu einer Trikuspidalklappeninsuffizienz führen. Der Mechanismus dahinten ist die Vergrößerung aber auch die Geometrieveränderung des rechten Ventrikels. Das führt zu einer Erweiterung des Trikuspidalklappenannulus mit gestörter Koaptation der Segel. Was unsere Studie beiträgt, ist das dieser Prozess in den meisten Fällen aus der klinischen Praxis potentiell reversibel ist. Wenn die RVOT Dysfunktion durch einen interventionellen Pulmonalklappenersatz beseitigt wird, ist nicht nur die RV Erweiterung aber auch der Trikuspidalinsuffizienz-Grad rückläufig.

Anderseits, was für die tägliche klinische Praxis wichtiger ist, brauchen Patienten mit einer RVOT Dysfunktion und einer sekundären Trikuspidalklappenstenose nicht unbedingt eine chirurgische Behandlung mit Pulmonalklappenersatz und gleichzeitiger

Trikuspidalklappenplastik. Der perkutane Pulmonalklappenersatz bietet für sie eine gute und viel schonendere Alternative an. Diese Patienten profitieren von dem interventionellen Pulmonalklappenersatz genauso viel wie die Patienten, die keine Trikuspidalklappeninsuffizienz haben. Offen bleibt die Frage, wann der richtige Zeitpunkt für einen Pulmonalklappenersatz ist. Möglicherweise wird sich der Trend zu früheren Interventionen entwickeln, allerdings ist das Vorhandensein einer bedeutsamen Trikuspidalklappeninsuffizienz kein Zeichen, dass es schon zu spät ist.

Zusammenfassend fügen unseren zwei Studien zusätzliche Information über die Indikationen zum interventionellen Pulmonalklappenersatz hinzu. Initial wurde die Melody Klappe für das Verlängern des Lebens von RV-PA Conduits bei selektierten Patienten entwickelt. Mittlerweile ist es bekannt, dass diese Klappe und auch die später zum perkutanen Pulmonalklappenersatz zugelassene Sapien Klappe deutlich länger eine Reinterventionsfreiheit gewährleisten. Unsere zwei Studien zeigen, dass diese Methode auch für bestimmte Patienten mit „nativen“ oder Conduit-freien RVOTs aber auch für Patienten mit bedeutsamer sekundären Trikuspidalklappeninsuffizienz sehr gut geeignet ist. Damit könnten mehr Patienten von dieser innovativen Behandlungsmethode profitieren.

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Percutaneous pulmonary valve implantation in patients with dysfunction of a "native" right ventricular outflow tract — Mid-term results☆

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ABSTRACT

Background: To investigate the feasibility and mid-term results of percutaneous pulmonary valve implantation (PPVI) in patients with conduit free or "native" right ventricular outflow tracts (RVOT).
Methods and results: We identified all 18 patients with conduit free or "native" right ventricular outflow tract, who were treated with percutaneous pulmonary valve implantation (PPVI) in our institution. They were divided into two groups – these in whom the central pulmonary artery was used as an anchoring point for the preparation of the landing zone ($n = 10$) for PPVI and these, in whom a pulmonary artery branch was used for this purpose ($n = 8$). PPVI was performed successfully in all patients with significant immediate RVOT gradient and pulmonary regurgitation grade reduction. Four patients had insignificant paravalvular regurgitation. In one patient the valve was explanted after 4 months because of bacterial endocarditis. A follow-up of 19 (4–60) months showed sustained good function of the other implanted valves. The MRI indexed right ventricular end diastolic volume significantly decreased from 108(54–174) ml/m^2 before the procedure to 76(60–126) ml/m^2 six months after PPVI, $p = 0.01$.
Conclusions: PPVI is feasible with good mid-term results in selected patients with a "native" RVOT without a previously implanted conduit. Creating a stable landing zone with a diameter less than the largest available valve (currently 29 mm) is crucial for the technical success of the procedure. Further studies and the development of new devices could widen the indications for this novel treatment.

1. Introduction

Percutaneous pulmonary valve implantation, originally introduced to treat RVOT dysfunction and reduce the total number of open heart surgeries during a patients' life [1], is today the preferred treatment mode for RVOT dysfunction in many centers [2–5]. In the original first patient cohort of PPVI a "native" RVOT, that is a RVOT without a previous surgically implanted biological valve as a landing zone, was a risk factor for stent/valve-dislodgement during PPVI [6]. At present, surgical correction of tetralogy of Fallot is performed with excellent long-term results. However, many patients after a RVOT reconstruction with a transannular patch develop severe pulmonary regurgitation and need pulmonary valve replacement later on [7]. In 2009 Momenah et al. reported on successful PPVI in four patients with "native" RVOT after surgical TOF repair with transannular patches and severe pulmonary regurgitation [8]. PPVI in these patients was feasible, only if a reliable landing zone could be established by prestenting of the central PA. Since then there have been case reports and small case series for PPVI in "native" RVOT [9–13]. We report on our experience with PPVI in patients with RVOT dysfunction without a valved conduit in place ("native RVOT") and on our mid-term results.

2. Methods

The current study includes all PPVI patients from the German Heart Center Munich who had been treated previously without the use of a valved conduit. All patients were informed in detail about the off label nature of the procedure and gave informed consent before proceeding with the catheter intervention.

2.1. Indications for PPVI and preparation of the patients

The patients typically had been treated by a previous surgical procedure, usually a transannular RVOT-patch and had residual lesions including stenosis of the pulmonary trunk and/or branch PAs, pulmonary regurgitation or a combination of both. The indications for the intervention were met according to the usual criteria for PPVI in our

Abbreviations: PPVI, percutaneous pulmonary valve implantation; RVOT, right ventricular outflow tract; cMRI, cardiac magnetic resonance imaging; RV, right ventricle; PA, pulmonary artery.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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institution [2]. Standard preparation for the procedure included a detailed medical history and examination, 12 lead ECG, echocardiography, chest x-ray, an exercise test and cMRI.

2.2. PPVI technique

The first step was to create of a stable landing zone for the percutaneous valve with prestenting, which required some narrowing along the RVOT/PAs that could accommodate a stent. Our study population included two types of patients. The first group had a stenosis in the RVOT/central PA, where a stent could be implanted and served as a landing zone for the percutaneous pulmonary valve. In the other group of patients, the origin of the branch PAs was treated with short stents, into which longer stents were implanted, which proximal parts served as landing zones for the percutaneous pulmonary valves.

A detailed angiographic interrogation of the RVOT and the branch PAs in different projections defined the treatment strategy based on the maximal and minimal RVOT diameter and the presence of branch PA stenoses. Balloon interrogation of the RVOT showed vascular compliance and gave information on a balloon waist, which could serve as a landing zone. The anatomy of the coronary arteries in relation to the RVOT was assessed by balloon inflation in the RVOT with a simultaneous aortogram and selective coronary injections, if needed.

2.2.1. PPVI in patients with central PA stent anchoring

A balloon test was performed after a diagnostic angiogram into the main PA. PPVI was considered feasible, if the chosen balloon presented a waist of <28 mm diameter, since the largest available valve for PPVI has an external diameter of 29 mm (Sapien XT 29 mm, Edwards Livesciences Corp, Irvine, CA); in these patients a large stent was implanted into the main PA (Fig. 1a). In larger vessels (>28 mm diameter), PPVI was thought to be impossible. The next step was implantation of the percutaneous pulmonary valve in the prestented area (Fig. 1b). Postdilatation with high pressure balloons was performed in some cases to achieve optimal expansion of the valved stent and for best alignment to the RVOT.

2.2.2. PPVI in patients with branch PA stent anchoring

In these patients the creation of a stable landing zone involved a more complex catheter technique. The proximal branch PA was initially stented with a short stent as a future anchoring base (Fig. 2a). The next step was scheduled six to eight weeks later and included implantation of a longer bare metal stent, anchored into the prestented branch PA, so that the longer proximal part of this stent reached the main PA. A 0.0014′ coronary guidewire was advanced through the struts of this stent into the "jailed" contralateral PA. After a coronary balloon (4–6 mm), introduced through a coronary guide catheter (6F), was inflated through the stent, the catheter could be advanced allowing the placement of a 0.035 in. guide wire. The stent struts were then opened widely with high pressure balloons until the orifice of the PA was completely open. If this PA was stenotic or somewhat distorted by previously implanted long stent, another stent was then delivered, thus creating a Y-stent construct (Fig. 2b). After ensuring a stable landing zone and unimpeded flow to both PAs, PPVI into the central PA was done (Fig. 2c). Again, in some patients postdilatation was performed in order to achieve a good hemodynamic result.

2.3. Postimplantation care

Immediately after implantation invasive assessment of the new pulmonary valve was performed. All patients received 3 doses of a 2nd generation cephalosporine and Aspirin 100 mg for 6 months. Clinical, X-Ray and echocardiographic assessment were performed before discharge. An outpatient follow-up visit was recommended 6 months later including a cMRI and an exercise test.

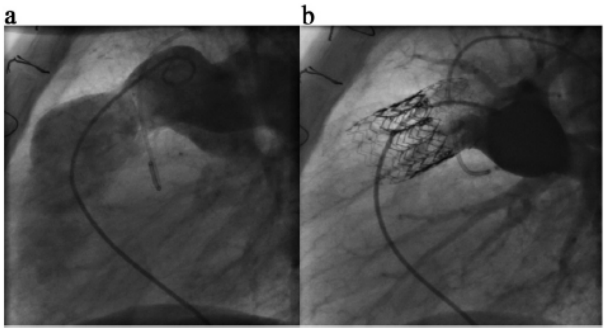

Fig. 1. A patient (case number 1) with central PA stent anchoring. a. Enlarged RVOT and severe pulmonary regurgitation after tetralogy of Fallot correction with transannular patch. b. After prestenting of the main PA with an Andra 57 mm Stent on a 28 mm Z-Med Balloon (Numed Inc., Hopkinton, NY) a Sapien XT 29 valve was implanted.

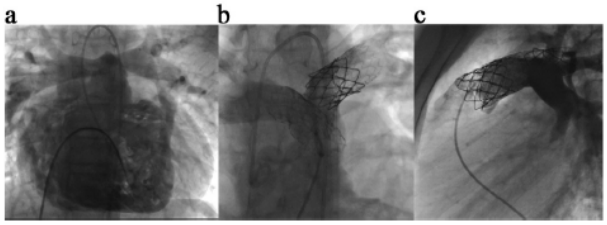

Fig. 2. A patient (case number 13), in whom a branch pulmonary artery was used for anchoring of the landing zone. a. Dilated RVOT and proximal stenoses of both branch pulmonary arteries after Tetralogy of Fallot repair with a transannular patch. b. Initially a 22 mm bare metal CP stent was implanted into a left PA stenosis. It served as an anchoring base for a Y-stent construct (57 mm Andra stent into the left pulmonary artery and 48 mm Andra stent into the right pulmonary artery). c. A Melody valve was implanted with good result with minimal paraprostetic regurgitation.

2.4. Statistical analysis

Results are presented as median values with range. Patients' characteristics before and after PPVI were compared with the Wilcoxon signed-ranks test. A p-value $p < 0.05$ was considered significant.

3. Results

Between December 2006 and May 2016 191 patients were treated with PPVI in our institution. Eighteen patients had a "native" RVOT and were included in the study. The median age at PPVI was 19 (8–43) years and median weight 56 (19–110) kg. Diagnoses of the patients, along with other characteristics are presented in Table 1. The indication for the intervention was pulmonary regurgitation in 9/18 patients, pulmonary stenosis in 2/18 patients and mixed lesion with pulmonary stenosis and regurgitation in 7/18 patients. Two patients did not receive cMRI before the procedure – one had a pacemaker and the other one complained of insurmountable claustrophobia. The median indexed RV end diastolic volume of the other 16 patients was 110 (54–174) ml/m^2.

Balloon sizing of the RVOT was performed in all patients and dependent on the anatomy, the prestenting strategy for creating a landing zone for the percutaneous valve was determined. Procedural characteristics of the patients are presented in Table 2.

3.1. Patients with RVOT stenosis.

Ten patients (case numbers 1–10) had some stenosis in the RVOT or the main PA, which had an appropriate size and was rigid enough to accommodate a stent. The median minimal diameter of the RVOT in these patients was 12 mm (7–18 mm) and the median maximal diameter of the RVOT was 29 mm (19–45 mm). In 8 patients prestenting was performed with 1 stent, and in two patients 2 stents were used. In 9 patients the percutaneous valves were implanted during the same catheterization and in 1 patient the implantation was postponed after initial prestenting for 3 months. Nine Melody (Medtronic Inc., Minneapolis, MN) und 1 Sapien XT 29 valves were used in these patients.

3.2. Patients with branch PA stenosis

In eight patients (case numbers 11–18) the RVOT was largely dilated, but they had some narrowing of the branch PAs, which served as an anchoring site for the construction of the landing zone. The median minimal diameter of the RVOT in these patients was 17 mm (16–26 mm) and the median maximal diameter of the RVOT was 33 mm (24-47 mm). The landing zone construct was created with 2 stents in 4 patients, with 3 stents in 3 patients and with 4 stents in one patient. Seven Melody and one Sapien XT 26 valves were implanted in these patients. The procedure was performed during 2 catheterizations in 3 patients and during 3 catheterizations in 5 patients.

Table 1
Characteristics of the patients.

Patient no	Sex	Age (y)	Weight (kg)	Diagnose	Non cardiac diagnose	Operation	Type of RVOT	NYHA	iRVEDV (ml/m²)	PR fraction (%)	Indication for PPVI	Additional information important for the indication for PPVI
1	M	34	63	PSt		RVOT enlargement	TAP	2	119	37	PR	Declining physical capacity
2	F	8	35	TOF, AVSD	Trisomy 21	Correction	TAP	2	n.m.	n.m.	PSt + PR	50% systemic RV pressure
3	F	14	56	PAtr, VSD		Correction	TAP	1	104	27	PSt + PR	Increasing RV pressure
4	M	32	59	TOF	Situs inversus	Correction	Subvalvular RVOT patch	1	73	18	PSt + PR	70% systemic RV pressure
5	F	16	68	TGA, VSD		1.ASO, PAB 2. VSD closure + debanding	Supravalvular PSt	1	54	6	PSt	70% systemic RV pressure
6	F	21	56	TOF		Correction	Subvalvular PSt	2	64	5	PSt	60% systemic RV pressure
7	F	16	79	TOF		Correction	TAP	2	69	21	PSt + PR	Declining physical capacity
8	M	13		TOF	Partial trisomy 14	Correction	TAP	3	108	27	PSt + PR	2/3 systemic RV pressure
9	M	30	89	TOF		Correction	Valveless RV-PA Connection	2	n.m.	29	PSt + PR	80% systemic RV pressure + severe PR
10	M	10	19	TOF, atretic LPA		Correction	TAP	2	114	18	PSt + PR	Systemic RV pressure
11	M	43	110	TOF		Correction	TAP	3	113	40	PR	Severely symptomatic
12	M	28	52	TOF, AVSD	Trisomy 21	Correction	Unknown	3	174	37	PR	Declining physical capacity
13	M	39	54	TOF		Correction	TAP	2	140	43	PR	RVEF 42%
14	F	13	37	TOF	22q11 deletion	Correction	TAP	2	153	38	PR	RV dilatation
15	M	15	62	TOF		Correction	TAP	2	101	28	PR	Declining physical capacity
16	F	43	49	TOF		Correction	TAP	2	112	35	PR	Declining physical capacity
17	F	38	58	TOF		Correction	TAP	2	144	30	PR	Declining physical capacity
18	M	9	28	TOF		Correction	TAP	1	104	50	PR	Severe PR

Abbreviations: M – male, F – female, iRVEDV – indexed right ventricular end diastolic volume, PR – pulmonary regurgitation, M – male, W – female, PSt – pulmonary stenosis, TAP – transannular patch, n.m. – not measured, TOF – Tetralogy of Fallot, AVSD – atrioventricular septal defect, PAtr – pulmonary atresia, VSD – ventricular septal defect, TGA – Transposition of the great arteries, ASO – Arterial switch operation, PAB – Pulmonary artery banding, LPA – left pulmonary artery, RV – right ventricle, PA – pulmonary artery, RVEF – right ventricular ejection fraction.

3.3. Procedural complications

In case number 11 stent infolding occurred during an attempt to prestent the left PA with a 57 mm Andra stent (Andramed GmbH, Reutlingen, Germany) on a 30 × 60 mm VACS balloon (Osypka AG, Rheinfelden-Herten, Germany). The infolded stent was crossed with a second catheter, dilated and anchored safely into the left PA. A second 57 mm Andra stent was implanted proximally, and was opened to the right PA as described above. PPVI was performed without additional complications. In case number 17 we intended to use the right PA as an anchoring point, however the stent, that was deployed there, dislocated into the dilated RVOT. It was possible to dilate the stent with a double balloon technique and fix it to the RVOT. Then, the left PA was prestented and PPVI was uneventful.

3.4. Outcome of the patients

Immediate invasive interrogation of the newly implanted pulmonary valves showed a significant reduction of the peak-to-peak gradient between the RA and the PA (before PPVI – 21 (3–57) mm Hg vs. after PPVI – 7 (0–18) mm Hg, $p = 0.001$), no pulmonary regurgitation in 14 and a mild pulmonary regurgitation in 4 cases. In one patient the intervention was performed shortly before the preparation of the manuscript and he is currently waiting for his first follow-up visit. One patient, followed up in another institution, was contacted by phone and was free of any additional interventions and two patients were lost to follow-up. Fifteen patients were followed up at a median time of 19 (4–60) months. Patient number 4 developed bacterial endocarditis 4 months after implantation of a Melody valve. The patient presented with fever, positive blood cultures with *Staphylococcus epidermidis*, a vegetation on the Melody valve and an increase of the gradient across the valve up to 55 mm Hg. Aspirin therapy was admitted regularly, according to the patient. After 6 weeks of antibiotic treatment and persistence of the increased gradient, the percutaneous valve was explanted surgically and a homograft was implanted with a good result and no endocarditis recurrence. Echocardiographically, in the other 12 patients valve function without an increase of pulmonary regurgitation was sustained and in two patients a new, mild and insignificant pulmonary regurgitation was diagnosed. The Doppler derived peak instantaneous gradient across the pulmonary valve did not increase significantly immediately after the intervention – 8(0–18) mm Hg until the last follow-up – 13(0–35) mm Hg, $p = 0.16$. In the patients who were available for cMRI after PPVI ($n = 12$), the indexed RV end diastolic volume significantly decreased from 108(54–174) ml/m² before the procedure to 76(60–126) ml/m² six months after PPVI, $p = 0.01$.

4. Discussion

This study provides additional evidence that PPVI is feasible and safe in selected patients with "native" RVOTs. Mid-term follow-up shows sustained excellent hemodynamic results, which are comparable to that of patients, who had a classical PPVI indication.

PPVI represents an interventional method for sparing surgeries in patients with RV-PA conduits [2–5]. Extending the indications for this type of intervention to conduit free "native" RVOTs may have a significant impact on the management of many patients. Boudjemline et al. [14] reported the use of a "downsize" stent containing a bovine valve into dilated RVOTs in animals. The PPVI patient series of Momenah et al. [8] included four patients with RVOT dysfunction after transannular patch implantation. Other small case series with different techniques involved prestenting of the main PA [9,10,12,13] or introduced the "Russian doll" and the "pulmonary jailing" technique [11]. In our report we share our experience with the use of valved stents in "native" RVOTs, including two different types of patients.

The RV-PA conduits of the patients, who are classically indicated for PPVI are typically non-distensible tubes, often with pronounced calcifications, making them rigid shells and thus ideal for accommodating

Table 2
Procedural details of the patients.

Patient no	Landing zone anchoring point	Minimal RVOT diameter	Minimal balloon sizing diameter	Maximal RVOT diameter	Type of stents for prestenting	Number of catheterizations for the PPVI	Valve	Postdilatation	Procedural Complications
1	MPA	17	23	45	Andra 57	1	Sapien XT 29	No	
2	MPA	8	14	24	Andra 26	2	Melody BIB 18	No	
3	MPA	15	15	30	Max LD 36[a]	1	Melody BIB 22	Atlas 22[b]	
4	MPA	12	18	26	2× Max LD 36	1	Melody BIB 22	Atlas 22	
5	MPA	9	12	22	Max LD 36	1	Melody BIB 20	Atlas 22	
6	MPA	12	16	37	CCP 34	1	Melody BIB 20	Atlas 20	
7	MPA	13	15	29	CCP 34	1	Melody BIB 22	Atlas 20	
8	MPA	10	14	19	Max LD 26	1	Melody BIB 20	Atlas 20	
9	MPA	18	18	37	CCP 34	1	Melody BIB 22	Atlas 22	
10	MPA	7	8	28	CCP 28, MaxLD 26	1	Melody BIB 18	No	
11	LPA	26	26	47	2× Andra 57, CCP 39	3	Sapien XT 26	No	Stent infolding
12	LPA	16	16	33	Andra 39, Max LD 26	2	Melody BIB 22	No	
13	RPA	22	22	46	Andra 57, Andra 39	2	Melody BIB 22	No	
14	LPA	16	17	30	Max LD 26, Andra 57	2	Melody BIB 20	No	
15	LPA	16	25	28	CP 22, 2xAndra 57, Max LD 26	3	Melody BIB 22	No	
16	LPA	17	23	24	CP 34, Andra 26	3	Melody BIB 22	No	
17	LPA	17	17	33	Max LD 16, Andra 57, CCP 28	3	Melody BIB 22	Atlas 22	
18	LPA	19	20	35	Andra 13 mm, Max LD 26, Andra 57	3	Melody BIB 22	no	RPA Stent dislocation

[a] MaxLD (ev3 Endovascular, Inc., Plymouth, MN).
[b] Atlas (BARD Peripheral Vascular, Inc., Tempe, AZ).

stents during PPVI. The different characteristics of RVOT of the patients we treated require different PPVI techniques. The first group has a stenosis of the main PA, which is the main indication for PPVI and is often combined with considerable pulmonary regurgitation. The technique of PPVI in such cases is principally similar to that of the "classical" patients and involves presenting for preparation of a landing zone for the valved stent. Importantly, these RVOTs are not calcified and tend to be distensible which predisposes to dislocation or even embolization of the stents. Balloon interrogation with large and long balloons at low inflation pressure proved to be very useful to prevent this complication. The elastic properties of the Pas can be shown and a balloon waist signifies where a stent can be safely delivered, preparing the landing zone for the valved stent.

The other group of patients have wide RVOTs, typically after surgical corrections with transannular patches and are indicated for the intervention because of pulmonary regurgitation. This involves a more complex and technically challenging procedure and requires some narrowing of a branch PA, which can serve as an anchoring point for fixing the stent construct for the landing zone for PPVI. In contrast to the concept of "PA jailing" [11], our technique involved routine opening of the stent struts to the contralateral PA, thus surely creating unobstructed flow to both branch PAs. Challenging in these patients is to prevent paravalvular regurgitation. There should be a narrower zone across the RVOT, which is smaller than the largest available valve and can be effectively sealed by its covered stent. Following this rule, good results could be obtained in our patients – four had paravalvular regurgitation and it was not significant in any of them. Currently, the largest available valve has an external diameter of 29 mm (Edwards Sapien XT 29) and this represents a limitation for the interventional treatment of such patients. The development of new devices, especially designed for "native" RVOTs could enable the percutaneous treatment of larger RVOTs [15]. Stent dislocation is possible also in this type of patients. The first short stent that is used as an anchoring point for the construct of the landing zone is implanted into a narrower but not really stenotic region. We observed stent dislocation in one patient, in whom the intended implantation zone in the right PA was obviously not suitable to accommodate a stent. As the stability of this first stent is of paramount importance, we suggest delaying the next interventional steps for few months to allow vessel wall ingrowth in it. This treatment involves extensive stenting in a zone, which is predisposed to need further interventions. This may make future surgery of the RVOT difficult and we believe that these cases have to be discussed in the heart team with congenital cardiac surgeons before the procedure.

This study shows a positive effect of PPVI on cMRI derived RV dimensions in patients with "native RVOTs". Right ventricular end diastolic volumes declined significantly as described for patients with RV-PA conduit dysfunction [16]. The mid-term durability of PPVI for this indication was good, only one patient needed repeated treatment because of endocarditis. This complication is well known in "standard" patients in PPVI and patients with "native" RVOTs seem to be at risk as well. Further studies are needed for estimation of the incidence and risk factors for bacterial endocarditis in these patients.

This study reports on our initial experience with PPVI in patients with a "native RVOT" and has some limitations. The treatment is technically demanding. Although our patient number is small and the follow-up is relatively short, to our knowledge this is one of the largest cohort treated by PPVI for this indication. However, only limited conclusions can be drawn so far and further studies are needed.

5. Conclusion

PPVI is feasible in selected patients with "native" RVOTs without previously implanted RV-PA conduits. Due to the elastic properties of the central PA a landing zone has to be created with balloon expandable stents. It can be created by anchoring stents in the main - or branch pulmonary arteries depending on the specific anatomy. At present the limiting factor is the availability of large valves. The mid-term hemodynamic outcome of our group of patient was excellent. The only follow-up complication was bacterial endocarditis. Studies on larger numbers of patients are needed in order be able to create precise indications for this intervention and predict the outcome.

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Conflict of interest statement

Andreas Eicken is proctor for the Melody Valve, Peter Ewert – proctor for the Melody and the Sapien XT valve. Alfred Hager received

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Tricuspid Regurgitation Does Not Impact Right Ventricular Remodeling After Percutaneous Pulmonary Valve Implantation

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ABSTRACT

OBJECTIVES This study sought to investigate the impact of tricuspid regurgitation (TR) on right ventricular function after percutaneous pulmonary valve implantation (PPVI).

BACKGROUND PPVI provides a less invasive alternative to surgery in patients with right ventricular-to-pulmonary artery (RV-PA) conduit dysfunction. Recovery of the right ventricle has been described after PPVI for patients with pulmonary stenosis and for those with pulmonary regurgitation. Additional TR enforces RV dysfunction by supplemental volume overload. Limited data are available on the potential of the right ventricle to recover in such a specific hemodynamic situation.

METHODS In a matched cohort study, we compared patients who underwent PPVI with additional TR with those without TR.

RESULTS The degree of TR improved in 83% of the patients. In our patients (n = 36) exercise capacity and right ventricular volume index improved similarly 6 months after PPVI in patients with and without important TR. None of them had significant TR in the long-term follow-up of median 78 months.

CONCLUSIONS PPVI improves not only RV-PA-conduit dysfunction, but also concomitant TR. In patients with a dysfunctional RV-PA conduit and TR, the decision whether to fix TR should be postponed after PPVI. (J Am Coll Cardiol Intv 2017;10:701–8)
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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

PPVI = percutaneous pulmonary valve implantation

PR = pulmonary regurgitation

PS = pulmonary stenosis

PVR = pulmonary valve replacement

RV-PA = right ventricle to pulmonary artery

RVEDVI = right ventricular end-diastolic volume index

RVOT = right ventricular outflow tract

TR = tricuspid regurgitation

Vo_2 peak = peak oxygen uptake

In patients with right ventricular outflow tract (RVOT) conduit dysfunction, percutaneous pulmonary valve implantation (PPVI) is a less invasive therapeutic option than repeated cardiac surgery (1). PPVI proved to be safe and effective in several studies and at present is the preferred treatment option for RVOT conduit dysfunction in many centers (2–5). In prior studies, beneficial effects of PPVI were documented irrespective of the prevailing hemodynamic indication: RVOT stenosis, pulmonary regurgitation (PR), or a combination of stenosis and regurgitation (6,7). Sustained improvements in hemodynamics were shown up to 7 years post-PPVI (8).

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In addition to RVOT dysfunction, some patients referred for PPVI present with moderate to severe tricuspid valve regurgitation (TR). This may be caused by various factors, including a congenitally dysplastic tricuspid valve, RV pressure and/or volume overload, or sequela of preceding surgical procedures. Limited data are available on the potential of the RV to recover in such a specific hemodynamic situation. Current guidelines suggest a surgical approach if RVOT dysfunction is combined with moderate to severe TR (9,10). However, if restoring RVOT function by PPVI improves right heart hemodynamics significantly, the clinical impact of TR may be reduced and surgery may thus be avoidable (11). Therefore, the objective of the present matched cohort study was to investigate the impact of TR on right ventricular function after PPVI.

METHODS

PATIENT SELECTION. Between December 2006 and December 2014, a total of 173 patients underwent PPVI at the German Heart Center Munich. Twenty-two of these patients had moderate or severe TR according to echocardiographic criteria (12) before PPVI and constitute the study cohort (TR cohort, TR patients). Patients were evaluated with a standardized protocol including the following: history, echocardiography, cardiac magnetic resonance imaging (CMR), cardiopulmonary exercise testing, and assessment of New York Heart Association functional class. For every patient with significant TR, a matched control subject was selected with comparable clinical findings but without additional TR (control cohort). According to study protocols, all cases and control subjects were evaluated before PPVI and 6 months after PPVI.

Control subjects were matched to patients with TR according to the following criteria. In detail, we made sure to compare patients: 1) having the same pulmonary valve pathology, either pulmonary stenosis (PS), PR, or a combination of both; 2) with similar indexed right ventricular end-diastolic volume (RVEDVi); and 3) with New York Heart Association functional class state that was the same or differed no more than 1 class. Additionally, the underlying cardiac diagnosis, sex, age at PPVI, and number of previous surgeries were also taken into consideration. PS was defined as a peak invasive right ventricular-to-pulmonary artery (RV-PA) gradient more than 40 mm Hg, and PR was defined as a regurgitant fraction more than 20% by CMR. Patients with mixed valve disease (i.e., meeting both PS and PR criteria) were compared with similar patients with mixed disease. For statistical evaluation, patients with mixed disease were analyzed either with the PS or PR cohorts, depending on which was the dominant pathophysiology.

In 4 patients it was not possible to find a matched pair, in 3 because the RVEDVi differed significantly and in 1 because of a unique congenital heart defect (congenitally corrected transposition of the great arteries). Those 4 patients were excluded from further evaluation. Thus, the study group consisted of 18 patients with pulmonary valve dysfunction and significant TR, who were compared with 18 matched control subjects treated by PPVI who did not have relevant TR.

CARDIOPULMONARY EXERCISE TESTING. All patients underwent a symptom-limited cardiopulmonary exercise test on an electronically braked bicycle in a sitting position according to international guidelines (13). Patients cycled according to a ramped protocol with a 3-min warm-up at 0 W followed by a rampwise increase of load with 10, 15, 20, or 30 W/min with the aim of reaching an exercise duration of 8 to 12 min. They were encouraged to exercise until exhaustion. Oxygen uptake was measured breath by breath by a metabolic cart (Vmax 229, SensorMedics, Viasys Healthcare, Yorba Linda, California). Peak oxygen uptake was defined as the mean oxygen uptake in the 30-s period that was highest throughout the exercise test.

CARDIAC MAGNETIC RESONANCE IMAGING. CMR was performed at 1.5 T (Symphony Maestro Series and Avanto, Siemens Medical Solutions, Erlangen, Germany). Retrospective gated cine CMRs of the heart were acquired in the vertical long-axis, 4-chamber, and short-axis views that included the extent of both ventricles, and 2 long-axis planes of the RVOT for through-plane flow quantification. Aortic and PA flow

data were acquired with a flow-sensitive gradient echo sequence during free breathing. Regurgitant fractions were calculated from forward and backward flow across the valve. For volume measurements of the RV, endocardial contours were traced, excluding papillary muscles, trabeculae, and the moderator band from the blood volume.

STATISTICAL ANALYSIS. Data were analyzed with a standard statistical package (SPSS version 22.0, SPSS Inc., Chicago, Illinois). All continuous variables were expressed as median and minimum-maximum. Pre- versus post-PPVI data were analyzed with the 2-tailed Mann-Whitney *U* test. For continuous data, patients with pulmonary valve dysfunction and additional TR were compared with control subjects using a 2-tailed paired Student *t* test. For statistical analysis of the changes in the degree of TR, the Wilcoxon signed rank test was performed. Statistical significance was inferred when $p < 0.05$.

RESULTS

BASELINE CHARACTERISTICS. The median age of all cases and control subjects included in the study was 21 years (mean, 22.2 ± 7.9 years), the youngest patient being 10 years and the oldest 39 years of age. The group comprised 14 female and 22 male patients. Overall, 18 patients had an underlying cardiovascular diagnosis of tetralogy of Fallot, 9 had pulmonary atresia with ventricular septal defect (n = 9), 8 had truncus arteriosus (n = 8), and 1 had pulmonary atresia with intact ventricular septum (n = 1). Individual patient data are listed in Table 1.

All patients had undergone a median of 2 prior surgical interventions, and all had undergone corrective surgery with RV-PA conduit. Most of the patients were in New York Heart Association functional class II (n = 32), whereas 3 were in functional class I and 1 was class III.

The median peak oxygen uptake ($Vo_{2\ peak}$) was 28.5 ml O_2/kg/min (mean, 27.5 ± 7.4 O_2/kg/min), and ranged from 15 to 44 ml O_2/kg/min. Among patients referred for PPVI because of predominant PR, the median regurgitant fraction calculated by CMR was 33% (21% to 43%). Patients with prevailing PS had a median RV-PA peak systolic pressure gradient at cardiac catheterization of 46 mm Hg (27 to 83 mm Hg). The median central venous pressure (measured in the right atrium) was 8 mm Hg (3 to 17 mm Hg), with no difference between patients with and without TR ($p = 0.29$). The median RVEDVi of all patients included in the study was 100 ml/m² (mean, 109.3 ± 34.4 ml/m²) with a range of 61 to 185 ml/m².

PEAK SYSTOLIC PRESSURE GRADIENTS AND PULMONARY REGURGITATION. PPVI was performed successfully in all patients, with no significant procedural adverse events. Patients with pulmonary valve pathology and TR received PPVI at a median age of 22 years (10 to 34 years), which was similar to those without TR, whose median age was 22.5 years (13 to 39 years; $p = 0.19$).

In patients with predominant PR, the regurgitant fraction was significantly reduced after PPVI, from a median of 33% (21% to 43%) to 1% (0% to 3%; $p < 0.001$). In patients with PS, the peak invasive RV-PA systolic pressure gradient was reduced significantly from 46 ± 12 mm Hg to 14 ± 5 mm Hg ($p < 0.001$). Comparing patients with TR with control subjects showed no significant difference in the reduction of PR or PS.

ECHOCARDIOGRAPHIC EVALUATION OF TR. In all patients, echocardiographic data were evaluated for at least 8 years before PPVI. In all of them, TR developed gradually over time, with absent or trivial TR initially that increased to mild and later to moderate or severe. None of them had a sudden increase of TR after surgery.

After PPVI, the degree of TR improved in 15 of 18 (83%) study patients ($p < 0.001$) 6 months after implant. In 3 of 18 (16%) study patients it remained unchanged. Patients in the TR cohort were followed for a median of 6.5 years (8 months to 9.3 years) after PPVI, and at the latest follow-up visit, none had significant TR. In 15 patients, follow-up TR was trivial and in 3 it was mild. In 1 patient whose TR initially improved to trivial, it later become mild in the context of recurrent stenosis of the melody valve. Detailed data are presented in Table 1 and Figure 1.

RIGHT VENTRICULAR END-DIASTOLIC VOLUME INDICES. Patients in the TR cohort had a median RVEDVi before PPVI of 100 ml/m² (71 to 182 ml/m²). After 6 months, RVEDVi decreased significantly to 88 ml/m² (60 to 152 ml/m²; $p < 0.001$). Patients without TR also had a median pre-PPVI RVEDVi of 100 ml/m² (61 to 185 ml/m²), which decreased to 80 ml/m² (59 to 162 ml/m²; $p < 0.001$). Complete results are depicted in Table 1. There was no difference in RVEDVi between patients with and without TR, either at baseline or after PPVI (baseline, $p = 0.63$; after PPVI, $p = 0.20$). There was also no difference between groups in the magnitude of decrease in RVEDVi ($p = 0.57$). In TR patients, RVEDVi decreased a median of 16 ml/m² (3 to 65 ml/m²) and in patients without TR it decreased by a median of 15 ml/m² (2 to 78 ml/m²). The results are listed in Table 2 and depicted in Figure 2.

TABLE 1 Demographic and Clinical Characteristic of All Patients

Patient #	Sex	Diagnosis	Indication for PPVI	Age at PPVI, yrs	NYHA Functional Class Before	Previous Surgeries	CVP a/v/m	RVEDVI, ml/m²		Vo_2 Peak, ml/kg/min		TR			
								Before	After	Before	After	Before	After PPVI	After Follow-Up	Follow-Up, months
1*	Male	TOF	PR	13	2	3	10/12/8	130	119	44	45	Severe	Mild	Trivial	76
2†	Male	TOF	PR	15	1	2	10/10/8	151	107	34	36				
3*	Female	TAC	PR	33	2	3	17/19/17	90	78	21	22	Moderate	Moderate	Mild	85
4†	Female	TAC	PR	33	2	3	9/7/6	103	99	15	20				
5*	Male	TOF	PR	34	2	2	8/10/7	138	73	17	20	Moderate	Trivial	Absent	61
6†	Male	PA, VSD	PR	30	2	2	7/6/5	109	66	33	38				
7*	Male	TOF	PR	33	1	2	6/9/6	128	117	30	32	Moderate	Mild	Trivial	91
8†	Male	TOF	PR	21	2	2	17/16/15	94	78	29	30				
9*	Male	TOF	PR	23	2	3	7/9/6	182	152	25	26	Moderate	Trivial	Trivial	42
10†	Male	TOF	PR	39	2	2	12/11/10	175	126	34	36				
11*	Male	TOF	PR	22	2	2	7/10/8	93	65	22	24	Moderate	Trivial	Trivial	107
12†	Male	PA, VSD	PR	30	2	2	7/6/5	109	60	33	38				
13*	Female	TOF	PR	16	2	2	10/11/9	172	130	37	37	Moderate	Trivial	Mild	80
14†	Female	TOF	PR	18	2	2	10/8/8	185	107	32	44				
15*	Female	TOF	PR	14	2	1	9/10/9	98	95	29	29	Moderate	Moderate	Trivial	86
16†	Female	PA, VSD	PR	16	2	2	12/10/9	94	65	36	35				
17*	Male	PA, VSD	PS	10	2	3	5/8/4	89	86	43	46	Moderate	Absent	Trivial	68
18†	Male	PA, VSD	PS	13	2	3	8/8/6	61	59	26	32				
19*	Male	PA, VSD	PS	23	2	3	7/11/8	113	80	31	34	Moderate	Mild	Trivial	27
20†	Male	PA, VSD	PS	21	2	4	4/4/3	100	90	22	30				
21*	Male	PA, IVS	PS	16	2	2	16/15/12	142	110	36	49	Severe	Severe	Trivial	60
22†	Male	TOF	PS	17	2	2	7/6/5	112	85	30	30				
23*	Female	TOF	PS	25	2	3	7/9/8	134	109	16	28	Moderate	Mild	Trivial	112
24†	Female	PA, VSD	PS	28	3	2	18/15/14	84	73	18	21				
25*	Male	TOF	PS	31	2	3	10/12/10	101	82	19	22	Severe	Moderate	Trivial	88
26†	Male	TOF	PS	36	2	2	9/9/6	100	95	20	24				
27*	Female	TAC	PS	13	2	1	7/9/6	99	91	26	27	Severe	Moderate	Mild	92
28†	Female	TAC	PS	14	2	2	8/7/6	69	67	31	31				
29*	Female	TOF	PS	16	2	2	10/11/8	71	67	21	24	Moderate	Mild	Trivial	60
30†	Female	PA, VSD	PS	17	2	3	10/10/9	71	59	30	31				
31*	Female	TAC	PS	22	2	3	11/12/12	81	60	23	21	Moderate	Trivial	Trivial	93
32†	Female	TAC	PS	20	2	2	10/9/8	93	67	23	23				
33*	Male	TAC	PS	15	2	1	7/10/8	79	71	24	25	Moderate	Trivial	Trivial	8
34†	Male	TAC	PS	15	1	3	12/11/10	84	81	28	30				
35*	Male	TOF	PS	29	2	2	13/14/13	92	89	34	35	Moderate	Trivial	Trivial	62
36†	Male	TOF	PS	26	2	2	8/8/7	108	95	18	35				

*Patients with pulmonary valve dysfunction and additional TR. †Selected matched pairs corresponding in sex, diagnosis group, age at PPVI, and RVEDVI measured by cardiac magnetic resonance imaging. The functional state of the patients is indicated according to NYHA functional classification.

a = "a"-wave, CVP = central venous pressure; m = mean pressure in mm Hg; NYHA = New York Heart Association; PA IVS = pulmonary atresia and intact ventricular septum; PA VSD = pulmonary atresia with ventricular septal defect; PPVI = percutaneous pulmonary valve implantation; PR = pulmonary regurgitation; PS = pulmonary stenosis; RVEDVI = right ventricular end diastolic volume index; TAC = truncus arteriosus communis; TOF = tetralogy of Fallot; TR = degree of tricuspid regurgitation classified according to echocardiographic guidelines in none or trivial, mild, moderate, and severe; v = "v"-wave; Vo_2 peak = peak oxygen uptake.

EXERCISE TESTING. Compared with baseline, functional parameters improved in all patients 6 months after PPVI. Pre-PPVI median $Vo_{2\ peak}$ in index patients and matched pairs was 28.4 ml O_2/kg/min (15.1 to 44 ml O_2/kg/min). This improved significantly to 30 ml O_2/kg/min (20 to 49 ml O_2/kg/min; $p < 0.001$). The median pre-PPVI mean work load was 2.3 W/kg (1 to 3.4 W/kg) and improved significantly to 2.5 W/kg (1.3 to 3.7 W/kg; $p < 0.001$). The difference in Vo_2 between patients with and without TR did not differ at baseline ($p = 0.96$) or after PPVI ($p = 0.41$).

To assess the relationship between baseline TR and functional outcome, the improvement of peak Vo_2 was compared between patients with significant TR and control subjects. In patients with TR, the $Vo_{2\ peak}$ improved from a pre-PPVI median of 25.5 ml O_2/kg/min (16 to 44 ml O_2/kg/min) to 27.5 ml O_2/kg/min (20.4 to 49 ml O_2/kg/min; $p = 0.009$). In control subjects, only the median peak Vo_2 improved from 29.4 (15.1 to 36) to 31 (20 to 43.6) ml O_2/kg ($p = 0.001$). Despite the fact that in both groups the $Vo_{2\ peak}$ improved 6 months after PPVI, the

improvements were similar and not significantly different between groups (p = 0.32). These results are depicted in Figure 2.

Similar results were observed regarding improvement in workload. Before PPVI, the median workload in patients with TR was 2.0 (1.2 to 3.5) W/kg, which increased to 2.2 (1.5 to 3.6) W/kg after PPVI (p = 0.001). In control subjects without TR, median workload increased from 2.5 (1 to 3.4) W/kg to 2.6 (1.3 to 3.7) W/kg, (p = 0.001). As shown in Table 2, there were no significant differences in workload between patients and control subjects either at baseline (p = 0.56) or after PPVI (p = 0.52), and no difference in the amount improvement (p = 0.85).

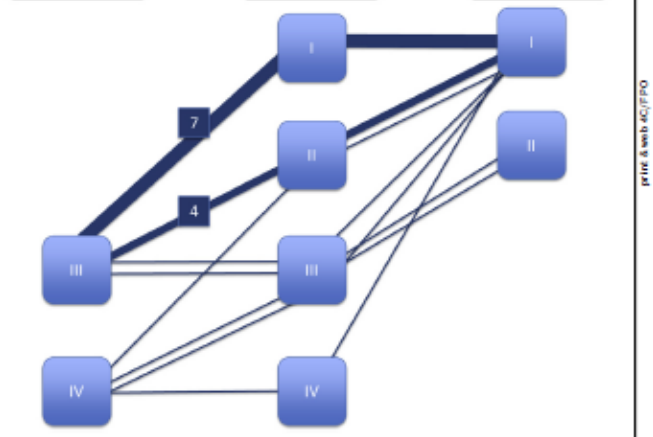
DISCUSSION

This matched cohort study shows that in most patients with RVOT conduit dysfunction and moderate to severe TR, PPVI leads to a sustained reduction in TR. The increase in exercise tolerance and reduction of RVEDVi after PPVI did not differ according to the presence or absence of significant baseline TR.

In the setting of increased afterload from PS or volume overload from PR, the RV undergoes a series of adaptations to maintain stroke volume. The potential of the RV to recover when abnormal loading conditions are relieved has been reported for patients with PS and/or PR (6,14). In addition to dysfunction of the RV-PA conduit, some patients present with important TR, which may be secondary/functional and the result of adaptive mechanisms of the RV (15), a sequela of previous surgical procedures, or related to a primary congenital abnormality of the tricuspid valve. Additional RV volume overload caused by TR can lead to a further rightward shift on the Frank-Starling curve. The potential for recovery of the RV in that specific hemodynamic condition has not been reported so far.

In our study population, exercise capacity and RVEDVi improved equally in patients with and without important TR. Following the current guidelines, surgery is recommended for treatment of RVOT dysfunction with concomitant moderate to severe TR (9,10). Surgery enables addressing both the pulmonary and tricuspid valves directly. The hypothesis of the current study was that treatment of RVOT dysfunction with PPVI, relieving PS, and providing a competent pulmonary valve would improve right heart hemodynamics and mechanics, with consequent reduction in the severity and clinical impact of TR. If this hypothesis were true, surgery could be postponed or potentially avoided altogether.

FIGURE 1 Improvement of TR Over Time



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Improvement in the degree of TR in patients with pulmonary valve pathology with additional TR. The **left column** depicts TR at baseline, the **middle column** shows the degree of TR 6 months after percutaneous pulmonary valve implantation, and the **right column** depicts degree of TR after a median follow-up of 6.5 years (8 months to 9.3 years). Each **thin line** represents a patient and indicates stagnation or improvement in the degree of TR in time. The **upper thick line** includes 7 patients, the **lower thick line** 4 patients. **Roman numbers** depict the degree of TR for the left side, **I** representing none or trivial TR, **II** mild, **III** moderate, and **IV** severe TR. PPVI = percutaneous pulmonary valve implantation; TR = tricuspid regurgitation.

DO WE HAVE TO ADDRESS SECONDARY TR?

Symptomatic patients with severe primary tricuspid valve dysfunction need surgery. However, in cases of a secondary TR, there is evidence that treatment of the underlying cause improves tricuspid valve function. For example, patients with severe pulmonary arterial hypertension caused by mitral regurgitation or other left heart disease often show regression of TR and almost one-third of them experience complete resolution of TR following mitral valve surgery without direct intervention on the tricuspid valve (16). Because of its functional physiology, secondary TR may diminish or disappear with improvement of right ventricular function and loading. In the context of right atrial or RV dilation caused by an atrial septal defect, amelioration of functional TR after interventional or surgical repair was described (17). In patients with at least moderate TR, significant improvement in tricuspid valve function occurs after surgical pulmonary valve replacement (PVR), irrespective of concomitant tricuspid valve annuloplasty (18).

In this series, TR gradually developed over years in all patients and was not related to surgery. This

TABLE 2 Hemodynamic and Functional Parameters From Patients With Pulmonary Valve Pathology With and Without Additional TR

		Pulmonary Valve Pathology With TR	Pulmonary Valve Pathology Without TR	p Value
RVEDVI, ml/m²	Pre	100 (71 to 182)	100 (61 to 185)	0.628
	Post	88 (60 to 152)	80 (59 to 126)	0.203
	p value	*<0.0001*	*0.0002*	
Peak Vo_2, ml/m²	Pre	25 (16 to 44)	29 (15 to 36)	0.936
	Post	28 (20 to 49)	31 (20 to 41)	0.406
	p value	*0.009*	*0.001*	
Work load, W/kg	Pre	2 (1.8 to 2.4)	2.5 (1.0 to 3.5)	0.563
	Post	2.2 (1.5 to 2.6)	2.6 (1.3 to 3.7)	0.521
	p value	*0.001*	*0.001*	
Absolute change in RVEDVI after PPVI, ml/m²		16 (3 to 65)	15 (2 to 78)	0.575
Absolute change in peak Vo_2 after PPVI, ml/m²		1.4 (-2 to 13)	2.6 (-1 to 17)	0.328
Absolute change in work load after PPVI, W/kg		0.16 (-0.2 to 0.7)	0.3 (-0.5 to 0.8)	0.851

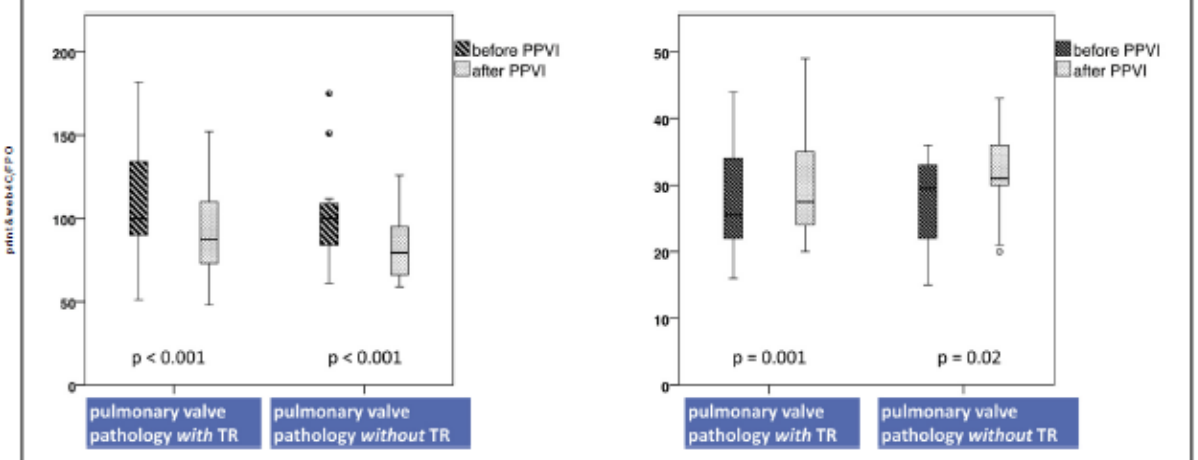
Values are median (range). Pre- and post-interventional values of patients. The minimal and maximal values are stated in parentheses. The p values in *italics* indicate statistic between pre- and post-PPVI values. The p values in nonitalics indicate statistic between patients with pulmonary valve pathology with additional TR and those without TR.

Abbreviations as in Table 1.

suggests that the mechanism might be associated with hemodynamic changes in the pressure or volume loaded RV. After PPVI, TR improved in most patients. The RVEDVi decreased significantly, which may have improved remodeling of the RV. The hemodynamic improvements and RV remodeling seemed to positively influence tricuspid valve function. Indeed, the larger RVEDVi after PPVI in the TR group suggests that the RV remained volume loaded in patients who had concomitant TR at baseline. This seems to be supported by the exercise testing findings, with higher workload and peak Vo_2 in patients without TR. However, even if differences were minimal and in 3 patients (16%) TR did not improve immediately after PPVI, none of the patients had significant TR during long-term follow-up. These results are in concordance with a recent study that documented sustained hemodynamic improvement of tricuspid valve function after PPVI at midterm follow-up (11).

DO PATIENTS WITH RVOT DYSFUNCTION BENEFIT FROM CONCOMITANT SURGERY ON THE TRICUSPID VALVE? The hypothetical advantage of surgery over PPVI in patients with RVOT dysfunction and significant TR is that there is the possibility to repair both dysfunctional valves at the same time. But in some patients with severe TR who undergo tricuspid annuloplasty, significant TR remains (19). Tricuspid valve repair usually is associated with a low perioperative risk (20). However, when reconstruction fails or is not feasible, valve replacement becomes inevitable. Compared with tricuspid valve repair, valve replacement is associated with reduced late

FIGURE 2 Decrease of RVEDVI and Increase of Peak Oxygen Uptake After PPVI



Decrease of the RVEDVI **(left panel)** and increase of the maximal oxygen uptake **(right panel)** after PPVI. The RVEDVI is measured in ml/m² and the maximal oxygen uptake in ml/kg/min. In each panel the **dark striped box** presents the data before PPVI and the **light checked box** presents the data after PPVI. The **box plots on the left side of the panel** depict the results of patients with pulmonary valve dysfunction and additional TR. The **box plots on the right side** depict the results of patients without additional TR. RVEDVI = right ventricular end-diastolic volume index; other abbreviations as in Figure 1.

survival (21). Additionally, in patients with repaired tetralogy of Fallot and both RVOT dysfunction and at least moderate TR, significant improvement in RV size and function occurs after PVR with or without tricuspid valve repair. This suggests that tricuspid valve repair at the time of PVR may not be superior to PVR alone (22).

Bokma et al. (23) compared the results of PVR alone with those with concomitant tricuspid annuloplasty in patients with repaired tetralogy of Fallot and severe TR. Irrespective of early post-operative TR reduction, patients with severe preoperative TR were at high risk for adverse clinical events after PVR in long-term follow-up. This may reflect the fact that the presence of TR is a marker of more advanced disease and an indication for PPVI or PVR to prevent irreversible RV damage. However, meticulous evaluation is needed to rule out patients with dysplastic tricuspid valves, because addressing just the pulmonary valve is a potentially deficient strategy in such patients.

WHEN SHOULD WE TREAT RVOT DYSFUNCTION? The optimal timing for PVR is still under debate because no controlled, randomized studies are available. In 1 study, RV size did not return to normal after PVR in patients with a RVEDVi more than 170 ml/m² (24). Oosterhof et al. (25), reported that RV volume returned to normal if PVR was performed before the RVEDVi reached 160 ml/m². Another large study reported that RV remodeling was possible in patients <17.5 years of age with a RVEDVi <150 ml/m² (26). In contrast to these data, it was shown that in young patients with a mean age of 14 years, the RVEDVi normalized after PVR even if RVEDVi exceeded 200 ml/m² before surgery (27). This suggests that the potential of the RV to remodel decreases with age and that there is not completely fixed "point of no return" for RV dilation. In our patients, PPVI was performed at a mean RVEDVi of 111 ml/m² at a mean age of 21 years. Compared with published surgical series, the patients included in our study were older and had less severe RV dilation. This may be explained in part by the method of assessing the RVEDV in CMR. Exclusion of papillary muscles, trabeculae, and the moderator band from the RV volume automatically results in smaller volume indices. However, PPVI has improved functional outcome even in patients with preserved RV function and underlines the earlier timing of PPVI (28).

STUDY LIMITATIONS. This is a retrospective matched cohort study with a relatively small number of patients, and thus the findings cannot be generalized. Also, the study might be underpowered and accordingly subject to type II error. In addition, the patients in this series with significant TR generally had modest functional impairment and RV enlargement at baseline, and do not represent the more severe end of the clinical spectrum of patients with RVOT dysfunction and RV volume overload related to PR and TR. Accordingly, the findings of this study may not reflect expected outcomes in patients with more severe RV dilation and/or symptoms of right heart failure.

CONCLUSIONS

This study shows that in patients with RVOT conduit dysfunction and moderate to severe TR, PPVI leads to improvement in TR in most cases. The beneficial effects of PPVI, including improved clinical symptoms and exercise tolerance, along with RV remodeling, were similar in patients with and without significant baseline TR. This study supports the idea of primary catheter intervention in cases of RVOT dysfunction and secondary TR. However, if significant TR persists, close clinical surveillance is indicated to prevent irreversible damage of the RV.

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PERSPECTIVES

WHAT IS KNOWN? PPVI is a less invasive therapeutic option in patients with RVOT conduit dysfunction than repeated cardiac surgery. Current guidelines suggest a surgical approach if RVOT dysfunction is combined with moderate to severe TR.

WHAT IS NEW? In patients who underwent PPVI with additional TR, degree of TR improved in 83% 6 months after the intervention. None of them had significant TR in the long-term follow-up.

WHAT IS NEXT? In patients with a dysfunctional RV-PA conduit and additional TR, the decision whether to fix TR should be postponed after PPVI if TR is secondary in nature.

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KEY WORDS PPVI, pulmonary valve replacement, RVEDVi, tricuspid regurgitation

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