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Prosthetic valves in the pulmonary position

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Prosthetic valves in the pulmonary position

Hanna Pragt

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Introduction

Over the past decades, treatment options for congenital heart disease have expanded and improved. As a result, life expectancy of patients with Congenital Heart Disease (CHD) has increased, with more patients entering adulthood with CHD.^{1,2} As a result, new issues have emerged, such as the longevity of prosthetic cardiac valves in these patients, that are much younger than the non-CHD patients. In addition, the quality of life of these patients has become a concern, because younger patients have different expectations of life as compared to the conventional much older age groups.

Valve replacement is a common procedure among patients with CHD and, in contrast to other patient groups, pulmonary valve placement particularly is a frequent procedure.³⁻⁶ Pulmonary valve replacement is mostly seen in patients with Tetralogy of Fallot, or with a transposition of the great arteries. Also, in case of a dysfunctional aortic valve, occasionally the pulmonary valve is transplanted into the aortic position, whilst a prosthetic valve is placed in the pulmonary position: the so-called "Ross" procedure. Then children with CHD can easily outgrow their prosthetic valve, which is one of the major concerns, because this can lead to repetitive valve replacement.

The aortic and pulmonary valve have a similar appearance, however the hemodynamic circumstances in which they function differ, in particular in the ambient pressures. While the right ventricle is a low-pressure system, the left ventricle is a high-pressure system. The elastance of the left ventricle is higher than the right ventricle,⁷ yet the right ventricle is much more compliant than the left ventricle.⁸ However, Dell'Italia and Santamore have shown that left and right ventricle have many similar pump properties, as the flow profiles over the aortic and pulmonary valve are comparable, however there are also distinct differences.^{9,10} The lower pressures can explain why the fact that pulmonary valves are larger than aortic valves as Poiseuille's law dictates that the product of diameter and pressure drop is constant when all other parameters are constant.^{11,12} As pressure drops in the right ventricle are always smaller than the left ventricle under normal circumstances, as a consequence the pulmonary valve diameter must be larger than the aortic valve.

Pulmonary valve replacement can be performed either surgically or by a transcatheter approach where the valve is inserted with a catheter through the femoral vein. Currently trans-catheter pulmonary valve replacement is often used as a valve-in-valve solution to delay surgical intervention. Although results of transcatheter pulmonary valve replacement look promising^{13,14}, there are also signs of increased risk for endocarditis.¹⁵⁻¹⁷ In this thesis we focus on the use of surgical prosthetic valves in the pulmonary position and on ways to improve the design of these usually LV designed valves for the RV.

Manufacturers

There are 5 major manufacturers of heart valve prosthetics that dominate the vast majority of the market, Table 1 shows the manufacturers and the valve types they produce as of 2019:

- **Abbott:** After the acquisition of St. Jude Medical, Abbott now produces the mechanical and prosthetic tissue valves of the St. Jude medical portfolio. St. Jude medical began the production of prosthetic heart valves in 1976, St. Jude also produces transcatheter valves.
- **Cryolife:** Was founded in 1984 and is originally specialized in low temperature acquisition, preservation and distribution of human heart valves. After acquiring On-X Medical in 2016 they incorporated their mechanical prosthetic valve into their portfolio.
- **Edwards Life Sciences:** Has been established in 1958 with the start of their first artificial heart valve. In 1960 the first Starr-Edwards valve was successfully implanted into a patient. Currently Carpentier Edwards specializes in bioprosthetic heart valves only.
- **LivaNova:** In 2019 the Sorin group merged with Cyberonic resulting in the new company LivaNova. Sorin was founded in 1956; with the purchase of Shiley in 1992, Sorin entered the cardiovascular market. In 2002 the Carbomedics group including Mitroflow were purchased by the Sorin group. Livanova produces both mechanical as well as bioprosthetic heart valves
- **Medtronic:** Medtronic was founded in 1949, in 2018 Medtronic was the largest global medical device company. In 2010 they acquired ATS Medical, giving them a position in the mechanical valve market. Medtronic also produces bioprosthetic valves, transcatheter valves and valves from bovine jugular veins designed for the pediatric patient that can be used both surgically as well as catheter based.

Pulmonary prosthetic valves

There are three valves that have been designed for use in the pulmonary position. The Contegra and the Melody valve, both manufactured by Medtronic and the transcatheter Sapien XT transcatheter valve manufactured by Edwards Lifesciences. The Sapien XT is a valve designed out of bovine pericardial tissue, only suitable for transcatheter implantation. Both the Contegra as the Melody valve consist out of bovine jugular vein tissue, the Contegra valve is a surgical valve and the Melody valve a transcatheter valve. Both the Contegra and Melody valve are limited in size and therefore not suited for most adults. As for all biological tissue structural valve deterioration is a problem reducing the lifespan of these valves. The results on the Contegra valve have been mixed, there are indications for a reduced lifespan and increased risk for endocarditis compared to other prosthetic valve options.^{18–20}

Table 1, Heart valve manufacturers

	Homograft	Porcine bio-prosthetic valves	Pericardial bioprosthetic valves	Jugular vein bioprosthetic valve.	Mechanical prosthetic valves	Trans-catheter pulmonary valves
Abbott			<ul style="list-style-type: none">• Epic / Biocor• Trifecta Aortic		<ul style="list-style-type: none">• Regent• Master	
Cryolife	<ul style="list-style-type: none">• Cardiac allografts				<ul style="list-style-type: none">• On-x prosthetic valves	
Edwards life sciences			<ul style="list-style-type: none">• CE Perimount Family• Inspiris Resilia• Inuity Elite			<ul style="list-style-type: none">• Sapien XT
LivaNova			<ul style="list-style-type: none">• Perceval• Solo smart• Crown PRT• Pericarbon		<ul style="list-style-type: none">• Carbomedics• Bicarbon	
Medtronic		<ul style="list-style-type: none">• Hancock 2• Freestyle• Mosaic	<ul style="list-style-type: none">• Avalus	<ul style="list-style-type: none">• Contegra		<ul style="list-style-type: none">• Melody

Homograft

One of the most widely used solutions for pulmonary valve replacement is the use of homografts/allografts: human donor valves. The major complication for the use of homografts is their limited availability, which is the case for all human donor tissues. Depending on location and size, the availability of homografts can vary. In the Netherlands human donor valves are distributed by the Dutch Transplantation Foundation according to established criteria and stored by ETB Bislife. Another issue with homografts can be tissue rejection, which is a risk for all donor material.

Studies have shown varying results of the use of homografts in the pulmonary position with freedom from reintervention at 10 year follow up varying between 35% and 83%.^{21,22} Most homografts eventually fail due to structural valve deterioration leading to valve regurgitation and/or stenosis. The lifespan of homografts as well as other biological valves appears to be shorter in the pulmonary position, most likely due to the young age of the recipients. Young age has been associated with earlier onset of degeneration.^{23 24}

Biological valves

One of the other widely used options for pulmonary valve replacement is the off-label use of bioprosthetic aortic valves. All surgical bioprosthetic valves except the Contegra, Melody and Sapien XT valve have been designed for the valves in the left ventricle, either the aortic or the mitral position. Physiological conditions differ between the left and the right ventricle. Where the left ventricle functions under a high-pressure condition, on average 120 mmHg systolic and 80 mmHg diastolic, the right ventricle functions

under low pressure conditions of on average 20 mmHg systolic and 10 mmHg diastolic. Research into the hemodynamic behavior of prosthetic heart valves have been focused on the aortic and mitral valve conditions.²⁵⁻²⁷ The difference in pressure conditions between left and right ventricle could potentially influence the hemodynamic behavior of biological prosthetic heart valves. Other research into the hemodynamic behavior of bioprosthetic valves suggests that the intrinsic structural characteristics of the materials used for leaflets and stents also influences the hemodynamic behavior of bioprosthetic valves.²⁸

Biological prosthetic valves are made either out of porcine aortic cardiac valve tissue or bovine pericardial tissue. The valves can be either stented (sewn onto a frame) or stentless; furthermore, there are so-called sutureless valves on the market, mounted in a stent. Biological valves have a proven track records in the aortic and mitral position.²⁹⁻³¹ Clinical results of bioprosthetic valves in the pulmonary position have been mixed in terms of durability and reoperation, also the results between the different biological valve types have not been uniform³²⁻³⁸. Biological valves appear to have a reduced lifespan in the pulmonary position. Besides the different hemodynamic conditions also the difference in age is a major factor. In general, patients requiring a prosthetic heart valve due to congenital heart disease are much younger than the general population requiring aortic or mitral valve transplantation. Younger age has been associated with increased degeneration of bioprosthetic valves.^{33,39}

Mechanical valves

Besides biological valve implants also mechanical valve implants can be an option for the pulmonary position. Mechanical prosthetic valves are an interesting option for young patient because they do not degenerate and have the potential of a much longer lifespan in the pulmonary position. Large studies with long-term follow-up of mechanical valves in the pulmonary position have been lacking. Studies on mechanical valves in the pulmonary position have been heterogeneous in design.⁴⁰

Prosthetic valvar thrombosis is of serious concern for the use of a mechanical prosthetic valve in the pulmonary position. In the aortic mitral position mechanical valve thrombosis incidents range between 0% and 0.6 % per patient-year.⁴¹⁻⁴⁴ In the pulmonary position average valvar thrombosis rates of 2.2 % per year were reported at an average follow-up of 73 months.⁴⁰ To prevent valvar thrombosis lifelong use of anticoagulation is required when a mechanical valve is implanted. Especially for young females with a wish for future pregnancies the use of anticoagulation is a risk factor.⁴⁵

Currently all widely used mechanical valves are of the bileaflet type, this type of valve consists out of two leaflets that rotate around four hinges. Mechanical valve thrombosis in bileaflet mechanical valves almost always originates in the hinge region of the valve.⁴⁶ In aortic circumstances these hinges are flushed with a diastolic pressure gradient of

approximal 80mmHg pressure difference. The washout of the hinges of mechanical valves has been demonstrated to be crucial under aortic conditions.⁴⁷ The pressure difference over the closed valve produces regurgitant flows that wash the hinges free of micro-clots, this prevents clots from growing and embolizing when larger.^{48,49} The flow behavior of mechanical valves under pulmonary conditions, with a much lower pressure difference has not been studied. It is reasonable to assume that these lower pressures will result in less regurgitant flow through the hinges. It could very well be that these lower flows influence the washing mechanism of mechanical valves and consequently the thrombus formation.

Quality of life and prosthetic heart valves.

Life expectancy of the congenital heart disease population has increased in the last decades, to a point where currently there are more adults than children with congenital heart disease in western Europe.³ With the increasing lifespan of these patients more emphasis lies on the Quality of Life.⁵⁰ Current literature is not uniform on the Quality of Life of patients with congenital heart disease as compared to the general population, although most studies do show a reduction in physical Quality of Life.⁵¹ Specific research on the Quality of Life of congenital heart disease patients with a prosthetic valve is lacking, most research has focused on the medical outcome in terms of risk of mortality and reoperation.

Patients with prosthetic valves face specific problems, like anticipated reoperation due to degenerated prosthetic valves, difficulties for future pregnancy's and the risks of anticoagulation.⁵² These specific problems could very well influence the Quality of Life of these patients.

Aim of this thesis.

In this thesis we aim to give insight into the functionality of prosthetic valves in the pulmonary position and the outcomes after pulmonary valve replacement. We also present a new valve system for pulmonary valve replacement. In **chapter 1** we will present the functionality of mechanical prosthetic valves in the pulmonary position, with a special interest in the prevalence and treatment of prosthetic valve thrombosis. In **chapter 2** the mechanism of hinge washing in the pulmonary position is studied in a test set-up, to give insight in the mechanism of valvar thrombosis of mechanical prosthetic valves in the pulmonary position. In **chapter 3** a new design of a mechanical prosthetic valve for the pulmonary position is described. In **chapter 4** the functionality of a pericardial prosthetic valve in the pulmonary position is described in a clinical study. In **chapter 5** the hemodynamic functionality of a pericardial prosthetic valve in the pulmonary position is studied in an in vitro setting to give insight in the functionality of these valves

in the pulmonary position. In **chapter 6** the influence of prosthetic heart valves on the Quality of life of patients with congenital heart disease is studied.

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1

Mechanical valves in the pulmonary position: an international retrospective analysis

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ABSTRACT

Objective: Life expectancy of patients with congenital heart disease has improved over the past decades, increasing the need for a durable pulmonary prosthetic valve. Biological valves in various forms have become the valve of choice for pulmonary valve replacement (PVR), but structural valve deterioration is unavoidable in the long term. Use of a mechanical valve could be an alternative, but data on long-term outcomes are sparse.

Methods: We retrospectively collected and analyzed data on 364 patients with mechanical valves implanted in the pulmonary position between 1965 and 2014. The data originate from medical centers in Barcelona (Spain), Graz (Austria), Groningen (the Netherlands), Munich (Germany), Rochester (United States), Seoul (Republic of Korea), and Tehran (Iran).

Results: Median follow-up duration was 4.26 years (range, 0-27 years), mean age at implantation was 27.16 ± 12.2 years. Tetralogy of Fallot was the most common primary cardiac diagnosis, with a subgroup of 69.8%. Freedom from valvular thrombosis was 91% (95% confidence interval (CI), 87%-94%) at 5 years and 86% (95% CI, 81%-91%) at 10 years post -PVR. With a success rate up to 88%, thrombolysis was a successful therapy. Freedom from reoperation was 97% (95% CI, 94%-99%) at 5 years post -PVR and 91% (95%CI, 85%-95%) at 10 years.

Conclusions: Mechanical PVR is associated with a limited risk of valvular thrombosis. Thrombolysis was an effective treatment in the majority.

Glossary of abbreviations

INR= international normalized ratio

IOD= inner orifice diameter

LVEF= left ventricular ejection fraction

MPVR= mechanical pulmonary valve replacement

PVR= pulmonary valve replacement

TAPSE= tricuspid annular plane systolic excursion

TOF= tetralogy of Fallot

INTRODUCTION

Pulmonary valve replacement (PVR) is among the most common procedures in patients with right-sided congenital heart disease.^{1,2} No valve prostheses have been designed specifically for the pulmonary position, for which reason aortic valve prostheses (both tissue and mechanical) are usually used in the pulmonary position. Exceptions are jugular venous xenograft valves that are available in a limited size range of 12 to 22 mm diameter and pulmonary allografts (homografts). Aortic tissue prosthetic valves in various models and allografts have been the valves of choice for particularly adult PVR² because of a low risk of thrombosis without the need for anticoagulation. However, tissue valves have a limited lifespan caused by structural valve degeneration,^{3,4} which seems to occur earlier in the pulmonary than in the aortic position, rendering reinterventions unavoidable in all but elderly patients.

Mechanical prosthetic valves have been the gold standard for left -sided valve replacement in patients younger than age 60 years and could be a viable alternative to bioprostheses for patients in need of a PVR, particularly for patients with high surgical risk and patients already using anticoagulation agents. However, there are serious concerns about the higher risks of valvular thrombosis in right-sided mechanical valves as well as the bleeding risk resulting from lifelong anticoagulation use.

A recent meta-analysis on mechanical PVR (MPVR) showed an average valvular thrombosis occurrence of 2.2% at an average mean follow-up of 73 months (range, 8-180 months).⁵ However, this study was limited by a stark heterogeneity between studies and no time -related analysis was possible. A large study on the long-term functionality of MPVR is missing in the current literature.

The objective of this study was to evaluate medium- to long-term results of MPVR, using a large multicenter database combining updated data from the 7 largest studies worldwide from 2009 to 2015,⁶⁻¹² with a focus on valvular thrombosis as a primary end point. Thrombolysis, reoperation, and death were chosen as secondary end points because death is more associated with cardiac failure than with the prosthetic valve, whereas thrombolysis and reoperation are the result of the primary end point.

METHODS

Study design

This study was designed as a multicenter retrospective study to observe the long-term functionality of a first MPVR. The primary end point was first valvular thrombosis, whereas secondary end points were thrombolysis, reoperation, and mortality. To minimize patient -related factors (such as thrombophilia), follow-up of second mechanical valves

introduced at reoperation were not further analyzed. All corresponding authors of articles with a minimum of 15 mechanical pulmonary valves published between May 2009 and May 2015⁶⁻¹² agreed to participate in this retrospective chart review study, where the data were to be completed and updated from the time of their original publication. Patients diagnosed with carcinoid heart disease were excluded from the study due to the poor prognosis associated with carcinoid heart disease. Data Transfer agreements are in place between all institutions and the University Medical Center Groningen.

Data collection

All data were de-identified and compiled at the time of collation into the clinical database. Institutional review board approval was obtained by each separate institution before the collection of the data. Applicable legislation in the Netherlands stipulates that retrospective anonymized chart research is not subjected to institutional review board review. Ethics review was not deemed necessary upon question of individual Ethics review boards. Data were collected retrospectively, using electronic and paper patient records. No identifiers were linked to patients in this collective database. Centers from the following towns contributed to this study: Barcelona, Spain (7); Graz, Austria (10); Groningen, The Netherlands (8); Munich and Lubeck, Germany (9); Rochester, Minnesota; Seoul, Republic of Korea (11); and Tehran, Iran(6). Data were collected and entered by the individual centers in a predetermined data submission file. We used the following parameters:

- Patient characteristics: age, gender, original diagnosis, previous surgeries, concomitant medication, and previous pregnancies.
- Procedural information: prosthetic valve brand, model and labeled size, date of implantation, concomitant procedures, complications, antithrombotic regimen, tricuspid annular plane systolic excursion (TAPSE), left ventricular ejection fraction (LVEF), and postoperative valve flow velocity, determined by continuous wave Doppler echocardiography.
- Follow-up information: valvular thrombosis, death, cause of death, valve replacement, thrombolysis of valvular thrombosis, date of the last follow-up visit, and pregnancies.

Transthoracic echocardiography was recorded within 1 year postoperatively. Local protocols were followed for obtaining and evaluating the echocardiographic images. Right ventricular systolic dysfunction was defined as TAPSE < 16. Moderately impaired left ventricular systolic dysfunction was defined as a LVEF < 45% and severe dysfunction as a LVEF < 30%. The variable "thrombosis" also includes pannus because the difference is often not obvious.

Labeling of prosthetic heart valves has changed over the years, although not all manufacturers adhere to the applicable International Standards Organization standards. The tissue annulus diameter of the patient is meant to reflect the labeled size. Thus, the labeled size reflects the inner orifice diameter (IOD) in supra-annular valves and the outer diameter in intra-annular valves. To take into account as many aspects as possible, we collected the IOD of all prosthetic valves from the manufacturer's specifications. Thus, IOD was chosen instead of the in vitro determined effective orifice area because of additional inconsistencies in the applicable methods used for measuring the effective orifice area. All data files were merged into 1 database and prepared for analysis at the University Medical Center Groningen

Pulmonary valve replacement procedures

Operative procedures and valvular selection were performed according to local standards at the time of surgery.⁶⁻¹² Uniformly, PVR was performed through a median sternotomy with the use of cardiopulmonary bypass. Follow-up visits were scheduled regularly according to local guidelines. International normalized ratio (INR) was targeted between 2.3 and 4.5 for all centers; table 1 shows Target INR levels for the individual centers.⁶⁻¹²

Table 1 baseline characteristics and Endpoints, distribution between centers

	Barcelona	Graz	Groningen	Munich	Rochester	Seoul	Tehran	Total
N	34	22	65	19	52	53	119	364
Age at PVR, y	35.1 ± 10.8	23.5 ± 6.5	34.1 ± 12.0	25.6 ± 9.6	31.6 ± 14.1	13.9 ± 5.8	25.96 ± 9.3	27.16 ± 12.2
Gender, male	70.6%	77.3%	60%	68.4%	61.5%	67.9%	58.8%	63.5%
Follow-up, y	7.5 (0-27.4)	5.6 (0-9.3)	6.2 (0-21.3)	12.6 (8.1-15.9)	6.4 (0-24.76)	4.9 (0.4-26.1)	2.3 (0-5.7)	4.26 (0-27.4)
Previous surgeries	0.91 ± 0.5	2.0 ± 0.9	1.6 ± 0.8	3.2 ± 1.5	2.2 ± 1.2	1.9 ± 1.2	1 ± 0	1.6 ± 1.0
Labeled valve size, mm	23 (21-29)	25 (21-29)	25 (21-29)	23 (21-27)	25 (21-33)	23 (17-27)	25 (21-29)	25 (17-33)
Target INR	2.5-3.5	3.5-4	2.4-4	3-4.5	3/3.5*	2-3	2.3-3.5	

Abbreviations: PVR: Pulmonary Valve Replacement, INR: International normalized ratio, *patients with concomitant tricuspid valve replacement.

Thrombolysis

Protocols regarding thrombolysis have changed over time, due to the long period of inclusion and follow-up period of this study. No uniform thrombolysis protocol was present in all inclusion sites except for Munich and Tehran (Appendix E1).

Statistics

Continuous data are presented as means with standard deviations or medians with range, as appropriate. Frequencies are displayed as absolute numbers and percentages. Follow-up time was calculated between the date of PVR and the date of last follow-up, valvular thrombosis, redo-PVR, or death. Survival analyses were performed on a patient level. Competing risk analysis techniques were applied for the end points. Cumulative incidence curves were computed to display the event probabilities during the follow-up. Cox proportional hazard methodology was used to determine univariate and multivariate relationships between the covariates and time to event. Gender, hospital, and age were corrected for in our multivariate model. Most statistical analyses were performed using IBM -SPSS statistics version 22.0 (IBM-SPSS Inc, Armonk, NY). The cumulative incidence graph was generated using STATA version 14.0 (StataCorp LP, College Station, Tex).

RESULTS

We retrospectively collected data on 364 patients who received a first mechanical aortic valve prosthesis in the pulmonary position from 1965 to 2014. The number of patients per center varied from 19 to 119. Patient inclusion time periods varied widely across the different centers (Figure 1). The total number of patient-years was 2047 and there was a total of 35 first thromboses (1.7%/patient-year; 95%confidence interval [CI], 1.2%-2.4%) and 20 reoperations (1.0%/patient-year: 95%CI, 0.6%-1.5%).

Baseline characteristics are shown in Table 2. Mean age was 27.16 ± 12.2 years at the time of MPVR (range, 1-71 years). Tetralogy of Fallot (ToF) was the primary cardiac diagnosis in 69.8%. In 94.9% (241 out of 254) of ToF cases, a total repair had been done before MPVR. The median number of prior cardiac surgeries was 1 (range, 0-7). In 10 cases, no previous procedures had been performed. Median follow-up was 4.26 years (range, 0-33 years), 152 patients had a follow-up of more than 5 years, and 58 patients had more than 10 years of follow-up. Of the female patients, 11 had been pregnant before the MPVR. Four patients were pregnant whilst having an MPVR. Two patients experienced valvular thrombosis relating to pregnancy.

There were 241 St Jude Medical (St Paul, Minn) valves implanted (66.2%), 76 Sorin Caromedics valves (Liva- Nova, London, United Kingdom) (20.9%), 16 ATS valves (Medtronic, Dublin, Ireland) (4.4%); 11 Sorin Bicarbon valves (3.0%); 5 On-X valves (CryoLife Inc, Kennesaw, Ga) (1.4%), and 1 (0.3%) Duromedics valves (Edwards LifeSciences, Irvine, Calif), all of the bileaflet type. Eleven tilting disc valves were implanted: 7 Bjork-Shiley (Pfizer, New York, NY) (1.9%), 4 Omnicarbon (1.1%) (MedicalCV, Inver Grove Heights, Minn), 2 caged-ball Starr-Edwards (0.5%) (Edwards LifeSciences), and 1 Gott valved con-

duit was used. The median labeled valve size was 25 mm (range, 17-33 mm), the median IOD was 20.5 mm (range, 14.8-24.9 mm). Right ventricular outflow tract repair was the most frequently performed concomitant procedure (Table 2). Of all patients, 28% had an LVEF <45% postoperatively (Table 3). As anticoagulant, warfarin was used in 64.8% (N = 236), acenocoumarol in 105 (28.8%), and phenprocoumon in 16 (4.4%). One patient was only treated with acetylsalicylic acid and for 6 patients the anticoagulation regimen was unknown due to immediate reoperation or to early operative mortality.

Figure 1. Pulmonary valve replacement by year of surgery, color coded by participating center

Valvular Thrombosis.

There were 35 of 364 (9.6%) reported cases of first valvular thrombosis. Median time between PVR and first valve thrombosis was 2.9 years (range, 0.3-23.2 years). Cox regression calculated freedom from first thrombosis at 5 years was 91% (95%CI, 87%-94%), at 10 years ,86% (95%CI, 81%-91%), and at 15 years 79% (95%CI, 70%-87%) (Figure 2 and Table E1). No valvular thrombosis occurred for the single patient taking acetylsalicylic acid. There seemed to be a relationship between labeled valve size and occurrence of thrombosis, but when repeating the analysis for the IOD, no relationship was found with valvular thrombosis (hazard ratio, 0.99; 95%CI, 0.76-1.3; P= .936). We did detect a center effect in our study; however, when correcting for center, both as a fixed or random effect, there was no influence on outcome.

Table 2 Original diagnosis, previous procedures and concomitant procedures

	N	%
Original diagnosis		
Tetralogy of Fallot	254	69.8
Transposition of the great arteries	8	2.2
Pulmonary valve atresia	27	7.4
Pulmonary valve stenosis	17	4.7
Double outlet right ventricle	13	3.6
Truncus arteriosus	22	6.0
Aortic valve disease	21	5.8
Other	7	1.9
Previous procedures		
Aortic pulmonary shunt	53	14.3
Pulmonary valvotomy	40	11.0
Total repair tetralogy of Fallot	241	66.2
Ross	20	5.5
Rastelli procedure	20	5.5
Patent ductus arteriosus correction	4	1.1
Aortic valve replacement	21	5.8
Mitral valve replacement	4	1.1
Pulmonary valve replacement	89	24.5
Tricuspid valve replacement	7	1.9
Other procedures	70	19.2
C Concomitant procedures during mechanical pulmonary valve replacement		
Right ventricular outflow tract repair	114	31.3
Tricuspid valve repair	49	13.5
Mechanical aortic valve replacement	41	11.3
Ventricular septal defect closure	21	5.8
Mechanical tricuspid valve replacement	18	4.9
Mechanical mitral valve replacement	10	2.7
Total repair tetralogy of Fallot	6	1.6
Rastelli procedure	3	0.8
Pacemaker implantation	8	2.2
Other procedures	61	16.8

TABLE 3. Postoperative transthoracic echocardiogram characteristics

Parameter	Result	Valid N
Pulmonary valve flow velocity, m/s	2.1 ± 0.62	302
Tapse < 16	69.2% (128/185)	185
Left ventricular ejection fraction < 30%	3.1% (9/290)	290
Left ventricular ejection fraction 30%-45%	25.9% (75/290)	290
Left ventricular ejection fraction > 45%	71% (206/290)	290

Inclusion of gender, age, year of implantation, primary cardiac diagnosis, valve brand, type of anticoagulation, simultaneous valve replacements, and prior surgeries and conduit resulted in no correlation of any variable with valvular thrombosis, both univariate nor multivariate.

In 26 of 35 cases (74.3%) of valvular thrombosis, thrombolysis was performed, as shown in figure 3. Thrombolysis was successful in 22 of 26 cases (84.6%). In 4 cases, thrombolysis was unsuccessful and reoperation ensued. In 3 cases, reoperation was later necessary after initial successful thrombolysis (at 0.2, 3.7, and 6.2 years, respectively, after thrombolysis). In 1 case, there were 3 successful thrombolysis procedures. Median follow-up after first thrombolysis was 1.5 years (range, 0-7.6 years).

Figure 2, Competing risk analysis, for valvular thrombosis (*Thromb*), reoperation (*Re-Op*), and death. Incidences for reoperation and valvular thrombosis are presented as 1-Thrombosis and 1-ReOp.

Reoperations

In 20 of 364 cases (5.5%) the prosthetic valve was replaced; 16 of 20 (80%) reoperations were indicated by valvular thrombosis: 1 patient outgrew the prosthesis, the reason for reoperation in the remainder is unknown. The mean time to valve replacement was 7.6 ± 5.5 years. Freedom from reoperation at 5 years was 97% (95%CI, 94%-99%), 91% at 10 years (95%CI, 85%-95%) and 81% at 15 years (95%CI, 71%-90%). Figure 2 shows the freedom from reoperations over time in a cumulative incidence graph depicting the competing risks. In 6 of 20 patients, their redo valve was an MPVR, which we chose not to include for further analysis. For the other patients, the valve received at reoperation is unknown due to the historical nature of this study. From the 20 patients who had a prior

Ross operation, 16 patients had an MPVR in either the aortic or mitral position and were thus already taking anticoagulation medication, for 4 other patients there were different reasons to choose an MPVR.

Figure 3, Flow chart of treatment of valvular thrombosis in pulmonary mechanical valves.

Mortality

There were 31 of 364 (8.5%) reported deaths, of which 7 of 31 occurred operatively (22.6%), 15 of 31 (48.4%) were cardiac deaths (right ventricle failure, arrhythmias, or sudden death), and in 9 cases the cause was unknown (29.0%). Mean age at death was 40.3 ± 16.0 years (range, 5.3-75.5 years). Of the cardiac deaths, none were valve related. There was 1 death due to pulmonary hemorrhage with INR level >7. There were no thrombosis-related deaths reported. Survival post -PVR at 5 years was 95% (95%CI, 92%-97%), 91% at 10 years (95%CI, 85%-95%), and 79% at 15 years (95%CI, 67%-88%) (Figure 2).

DISCUSSION

The unique size of this study was only possible by combining data from the 7 participating centers, from which we accumulated 364 patients who had a first MPVR performed from 1965 until 2014. By doing so, we created the largest comprehensive dataset so far on MPVR and we were able to provide the most realistic evaluation of mechanical prosthetic valves in the pulmonary position until now.

Valvular thrombosis has always been the major concern with the use of mechanical valves in the pulmonary position. The rate of thrombosis, despite anticoagulation, has always been reported to be appreciably higher than in the aortic position. We found a relatively linear rate of valvular thrombosis of about 1.7% per patient year. Dunne and colleagues⁵ published recently a meta-analysis of 19 studies up until 2013, but regrettably could not perform a detailed time-related analysis on the occurrence of valvular thrombosis, so that study does not provide insight into that crucial observation over time (5). Our results confirm a higher incidence of valvular thrombosis for mechanical valves in the pulmonary position compared with the literature on aortic and mitral position; reported thrombosis incidences range between 0% and 0.6% per patient-year.¹³⁻¹⁷ However, we should be careful when comparing different populations, particularly because patients receiving a pulmonary valve in most cases have a more complex medical history and surgical background than have patients receiving aortic and mitral valves and, in addition, usually are much younger. On the other hand, thrombosis of right-sided prosthetic valves may be underdiagnosed because partial and nonobstructive thrombosis as well as minor emboli may remain subclinical for a long time. The higher propensity for thrombus formation in the right ventricle is most likely related to its lower pressures and the mechanism of mechanical valves. Whether or not the incidence of thrombus formation is also larger in tissue prostheses in the right ventricle is unknown.

Thrombolysis was found to be remarkably successful in our cohort, with a success rate of 84.6%. The 2014 American Heart Association/American College of Cardiology guidelines advise fibrinolytic therapy as “reasonable” for thrombosed right-sided prosthetic heart valves,¹⁸ which might be changed to “recommended” based on our findings. We presume, because we have no evidence, that this might apply to the tricuspid position as well. Nonetheless, we should be aware that information on the complications of thrombolysis is not available and did not surface in the current study. more research is necessary on the long term effect of thrombolysis on the treatment of valvular thrombosis.

Although we did not find any relevant predictors for valvular thrombosis, several factors could influence its occurrence. Local circumstances and practices could influence the occurrence of valvular thrombosis, most notably the availability of universally adequate antithrombotic services. In addition, the frequency of screening during the

early stages after PVR could play a role in detecting and treating early thrombi. Non-compliance with anticoagulation therapy has been shown to play an important role in the incidence of valvular thrombosis. These factors could play an important role in the center effect we detected.

Because the objective of this study was to analyze valves instead of centers, we lacked adequate parameters to make a valid analysis between centers.

Reintervention rates (both catheter-based and reoperation) in our study are lower than in the large Nomoto study¹⁹ with 611 biological valves: our MPVR study showed 97% freedom of reoperation only at 5 years postoperatively and 91% at 10 years post-PVR. These observations were not equal for all valve brands. Nomoto reported a Kaplan-Meier estimate of 80% freedom from reintervention at 5 years for the Mitroflow (LivaNova, London, United Kingdom), but 80% at 8 years out for Perimount pericardial valves⁽¹⁹⁾ (Edwards Lifesciences).¹⁹ Studies with similar populations are heterogeneous and provide less information for comparison, but the impression is that their results vary between Nomoto and the work by Babu-Narayan,²⁰ who reported much better results in a study of 220 patients (20). Table 4 presents recent relevant literature on biological valves in the pulmonary position.¹⁹⁻²⁷ Because younger age has been associated with higher rates of tissue valve degeneration and subsequent replacement, we did not include studies with predominantly young children in Table 4. Pulmonary homografts were only reported by Van de Woestijne and colleagues,²⁵ who reported an 83% freedom from homograft replacement at 10 years in an adult ToF population.

Although with biological valves a younger age at implantation is associated with higher rates of valve degeneration,²¹ we saw no association between age at implantation and reoperation for mechanical valves. Arguably, tissue valves offer the advantage of not needing anticoagulation, whereas future replacements could be performed by transcatheter valve-in-valve procedures. Although percutaneous procedures are currently fashionable, even medium-term results of these procedures are lacking, yet there is an emergence of articles on an associated elevated endocarditis risk of up to 3% per patient year.²⁸⁻³⁰ Current literature on longer-term results of tissue valve prosthetic performance in the pulmonary position (without valve-in-valve procedure) is so heterogeneous as to preclude formal comparison with this study, but mechanical valves seem not to do worse. The obvious advantage of catheter-based tissue valve implantation is that the procedure is far less traumatic and patient recovery is more rapid. Future development of mechanical valve prostheses specifically designed for the right ventricle might even improve upon the current propensity for thrombosis of 1.7% per patient-year and reoperation of 1.0% per patient-year. Finally, a normal pulmonary valve is a larger valve than the aortic valve in each individual because of the lower pressures involved.

TABLE 4. Relevant literature on biological pulmonary valve replacement

First author	Country	Publication year	ToF%	Inclusion period	Total patients	Follow-up, y	Men	Age
Nomoto ¹⁹	USA	2016	68.6	1996-2014	611	3.0 (1.1-5.3)	367 (60%)	17.8 (11.9-27.3)
Oliver ²¹	Spain	2015	71	1990-2013	114	7 (13-34)	68 (59.6%)	23 (13-34)
Schubert ²²	USA	2015	57	2008-2013	84	2.5 (0.2-5.6)	52 (61.9%)	18.3 (0.8-62.1)
Babul-Narayan ²⁰	UK	2014	100	1993-2010	220	Homograft 4.3 (1.6-9.4), xenograft 2.4 (1.0-4.3)	128 (58.2%)	32 (16-64)
Sabate-Rotes ²³	USA	2014	100	1973-2012	278	7.3 ± 6.8 (1-34)	148 (53%)	31.4 ± 16.4
Chen ²⁴	USA	2013	53.4	1992-2008	161	(months) porcine 24 (0.03-135), pericardial 58 (1-181)	Porcine 48 (65.7%), pericardial 58 (59.8%)	Porcine: 19 (4-66), pericardial: 16 (0.5-72)
Van de Woestijne ²⁵	NL	2011	100	1987-2009	126	8.1 ± 5.6 (0.04-21.2)	72 (57.1%)	28.1 ± 12.2
Shinkawa ²⁶	USA	2010	64	2002-2009	73	2.6 (0.2-8.0)	44 (60.2%)	17.3 (2.1-64.3)
Fiore ²⁷	USA	2008	?	1995-2006	82	(mo) Porcine 20 ± 27, pericardial 42 ± 21, homograft 49 ± 40	53 (64.6%)	22.2 ± 13.0

ToF, Tetralogy of Fallot; UK, United Kingdom; NL, The Netherlands.

TABLE 4. Continued

Freedom reintervention 5 y	Freedom reintervention 10 y	Freedom reintervention 15 y	Survival 5 y	Survival 10 y	Survival 15 y	Porcine	Pericardial	Homograft	Mechanical	Other
611	93.7%	75.6%								
85	21	48	95%	71%	41%					
84	81%									
72	31	117	98%	96%						
211	37	27	3	97.0%	84.7%	75.1%	96.8%	83.1%	79.6%	
73	58	94.0%	36.0%							
133	83%	70%	95%	91%	80%					
73	97.70%	100%								
49	18	15	92%	Pericardial/78%	35%	Homograft porcine/homograft				

Thus, there are probably limits to which we should narrow the pulmonary valve with valve-in-valve procedures without inflicting an undue burden on the right ventricle, particularly of young patients and on exercise.

Bleeding complications were not recorded in this study, which arguably constitutes a major limitation. The reason for not recording bleeding complications is the historic nature of the study, and many patient files were incomplete. In addition, many patients are and were not followed-up by cardiologists from the center performing the operation. On the contrary, many received follow-up from remotely located cardiologists and feedback about such complications is vastly incomplete. Because we knew any attempt at collecting data on bleeding would appreciably underestimate the incidence, we decided not to do so. However, because the target INR is usually in the range of mechanical mitral valve prophylaxis, we presumed the bleeding incidences to be in that range.

In our study, a relatively high percentage (70%) of patients with available echocardiogram data appeared to have right ventricle systolic dysfunction 1 year after surgery, as measured by TAPSE. However, one should be careful with use of TAPSE as a parameter in this population particularly because of the high rates of previous surgeries. TAPSE is systematically reduced after cardiac surgery and does not always reflect true right ventricle dysfunction. Longitudinal right ventricle excursion is usually reduced after surgery, but if radial contraction is preserved, the ejection fraction may be normal.³¹ This imposes limitations to our interpretation of the echocardiography data available.

Almost no valve-related death was found in our study: there was 1 death due to hemorrhage and none due to thrombosis or reoperation. For 9 patients cause of death was unknown, so it is impossible to comment on the cause of their deaths. All-cause survival was comparable to other pulmonary valve replacement cohorts, with 95% at 5 years and 91% at 10 years.²⁵

LIMITATIONS

The nonrandomized and retrospective nature of this study including a number of heterogeneous populations are major limitations of this study. In addition, we updated studies that had already been published, so that publication bias undeniably plays a role. Within this population there is substantial variance; for instance, time period of inclusion, underlying cardiac conditions, and number of surgeries, contributing to heterogeneity of this cohort. Bleeding events were not registered in this study due to its historic nature and the likely underreporting inherent to such a study. In addition, local cardiologists remotely located from the center performing the operation followed -up with many patients and communications were not always recorded. Nonetheless, we have no reason to expect a higher incidence of bleeding events compared with mitral

valve implantations because this is not related to the valve position but rather to INR control. Where the strength of this study lies is in its global nature. at the same time, a major limitation of the study is heterogeneity. Another limitation is the nonstandard anticoagulation management among institutions and throughout the study period, because anticoagulation control is crucial for the functional integrity of a prosthesis.³²

CONCLUSION

A mechanical valve can be a valid choice for PVR. MPVR is associated with a limited risk of valvular thrombosis, for which thrombolysis was an effective treatment in the majority of affected patients. Reintervention rates over 10 years were superior to reported rates of biological aortic valvular prostheses and similar to pulmonary allografts. Nonetheless, we do not advise use of MPVR for patients with an elevated risk of thrombosis, such as women foreseeing a possible pregnancy^{33,34} and patients likely to be noncompliant with anticoagulation therapy.

Conflict of Interest Statement H.P. and T.E. own rights to a patent for a mechanical valve design for the pulmonary position. No funding was provided for this study. All other authors have nothing to disclose with regard to commercial support.

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CONGENITAL: PULMONARY VALVE

SUPPLEMENTARY MATERIALS

APPENDIX E1, THROMBOLYSIS PROTOCOLS SUMMARY in order of preference.

1. Tehran:

- a. Streptokinase: start with 250,000 IU, then 100,000 IU/h infusion for 24-72 hours. Last two years:
- b. Reteplase: 2 successive doses of 10 U at 30 min intervals,
- c. Alteplase: 10 mg stat then 90 mg during 90 min infusion.
- d. For children SK 50 to 100 U/kg/h for 48-72 hours.

2. Munich:

- a. Alteplase: 0.5-1.0 mg/kg as short infusion for 30-60 min, then 0.5-1.0 mg/kg/day. When no result or no lab results consider local thrombolysis. Always Heparin 5000 IU/m²/day to begin with, then tune to 1.5-2 times higher PPT (Increase of PPT is controversial with Alteplase) .
- b. Urokinase systemic thrombolysis: 4400 U/kg for 10-20 min, then 4400 U/kg/h, Urokinase local thrombolysis: 1500 U/kg for 10-20 min, then 1500 U/kg/h.
- c. Streptokinase systemic thrombolysis: 3500-4000 U/kg for 30 min, then 1000-1500 U/kg/h for 12-72 h.

Table E1. Cumulative incidences

Event	Time point, y	Cumulative incidence	95% Confidence interval
Death	5	0.05	0.03-0.08
Death	10	0.09	0.05-0.15
Death	15	0.21	0.12-0.33
Reoperation	5	0.03	0.01-0.06
Reoperation	10	0.09	0.05-0.15
Reoperation	15	0.19	0.10-0.29
Valvular thrombosis	5	0.09	0.06-0.13
Valvular thrombosis	10	0.14	0.09-0.19
Valvular thrombosis	15	0.21	0.13-0.30

2

Influence of transvalvar pressure gradient on hinge washing in closed mechanical prosthetic cardiac valves under pulmonary pressure conditions; a comparative in vitro study.

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ABSTRACT

Objective: Hinge washing is a crucial factor in the prevention of mechanical prosthetic valvar thrombosis, especially in the pulmonary valve position. The aim of this laboratory study was to determine the relationship between pressure difference and the amount of hinge washing in the closed position, using the pressures that are normal for the right ventricle and pulmonary artery.

Methods: In an in vitro setting, four different bileaflet mechanical valves were tested for hinge washing in closed position. Based on similarity in inner diameter (range: 20.5-21.4 mm), the following valves were tested: Abbott SJM Regent size 23, Cryolife On-X size 23, LivaNova Carbomedics-R size 25, Medtronic Open Pivot (M-OP)-A size 25. Tests were carried out in a range between 3 and 100 mm Hg pressure difference, using water as a test fluid. The amount of leakage per minute through the closed valve was measured.

Results: All four valves showed an increase in leakage with increasing transvalvar gradient, and the relationship between pressure and leakage behaves in logarithmic fashion. Leakage under normal pulmonary diastolic pressure conditions (10 mm Hg) was between 23.3% and 29.3% of the leakage under aortic diastolic pressure conditions (80 mm Hg). The Cryolife On-X valve showed the highest closed leakage volume under pulmonary conditions (10 mm Hg) 0.254 ± 0.01 (L/min), where the Medtronic M-OP showed the lowest leakage volume with 0.125 ± 0.014 (mL/min). Conclusion: Hinge washing is related to transvalvar pressure difference in closed position. Valve brands differed significantly from each other in the amount of hinge washing.

Glossary of abbreviations

ANOVA= analyses of variance

M-OP= Medtronic Open Pivot

CarboR= LivaNova Carbomedics R

IOD= inner orifice diameter

ON-X= Cryolife On-X

P= pressure difference

Regent= Abbott SJM Regent

SD= standard deviation

TAD = tissue annulus diameter

INTRODUCTION

Prosthetic valvar thrombosis is one of the most common complications of mechanical prosthetic valves in the pulmonary valvar position. In contrast, prosthetic valvar thrombosis is rare in the aortic position for which these prostheses have been designed so successfully.^{1,2} For the most commonly used bileaflet valves, valvar thrombosis in most cases originates from the hinges.³ These hinges are flushed under aortic circumstances by a pressure gradient of about 80 mm Hg between aorta and the left ventricle that produces small turbulent flows while the valve is in closed position. These small regurgitant flows through the hinges wash them free of microclots, to prevent clots from growing and subsequently embolizing.^{4,5} Jun et al have demonstrated that the washout of these hinge regions during closed position appeared to be crucial under aortic conditions.⁶

The extensive research in the field of mechanical prosthetic valves has been focused on the aortic and mitral position and related physiology, because these valves are replaced most frequently.^{5,7} However, patients with a congenital cardiac defect more often require replacement of the diseased or absent pulmonary valve.^{8,9} In this pulmonary position, however, these very same valvar prostheses are beset by a substantial propensity for clotting, for which reason tissue valves have been popular for pulmonary valve replacement, even though their reoperation rates are high.^{10,11} Recent follow-up suggests, nonetheless, that mechanical valves proved actually to be surprisingly promising for this position, despite the higher propensity for clotting.^{1,2} Little is known about the flow behavior of mechanical valves in the pulmonary position under the much lower pulmonary pressures, which will result in less flow through the hinges in closed position. The precise relationship between pressure and flow has not been investigated, let alone for different brands or models. It is conceivable that these (yet unquantified) lower flows are insufficiently capable of washing the currently existing valvar hinges free of microclots and are thus causal for the higher incidence of clot formation.

The aim of this in vitro study was to determine the relationship between pressure difference and the amount of hinge washing in the closed position, using the pressures that are normal for the right ventricle and pulmonary artery. Particularly, the differences, if any, between valvar brands or models can well be relevant for the choice of pulmonary valvar mechanical prosthesis.

MATERIALS AND METHODS

A static in vitro model was developed to determine accurately the relationship between pressure and the amount of hinge washing in closed position (Figure 1). The model consists of a water container, various sizes of tubing with a 25 mm diameter that were

connected to the container, a customized valve holder, and a stand to keep the valve holder in place. For each valve, an individual valve holder was designed to make sure that no paravalvar leakage was possible. The model was loaded with a constant pressure that could be varied by adjusting the height of the water container. A pressure gauge connected to a Philips Intelli-Vue MP70 (Amsterdam, Netherlands) monitor was used to monitor the pressure. The regurgitant volume was determined by weighing the regurgitant water using a digital measuring scale. Testing was done with pressures ranging between 3 and 100 mmHg, which is the average range of diastolic pressure differences over the aortic and pulmonary valves. Each measurement was done over a period of 60 seconds with the valve continuously in closed position; for each sample, the measurement was repeated nine times. We expected that the amount of hinge washing (and not the leakage between the leaflets and between the leaflets and the housing) was by far the most dominant part of the total regurgitant volume in this setup. To confirm this, a qualitative assessment by eye was done and photographs were taken (H.P. and T.E.).

Figure 1, Test set-up.

VALVAR PROSTHESES

Valves of four major mechanical heart valve producers were used: Medtronic Open Pivot (M-OP; Medtronic plc, Dublin, Ireland), Cryolife On-X (On-X; Cryolife Inc, Kennesaw,

Georgia), LivaNova (Livanova plc, London, United Kingdom)—Carbomedics R (CarboR), and the Abbott (Abbott Laboratories, Lake Buff, Illinois) SJM Regent (Regent) valves. To make a sensible comparison, valves were selected with similar internal orifice diameters (IOD) instead of tissue annulus diameter (TAD), as according to International Standards Organization standard (ISO; Standard 5840-2: Cardiovascular Implants, Cardiac Valve Prostheses, Surgically Implanted Heart Valve Substitutes) valvar label should reflect TAD. We derived the IOD from sizes 23 and 25 from the manufacturer's specifications and, in addition, measured the IOD using a Vernier calliper. We chose prosthetic valves from these four brands so that the standard deviation (SD) of the four IOD's was as small as possible.

STATISTICS

Continuous data are presented as means and SDs. Spearman rank correlation coefficient was used to determine the correlation coefficient between leakage pressure. Curve fitting was used to find the best fit for relationship between pressure and valvar leakage for the four different valves. To determine differences between the four valve brands, analysis of variance testing was used. We performed a logarithmic transformation on the dependent variable leakage and the predictor variable pressure. A P value <.05 was considered statistically significant. For all statistical analyses, IBM SPSS Statistics version 23 was used.

RESULTS

The IOD of the sizes 23 and 25 of the four manufacturers are shown in Table 1. We found no difference between our own IOD measurement with the Vernier calliper as compared to the diameters as supplied by the manufacturers. The mean IOD of the size 23 valves was 20.0 mm (SD: 1.6 mm) and of the 25 valves 21.9 mm (SD: 1.5 mm). The percentage range of the difference from the mean was -7.6% to + 6.9% for the size 23 valves and -6.5% to + 6.7% for the size 25 valves. When we chose valves, irrespective of their label, to have the least SD, the mean IOD was 21.0 mm (SD: 0.45 mm). The percentage range of the difference from the mean then diminished to -2.5% to +1.8%. This led us to the choice of the following valves in our experiments: M-OP size 25, On-X size 23, CarboR size 25, Regent size 23.¹²⁻¹⁵

The leakage through the hinges was by far the largest of the entire regurgitant volume as could clearly be distinguished by direct observation (Figure 2). However, as the regurgitating fluid mixes right after having passed the valve, we found it impossible to

separate these streams so as to make a reliable quantitative distinction between the two elements of regurgitation. There seemed not to be an obvious difference between the valves, so that the total regurgitant volume seems to allow for a realistic comparison between the hinge washing of the valves.

Table 1. Internal Orifice Diameter in Millimeters.^a

Valve label	23	25	chosen size	choice
Medtronic M-OP	18.8 (-6.1%)	20.8 (-5.1%)	25	20.8 (-1.1%)
Cryolife On-X	21.4 (+6.9%)	23.4 (+6.7%)	23	21.4 (+1.8%)
Sorin/Carbomedics R	18.5 (-7.6%)	20.5 (-6.5%)	25	20.5 (-2.5%)
St. Jude regent	21.4 (+6.9%)	23.0 (+4.9%)	23	21.4 (+1.8%)
Mean	20.0	22.0		21.0
Standard Deviation	1.6	1.5		0.45

Abbreviations: IOD, internal orifice diameter; M-OP, Medtronic Open Pivot.

a Given IOD by the manufacturer and the deviation from the mean in percentage.

Figure 2, Image of valve leakage in closed position, A= Cryolife On-X size 23, B = Abbott SJM Regent size 23.

As expected, regurgitant volume (leakage) was positively correlated with pressure, $p = 0.93$, $P < .001$; all four valves showed an increase in leakage with increasing pressure (Figure 3). The increase in leakage volume was linear in the test pressure range from 3 to 10 mmHg, with higher pressures the leakage increased in logarithmic fashion. The difference in leakage between 3 and 5 mmHg pressure tests was not statistically significant. All valves differed significantly on mean leakage volumes ($P < .001$). The CarboR had 6.7% less leakage as compared to the On-X valve as reference, because it has the most leakage. The leakage of the Regent and M-OP valves was 60.4% and 53.8% less, respectively. In the high-pressure test area, the On-X and CarboR valve showed much

higher leakage volumes at 80 mmHg than the Regent and the M-OP valve: The On-X and the CarboR-valves show, respectively, a leakage of 596 ± 7 mL/min and 495 ± 30 mL/min, compared to 305 ± 13 L/min and 337 ± 33 mL/min for the Regent and the M-OP valve. In the low-pressure test area, the On-X and CarboR valve showed higher leakage, respectively, 77 ± 21 mL/min and 90 ± 6 mL/min at 5 mmHg, than the Regent and the M-OP, respectively, leaking 44 ± 3 and 48 ± 4 L/min at 5mmHg.

Figure 3, Valve leakage in the closed position, **Leakage = $e^{(C+B \cdot \ln(P))}$**

SJM= Abbott SJM Regent size 23, ONX= Cryolife On-X size 23, SCR= LivaNova Carbomedics R-reduced size 25, ATS = Medtronic Open Pivot –A size 25.

The leakage under pulmonary pressure (10 mm Hg) was 23.3% of that in the aortic pressure (80 mm Hg) for the Regent valve, 24.3% for the M-OP valve, 27.7% for the On-X valve, and 29.3% for the CarboR valve. In the most leaking On-X valve, the corresponding leakage dropped from 596 to 165 mL/min, which is a 72.3% decrease. In the least leaking Regent valve, the leakage volume flow decreased from 347 to 71 mL/min, which is 79.5%

less. The proportional difference in hinge leakage between the Regent and On-X valves then differs from $347/596 = 58.2\%$ at 80 mm Hg versus $71/165 = 43.0\%$ at 10 mm Hg.

Several regression models were tested to find the best relationship between pressure p and valve leakage; the following model provided the highest coefficient of determination (R^2) for the relationship between pressure and leakage.

"Leakage= e^{^(C+B*ln(p))},"

p = pressure difference (mmHg)

In Figure 3, the regression function and the regression parameters are shown, values for C and B can be found in Figure 3. Figure 4 shows a detailed figure of the low-pressure circumstances.

Figure 4, detailed valve leakage in closed position up to 20 mmHg. **Leakage=e^{^(C+B*ln(P))}**, SJM= Abbott SJM Regent size 23, ONX= Cryolife On-X size 23, SCR= LivaNova Carbomedics R-reduced size 25, ATS= Medtronic Open Pivot –A size 25.

DISCUSSION

This study has quantified the logarithmic relationship between pressure and regurgitant hinge flow in four major brands of mechanical valvar prostheses. In addition, we have demonstrated that there is considerable difference in hinge leakage between these four brands of aortic cardiac valvar prostheses. The relationship between pressure and leakage is logarithmic at pressures over 10 mm Hg and may be virtually linear at lower pressures. This implies that the leakage flow at pressures over 10 mm Hg is most likely diminished by turbulence, because a laminar flow would have yielded a linear relationship according to the Hagen-Poiseuille law. In addition to the quantification of the flow–pressure relationship, the location of the leakage flow occurs predominantly through the hinges. These hinges allow for a complex shape of the channel through which the water flowed, this shape being an element we did not investigate in this study. This means that the flow at lower, diastolic pulmonary pressure range is not turbulent and behaves according to the Hagen-Poiseuille law.

The amount of hinge leakage of these mechanical valvar prostheses under 10 mm Hg was about a quarter of the amount under 80 mm Hg. Obviously, these valves have not been designed for these low pressures. Furthermore, we have shown for the first time, to the best of our knowledge, that there is a substantial difference in this respect between valvar brands. Unknown is whether this difference plays a role in a possible difference between brands in the propensity for clot formation under pulmonary pressures.

The fact that we used water as test fluid means that the regurgitation of blood will be less than our measurements indicate, as the viscosity of blood is three to four times higher than the viscosity of water. Blood viscosity, however, is not a static factor as it is a so-called “non-Newtonian fluid.” Being non-Newtonian means that viscosity increases when shear rate goes down with lower flow (through lower pressure), thus with decreased vessel (channel) diameter such as a hinge. Nonetheless, we can think of no argument why the comparison between the valves would not be valid, because the magnitude of the non-Newtonian phenomena is limited. In addition, a pressure gradient of 10 mm Hg coincides with a Doppler velocity of about 1.6 m/s, where turbulence does not play a role. Thus, the regurgitant flow through the hinges is laminar in the pulmonary pressures. Furthermore, the viscosity conundrum cannot be solved using a water/glycerol mixture to mimic blood viscosity, because water/glycerol does not possess this “non-Newtonian” property. Instead, as the viscosity is three to four times higher than that of water/glycerol, the flow will proportionally decrease, in accordance to Poiseuille law. Turbulence ensued with increasing pressure above 10 mm Hg, leading to nonlinear increasing resistance, but did so for all tested valves in the same fashion. Arguably, the testing should have been done with blood; however, blood is a prohibitively inconvenient test fluid and would not have an advantage, particularly for pulmonary

pressures. Thus, both water/glycerol and blood were not used, because in our conviction, the results reflect effective differences between aortic and pulmonary position.

Although the vast majority of the leakage flow is due to hinge leakage, the design of the bileaflet valves also includes some additional leakage flow through the so-called “B-datum gap” (the point where the two leaflets touch each other in closed position) and the periphery gaps (minor gap between the leaflets and the housing).⁴ Although we could not quantify these different areas of leakage, our observation also confirms that the vast majority of the leakage occurred through the hinges. We are not aware of data quantifying the difference between these two areas of leakage. It is important to recognize that these values are all measurements over a continuous period of one minute, where the average adult heart beats 70 times per minute at rest. During one heartbeat, the valve is closed during approximately two-thirds of a cardiac cycle, which means that the average leakage per minute has to be divided by approximately 47 to obtain the value per heartbeat.

In this study, we focused on hinge washing in mechanical prosthetic valves, and it must be noted that hinge washing can only have one valvar design characteristic of several that may influence valvar thrombosis.⁴ An important influence on the formation of valvar thrombosis is the intrinsic hemodynamic properties of the valvar design.^{16–18} Since valvar thrombosis is a highly complex phenomenon, there are other factors that could play a role in the development of a thrombosed valve. Nonetheless, hinge washing may play an important role in thrombus formation, and because it is quantifiable, it became the parameter of interest in this study.

Although similar research has not yet been published, Bottio et al did an in vitro comparison with four different valvar brands that are suitable for the replacement of a systemic atrioventricular valve (mitral and tricuspid) in children.¹⁹ Of the four valves they tested, the On-X and the Regent valves coincide with the group of valves we tested. In contrast to our setup, they compared the valvar leakage under pulsatile conditions in a closed system, where pressures varied from 120 to 80 mm Hg, whereas for the pulmonary position, we focus on much lower pressure circumstances. The size of the valves they used varied from 18 to 19 mm; however, for the pulmonary position, these small sizes are hardly ever used. Although the setup is different from our study, they also found a higher average closed leakage volume for the On-X as compared to the Regent valve, which is in line with our results. Jun et al have shown that the “hinge gap width” of mechanical valves is essential for thrombus formation. For aortic valves, a larger hinge gap width was associated with increased shear stresses and increased washout.⁶ For the pulmonary position, the optimal hinge geometry might very well differ from the aortic position, most likely creating more washout potential. Our previous clinical research was underpowered to determine differences between brands.¹ The average rate of valvar thrombosis in the pulmonary position for all valve models was about 1.7% per patient year.

LIMITATIONS

Limitation of this study is that we compared single samples of four different cardiac valves, not considering the possibility of relevant differences between samples of the same size and valvar make. We have not found publications elaborating on the tolerance that the manufacturers allow in their production series, while the manufacturers themselves are not transparent about this feature. Furthermore, in this setup, we could not quantify the difference between regurgitant flow through the hinges and flow in between the leaflets and the housing, although visual observation indicated the majority of regurgitant flow to originate from the hinges.

Another potential limitation of our study was the usage of water for our experiments, as valve leakage and clot formation are influenced by fluid viscosity. Testing our research question with blood is prohibitively complicated. For discovering the basic principles of leakage in mechanical valves and the basic differences between valves, water was an exceedingly convenient and theoretically acceptable test fluid,¹⁹ with the additional advantage of being freely available.

CONCLUSION

Hinge washing has been shown to be related to the fluid pressure applied in closed position. Remarkable differences have been noticed between the different valve brands under pulmonary conditions. With the outcome of this research, we aim to provide knowledge that could be of use in selection of prosthetic valves for pulmonary valvar positions.

Conflict of Interest: HP and TE own rights to a patent for a mechanical valve design for the pulmonary position. (US: 2018/14929A1; EU: 16718495.1-1664; China: 173605PCT-CN). No funding was provided for this study.

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3

Development of a mechanical prosthetic heart valve for the right ventricle.

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BACKGROUND

Patients with congenital heart disease often require a heart valve replacement, where a replacement of the pulmonary valve is one of the most common replacements. For the replacement of a pulmonary valve there are several options, including; homografts, Contegra grafts, Melody trans catheter grafts, biological valves and mechanical valves. Since allografts are human donor tissue these valves are considered to be a transplantation instead of a prosthetic valve. Allografts are limited both in lifespan and in availability as are all donor tissues. The Contegra and Melody valves are made out of bovine jugular veins and are solely designed for usage in the pulmonary position, furthermore they are limited in size which makes them unsuitable for most adults. The bovine pericardial and porcine aortic xenograft valves are widely used options for pulmonary valve replacement (PVR) but have a limited lifespan due to valve degeneration, making valve re-operation unavoidable particularly in a young population^{1,2}

In the aortic and mitral positions mechanical valves are predominantly used for younger patients according to current guidelines^{3,4}. In contrast to the pulmonary position xenograft or biological valves have long been regarded as the gold standard, which is probably still the case. Mechanical valves have been associated with higher incidences of valvar thrombosis and for that fact are not considered as a good option for PVR. Our study on the long-term follow-up of mechanical valves in the pulmonary position (chapter 1) has shown that, although prosthetic valvar thrombosis is increased compared to aortic and mitral position, treatment with thrombolysis was highly successful. In terms of reoperation, rates for mechanical PVR were decreased or similar to those of biological PVR⁵. This research highlights the potential for mechanical valves in the pulmonary position. Nonetheless, the biggest hurdle in the use of mechanical valves for the pulmonary position remains valvar thrombosis. When valvar thrombosis could be reduced, mechanical valves could play an important role in the replacement of pulmonary valves. This would potentially have the additional benefit of the absence of valve degeneration.

Current mechanical heart valves have all been designed for use in the left ventricle, in the aortic or mitral position, in which they function very well⁶⁻⁹. Mechanical heart valves specifically designed for the right ventricle do not exist. Currently all available mechanical heart valves on the market in western-Europe and the USA are of the bileaflet type, the valves that are currently in use are listed in table 2.

All valves exist out of two leaflets that rotate in or around a hinge. All valves except for the ATS valve have a cavity pivot as a hinge design, where the ATS has an open pivot hinge design¹⁰. For the ATS the hinge is designed with an extruded hinge, the other valve designs all have a hinge cavity. The valves with a cavity pivot design differ on their hinge region on the shape of their hinge cavities, the angle of the leaflets and on the movement of the leaflets.

Previous research has shown that valvar thrombosis mostly originates in the hinges of mechanical heart valves¹¹. These hinges have been designed to have regurgitant flows to wash them free from micro-emboli. In our previous study (chapter 2) we have shown that hinge washing is influenced by pressure difference. The leakage under normal pulmonary pressure (10mmHg) ranged from 23.3% to 29.3% of the leakage under normal aortic pressure (80mmHG). This reduced washing of the hinges is very likely to contribute to the increased thrombus formation of mechanical heart valves in the pulmonary position.

None of the current biological valves are durable in the pulmonary position, in contrast to mechanical valves that show potential for longer durability⁵. We aimed to design a new mechanical prosthetic valve for the pulmonary position.

Design strategy

Central objective is to increase the amount of hinge leakage under pulmonary pressures, to allow for the same amount of blood passing through the hinges as in aortic valvar prostheses under aortic pressures. Increase of the valvar leakage through the hinges in closed position can be achieved in several ways:

- Enlarging the hinge area to create more space between the leaflet ears and the hinge region, allowing more blood flow through the hinges.
- Creating a passageway in that part of the leaflets that are adjacent to the hinge, allowing more blood flow via the hinge in closed position

We decided to create a passageway in the leaflets to allow more blood flow through the hinge region in closed position. To facilitate an easy production process, adaptation of already existing models were considered as a promising option. This will require minimal adaptation of already existing production process, keeping costs at a minimum. When the structural design and the sewing ring are maintained, just as in already existing models, surgical procedures require no adaptations.

Patient group

The target group for this design are patients who require a replacement of the pulmonary valve, with the main focus on patients that have been full grown. Initially women anticipating to conceive are not considered to be the primary target group for this design, as they encounter specific problems with Vitamin K antagonists. Also patients with pulmonary hypertension are not part of the targeted patient group, as their pulmonary artery pressures are much higher, which would result in more than required hinge leakage.

Type	Origin	Anticoagulation	Rejection	Problems
Allograft	Human donor tissue	No	Yes	Rejection Ultimate Leakage / Stenosis
Contegra® (Bovine Jugular valved vein)	Bovine jugular vein	No	No	Calcification/Endocarditis Limited sizes (<=22mm) Leakage / Stenosis
Melody® (stented Contegra)	Bovine jugular vein	No	No	As above/Endocarditis ++ Stent Fracture
Tissue Pericardial	Bovine pericardial tissue	No	No	Stiff leaflets > Leakage / Stenosis
Tissue Valvar	Porcine heart valve	No	No	Calcification > Leakage / Stenosis
Mechanical	carbon/ titanium	Yes	No	Thrombosis

Figure 1, close-up image of the widely used cavity pivot design

Table 2 mechanical prosthetic heart valves

Manufacturer	valve type	Valve material	Hinge design
LivaNova (former Sorin)	Carbomedics series	Leaflets: graphite core coated with pyrolytic carbon Housing: pyrolite carbon, titanium stiffening bands	Cavity pivot
LivaNova (former Sorin)	Bicarbon series	Leaflets: pyrolytic carbon Housing: titanium coated with carbofilm.	Cavity pivot
Abott (former St. Jude)	Regent series	Leaflets: pyrolytic carbon Housing: pyrolytic carbon	Cavity pivot
Abott (former St. Jude)	Master series	Leaflets: pyrolytic carbon Housing: pyrolytic carbon	Cavity pivot
Cryolife (former On-X)	ON-X	Leaflets: On-X® carbon deposited on a graphite substrate, impregnated with 10 % tungsten Housing: graphite substrate coated with On-X® Carbon.	Cavity pivot
Medtronic (former ATS)	ATS	Leaflets: pyrolytic carbon coated over a graphite substrate. Housing: pyrolytic carbon	Open pivot

Requirements

Stakeholders analysis

When designing a new implant, it is important to consider all stakeholder (individuals and groups) that will affect or will be affected by the new mechanical prosthetic heart valve for the right ventricle. An overview off all stakeholders and their goals, expectations, essential knowledge and deficiencies is presented in table 3. The stakeholders are essential in formulating the requirements and desires for the new mechanical valve implant. Based on their specific demand and wishes for the valve a list of requirements and desires was made for the new valve implant.

Functional requirements

1. The newly designed mechanical heart valve should decrease thrombus formation in the hinges when placed in the pulmonic position by at least 10%.
2. This should be realized by increasing the volume through the hinge region of bi-leaflet heart valves by at least 50 %, up to normal aortic levels.

Material requirements

1. Materials should be blood compatible, as they will be located within the heart.
2. Materials should have low thrombotic properties to prevent thrombus formation as much as possible.

Desires

1. It would be desirable that the newly designed mechanical heart valve is suitable for both the pulmonary as the tricuspid position. The tricuspid position requires a larger valve diameter.
2. Materials should be known materials for the production of mechanical heart valves.
3. Similar hinge washing patterns as in the left ventricle should be chosen.

Table 3, Stakeholder analysis

stakeholders	Individual	Main goal	Essential knowledge	Deficiency
Development	Researcher 1	Design/ testing	Function and design of implants	Clinical knowledge
	Researcher 2	Design	Function and clinical implantation of implants	Design knowledge
Industry	Manufacturers/ distributors	Production/Selling	Manufacturing process, market	Function of implant
Finance	Insurance	low priced treatment	Competition	Clinical and design knowledge
	Patients	Good price/quality	Personal budget	Clinical and design knowledge
Diagnostics	Cardiologist	Proper diagnosis	Valve functionality	Technical knowledge
consumption	Patients	Proper functioning heart valve	Comfort	Functioning of implant
Application	Surgeons	Proper functioning heart valve, successful surgery	Surgical technique	Technical knowledge
Regulations	Regulatory affairs	Safety of the implant	Knowledge of guidelines	Functioning of implant

Final design

The final design is applicable to all existing bileaflet heart valves that are currently on the market. The housing of the valve and the hinge remain identical to the original design. The leaflets of the hinges will be adapted to allow for additional blood flow through the hinge region. In the presence of a cavity pivot hinge design, each leaflet will have two additional spaces within each ear of the leaflet, so four spaces will be added to each leaflet, making a combined total of 8 spacing's in the entire valve design as shown in figure 2. In figure 3 the leaflet design for the open pivot hinge design is shown. For the open pivot hinge one cavity was added to the leaflet, positioned at the hinge region as shown in figure 3. Due to the low pressure conditions shear stresses will remain low and minimal turbulence is expected. The final design has been published in a European and US patent.

Figure 2, Design of the new prosthetic valve for the cavity pivot design, 1 = thickened wall section of the valve body, 2,3 = ear passageways, 4= raised bands, 5= exterior circumferential groove, 6= laterally extending ears of the leaflet.

Figure 3, Design of the new prosthetic valve for the open pivot design, 1= valve body passageway for blood flow, 2= interior surface of the valve body, 3= recess in the side edge of the leaflet, 4= knob on the interior surface of the valve body, 5= leaflet passageway

Functional prototype

The functional prototype has been created in collaboration with the Research Instrument Manufacturing Department of the University Medical Center Groningen (UMCG). The prototype was based on the Carbomedics R-reduced valve but can also be achieved for any of the other available bileaflet valve models. The suture ring from an original 25 mm Carbomedics r-reduces was removed from the housing to allow dismantling of the valve. After carefully removal of the leaflets 4 incisions were made in the leaflet ears, two on each side as shown in figure 4. Initial incisions had a depth of 0.25 mm and a width

of 0.5 mm for each incision (figure 5), The valve was reassembled, where the suture ring was not reinstalled to make further adaptations possible, as shown in figure 6. The valve was put in a custom made holder to prevent paravalvar leakage. The new heart valve design will only require an additional step in the manufacturing of the leaflets. There are two production options, either the mold will be adapted or the original leaflets will be altered after fabrication.

Figure 4, prototype leaflet with leaflet passage-ways.

Figure 5, spacing's in the leaflet design, 1; width , 2; dept.

Testing of the functional prototype

Materials and methods

The functional prototype as described above was utilized in the test set-up. Testing was performed in a static in-vitro model to determine the relationship between pressure and valvar leakage (figure 7). The model is based on water pressure kept at a constant level, that was varied by adjusting the height of the water container. Pressure was monitored with the use of a pressure gauge connected to a Philips Intelli-Vue MP70[®] monitor. The leakage volume

was collected and measured to determine the flow volume of leakage of the valve in closed position. Testing was done in the range between 3 and 80 mmHg, which is the approximate range of the diastolic pressures between pulmonary and aortic diastolic pressure. Measurements were taken over a period of 1 min, each measurement was repeated 3 times.

Figure 6, prototype with leaflet passageways.

Figure 7, In-vitro testing set-up.

After each set of measurements, the results were evaluated. When the desired flow volume was not reached the cavities were enlarged in small incremental steps until the desired amount of fluid leakage was attained. The aim was to approximately reach the same amount of fluid leakage of the original valve under 80 mmHg at 10 mmHg.

Figure 8, Prototype testing results.

Results

The results of the in vitro-testing are presented in figure 8. We adapted the prototype in 4 steps until the desired leakage of 496 ml per minute was reached. The width of the cavity was 0.5 mm, in the first step the dept was 0.25 mm followed by 0.50, 0.75, in the final model the dept of the cavities was 0.875 mm (figure 2). The final prototype had a leakage volume for 454 ml at 10 mmHg as shown in figure 8.

Future perspective

For further development of our prosthetic heart valve for the right ventricle further in-vitro and in vivo testing is necessary. In vitro testing with blood or a blood mimicking fluid in a pulsatile system is necessary to evaluate the thrombogenic properties of the valve. Also, durability testing of the valve is necessary. Next, an in-vivo testing on animal models is warranted to prove the biocompatibility and the functionality of the mechanical valve. If animal trials are successful the next steps could be to start a clinical trial.

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4

A stented bovine pericardial prosthesis in the pulmonary position.

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ABSTRACT

Background: Pulmonary valve replacement is very common among patients with congenital heart disease. The Carpentier Edwards Perimount valve (Edwards Lifesciences, Irvine, Calif), which was originally designed for the aortic position is among the most implanted valves. We aim to describe the follow-up of this valve in the pulmonary position.

Methods: Patients with a Perimount valve implanted between 2003 and 2013 in the University Medical Center Groningen were followed for the primary end point reintervention, defined as surgical or transcatheter valve replacement. Secondary end point was the occurrence of valve failure, defined as significant valvular regurgitation or stenosis. Explanted valves were histologically examined.

Results: Forty-five patients (median age at operation 27.8 years, 55.6%women) had a mean follow-up duration of 5.8 ± 3.3 years. There were 7 reinterventions (5 surgical and 2 transcatheter). Freedom from reintervention was respectively $95\% \pm 4\%$ and $83\% \pm 8\%$ at 5- and 10- years of follow-up. Freedom from valve failure was $75\% \pm 4\%$ at 2 years, $65\% \pm 8\%$ at 5 years of follow-up and $57\% \pm 10\%$ at 10 years of follow-up. Morphology evaluation ($n = 4$) showed stiffened valves in the open position, with extensive fibrous tissue overgrowth on the leaflets and a variable proliferation of myofibroblasts.

Conclusions: The Perimount valve has adequate function in the pulmonary valve position at 5 years of follow-up, although after 10 years of follow-up valve failure and reinterventions are common. Explanted valves show retraction and stiffening of the leaflets due to a fibrotic layer on both sides of the leaflet.

Glossary of abbreviations

CE= Carpentier Edwards

CHD = Congenial Heart Disease

LVEF= Left Ventricular Ejection Fraction

MSB= Martius Scarlet Blue

RVOT= Right Ventricular Outflow Tract

PPEC= Percentage of Predicted Exercise Capacity

PVR= Pulmonary Valve Replacement

RVEDD = Right Ventricular End Diastolic Diameter

TAPSE = Tricuspid Annular Plane Systolic Excursion

VSD= Ventricular Septal Defect

INTRODUCTION

A wide spectrum of congenital heart diseases require pulmonary valve replacement (PVR) with or without reconstruction of the right ventricular outflow tract. There are several options for PVR, including homografts, bovine jugular vein conduits, mechanical prosthetic valves, and biological prosthetic valves. Homograft and bovine jugular vein conduits have limited availability and sizes, while mechanical valves are associated with higher rates of valve

thrombosis requiring lifelong use of anticoagulation medication.¹ As a result, biological aortic valve prostheses are widely used for PVR. When the occasion rises, the stented bovine pericardial Carpentier Edwards Perimount valve (Edwards Lifesciences, Irvine, Calif) is among the most implanted bioprosthetic valves in the pulmonary position.

Originally designed for left-sided valvular heart disease, the Perimount valve has shown excellent results in the aortic and mitral valve position.²⁻⁴ However, data on its durability and functionality in the pulmonary valve position are scarce. The Perimount valve has shown mixed results in the pulmonary position so far.⁵⁻¹² A large study by Nomoto and colleagues¹² showed very good results in terms of reintervention for the Perimount valve compared with the Mitroflow valve (Sorin Group USA Inc, Arvada, Colo), whereas the studies by Jang and colleagues^{7,11} suggested higher rates of valve failure for the Perimount valve compared with porcine valves. Of note, both studies were performed in a young population with a relative short follow-up duration. Most studies are limited in echocardiographic valve evaluation and others include heterogeneous populations in terms of implanted valve type and age.

More uniform long-term research on the functionality of prosthetic valves in the pulmonary position is essential to provide patients and physicians with a well-founded choice, when selecting a prosthetic valve for this position. In this retrospective observational study, we evaluate the Perimount valve in an adolescent/adult population. Both re-intervention rates as well as valve function (based on echocardiograph images) are evaluated, giving a complete representation of valve functioning.

METHODS

Patients

All patients in whom a Perimount aortic valvular prosthesis was implanted in the pulmonary position between 2003 and 2013 in the University Medical Center Groningen were included in this study. The Perimount series include the Perimount, Perimount Magna, and the Perimount Magna Ease valve. The valves consist out of bovine pericardial leaflets mounted on a flexible cobalt-chromium alloy stent. Valve choice was based on surgeon's

preference and patient's wishes. Valve replacement was performed through a median sternotomy with the use of cardiopulmonary bypass. Indication for PVR was based on a combination of criteria, including but not limited to, symptoms related to pulmonary regurgitation, QRS complex duration, right ventricular volume, right ventricular ejection fraction, maximum oxygen capacity uptake, left ventricular volume, ventricular tachycardia and tricuspid regurgitation. Data were retrieved retrospectively using electronically stored patient files up to October 2017. No identifiers were linked to patients in this database. Applicable legislation in the Netherlands stipulates that retrospective anonymized chart research is not subjected to institutional review board review.

End Points

The primary end point was reintervention, defined as surgical or transcatheter (valve-in-valve) replacement of the prosthetic heart valve. Secondary end point was the occurrence of prosthetic valve failure, which was defined as the occurrence of at least moderate regurgitation or moderate stenosis. The other secondary end point was endocarditis. Echocardiography Valve functioning was determined by standard clinical 2-dimensional transthoracic Doppler echocardiography performed by trained specialists as part of routine clinical care. The following parameters were evaluated with color and Doppler echocardiography: prosthetic valve regurgitation and stenosis, tricuspid valve regurgitation, all of which were graded according to European Association of Echocardiography/American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.¹³⁻¹⁵ Additionally, left ventricular function measured as left ventricular ejection fraction (LVEF), right ventricular function measured as tricuspid annular plane systolic excursion (TAPSE) and right ventricular end diastolic diameter (RVEDD) in the 4-chamber apical view were determined. Regurgitation and stenosis were evaluated postoperatively in the aftermath of a recent implantation and during regular outpatient clinic visit. Additional parameters were evaluated postoperatively and during the last outpatient clinic visit.

Exercise Capacity

Exercise capacity was evaluated using the percentage of predicted exercise capacity (PPEC), calculated by dividing the achieved exercise level by the predicted exercise level. Exercise capacity was evaluated as part of routine clinical care. Testing was performed using a bicycle ergometer or treadmill. Routine clinical care protocols were followed: the Bruce, modified

Bruce, 10Watt, or 15Watt programs. Patients were permanently monitored with echocardiogram, blood pressure, and oxygen saturation during the test. Exercise levels were evaluated using either maximum oxygen capacity or the maximum workload. Predicted

workload was calculated as described by Ascoop and colleagues,¹⁶ and predicted maximum oxygen capacity was determined with the Wasserman/Hansen equation.¹⁷

Pathologic Evaluation

Of the surgically explanted valves (N = 5), 4 valves were histologically examined and compared with a nonimplanted Perimount valve. Specimens were described macroscopically, and samples were formalin fixed and paraffin embedded according to standard operating procedures in our routine diagnostic pathology laboratory. Series of sections were cut at 4 mm thickness and mounted onto glass slides. We performed hematoxylin and eosin stain, Verhoeff-van Gieson stain, Alcian Blue stain, Van Kossa stain, and Martius scarlet blue stain using standard staining protocols. Besides histomorphology, slides were stained with different immunohistochemistry markers to differentiate between cell types. Alpha smooth muscle actin staining (clone 1A4; Agilent Technologies, Santa Clara, Calif) and Caldesmon (clone h-CD; Agilent Technologies) were performed to stain myofibroblasts. CD45 (clone 2B11pPD7/26; Roche Holding Ltd, Basel, Switzerland) was used to identify inflammatory cells. To identify endothelium, CD31 (clone JC40; Roche Holding Ltd) was applied.

Statistical Analysis

Normally distributed continuous variables are presented as mean $\pm$ standard deviation. Not normally distributed continuous variables are presented as medians and ranges. Dichotomous variables are presented as numbers and percentages. Paired samples Student t test was used to

compare LVEF, TAPSE, RVEDD, and PPEC postoperatively and at last visitation. In case of reintervention, the last visit before reintervention was considered for evaluating echocardiography parameters. Kaplan-Meier analyses and life tables were used to evaluate time to event. Cox proportional hazard methodology was used to determine relationships between the covariates and time to event. Age, gender, tetralogy of Fallot (TOF), number of sternotomies, labeled size, TAPSE, LVEF, PPEC, and RVEDD were evaluated as univariables, and all variables with a P value < .1 were included in a multivariable model. Additionally, a multivariate model including age and gender was created. All statistical analyses were performed with IBM SPSS Statistics version 23 (IBM-SPSS Inc, Armonk, NY).

RESULTS

We included a total of 45 patients who received a Perimount valve in the pulmonary position; this was 21.2% out of a total of 212 PVR patients between 2003 and 2013. Of

these 212 valves, 98 patients received a Contegra valve (Medtronic, Minneapolis, Minn) (46%) of which 9 were older than age 16 years at implantation, 47 received a mechanical valve (22%), 13 received a Melody valve (Medtronic) (6.1%), 5 received a porcine valve (2.3%), and 4 received a homograft (1.9%).

Baseline Characteristics

As depicted in Table 1, median age at time of valve implantation was 27.8 years (range, 15.1-59.2 years). There were 3 patients younger than age 18 years. The study sample comprised 55.6% women. The main underlying cardiac diagnosis was TOF (68.9%), followed by congenital pulmonary regurgitation and/or stenosis (24.4%). For the patients with TOF, median time between total correction and implantation of the Perimount valve was 25.5 years (interquartile range, 20.0-32.8 years). Of the patients included, 98% had at least 1 prior sternotomy. Median implanted valve size was 25mm (range, 23-29 mm), 22 (48.9%) of patients received a 25-mm valve.

Reintervention

Mean follow-up duration was 5.8 ± 3.3 years; mean age at follow-up was 39.1 ± 12.2 years. Two patients died during the follow-up period. One patient died in the early aftermath 3 days post-surgery related to postoperative cerebral ischemia. The other fatality was 3 years after PVR due to end-stage right ventricular heart failure, with a well-functioning valve. In total there were 7 reinterventions of which were 2 transcatheter (valve-in-valve) interventions and 5 were surgical reinterventions. Cumulative freedom from reintervention was $95\% \pm 4\%$ at 5 years, $83\% \pm 8\%$ at 10 years, and $12\% \pm 16\%$ at 15 years post implantation as shown in Figure 1. For 6 patients, severe valve regurgitation was the main reason for reintervention and for the remaining patient endocarditis was the cause for reoperation.

Secondary End Points

Freedom from valve failure (at least moderate regurgitation or moderate stenosis) was $75\% \pm 4\%$ at 2 years of follow-up, $65\% \pm 8\%$ at 5 years of follow-up and $57\% \pm 10\%$ at 10 years of follow-up. At final follow-up, 10 patients had severe regurgitation (22.2%), 3 patients had moderate regurgitation (6.7%), 9 patients had moderate stenosis (20.0%), and 1 patient had severe stenosis (2.2%). There was 1 patient with pulmonary valve stenosis without valvular regurgitation. In total, there were 5 cases of endocarditis (11.1% of the total study cohort). Cumulative freedom from endocarditis was $89\% \pm 5\%$ at 5 years post-PVR and $83\% \pm 8\%$ at 10 years post-PVR (Figure 2). Mean time to develop endocarditis was 3.03 ± 1.9 years (range, 0.89-5.22 years) after PVR. Right ventricular function measured by TAPSE improved from 14.3 ± 4.0 mm postoperatively to 16.9 ± 3.8 mm at final visit ($P < .001$), although the RVEDD increased from 41.9 ± 6.9 mm/m² postoperatively

TABLE 1. Baseline characteristics

Characteristic	Result
Female gender	25 (55.6%)
Number of thoracotomies	1 ± 1.0
0	1 (2.2%)
1	29 (64.4%)
2	9 (20.0%)
3	3 (6.7%)
4	2 (4.4%)
5	1 (2.2%)
Principal cardiac diagnosis	
Tetralogy of Fallot	31 (68.9%)
Pulmonary stenosis	11 (24.4%)
Truncus arteriosus	1 (2.2%)
Pulmonary atresia	1 (2.2%)
Aortic valve replacement	1 (2.2%)
Previous procedures	
Aortic pulmonary shunt	10 (22.2%)
Total correction	31 (68.9%)
Pulmonary valvulotomy	13 (28.9%)
VSD closure	4 (8.9%)
Pulmonary valve replacement	7 (15.6%)
Other	8 (17.8%)
History of endocarditis	2 (4.4%)
Valve size (mm)	25 (23-29)
Age at implantation (y)	31.26 ± 12.54*
Concomitted procedures	
RVOT correction	6 (13.3%)
VSD closure	1 (2.2%)
Tricuspid valve repair	4 (8.9%)
Other	3 (6.7%)
Echocardiographic variables	
Tricuspid regurgitation	15 (33.3%)
LVEF (%)	51.6 ± 5.0
TAPSE (mm)	14.3 ± 4.0
RVEDD (mm/m ²)	41.9 ± 6.9
PPEC (%)	67.4 ± 16.8

Values are presented as mean ± standard deviation, n (%), or median (range). VSD, Ventricular septal defect; RVOT, right ventricular outflow tract; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RVEDD, right ventricular end diastolic diameter; PPEC, predicted percentage exercise capacity. *Range, 15.1 to 59.2 years.

to 44.03 ± 6.0 mm/m² at last visit ($P = .001$). Postoperative left ventricular function was stable during follow up (LVEF $51.6\% \pm 5.0\%$ compared with $51.5\% \pm 6.7\%$ at last visit) ($P = .27$). Exercise capacity measured by PPEC was increased from $67.4\% \pm 16.8\%$ at first test postoperatively to $72\% \pm 15.7\%$ at final visit ($P = .05$). Univariate Cox proportional hazard analyses showed no effect on time to valve failure for age, gender, underlying disease (divided by TOF vs other), use of anticoagulation, RVDD, TAPSE, LVDD, and valve size. For time to reoperation RVDD was both univariable and in a multivariable model with age and gender, associated with reoperation (hazard ratio, 1.39; 1.04-1.85; $P = .027$). There were no other significant associations for any of these variables (Table E1).

Figure 1: Cumulative freedom from re-intervention and freedom from valve failure during 15-year follow-up of Carpentier Edwards Perimount valves in the pulmonary position, including the 95% Confidence Interval. Re-intervention is defined as surgical or transcatheter valve replacement. Valve failure is defined as: moderate or severe valve regurgitation or stenosis.

Figure 2: Cumulative freedom from endocarditis during a ten-year follow-up of Carpentier Edwards Perimount valves in the pulmonary position, including 95% Confidence Interval. Endocarditis was defined as clinically treated endocarditis.

Morphologic Findings

Among the explanted valves ($N = 5$) 1 valve was explanted due to active endocarditis and 1 patient was treated for suspected endocarditis years before the operation. The histologically examined valves ($n = 4$) showed severe malfunctioning due to thickening and valve retraction as shown in Figures 3 and 4. Histologically, all valves showed central collagenous thickening, with fibrosis on the surface on both sides of the leaflet (Table 2). This fibrosis showed variable proliferation of myofibroblasts (Figure 4). No valves showed an endothelial lining. One valve showed central dystrophic calcification. In ad-

Figure 3: Front and Back view of 3 explanted bovine pericardial Carpentier Edwards Perimount valves with retracted leaflets. A & B front and back view of Carpentier Edward valve with an implanted duration of 5 years, C & D front and back view of Carpentier Edwards valve with an implanted duration of 10 years, D & E front and back view of Carpentier Edwards valve with an implanted duration of 13 years.

dition, some valves showed fibrin deposition/thrombosis at the surface. Three out of the 4 valves showed inflammatory cells. Our findings were compared with a nonimplanted Perimount valve, which showed no inflammation, collagenous thickening, fibrosis, or endothelial lining at all (Figure 5).

Figure 4: Histomorphology of implanted bovine pericardial Carpentier Edwards Perimount valves in pulmonary position without (history of) endocarditis. Collagenous thickening of the valve is seen with fibrosis (A, B & C). In the fibrosis proliferation of smooth muscle cells is depicted (D). No endothelial cells (E) or inflammation (F) present. (A) Hematoxylin & Eosin staining, original magnification x2, (B) Verhoeff-van Gieson staining, original magnification 2x, (C) Martius Scarlet Blue staining, original magnification x10, (D) alpha Smooth Muscle Actin staining, original magnification x10, (E) Cluster of Differentiation 31 staining, original magnification x10, (F) Cluster of Differentiation 45 staining, original magnification x10.

Table 2: Histomorphologic characteristics of the valves that were examined

Valve	Collagenous thickening	Inflammation	Calcification	Myofibroblasts	Absence of endothelium	Thrombosis/fibrin	Fibrosis
Valve 1*	p	Focal p		p	p		p
Valve 2y	p	p		p	p	p	p
Valve 3	p		p	Focal p	p	p	p
Valve 4	p	Focal p		p	NA	Focal p	p
Control valve					p		

p, Present; *Focal p*, focal present; , absent; *NA*, not applicable. *Underwent previous treatment for endocarditis.y Active endocarditis.

Figure 5: Histomorphology of normal, unimplanted bovine Carpentier Edwards Perimount valve. No calcification, fibrosis or inflammation is present. (A) Hematoxylin & Eosin staining, original magnification x2, (B) Verhoeff-van Gieson staining, original magnification 2x, (C) Martius Scarlet Blue staining, original magnification x10, (D) alpha Smooth Muscle Actin staining, original magnification x10, (E) Cluster of Differentiation 31 staining, original magnification x10, (F) Cluster of Differentiation 45 staining, original magnification x10.

DISCUSSION

Bioprosthetic aortic valves are used off-label for replacement of pulmonary valves. For this purpose, the Perimount valve is among the most widely used stented bioprosthetic valves. There is a scarcity of data on the long-term functionality of these valves in the pulmonary position. The results of this study show that short-term freedom from re-intervention has been acceptable for the Perimount valve in the pulmonary position. Although numbers are limited after 10-year follow-up, prosthetic failure and reinterventions were common. There was no mortality specifically related to valve failure. All surgically explanted and examined valves showed the same features: Valve leaflets were degenerated and stiffened and complete closure was impossible. All explanted and examined valves showed extensive fibrotic tissue deposits. RVDD was univariable and multivariable associated with reintervention.

Reintervention

Reintervention rates up to 10 years were acceptable in our study, with a freedom from reoperation of 95% at 5 years after surgery and 83% at 10 years post implantation. Beyond 10 years, intervention rates are high; however, it should be noted that only 4 patients entered that interval. Comparing reintervention rates between studies is difficult because the timing of reintervention for pulmonary valve failure is subject to intense debate and often different among congenital heart centers.^{18,19} Our findings show comparable or better results on freedom from reintervention at 5 and 10 years of follow-up when compared with previous studies. These studies report a median freedom from reintervention of $95.2\% \pm 15.98\%$ (range, 50%-98.2%) for 5-year follow up,^{5-12,20} and 81.2% (66.4%-84.7%) for 10-year follow up.¹⁰⁻¹² However, most of these studies include a younger patient population. Young age has been frequently associated with an increased risk of valve failure.^{6,11} When comparing with the adult population with a valve described by Nomoto and colleagues,¹² freedom from reintervention was much higher in their study with 96.7% at both 5- and 10-year follow-up.

There has been a limited amount of studies reporting more than 10 years of follow-up after implantation. The study by Jang and colleagues¹¹ reported freedom from reintervention of 21.2% at 15 years of follow-up for both pericardial and porcine valves combined. In contrast, the study by Rotes and colleagues¹⁰ had a 75.1% freedom from reintervention at 15 years for a combined cohort of 13% Perimount valves and 76% porcine valves. In our study, we report 2 cases of successful implantation of a transcatheter valve in a failed Perimount valve. Also in literature, the option of valve-in-valve implantation in the pulmonary position seems promising.^{21,22} More long-term studies need to point out the reliability of this strategy.

Valve Failure

In our population we found a rather high rate of valve failure with a freedom from moderate to severe valve regurgitation of 67% at 5 years post implantation and 59% at 10 years post implantation. Echocardiographic evaluation of valve function has not been uniform between studies, most studies only reporting valve function at last follow up. Only the study by Lee and colleagues¹⁹ presented a time related analysis. Lee and colleagues¹⁹ presented a combined end point of valve failure and dysfunction, which was 92.2% at 5 years and 20.2% at 10 years.²⁰ Our relatively high rates of valve failure compared with the reoperation rates could be explained by the fact that a malfunctioning pulmonary valve is often tolerated quite well and timing of reintervention has been much debated.²³ Also, we recognize that the choice for moderate regurgitation and moderate stenosis as definition for valve failure is arbitrarily. Choices were made as we aimed to observe the process of valve deterioration.

Pathology

The explanted and histologically examined valves in our study showed stiffened leaflets that are completely retracted, likely to be caused by collagenous pannus overgrowth and the presence of myofibroblasts. To our knowledge the histology of this valve in the pulmonary position has not been studied before. Butany and colleagues²⁴ studied the morphology of explanted Perimount valves. However, they did not distinguish between valve locations. They showed pannus overgrowth in 69.9% of the explanted valves.²⁴ One of their valves also showed shortening of the cusp, but this valve had been implanted in the mitral position. Jang and colleagues¹¹ reported macrophage infiltration, fibrotic tissue deposits, and calcium deposits on explanted pulmonary valve prosthesis; however, they did not make a distinction between the different valve types used. A recent report by Sellers and colleagues²⁵ on transcatheter aortic valve replacement shows similarities with our findings, in a series of 23 explanted transcatheter aortic valves they showed the presence of thrombus that was followed by fibrosis. They found fibrosis on all valves implanted after 60 days, which is somewhat comparable with our results.²⁵ Although our sample size was limited the histologic results show a distinct pattern, more structural histological evaluation is necessary to determine the failure mechanism of (pericardial) bioprosthetic valves in the pulmonary position.

Limitations

Due to the retrospective nonrandomized observational nature of this study, follow-up durations within our cohort were random. In addition, the number of patients in our study population was limited and derived from a single center. Due to the limited sample size, our models are possibly underperforming. Additional larger long-term follow-up studies are warranted to investigate this valve in the pulmonary position.

CONCLUSIONS

The Perimount valve has adequate function in the pulmonary valve position at 5 years' follow-up, after 10-year follow-up valve failure and reinterventions are common in this relatively young cohort compared with the usual tissue valve recipients (Video 1). All explanted and histologically examined valves show a similar pattern of failure showing complete retraction and stiffening of the leaflets.

Conflict of Interest Statement Ms Pragt and Dr Ebels own rights to a patent for a mechanical valve design for the pulmonary position. Dr Mariani has been the recipient of an unrelated grant from Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

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5

Pulmonary versus aortic pressure behavior of a bovine pericardial valve.

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ABSTRACT

Background: The Carpentier Edwards Perimount Magna Ease aortic valvular prosthesis (Edwards Lifesciences, Irvine, Calif) has been among the most frequently and successfully used tissue prosthetic cardiac valves. Furthermore, this prosthesis has been used off-label in the pulmonary position. Until now, there has been a paucity of data regarding the functioning of tissue prosthetic valves under pulmonary conditions.

Methods: Using a pulse duplicator, hydrodynamic characteristics of a 21-mm and 25-mm Magna Ease valve were evaluated. Among parameters evaluated were leakage orifice area, closing time (ie, time required to close), and leakage duration. This procedure was performed under different pulmonic pressure conditions (15/5 mmHg, 28/11 mmHg, 73/32 mmHg) and normal aortic pressure (120/80 mm Hg) as a reference. Moving images were obtained using a Phantom MIRO M320S high-speed camera (Vision Research Inc, Wayne, NJ) at 600 frames per second and used to analyze valve area in closed position.

Results: Under normal pulmonic conditions (28/11 mm Hg) the leakage orifice area was $0.020 \pm 0.012 \text{ mm}^2$ for the 21-mm valve and $0.054 \pm 0.041 \text{ mm}^2$ for the 25-mm valve ($P = .03$). Hydrodynamic characteristics of the valves differed between pulmonary and aortic testing condition. Valve closing volumes were significantly lower under pulmonary hypotension and normal pulmonary conditions than under normal aortic conditions ($P < .05$).

Conclusions: Under normal pulmonary pressure conditions, the hydrodynamic characteristics of Magna Ease valves are significantly different compared with aortic conditions. Further research is needed to determine whether these results are associated with prosthetic valve failure.

Glossary of Abbreviations:

ANOVA = Analysis of variance

CE = Carpentier Edwards

EVA = Edwards valve analyzer

EOA = Effective Orifice Area

INTRODUCTION

A spectrum of congenital cardiac defects require the surgical replacement of the pulmonary valve. There are several options for pulmonary valve replacement (PVR), including homografts, bovine jugular vein conduits, and biological and mechanical prosthetic valves. Homograft valves are not always available and often have limited size options, yet bovine jugular vein conduits are limited in size and appear to be associated with an increased occurrence of infective endocarditis.¹ Mechanical valves are associated with a continuous risk of valvular thrombosis and require lifelong anticoagulation therapy.² These circumstances make biological valvular prostheses a widely used option for PVR, especially for adults.

The most frequently used prosthetic valvular prosthesis is the Carpentier Edwards Perimount Magna Ease (Edwards Lifesciences, Irvine, Calif) heart valve, the leaflet material of which is made out of bovine pericardial tissue. In the aortic position, results for the Perimount family of valves have been excellent, both in young and elderly populations.³ The durability of the Magna Ease valve has been shown to be promising in an in vitro test situation under aortic valvular pressure conditions.⁴ However, in the pulmonary position the clinical results of biological prosthetic valves have not been uniform.⁵⁻⁹

In this context, it is pertinent to remark that all prosthetic valves that are used in the pulmonary position for adults are originally designed for the aortic position. When valvular prostheses are implanted into the right ventricle they are exposed to hemodynamic conditions that are essentially different from the left ventricle, characterized in particular by much lower pressures. We hypothesize that the behavioral characteristics of bioprosthetic valvular prostheses are related to the systolic and diastolic pressures exerted upon the valve.

MATERIALS AND METHODS

Valves

For the in vitro simulation, the Carpentier-Edwards Perimount Magna Ease aortic 3300 TFX prosthetic valve was used. Prosthetic valves were tested in the sizes 21mm and 25 mm. These sizes were selected to represent the usual range of pulmonary prosthetic valves in adolescents and adults. Sewing ring and stitches of the valves were sealed after mounting in the test setup with silicone to prevent paravalvular leakage.

Testing Setup

Right and left ventricular conditions were simulated with the use of the Edwards Valve Analyzer (Edwards Lifesciences), a pulsatile flow system used to conduct hydrodynamic

testing. The system is powered by a piston driven pump, as shown in Figure 1. The system allows for testing according to Food and Drug Administration guidelines. Aortic and pulmonary testing was performed in the same test setup under the same flow profiles. To adapt the test setup to right ventricular conditions for pulmonary testing, the atrial reservoir and the afterload compliance chamber were adjusted to right cardiac conditions. An additional chamber was added to create more volume in the afterload compliance chamber. To make the Edwards Valve Analyzer operable for testing of the 21-mm and 25-mm pulmonary valves, respectively, a 29-mm and 31-mm Perimount mitral valvular prosthesis was used in the tricuspid position to complete the test system. The pulmonary and tricuspid valvular prostheses were matched based on normal native pulmonary and tricuspid valve sizes.^{10,11}

Figure 1, Schematic drawing of the Edwards Valve Analyzer (Edwards Lifesciences, Irvine, Calif). PT, Pressure transducer.

Images were obtained using a high-speed camera: model Phantom MIRO M320S (Vision Research Inc, Wayne, NJ) at 600 frames per second. Residual open valve areas, if any, in closed position was measured using the image processing software ImageJ (National Institutes of Health and the Laboratory for Optical and Computational Instrumentation, Washington, DC).¹² Stills were taken for 3 consecutive cycles when the valve was stable in closed position without resonances in the pressure measuring system and the forward flow was 0. Resonance is a phenomenon consisting of small repetitive pressure

differences initiated by the oscillation of the valve leaflets caused by a small periodic stimulus close to the natural frequency of the leaflets.

Test Conditions

We used 3 pulmonary valve-like test conditions and 1 aortic valve reference condition (Table 1), based on the ISO 5840-1 guidelines.¹³ We accepted a variance of 10% for arterial peak systolic pressure and arterial end diastolic pressure. For each valve size, 3 valves were tested and for each testing condition 10 measurements were taken from consecutive selected cycles. The following variables were evaluated:

- Mean pressure difference: Mean pressure difference (in millimeters mercury) over the prosthetic valve during forward flow;
- Forward flow volume: Flow volume (in millimeters) ejected through the prosthetic valve in a forward direction during 1 cycle (Figure 2);
- Forward flow duration: The time range (in milliseconds) within 1 cycle in which the flow through the pulmonary valve is in forward direction (Figure 2);
- Regurgitant volume: fluid volume (in milliliters) that flows through a prosthetic valve in reverse direction during 1 cycle (a combination of closing volume and leakage volume, where closing volume is defined as the volume that flows in reverse direction during the beginning of the closing period, when the leaflets start to move, until that very movement has stopped, and leakage volume is defined as the volume that flows in reverse direction after the end of the closing period until the beginning of the opening movement of the leaflets);
- Regurgitant fraction: Regurgitant volume expressed as a percentage of the forward flow volume;
- Closing volume: Proportion of the regurgitant volume (in milliliters) that is associated with the dynamics of valve closure during a single cycle (Figure 2);
- Closing time: The time interval (in milliseconds) associated with the dynamics of valve closure during a single cycle (Figure 2)
- Leakage volume: Proportion of the regurgitant volume (in milliliters) associated with leakage during the closed phase of a valve in a single cycle (Figure 2);
- Leakage duration: The time (in milliseconds) between the closure of the valve and the beginning of forward flow during a single cycle (Figure 2); and
- The effective orifice area (EOA) (in centimeters²):
$$EOA = \frac{Q_{vRMS}}{51,6 \times \sqrt{\frac{\Delta p}{\rho}}}$$

where Q_{vRMS} is the root mean square forward flow (in milliliters per second) during the positive differential period, Δp is the mean pressure difference (in millimeters mercury), and ρ is the density of the test fluid (grams per centimeters³).

Tests were performed using a phosphate buffered saline solution with a density of 1.006 g/cm³, at room temperature. Heart rate was maintained at 70 bpm, cardiac output was set at 5 L/min and systolic duration was kept at 35%.¹³

TABLE 1. Pressure conditions used for valve evaluation

Pressure condition	Peak systolic pressure (mm Hg)	End diastolic pressure (mm Hg)
Pulmonary		
Hypotension	15	5
Normotension	28	11
Severe hypertension	73	32
Aortic*		
Normotension	120	80

*Reference condition.

Figure 2, Edwards Valve Analyzer (Edwards Lifesciences, Irvine, Calif) output for pulmonic normotensive (28/11 mm Hg) condition (size 21 mm). Distance between points 1 and 2 indicate forward flow duration. Distance between points 2 and 3 indicate closing time and closing volume. Distance between points 3 and 4 indicate leakage duration and leakage volume.

Statistical Analyses

Continuous variables are presented as mean $\pm$ standard deviation. Repeated measures analysis of variance with Bonferroni testing was used to compare means between different test conditions, and analyses were stratified by valve size. Valve size was added to the unstratified model to detect differences between valve size. All statistical analyses were performed using an IBM SPSS Statistics version 23 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Flow and pressure profiles generated under pulmonary condition are shown in Figure 2, and were deemed adequate for evaluation.¹⁴ Some resonance in the flow and pressure curves under low-pressure conditions was observed.

The video images illustrate an increase in closing time with decreasing pressures. Video 1 shows the opening and closing of a 25-mm valve under normal pulmonary conditions and Video 2 under normal aorta conditions. During testing under the normal (28/11 mm Hg) and hypotensive (15/5 mm Hg) pulmonary pressure conditions, the valve did not completely close (Figure 3), thus leaving a regurgitant opening. Under normal pulmonary testing conditions (28/11 mm Hg), the area of the regurgitant opening in closed position was $0.020 \pm 0.012 \text{ mm}^2$ for the 21-mm valve and $0.054 \pm 0.041 \text{ mm}^2$ for the 25-mm valve ($P = .03$). For hypotensive pulmonary testing conditions (15/5 mm Hg) the regurgitant area was $0.097 \pm 0.026 \text{ mm}^2$ for the 21-mm valve and $0.19 \pm 0.13 \text{ mm}^2$ for the 25-mm valve ($P = .041$) (Figure E1).

Figure 3, Perimount Magna Ease (Edwards Lifesciences, Irvine, Calif) valve in closed position. A, 25-mm valve under normal aortic testing conditions (120/80 mm Hg). B, 25-mm valve under normal pulmonary testing position (28/11 mm Hg). C, 25-mm valve under pulmonary hypotension testing conditions (15/5 mm Hg). D, 21-mm valve under normal aortic testing conditions (120/80 mm Hg). E, 25-mm valve under normal pulmonary testing position (28/11 mm Hg). F, 21-mm valve under pulmonary hypotension testing conditions (15/5 mm Hg).

Closing duration was, 54.6 ± 3 ms for a 25-mm valve compared with 42.9 ± 3.2 ms ($P<.001$) for the 21-mm valve, leakage duration was 524 ± 3.9 ms compared with 539 ± 3.5 ms ($P<.001$), respectively, under 28/11 mmHg and 120/80 mm Hg. Closing time decreased with increasing pressure conditions, whereas the leakage duration increased. Leakage duration is the period in which the valve is in closed position. Figure 4 shows the difference between the aorta reference and pulmonary testing conditions in percentages for the forward flow duration, leakage duration, and closing time. Under all pulmonary test conditions, the closing time and leakage duration differed significantly from the aortic position ($P<.001$). The forward flow duration was significantly longer for the pulmonary hypotension testing condition (15/5 mm Hg) compared with the aortic position ($P<.001$).

Figure 4, percentage of forward flow duration, closing time and leakage duration for the different pressure conditions compared to normal aortic conditions, for a 21mm and 25 mm Magna Ease prosthetic heart valve. Values for forward flow duration, closing time and leakage duration at aortic conditions (80 mmHg) were set at 100%.

Valvular closing volumes were significantly lower under hypotensive and normal pulmonary conditions than under normal aorta conditions ($P<.05$). Between pulmonary

hypertensive conditions and aorta conditions there was no significant difference (Table 2). With increasing pressures, the total closing volume is larger, despite the decrease in closing time. The leakage volume does not show a distinctive trend with pressure (Table 2). As could be expected, the mean systolic pressure difference over the prosthetic valve decreased with decreasing pressure conditions (Table 2). For both valves, the systolic pressure drop for the pulmonary testing conditions differed significantly ($P < .001$) from the reference aorta condition. Under all testing conditions, the mean pressure difference over the 25-mm valve was lower than over the 21-mm valve. EOA was higher for the 25-mm valve compared with the 21-mm valve, as was expected. With decreasing pressure differences, the EOA also decreases, with a significant difference between normal aortic conditions and all pulmonary conditions for both valve sizes ($P < .001$).

TABLE 2. Outcome variables under different testing conditions for each valve size

Condition	Mean pressure difference (mmHg)		Forward flow volume (mL)		Closing volume (mL)
	21 mm	25 mm	21mm	25mm	21 mm
Hypotension	11.89 ± 1.4y	6.74 ± 0.43y	72.23 ± 0.78y	72.24 ± 1.0 y	0.63 ± 0.13y
Normotension	13.28 ± 0.73y	7.79 ± 0.15 y	71.32 ± 0.38	71.04 ± 0.72	0.72 ± 0.16z
Hypertension	14.83 ± 0.46y	8.85 ± 0.10y	70.79 ± 0.43y	70.71 ± 0.31z	0.80 ± 0.13
Normal aortic	17.46 ± 0.65	10.54 ± 0.12	71.33 ± 0.57	70.97 ± 0.33	0.86 ± 0.16

*Conditions were defined as hypotension: 15/5 mm Hg, normotension 28/11 mm Hg, hypertension: 73/32 mm Hg, and normal aortic: 120/80 mm Hg. y $P < .001$ compared with the normal aortic reference value. z $P < .05$ compared with the normal aortic reference value.

TABLE 2. Continued

Closing volume (mL)	Leakage	volume (mL)	Regurgitation	fraction (%)	Effective orifice area (cm ²)	
25 mm	21 mm	25 mm	21 mm	25 mm	21 mm	25 mm
1.04 ± 0.28y	0.54 ± 0.15y	1.06 ± 0.32	1.63 ± 0.27y	2.91 ± 0.53y	1.69 ± 0.035y	2.31 ± 0.089y
1.21 ± 0.18y	0.48 ± 0.15y	1.13 ± 0.37	1.85 ± 0.36y	3.42 ± 0.68	1.72 ± 0.033y	2.34 ± 0.029y
1.42 ± 0.30	0.69 ± 0.26z	0.97 ± 0.32	2.20 ± 0.47z	3.51 ± 0.80	1.75 ± 0.050y	2.38 ± 0.031y
1.53 ± 0.28	0.94 ± 0.35	1.15 ± 0.44	2.59 ± 0.66	3.87 ± 0.93	1.80 ± 0.052	2.43 ± 0.022

Regurgitant fractions were significantly decreased in normal (28/11 mm Hg) conditions for the 21-mm valve and under hypotensive (10/5 mm Hg) pulmonary conditions for both the 21-mm and 25-mm valves compared with aorta conditions (120/80 mm Hg) ($P < .001$) (Figure 5). For all valve sizes and testing conditions, the regurgitant fractions were considerably below 10%, the minimum requirement set by ISO for aortic valves.¹⁵

Figure 5, Boxplot for the regurgitant fractions of 21-mm and 25-mm Magna Ease (Edwards Lifesciences, Irvine, Calif) prosthetic heart valves under normal aortic, pulmonary hypotension, and normal pulmonary conditions. For each testing condition, 30 measurements were taken. Upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of nonoutliers. Extra dots represent outliers.

DISCUSSION

Although virtually all prosthetic cardiac valves have been designed for the aortic and mitral positions, they are also implanted, albeit off-label, in the pulmonary position. To the best of our knowledge, prosthetic valves designed specifically for use in the pulmonary position in adults do not exist yet. In this study we have shown that the Pericardial Magna Ease prosthetic cardiac valves behave differently under pulmonary conditions compared with aorta conditions in an in vitro test setup. Under pulmonary conditions compared with aorta test conditions, the pericardial Magna Ease valve had an increase in closing time and a reduction in leakage duration and volume, a decrease in pressure difference, and a decreased EOA. Because systolic pressure difference over a valve is in the denominator of the formula for EOA, identical valves have a lower EOA in the pulmonary position than in the aorta position. Therefore, a normal pulmonary valve is larger than an aorta valve.

Video recordings of the leaflet motion during the cardiac cycle showed that all valves do not close completely during diastole, without resonances under pulmonary testing conditions, in contrast to aorta conditions where full closure is always attained. Resonance can be caused by a rapidly decreasing oscillation of the volume because the prosthetic valve is not fully closed. A similar phenomenon can sometimes be seen within a pressure measuring setup at low pressures. Nonetheless, within the right ventricle this is likely to be not hemodynamically relevant, as far as regurgitant volume is concerned. Nonetheless, under pulmonary conditions the tension within the leaflets and the wall tension in the pulmonary artery is much lower than under aorta conditions, which may well contribute to long-term behavior.

The flow profiles created under pulmonary testing conditions and especially the hypotensive (10/5 mm Hg) testing conditions showed some resonance in both the flow and pressure curves. In the video images we observed these resonances during the closing of the valve. Most likely this is the natural behavior of the valve in a pulmonary position; however, we cannot be totally sure that the resonance in the testing system itself did not influence these patterns.

Although there has been no report on the opening and closing behavior of prosthetic heart valves under right ventricular conditions, some studies evaluated the opening and closing times of prosthetic heart valves under left ventricular conditions. Furthermore, there have been reports of increased opening and closing durations for pericardial valves compared with porcine valves.^{16,17} In a study by Bottio and colleagues,¹⁸ the Perimount valve showed lower closing volumes compared with other pericardial valves. In another study on the opening and closing behavior of pericardial valves by Tasca and colleagues,¹⁹ the opening and closing behavior was not influenced by the position of the pericardial leaflets, but rather depended on the intrinsic structural characteristics of the material used for stents and leaflets. These results suggest that changes of the material could potentially adapt valves for the pulmonary position.¹⁹

Although the hydrodynamic characteristics of bioprosthetic valves under pulmonary conditions have not been published before, the valve has been extensively tested under aorta and mitral conditions, both in vitro and in vivo. Both in vitro and clinical results of the valves in the aortic position have shown excellent results compared with other biological prosthetic heart valves.^{4,20,21} The Perimount Magna Ease series has been reported to have the best hydrodynamic properties in terms of EOA and pressure gradient compared with both porcine and other pericardial bioprosthetic valves.^{16,18,20} The slight decrease we found in the EOA under pulmonary conditions will most likely have little effect on the hemodynamic functioning because pulmonary prosthetic valves are generally larger than aortic valve implants.

Previous clinical studies showed a reduced lifespan of biological valves in the pulmonary position.^{9,22} However, there are many factors other than pressure differences that could influence this process. Extreme caution with translating our in vitro findings to the clinical practice is warranted. We could speculate that incomplete closure of the valve accelerates reduced motion of the leaflets, which could possibly influence pannus overgrowth onto the valve leaflets. The latter could potentially contribute to degeneration of the leaflets. It is unlikely that the incomplete closure has a direct effect on right ventricular function because the regurgitant fraction and leakage volume do not increase with decreasing pressures. In fact, regurgitant fractions decreased with decreasing pressures and stayed below 5% for all pulmonary testing conditions.

In this study we demonstrated that under similar circumstances 25-mm valves had a longer valve closing time and a larger leakage surface compared with 21-mm valves

under similar testing conditions. This could give reason to pay even more attention to the size of a prosthetic pulmonary valve. In general, surgeons are likely to oversize a prosthetic pulmonary valve. In most patients requiring PVR the right ventricular outflow tract has been surgically altered (eg, Fallot patients), in such a way that it invites for implantation of a larger valve. These results are difficult to translate directly into clinical behavior. This requires further research before making changes to the clinical practice.

The lifespan of patients with congenital heart disease has increased drastically in past decades. Currently there are more adults than children with congenital heart disease²³ Pulmonary prosthetic valve replacements under both teenagers and adults are increasingly performed. More research of the hydrodynamic functionality and clinical results of prosthetic valves under pulmonary conditions are necessary to be able to evaluate which treatment option is most successful in these patients. We hope this research is a first step in that direction.

Limitations

Tests were performed using a saline solution and for all testing we have used the same flow profile. Although flow profiles over the aorta and pulmonary valve are quite similar, we do recognize that there are some minor differences in flow profiles that we did not take into account.¹⁴ In our test setup we used the same ventricular simulator, not taking into account the difference in elastance between the ventricles.²⁴ Although it is not likely that this influences the basic principles of our results, because Dell'Italia and Santa-more²⁵ showed that although the right ventricle is more complex, the pump properties are comparable to the high-pressure left ventricle. In this study all tests were performed using a saline solution with a density of 1.006 g/cm^3 , whereas blood has a density of 1.06 g/cm^3 . Although the difference in density will probably lead to different absolute numbers, the difference in proportions will likely be minimal. For demonstrating initial differences in in vitro testing, saline is an accepted fluid.

CONCLUSIONS

Under normal pulmonary pressure conditions, Perimount Magna Ease valves do not reach complete closure yet demonstrate minimal leakage. Within the right ventricle this is likely not hemodynamically relevant. Hydrodynamic characteristics of the valves were significantly different from aortic conditions. Further research is needed to evaluate whether or not these results are associated with potential increased risk of prosthetic valve failure in the pulmonary position.

Conflict of Interest Statement

Testing setup and materials were provided by Edwards Lifesciences, Irvine, Calif. Ms Pragt and Dr Ebels own rights to a patent for a mechanical valve design for the pulmonary position. Dr Mariani has been the recipient of an unrelated grant from Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

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FIGURE E1. Area (mm²) of valve opening during steady closure of the valve, showing the area that remains open when the valve is closed in steady position for a 21-mm and a 25-mm Manga Ease (Edwards Lifesciences, Irvine, Calif) prosthetic heart valve. For each testing condition 30 measurements were taken. Upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of nonoutliers. Extra dots represent outliers.

Videos

Video 1

Opening and closing of a 25 mm Carpentier Edwards Magna Ease valve under normal pulmonary pressure condition (28/11 mmHg)

Video 2

Opening and closing of a 25 mm Carpentier Edwards Magna Ease valve under normal aortic pressure condition (120/80 mmHg)

6

Quality of life among patients with congenital heart disease after valve replacement.

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ABSTRACT

Most studies concerning valve replacement in congenital heart disease (CHD) focus on surgical morbidity and mortality. However, with the increased life expectancy of these patients, the focus shifts to quality of life (QOL). The aim of this study was to report and compare the QOL of CHD patients after valve replacement with the general population and to find factors associated with QOL. In a multicenter cross-sectional observational study of adults with CHD, QOL was measured with the RAND-36 questionnaire (a health-related QOL questionnaire, with 8 domains scoring from 0 to 100; higher scores indicate a better QOL). Functional status was measured with exercise capacity testing. Uni- and multivariable linear regression was used to find associations with QOL. In total, 324 patients with CHD and a prosthetic valve were included in this study. CHD patients with a valve replacement scored significantly lower than the general population on the general health, vitality, and social functioning domains ($P < 0.05$). On the bodily pain domain, they scored significantly higher (less pain) ($P < 0.001$). Higher NYHA class was associated with a lower QOL for all domains, reflecting the importance of functional capacity. Other variables related to aspects of QOL were age, gender, exercise capacity, and employment status. Adult patients with CHD and a prosthetic valve have lower scores on the QOL domains general health, vitality, and social functioning as compared to the general population. NYHA class was negatively associated with all QOL domains. Health care professionals should be aware of these patterns in counseling patients.

Glossary of Abbreviations:

ASD = Atrial Septum Defect

AVR = Aortic valve replacement

CHD = Congenital heart disease

CMR = Cardiac magnetic resonance

CONCOR = Dutch congenital corvita

ECG = Electro cardiogram

HRQOL= Health related quality of life

LVEF = Left ventricular ejection fraction

MVR = Mitral valve replacement

PPEC = Percentage of predicted exercise capacity

PROSTAVA = Prostheses in adult congenital heart valve disease

PVR = Pulmonary valve replacement

QOL = Quality of life

TAPSE = Tricuspid annular plane systolic excursion

TVR = Tricuspid valve replacement

VO_{2peak} = Maximum oxygen capacity

VO_{2pred} = Predicted maximum Oxygen

W_{peak} = Maximum workload

W_{pred} = Predicted workload

BSA = Body surface area

INTRODUCTION

Life expectancy of patients with congenital heart disease (CHD) has improved in the last decades. Currently, there are more adults than children with CHD.¹ With the improved survival of patients having undergone surgery for CHD, quality of life (QOL) becomes more and more important in this population.^{2,3} Literature has not been conclusive on the QOL of adults with CHD. Most studies conclude that adults with CHD have a reduced QOL on the physical domains as compared to the general population,⁴ although there are also studies suggesting that there is no reduction of QOL compared to the general population.⁵⁻⁷

Many patients with CHD require valve replacement(s) at a certain moment in time. Current studies on adults with CHD and a prosthetic valve generally focus on the medical outcome in terms of risk of reoperations, mortality, and long-term valve functioning. The implantation of a prosthetic heart valve and its consequences could very well influence the QOL, as patients with a prosthetic heart valve encounter specific problems for example: the need for anticoagulation, the expected problems for future pregnancies (women), and the anticipated reoperations for degenerated prosthetic valves.⁸ To our knowledge, data on QOL in adult patients with CHD and a prosthetic heart valve are lacking. The 2 valves that are replaced most frequently in the congenital cardiac population are the aortic and the pulmonary valves.⁹

The aim of this study is to evaluate the QOL in adult CHD patients with a history of valve replacement and to compare these results with previously reported results in the general population. In addition, we set out to investigate possible associations with QOL and the influence of valve position on QOL, using the PROSTheses in Adult congenital heart Valve disease (PROSTAVA) cohort.¹⁰

METHODS

Patient Population

Patients were selected from the PROSTAVA study (NTR2112). The PROSTAVA study has been designed as a cross-sectional observational study; in 2011, all patients over 18 years with a prosthetic heart valve registered in the Dutch CONgenital CORvitia (CON-

COR) database¹¹ were approached to participate in the PROSTAVA study. The rationale and design of the PROSTAVA study have been previously described.¹⁰ Briefly, data were retrospectively collected on demography and medical history by patient record. Data on echocardiography, cardiac magnetic resonance (CMR), blood testing, and exercise testing were collected as part of routine clinical care. Additionally, patients were asked to fill out a QOL questionnaire and a general questionnaire including questions about sport participation, educational level, and employment. The general questionnaire can be found in Supplementary file 1. Employment was self-defined by the patient according to the questions in the general questionnaire.

For this study, patients with a prosthetic valve in either the aortic valve position (AVR), pulmonary valve position (PVR), tricuspid valve position (TVR), or mitral valve position (MVR) that completed the QOL questionnaire were selected from the PROSTAVA cohort. Patients with congenital corrected transposition of the great arteries were classified as TVR. Patients who did not complete the QOL questionnaire were excluded. This study was approved by the ethical committees of all the participating centers (coordinating center University Medical Center Groningen). Informed consent was obtained from all patients.

QOL Questionnaire

QOL was measured as health-related QOL and was defined as the individuals' perceived effect of health status on multidimensional physical and mental well-being. To assess health-related QOL, we used the Dutch version of the Medical Outcome Study 36-item General Health Survey (RAND-36), comparable with the ShortForm36 (SF36).¹² The freely available RAND-36 was selected because of the available Dutch reference population. The RAND-36 is a self-administered, health-related QOL questionnaire. It consists of 36 questions of which 35 questions are divided into the following 8 domains of QOL: physical functioning (the extent to which physical activities are limited), physical role limitations (the extent to which physical health interferes with daily activities), bodily pain (the presence and intensity of pain and its effect on normal activities), general health (a person's evaluation of their health status), vitality (the extent to which one feels energetic), social functioning (the extent to which normal social activities are limited), emotional role limitations (the extent to which emotional problems interfere with daily activities), and mental health (general mental health problems). From the last question, a ninth domain on health change (change in health over the past year) can be calculated. Since patients in this study do not have a similar follow-up duration, we did not analyze this domain. RAND-36 scores were converted to the 8 domain scales ranging from 0 to 100 according published guidelines.¹² Higher scores on the domains indicate a better QOL. Patients were asked to fill in the questionnaire at home and return it through regular mail. QOL scores in our cohort were compared with the reference

scores from the Dutch manual of the RAND-36. The reference group consists of 1063 persons over 18 years of age, from the northern part of the Netherlands, with a mean age of 44.1(range 18_89) years.^{12,13}

Exercise Capacity Testing

Treadmill or an upright bicycle ergometer was used for the determination of exercise capacity, according to local routine clinical care protocol (Bruce, 10, 15 Watt program). After a short-unloaded warm-up period, workload was increased stepwise, based on age, sex, height, and weight aiming for an exercise duration of 6_8 minutes. Patients were permanently monitored with ECG, blood pressure, and oxygen saturation during the test. Symptoms onset prompted the end of the test. Achieved workload was determined as either the maximum oxygen capacity (VO₂peak [mL/min/kg]) or the maximum workload (W_{peak} [watts]), depending on the hospitals resources. Predicted exercise levels were calculated with the Wasserman/ Hansen equation for predicted maximum oxygen (VO₂pred) uptake,¹⁴ and for predicted workload (W_{pred}) as described by Ascoop et al.¹⁵ To evaluate exercise capacity, we used the percentage of predicted exercise capacity (PPEC). This was calculated by dividing the achieved exercise level by the predicted exercise levels.

Echocardiography

To determine left and right ventricular function, left ventricular ejection fraction (LVEF) and tricuspid annular plane systolic excursion were determined using routine 2- dimensional and M-mode echocardiography. When image quality was sufficient, LVEF (%) was measured using Simpson's rule. In order to take into account the function of the valve, valve regurgitation and peak gradient were evaluated. An obstructed aortic or pulmonary prosthetic valve was defined as a peak gradient ≥ 36 mm Hg over the pulmonary or aortic valve (ie, similar or more than moderate stenosis).¹⁶⁻¹⁸ Valvar regurgitation was quantified according to current guidelines into 4 classes: no regurgitation, mild, moderate, and severe regurgitation.¹⁶

Cardiac Magnetic Resonance Imaging

CMR imaging was performed for the assessment of ventricular stroke volume and ventricular ejection fraction for both ventricles. CMR protocols and acquisitions used for assessment of ventricular volume have been previously described by our group in detail.^{19,20}

Statistical Analysis

Normally distributed continuous variables are presented as means and standard deviations, not normally distributed continuous variables are presented as medians, inter

quartile ranges, and ranges. Categorical variables are presented in absolute numbers and percentages. The different subscales of the RAND-36 questionnaire are presented as means and standard deviations even if not normally distributed, to give a uniform representation of the data. The Dutch reference group on the RAND-36 was also reported in means and standard deviations.¹³ If patients had repeated valve replacements in one position, the last implanted valve was considered for analyses. A single sample t test against a hypothesized mean was used for the comparison with the Dutch reference group, since for the reference group only means and standard deviations were available. An independent sample t test was used to compare AVR and PVR patient groups. Dichotomous variables were compared using the Fisher's exact test. Ordinal variables were compared using the Mann-Whitney U test. The sample size of our studies allows the use of parametric testing, even though some of the parameters are skewed.^{21,22} Associations with QOL were determined for the entire cohort. Uni- and multivariable linear regression analyses were used to study the association between QOL subcategories and patient and valve characteristics. Variables were selected based on previous literature as well as reasonable influence on QOL, including educational level, interval between implantation and questionnaire, valve type, valve position (AVR, PVR, combined PVR and AVR), age, gender, number of sternotomies, sport activity, employment, PPEC, valve functioning, tetralogy of Fallot, aortic stenosis, Marfan syndrome, and NYHA class. MVR and TVR patients were not taken into account due to the limited number of patients in these groups. All variables that were associated on univariable analyses, with one of the outcome parameters with $P < 0.10$, were included in the multivariable analysis. Models were selected using backward elimination. Multivariable analysis was used to adjust for multiple factors that are highly correlated, including initial diagnosis and procedural group. A P value of <0.05 was considered significant. For all statistical analysis, IBM SPSS Statistics version 23 was used.

RESULTS

Baseline Characteristics

There were 385 CHD patients with a prosthetic valve included in the PROSTAVA study (Fig. 1). Sixty-one patients (15.8%) were excluded from this study because they declined to participate in the QOL study. Patients who did not participate in the QOL study were significantly younger (36.1 ± 9.9 years) and more female (68.9%) as the patients who did participate in the study. The study sample comprised 324 patients, including 127 AVR, 112 PVR, 46 PVR and AVR, 9 MVR and AVR, 16 MVR, 11 TVR, 2 TVR and PVR, and 1 PVR, AVR, and MVR patient who underwent their prosthetic heart valve surgery between May 1977 and December 2012. Mean age at study inclusion was 40.6 ± 11.9 years (range

19-70) and 35.8% was female (Table 1). In the total population, 53.6% of patients had a mechanical valve, although there were large differences between subgroups. In the AVR group mechanical valves were predominantly the valve of choice (88.7%), where in the PVR group, biological valves were predominantly used (only 13.9% mechanical valves). There were 5 patients (1.5%) with a transcatheter valve. There were 19 patients (5.8%) who had a biological valve prior to their current mechanical valve and 1 patient (0.3%) who had a mechanical valve prior to his current biological valve. For 88 patients (27.2%), the current valve was the result of a first thoracotomy. In Table 2, the functional parameters of this population are presented, showing an average LVEF of $54.6 \pm 8.6\%$. Comparison With the General Population As shown in Figure 2 and Table 3, patients with CHD and a prosthetic valve scored equally to the Dutch reference population on the following domains: physical functioning, physical role performance, and mental health domains. On the following domains, the CHD group scored lower than the reference population: general health, vitality, and the social functioning scale. In contrast, on the bodily pain domain, the CHD population scored significantly higher.

Figure 1, Flowchart of PROSTheses in Adult congenital heart VALve disease (PROSTAVA) inclusion. AVR, aortic valve replacement; PVR, pulmonary valve replacement; TVR, tricuspid valve replacement; MVR, mitral valve replacement; QOL, quality of life questionnaire.

Table 1 baseline characteristics

Variable	N
N	324
AVR	127 (39.2%)
PVR	112 (34.6%)
AVR, PVR	46 (14.2%)
MVR, AVR	9 (2.8%)
MVR	16 (4.9%)

Table 1 baseline characteristics (continued)

Variable	N
TVR	11 (3.4%)
TVR, PVR	2 (0.6%)
MVR, AVR, PVR	1 (0.3%)
Age at inclusion (years)	40.6 ± 11.9
Female	116 (35.8 %)
BSA (m2)	1.9 ± 0.2
Number of prior median sternotomies*	
0	88 (27.2%)
1	139(42.9%)
2	63 (19.4 %)
3	27 (8.3 %)
4	4 (1.2%)
5	3 (0.9%)
Age at last implantation(years)	29.3 ± 12.03
Follow-up since last implantation (years)	10.4 ± 7.2
Valve type (% mechanical valves)	173 (53.6 %)
cardiac diagnosis n (%)	
Aortic valvar stenosis	138 (42.6%)
Tetralogy of Fallot	74 (22.8%)
Marfan syndrome	27(8.3%)
Pulmonary Atresia	16(4.9%)
Pulmonary stenosis	14(4.3%)
Aortic subvalvar stenosis	5 (1.5%)
Transposition of the great arteries	5(1.5%)
CC Transposition of the great arteries	5 (1.5 %)
Truncus Arteriosus	5(1.5%)
Ebstein	5 (1.5 %)
Mitral stenosis	4 (1.2 %)
AVSD	8 (2.5%)
Other	20(3.7%)
Unknown	1 (0.9%)
Questionnaire Education n (%)	
University	92 (39.1 %)
Secondary school	95 (40.4 %)
Primary school	48 (20.4%)
Sport (%)	180 (76.6%)
Employed, studying or retired	179 (76.8%)

AVSD=Atrial Ventricular Septum Defect, BSA= Body Surface Area, sport => 1 hour a week of physical activity,

* = Number of median sternotomies before last valve implantation

Table 2 functional parameters

Echo		N(324)
LVEF (%)	54.6 ± 8.6	262
TAPSE (mm)	17.5 ± 4.1	277
Valve insufficiency (N (%))	32 (9.9 %)	274
Valve stenosis (N (%))	72 (28%)	257
MRI		
LV stroke volume(mL)	97.74±25.79	141
LVEF (%)	55.30±7.9	141
RV stroke volume(mL)	95.51 ± 24.62	141
RVEF (%)	48.12±9.2	141
Cardiopulmonary exercise testing		
PPEC (%)	82.75± 22.49	265
NYHA-class		234
NYHA-class I	157(67.4 %)	
NYHA-class II	61(26.2 %)	
NYHA-class III	14(6.0 %)	
NYHA-class IV	1(0.4%)	

RVEF=Right Ventricular Ejection Fraction, LVEF= Left Ventricular Ejection Fraction, TAPSE=Tricuspid annulus plane systolic excursion, PPEC=Predicted Percentage Exercise Capacity.

Figure 2, Quality of Life evaluated by the RAND-36 questionnaire. A comparison between Congenital Heart Disease (CHD) patients with a prosthetic heart valve and a reference sample of the Dutch population, n= 324, * P values<0.05.

Table 3 QOL scores compared between groups and the general population

	General population (GP) (n=1063)	CHD with prosthetic valve (n= 309)	GP- CHD p value
Physical functioning	81.9 ± 23.3	83.2 ± 20.6	0.2
Physical role performance	79.4± 35.5	77.0± 36.7	0.25
Bodily pain	79.5 ± 25.6	85.7± 20.4	<0.0001
General health	72.7 ± 22.7	60.14 ± 23.1	<0.0001
Vitality	67.4 ± 19.9	63.9± 20.5	0.002
Social functioning	86.9 ± 20.5	79.2 ± 24.3	<0.0001
Emotional functioning	84.1 ± 32.2	81.7± 34.0	0.2
Mental health	76.8 ± 18.4	78.1± 16.9	0.2

CHD; congenital heart disease

Associations With QOL

We found NYHA class ≥2 to be significantly associated in the multivariable model with all domains of the RAND-36 (Table 4). Increasing age was associated with worse physical functioning. Being male was positively associated with the social functioning domain.

Table 4 variables associated with QOL domains

	univariable		multivariable	
	B (95 % CI)	P value R ²	Adjusted R ² B (95 % CI)	P value
Physical functioning		0.58	0.57	
Current age	-0.54(-0.73 to -0.36)	<0.001	-0.49(-0.68 to -0.30)	<0.001
Sport (Y/N)	12.3 (5.88to 18.73)	<0.001	3.25(-1.5 to 8.01)	0.2
Mech valve	-5.6 (-10.1 to -1.1)	0.02		
Employment (Y/N)	21.17 (15.15 to 27.2)	<0.001	11.40 (6.45 to 16.44)	<0.001
NYHA ≥2	-19.69(-23.36 to -16.02)	<0.001	-14.1 (-18.72 to -9.47)	<0.001
PPEC	0.36(0.26-0.46)	<0.001	0.32(0.23 to 0.42)	<0.001
PVR	6.32 (1.6to 11.0)	0.016		
Physical role performance		0.30	0.28	
Current age	-0.62(-0.95 to -0.28)	<0.001		
AVR	-10.16(-18.33 to -2.0)	0.015	-9.3 (-18.5 to -0.1)	0.05
PVR	12.73 (4.37 to 21.10)	0.003		
Employment* (Y/N)	27.27(16.3 to 38.23)	<0.001	18.7 (7.59 to 29.81)	0.001
NYHA ≥2	-23.04 (-30.09 to -15.99)	<0.001	-29.5 (-39.36 to -17.44)	<0.001
PPEC	0. 37(0.19 to 0.56)	<0.001	0.23 (-0.027 to 0.43)	0.03
Bodily pain		0.30	0.27	
Current age	-0.32(-0.50 to -0.13)	0.001		

Table 4 variables associated with QOL domains (continued)

	univariable			multivariable		
	B (95 % CI)	P value	R ²	Adjusted R ²	B (95 % CI)	P value
Mech valve	-4.3 (-8.80 to 0.14)	0.058			5.33 (-0.59 to 11.25)	0.08
NYHA ≥2	-12.63 (-16.77 to -8.49)	<0.001			-20.17 (-25.52 to -14.82)	<0.001
Employment (j/n)	12.36 (5.9 to 18.82)	<0.001				
Sport (j/N)	5.96(-0.58 to 12.5)	0.07			-4.15 (-10.12 to 1.80)	0.2
PPEC	0.18(0.075 to 0.28)	0.001			0.17 (0.046 to 0.28)	0.007
AVR	-6.8 (-11.32 to -2.28)	0.003			-11.72(-17.83to -5.61)	<0.001
PVR	6.95 (2.32 to 11.59)	0.003				
General health			0.24	0.22		
Current age	-0.31(-0.52 to -0.10)	0.004			-0.24 (-0.52 to 0.05)	0.1
Employment (j/n)	18.18 (11.28 to 25.08)	<0.001			10.99 (3.46 to 18.52)	0.004
NYHA ≥2	-17.49(-23.62 to -11.35)	<0.001			-10.24 (-17.19to -3.29)	0.004
PPEC	0.30(0.18 to 0.42)	<0.001			0.26 (0.12 to 0.40)	<0.001
AVR&PVR	6.99 (-0.21 to 14.20)	0.057			4.38 (-3.71 to 12.48)	0.3
Vitality			0.20	0.18		
Current age	-0.232(-0.41 to -0.034)	0.02				
Gender (f=reference)	4.84 (0.17 to 9.51)	0.04				
Employment (j/n)	11.53(5.19 to 17.86)	<0.001			6.83 (-0.056 to 13.61)	0.05
Sport (j/N)	6.33(-0.085 to 12.75)	0.05				
NYHA ≥2	-16.33(-21.77 to -10.89)	<0.001			-13.41 (-19.42 to -7.39)	<0.001
PPEC	0.21(0.10 to 0.31)	<0.001			0.16 (0.035 to 0.28)	0.01
AVR	-4.08 (-8.67 to -0.50)	0.08			-3.83 (-9.44 to 1.78)	0.2
PVR	6.54 (1.86 to 11.2)	0.006				
Social functioning			0.30	0.28		
Current age	-0.31(-0.53 to -0.08)	0.007				
Gender(f=reference)	6.8 (1.2 to 12.24)	0.02			6.97(0.81 to 13.10)	0.03
Employment(j/n)	10.78 (3.13 to 18.44)	0.006				
NYHA ≥2	-22.14(-28.52 to -15.76)	<0.001			-18.01 (-24.65 to -11.38)	<0.001
PPEC	0.26(0.014 to 0.38)	<0.001			0.26 (0.12 to 0.39)	<0.001
Mech valve	-8.76 (-14.03to -3.49)	0.001				
PVR	13.19 (7.78 to 18.60)	<0.001			12.08 (5.54 to 18.62)	<0.001
Emotional functioning			0.063	0.053		
Employment (j/n)	14.03 (3.18to 24.88)	0.01			9.69 (-2.57to 21.95)	0.1
NYHA ≥2	-15.38(-25.00to -5.76)	0.002			-14.67 (-25.31 to -4.03)	0.07
PPEC	0.17 (-0.012 to 0.35)	0.07				
Mental health			0.059	0.0438		

Table 4 variables associated with QOL domains (continued)

	univariable			multivariable		
	B (95 % CI)	P value	R ²	Adjusted R ²	B (95 % CI)	P value
Gender (f =reference)	3.73(-0.13 to 7.59)	0.06			2.85 (-1.80 to 7.50)	0.2
Employment	5.17 (-0.13 to 10.47)	0.06			2.70 (-2.78 to 8.17)	0.3
NYHA ≥2	-7.44(-12.12 to -2.76)	0.002			-6.84 (-11.69 to -1.98)	0.006
AVR	-3.13(-6.92 to 0.66)	0.1			-2.51 (-7.02 to 1.20)	0.3

Variables in the multivariate analyses (with P <0.1 in univariable analyses), *employed, studying or retired, PPEC= predicted percentage exercise capacity

Employment status was positively associated with the physical functioning, physical role performance, vitality, and general health domains. Increase in PPEC was associated with better physical functioning, physical role performance, social functioning, vitality, bodily pain, and general health scores (Table 4). A prosthetic valve in the AVR position was significantly associated with lower scores on physical role performance and bodily pain compared to the CHD population. A prosthetic valve in the PVR position was associated with significantly higher scores on social functioning compared to the CHD population. For both emotional functioning and mental health, the created models only explained a very limited amount of the variance, respectively 6.3% and 5.9%. In the separate analyses, we found the diagnosis Marfan associated with poorer bodily pain scores (P = 0.05), in contrary, TOF was associated with higher bodily pain scores (P = 0.01).

Valve Position

The results from our multiple regression showed that valve position was of influence on QOL score. Interestingly, both AVR and PVR had significant associations with 1 or more particular QOL domains, and therefore we performed for these 2 largest groups an additional comparison. Baseline characteristics for both groups are reported in Supplementary Table 1. Comparison on functional parameters showed that the PPEC was significantly lower in the PVR group compared to the AVR group (P = 0.001). PVR patients showed worse left and right ventricular function, as well on echocardiography as on CMR data (Supplementary Table 2). The PVR group scored better on all subscales of the QOL questionnaire compared to the AVR group, but significance was reached only on physical functioning, physical role functioning, bodily pain, vitality, and social functioning. For the general health, emotional functioning, and mental health domains, no significant differences were observed. Compared with the general population, both groups reported a significantly lower general health. Additionally, the AVR group reported significantly lower scores on physical role performance, vitality, and social

functioning. The PVR group reported significantly higher QOL on physical functioning and bodily pain compared with the general population (Supplementary Table 3).

DISCUSSION

The lifespan of patients with CHD has increased drastically over the last decades, putting more emphasis on QOL of this group. The results of this study show that adult CHD patients with a prosthetic valve experienced the same QOL in the domains physical functioning, physical role performance and mental health domains, and significantly worse QOL in the domains general health, vitality, and social functioning scale, as compared to the Dutch reference population (Fig. 3). The most important but not surprising association with QOL measures was NYHA class, and exercise capacity and employment status, of which the first 2 reflect the importance of functional capacity. Variables that are somewhat unexpected related to aspects of QOL were age and gender. Valve position was also of influence on some aspects of QOL, which somewhat of a surprise.

Figure 3: Comparison of Quality of life between patients with congenital heart disease and a prosthetic heart valve and a reference group from the general population. Quality of life was evaluated using 8 domains of the RAND-36 questionnaire of. * = $p < 0.05$,

Comparison With the General Population

To our knowledge, there is a very limited amount of studies on the QOL of CHD patients with a prosthetic heart valve. Chen et al did describe the QOL (SF36/SF10) in a series of bio prosthetic pulmonary valve replacements; however, the number of participants was very limited as they only had 34 adults and 17 children returning the questionnaire.²³ In our study concerning the physical QOL domains (general health, bodily pain, physical functioning, physical role performance), patients did not experience a reduction in the bodily pain, physical functioning, and physical role performance but did experience a

reduced general health score. The QOL of the general CHD population has been studied before as described in a systematic review by Fteropoulli et al.⁴ The majority of studies described by Fteropoulli report a reduction in QOL in the physical function domain, whereas we found no difference. Furthermore, Fteropoulli described that only a small minority of studies reported a better QOL for bodily pain when compared to a reference population. A finding that was, replicated in our study. An explanation for this could lie in the fact that maximum age in our population was only 70 years. Bodily pain is likely to increase with increasing age. Where the majority of studies on the general CHD population, as well as the study by Chen et al report no difference on the psychosocial domains, our population has reported a reduced score on 2 (vitality and social functioning) of the psychosocial domains (mental health, vitality, emotional functioning, and social functioning). Most prominent is the reduced QOL on the social function domain, while from the CHD studies only 2 other studies described by Fteropoulli also reported a poorer QOL on this domain.⁴ However, when comparing studies concerning CHD caution is warranted, the CHD population is an exceedingly heterogeneous population.

Associations With QOL.

In accordance with previous literature, we found NYHA class to be associated with all domains of QOL.²⁴ In addition, the effect of age, employment status, and functional performance on the physical functioning domain has also been reported before.^{4,24,25} The effect of employment was possibly underestimated in our questionnaire, as both volunteer work and a regularly paid job were considered as employment. Although we describe a much younger population, our finding that valve type (mechanical vs biological) has no effect on all of the QOL domains is in line with previous research²⁶ We do have to recognize that valve type was very unequally distributed between valve positions.

Valve Position

Our multivariate analyses showed that AVR was negatively associated with bodily pain and physical role performance, whereas PVR was positively associated with higher social functioning scores. When comparing these 2 groups, PVR patients score equally or better on QOL compared to the AVR on most domains, while paradoxically PVR patients have a reduced ventricular function and exercise capacity. This could conceivably be explained by their more complex medical history. PVR patients usually have been receiving medical and surgical treatment all of their lives. Therefore, PVR patients likely require more frequent monitoring in the context of the expectation of repeated surgeries. For 47.2% of the AVR patients, this was their first procedure, in contrast only 1.8% of the PVR patients did not have a prior thoracotomy. It has also previously been reported that for AVR patients, the first surgery is usually at a later stage in life.²⁷ Probably, patients with a

PVR have had more time to adapt to their CHD by means of their coping skills, where for AVR patients the burden of the CHD often strikes suddenly at a more mature stage of life. Muller et al have previously reported that a “sense of coherence” was a strong predictor for QOL in adults with CHD, where “sense of coherence” was defined as a psychological resource of health and well-being. Patients with a strong sense of coherence perceived the world as predictable, manageable, and meaningful.²⁸ We speculate that patients with a PVR have a stronger sense of coherence, having had a longer time of adapting to the limitations of their CHD. It might well be that, due to their prolonged adaptation time, patients with a PVR have been able to substitute their functional limitations, as suggested by Ormel et al.²⁹ When, for example, considering diabetes mellitus type I, another chronic disease with frequent hospital contact at a young age, we see that also in this group QOL has not been reduced.³⁰ This supports our supposition that due to adaptation, QOL in a population with chronic disease is less compromised in their perception of QOL. As suggested by Moons and Norekva, developing a sense of coherence can improve the QOL in patients with CHD.³¹ Education and supporting patients on their CHD from an early stage in life could be beneficial for the development of stronger sense of coherence. Special attention should be paid to the education and mental preparation of patients who have their first surgical treatment in their adult life.

Limitations

First, since this study was a nonrandomized observational study and, due the retrospective design, the populations were not homogeneous. Randomized studies are very unlikely to be possible in the very heterogeneous CHD population. Second, although the RAND-36 questionnaire is used worldwide to assess general QOL, the questionnaire is not a disease-specific questionnaire for patients with CHD. However, to compare with the general population, a disease-specific questionnaire is not suitable. For further research, the addition of a disease-specific questionnaire in a longitudinal design will be the next step. Third, although this study was a multicenter study all centers were from the Netherlands. Moons et al have previously reported that Dutch patient reported outcomes are among the best worldwide.³² Therefore, we have to be careful when translating these results to other countries. Fourth, due to the relatively large sample size, small differences in QOL scores on the RAND-36 scale may be statistically significant but not clinically relevant. The minimal clinically important difference has been introduced as the minimal difference in scores that is clinically relevant. The minimal clinically important difference for the RAND- 36 is typically in the range of 3_5 points.³³ Finally, given the fact that the QOL was measured cross sectionally, we were not able to investigate changes over time. There was no control on the time between surgery and the time of answering the QOL questionnaire. Despite these limitations, our findings contribute to the knowledge on the well-being of patients with CHD a prosthetic heart valve.

CONCLUSION

Compared to the Dutch reference population, adult patients with CHD and a prosthetic cardiac valve experienced the same QOL (physical functioning, physical role performance, and mental health domains) but significantly worse QOL in the domains general health, vitality, and social functioning. Factors associated with QOL measures were age, sex, NYHA class, exercise capacity, employment status, and the position of the prosthetic valve. Health care professionals should be aware of these patterns in counseling patients.

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SUPPLEMENTARY TABLES

Supplementary table 1 baseline characteristics for AVR and PVR patients

Variable	AVR	PVR	p
N	127	112	
Age at inclusion (years)	45.9±10.7	34.2±9.3	<0.001
Fe Male	39(30.7 %)	44(39.3 %)	0.2
BSA (m2)	2.0±0.23	1.9±0.25	0.007
Number of prior median sternotomies*			
0	60 (47.2%)	2(1.8%)	
1	35(27.6%)	64(57.7%)	
2	20(15.7%)	31(27.9%)	
3	11(8.7%)	11(9.9%)	
4	0	2(1.8%)	
5	1(0.8%)	1(0.9%)	
Age at last implantation(years)	33.4±10.6	26.0±11.2	<0.001
Follow-up since last implantation (years)	11.0±8.1	8.2±5.8	0.01
Valve type (% mechanical valves)	112(88.2 %)	19(17.0 %)	<0.001
Aortic cardiac diagnosis n (%)			
Aortic valvar stenosis	87(68.5%)		
Marfan syndrome	25(19.7%)		
Aortic subvalvar stenosis	5(3.9%)		
Other	10(7.9%)		
Pulmonary cardiac diagnosis n (%)			
Tetralogy of Fallot		73(65.2%)	
Pulmonary stenosis		13(11.6%)	
Pulmonary Atresia		16(14.3%)	
Transposition of the great arteries		5(4.5%)	
Truncus Arteriosus		4(3.6%)	
other		1(0.9%)	
Questionnaire	N=101	N=63	
education n (%)			
University	46(44.6%)	23(36.5%)	0.3
Secondary school	35(34.7%)	29(46.0%)	0.2
Primary school	21(20.8%)	11(17.5%)	0.6
Sport (%)	74(73.3%)	50(79.4%)	0.3
Employed, studying or retired	73(72.3%)	55(88.7%)	0.02

ASD=Atrial Septum Defect, BSA= Body Surface Area, sport => 1 hour a week of physical activity, * = Number of median sternotomies before last valve implantation

Supplementary table 2 Functional parameters for AVR and PVR patients

	AVR	PVR	P
Echo	N=123/127	N=95/112	
LVEF (%)	57.3 ± 6.4	52.8 ± 8.3	<0.001
TAPSE (mm)	19.4 ± 3.8	15.6 ± 3.0	<0.001
Valve insufficiency (N (%))	2(1.6%)	16(17.8%)	<0.001
Possible valvar stenosis (N (%))	45(35.4%)	20(19.4%)	0.006
MRI	N=39/127	N=76/112	
LV stroke volume(mL)	105.6 ± 31.8	94.6 ± 20.9	0.02
LVEF (%)	57.5 ± 8.7	54.8 ± 6.5	0.09
RV stroke volume(mL)	98.5 ± 29.5	95.0 ± 22.1	0.4
RVEF (%)	52.8 ± 9.9	44.9 ± 8.0	<0.001
Cardiopulmonary exercise testing	N= 98/127	N=93/112	
PPEC (%)	89.7 ± 23.8	78.4 ± 19.9	0.001
NYHA-class	N=102/127	N=64/112	0.3
NYHA-class I	68(68.0%)	49(77.8%)	
NYHA-class II	31(31.0 %)	12(19.0 %)	
NYHA-class III	1(1.0 %)	2(3.2 %)	
NYHA-class IV	0(0%)	0(0%)	

RVEF=Right Ventricular Ejection Fraction, LVEF= Left Ventricular Ejection Fraction, TPASE=Tricuspid annulus plane systolic excursion, PPEC=Predicted Percentage Exercise Capacity

Supplementary Table 3 QOL scores compared between AVR and PVR and the general population

	General population (GP)	AVR	PVR	GP-AVR p value	PVR-GP p value	AVR-PVR p value
Physical functioning	81.9 ± 23.3	80.9 ± 21.6	86.9 ± 20.5	0.6	0.006	0.02
Physical role performance	79.4 ± 35.5	70.49 ± 40.9	84.6 ± 29.3	0.01	0.106	0.002
Bodily pain	79.5 ± 25.6	82.0 ± 23.2	89.9 ± 16.3	0.2	<0.0001	0.002
General health	72.7 ± 22.7	57.6 ± 23.4	61.7 ± 21.8	<0.0001	<0.0001	0.2
Vitality	67.4 ± 19.9	61.2 ± 20.9	67.7 ± 17.7	0.001	0.9	0.008
Social functioning	86.9 ± 20.5	78.4 ± 25.3	87.6 ± 17.6	<0.0001	0.7	0.001
Emotional functioning	84.1 ± 32.2	79.9 ± 35.3	84.7 ± 30.4	0.2	0.8	0.3
Mental health	76.8 ± 18.4	76.2 ± 17.7	79.9 ± 15.9	0.7	0.04	0.08

CHD; congenital heart disease, AVR; aortic valve replacement, PVR; pulmonary valve replacement

General

Discussion

In this thesis features of the prosthetic heart valve in the pulmonary position have been analyzed. Overall, we can conclude that the use of prosthetic valves in the pulmonary valve is suboptimal, while life expectancy increased and, in particular, the Quality of Life of patients with a pulmonary prosthetic valve does not seem to be affected. Both functionality of prosthetic valves in the pulmonary valve position as well as the outcome after pulmonary valve replacement are suboptimal when compared to aortic valve prosthesis.

Figure 1, Different types of prosthetic valve prosthesis.

In general, prosthetic valves can be divided into two fundamentally different groups: mechanical and tissue valves. Tissue valves can be further subdivided into aortic valve bioprostheses and allografts and a pulmonary bioprosthesis. As there is a general shortage of donor tissues, this also goes for donor cardiac valves, that have by far the best longevity of all possible prosthetic valves. In this study we focused on aortic valve bioprostheses that have been used in the pulmonary position due to the shortage of allografts. Both types of valves are associated with advantages and as well as disadvantages of different nature, making the choice of valve difficult for patients and doctors alike. Several overlapping developments have led to varying popularity of these valves. Historically, mechanical valves were used primarily, which require anti-coagulation. But despite the anticoagulation mechanical valves remain associated with valvar thrombosis, that leads to premature reoperations. With the advent of biological (or tissue) valves, mechanical valves became less popular, as tissue valves seemed to function better as thrombosis was less of a clinical feature. However, the introduction of thrombolysis altered this equation, resulting in surprisingly good results for mechanical prostheses

as compared to tissue prostheses. At the same time catheter-based tissue valve replacement rendered operation unnecessary, lowering the threshold for this type of therapy. As this therapy is often also possible within previously installed tissue prostheses (valve-in-valve) mechanical prostheses became more out of fashion.

Primarily we focused on mechanical valves, in order to analyze what the contemporaneous results are with this, currently somewhat contentious choice of prosthesis. We described the long-term functionality of mechanical heart valves in the pulmonary position in a large multicenter study in chapter 1. The unique size of the study with a total of 364 patients was realized by combining the results of seven world centers, presenting the most realistic evaluation of mechanical valves in the pulmonary position currently available.

One of the main arguments in favor of the usage of a mechanical valve is the reduced risk for reoperation as compared to biological options, particularly taking the successful advent of thrombolysis into account. We showed a freedom from reoperation of 97 % at 5 years and 91 % at 10 years post implantation. When compared to biological valves in the pulmonary position the 10-year freedom from re-operation rates are higher for mechanical valves than for the majority of studies reporting on biological valves ranging between 35% and 96%.¹⁻⁸ As young age has shown to influence tissue degeneration we did not compare with studies with predominantly children.

The major concerns for the use of mechanical valves in the pulmonary position has been the increased risk of valvar thrombosis and the impossibility of catheter bound tissue valve-in-valve implantation. We found a relatively linear incidence rate of valvar thrombosis of 1.7 % per patient year. This finding confirms the higher incidence of valvar thrombosis when mechanical valves are used in the pulmonary position as compared to reported incidence rates in aortic and mitral position, which vary between 0% and 0.6% per patient-year.²⁻⁶ Although one should always be cautious when comparing different populations, because in general patients that receive a pulmonary prosthetic valve are younger and have a more complex medical history, that could be associated with these findings.

One of the remarkable findings of this thesis was that thrombolysis of thrombosed mechanical valves in the pulmonary position was very successful with a success rate of 84.6 %. This finding offers new opportunities for the use of mechanical valves. However, this study did not evaluate the complications of thrombolysis. More long-term research in to the effect of thrombolysis in mechanical pulmonary valve replacement is necessary. This includes research into bleeding complications.

The higher incidence of valvar thrombosis for mechanical valves when used in the pulmonary positions as demonstrated formed the background to investigate the causes of this propensity for thrombosis. Bi-leaflet valves are currently the gold standard in mechanical valve design. In these bi-leaflet mechanical valves thrombosis usually

originates in the hinge region.⁷ Bileaflet mechanical heart valves have been designed in such a way that the hinges are washed free from micro-emboli in closed position during diastole in an aortic position. Therefore, we evaluated the influence of the transvalvar pressure gradient on the washout of the hinges of mechanical prosthetic valves under pulmonary pressure (10 mmHg) conditions in chapter 2.

We demonstrated that under pulmonary pressure conditions (10mmHg) hinge leakage of mechanical valves is approximately 25 % of the amount of hinge leakage under aortic conditions (80mmHg). And we found the relationship between pressure and regurgitant hinge flow to be logarithmic at pressures over 10 mmHg. For pressures below 10mmHg the relationship was found to be linear, implying that leakage flows over 10 mmHg are influenced by turbulence. We confirmed observations that the majority of leakage occurs through the hinges, however the design of the bileaflet valve also includes leakage through the minor gap between housing and leaflets (the periphery gap) and at the point where two leaflets touch each other in closed position (B-datum gap).⁸

Furthermore, we found a considerable difference in valve leakage between valve models in this study. However, we do not know if this difference influence the propensity for clot formation when used in the pulmonary position, as hinge washing is only one valve characteristic influencing valvar thrombosis.⁸ The design of the prosthesis could contain other features that influence its propensity for thrombosis. Previous studies have also demonstrated the hemodynamic properties of the valve to be of influence in the process of valvar thrombosis.⁹⁻¹¹ It is reasonable to assume that hinge washing is one of the important hemodynamics influencing mechanical prosthetic valve thrombosis.

Although similar research under pulmonary conditions has not been published, our findings in this study were in line with research in terms of differences between valvar models in the amount of valve leakage.¹² Jun et al. have performed very relevant research in the field of valvar thrombosis. They demonstrated that a large hinge gap was associated with increased washout and increased shear stresses for aortic valves.¹³ It is likely that for the pulmonary position an increased washout is preferred. As pressure differences in the pulmonary position are much lower the increase of shear stresses will most likely be limited.

These results led to the design of a new mechanical valve more suitable for the pulmonary position in chapter 3. The design has not been published in a peer reviewed journal, but has been patented by the University Medical Center of Groningen, and as thus is publicly available. The focus of this new design is the increasing the washout of the hinges of bi-leaflet mechanical valves to reduce valvar thrombosis under pulmonary pressure conditions. The design consists of a modification of the leaflets, consisting of indentations in the hinge region of the leaflets to allow for more blood flow through that very hinge region.

The design has been tested under static in-vitro conditions, and showed that it was possible to reach the level of hinge leakage of regular aortic bi-leaflet valves. One of the advantages of this model is the increased potential for turbulence due to the adjusted hinge geometry, that could be instrumental in cleaning the hinge of micro-clots. Due to the low-pressure conditions in the right ventricle the shear stresses are unlikely to become excessive and it is likely that the adjusted design will cause moderate turbulence. However further in vitro and in vivo evaluation of the design is necessary. The flow pattern through the hinges as well as the strength of the redesigned hinges should be evaluated. To evaluate further and validate the design testing under pulsatile cardiac simulations should be performed, followed by in-vivo animal experiments to demonstrate safety and effectiveness.

Mechanical valves currently are in a decreasing period of popularity, due to the increasing usage of catheter bound valve implantations. Manufacturers, therefore, are currently investing less into new mechanical valve prosthetic developments, such as ours. Hopefully medical fashion will take a course that does enable renewed interest into our patented pulmonary prosthesis.

Biological valves have been by and far the gold standard for adults receiving a pulmonary prosthetic valve. The pericardial Carpentier Edwards Perimount biological valves in the pulmonary position in a single center cohort of relatively young patients receiving a pulmonary valve replacement, showed remarkable results in chapter 4. Intuitively, one might presume that tissue valves fare better when less loaded by pressure stretch upon the leaflets. However, the opposite proves to be the case. Tissue valves in the pulmonary position do far worse than the same prosthesis in the aortic position. Therefore, we examined explanted tissue pulmonary valve prostheses, both macro- and microscopically to find clues as to the cause of these disappointing results.

We showed a remarkable stiffening and degeneration of all explanted and examined valves, and they all showed extensive fibrotic tissue deposits. The 5 and 10 year freedom from re-operation were comparable or better in this study compared to relevant literature.¹⁴⁻¹⁹ When the re-operation rates are compared with those found in mechanical valves the surprising observation is that at 5 year follow up post implantation differences are minimal with a freedom from re-intervention of 97 % for the mechanical valve study. At 10 years follow up freedom from re-intervention in chapter one was 91 % where in this study freedom from re-intervention was 83%. This confirms the longer lifespan of mechanical prosthetic valves also for the pulmonary position. Although the study by Nomoto et al. also found freedom from re-intervention rates for the Perimount valve in an adult pulmonary valve replacement to be 96.7 % both at 5 and 10 year follow-up.¹⁸

In this study we reported 2 successful valve-in-valve implantations in a failing Perimount valve. The option of trans catheter valve-in-valve implantation seems promising and has been reported in literature, but more long term results are needed to establish

the reliability and the target population.^{20,21} The obvious draw-back is that the inserted valve-in-valve prostheses are smaller than the valves they are inserted into, thus promising a potential cycle of increasing stenoses until the next operation.

Besides re-intervention we also looked at valve failure, since a smallish functioning pulmonary valve is often tolerated quite well and the timing of re-intervention in patients with pulmonary valve failure has seen much debate.²² Only reporting re-intervention rates would give a totally incomplete insight into the functionality of this valve. Longitudinal evaluations of valve failure have been scarce in literature. Lee et al. presented a time related analyses of the combined endpoint valve failure and dysfunction with a reported freedom from event of 92.2% at 5 year past implantation and 20.2% at 10 years past implantation. We found freedom from valve failure to be 65% at 5 years and 57% at 10 years follow-up. It should be kept in mind that only a relatively small sample of the population was observed.

The remarkable pattern of completely retracted and stiffened leaflets most likely caused by collagenous pannus overgrowth and myofibroblasts, combined with the high rates of valve failure and re-intervention, were some of the triggers to investigate these mechanisms further and under the controlled conditions of a hemodynamic laboratory in chapter 5.

The results of our laboratory study into the behavior of the Carpentier Edwards Magna Ease valve demonstrated that this valve behaves differently under pulmonary conditions as compared to the reference aortic condition. Most remarkable differences were an increase in closing time and a decrease in leakage duration. This means that under pulmonic conditions the valve takes longer to close and the time the valve spends in closed position is shorter. Our video observation of the leaflet motion showed another difference in closing behavior between aortic a pulmonic testing condition. Under pulmonic conditions valves did not completely close under the ambient diastolic pressures, whilst under the aortic pressures full closure was always attained. However, due to the low-pressure conditions in the right ventricle, it is not likely that this incomplete closure contributes to differences in regurgitant volume, but it could influence the long-term behavior of the prosthetic valve.

Although similar research has not been published, research has been done into the hemodynamic behavior of bioprosthetic valves under left ventricular conditions. In both in vitro and in vivo stetting the Carpentier Edwards Perimount valve has shown good overall hemodynamic characteristics.^{23–25} Several studies have reported on the opening and closing hemodynamics of bioprosthetic valves. In some cases increased opening and closing duration for pericardial valves as compare to porcine valves was reported.^{26,27} The study by Tasca et al. showed that the opening and closing behavior of pericardial prosthetic valves was influenced by the intrinsic structural characteristics of the material used for stents and leaflets.²⁸ The study by Bottio et al. showed that

the closing volume differs between valve models, where the Perimount valves showed lower closing volumes compared to other pericardial valves.²⁹

Our results indicate that the position of implantation in the heart influences the durability and hemodynamic behavior of pericardial prosthetic valves. Although we do not have the complete picture and the failing mechanism of prosthetic heart valves is most likely influenced by many factors, pressure difference is likely one of these factors. When speculating about a possible mechanism, the incomplete closure and the increased closing time could facilitate pannus overgrowth which could potentially lead to degeneration of the leaflet. Also, it is unclear if and how valvar size in the pulmonary position might influence lifespan of the prosthetic valve. In addition, it is necessary to realize that age probably is also a considerable influence in this failing mechanism. To define the mechanism of failing and find improved therapies, more research in this field is necessary. Interestingly enough both mechanical as tissue valve prostheses behave differently under low pressure than the pressure they have been designed for, which may not surprise if phrased in this way, but it shows that we have to look for alternatives specifically designed for the pulmonic position.

While doctors worry about the longevity of the prostheses deployed, the patient has to deal with daily life. Life expectancy for patients with congenital heart disease has improved in the last decades, resulting in more adults as children with congenital heart disease.³⁰ Together with the improved survival rates for patients undergoing surgery for congenital heart defect quality of life (QOL) becomes a key component for these patients.^{31,32} In chapter 6 we demonstrated that the QOL of adult congenital heart disease patients with a prosthetic heart valve was significantly lowered on the general health, vitality and social functioning domain compared to the Dutch reference population. For the physical functioning, physical role performance and mental health domain there was no significant difference in QOL compared to the general population.

There has been very limited research in to the QOL of this specific population. Our results were in line with the finding of Chen et al. they also found no reduction on the QOL domains bodily pain, physical functioning, physical role performance but did find a reduction in general health.³³ Although research on this specific population is limited the QOL of the general congenital heart disease population has frequently been described. Remarkable is the fact that we found a reduction on the vitality and social functioning domain, where the majority of studies did not report any differences in this area.³⁴

We found NYHA class to be associated with all domains of QOL in accordance with the study by Apers et al.³⁵ Although this is not a very remarkable finding it does validate the use of the NYHA class. It also confirms the connection between functional capacity and QOL. As could be expected we found associations between the physical functioning domain and age, employment status and functional performance as was also previously reported.^{34–36} Remarkably, in this study was the negative associations with bodily pain

and physical role performance for patients with an aortic valve replacement and the positive association for patients with a pulmonary valve replacement for social functioning. In the sub analyses of the comparison between aortic valve and pulmonary valve patients, pulmonary valve patients scored equally or better on most domains. In contrast their ventricular function was reduced as was their exercise capacity. An explanation for this remarkable finding could be the more complex medical history and consequently the more frequent monitoring and treatment of patients with a pulmonary valve replacement. They possibly had more time to adapt to the physical and mental effects of their condition where for patients receiving an aortic valve replacement first surgery is very often during adulthood.³⁷ One could speculate that due to the longer adaptation time patients with a pulmonary valve replacement are able to substitute their functional limitations, as suggested by Ormel et al.³⁸ It has been shown that coping skills can be developed in patients with congenital heart disease.³⁹ Education and supporting patients with congenital heart disease from an early stage in life could be beneficial for their QOL.

Future perspectives

With the research described in this thesis a contribution was made to the knowledge on prosthetic valves in the pulmonary position. The results in this thesis demonstrate that there is a need for a suitable valve for the pulmonary position, tailored to the physiological circumstances of the right ventricle and the young age of this population. Currently available valve types each have their own limitations that tend to be more prone in the pulmonary position. With the increased life expectancy of congenital heart disease patients, the need for a better functional pulmonary valve is evident. A mechanical valve could be a good solution for part of this population, further research into the treatment and prevention of thrombus formation would enhance the possibilities for the use of mechanical valves. Further research into the failing mechanisms of biological valves in the pulmonary position will hopefully lead to valves with a long-lasting potential in the pulmonary position. In the future the option of transcatheter valve replacement is likely to gain popularity in pulmonary valve replacement. Especially the option of valve-in-valve replacement can be an interesting option to reduce the number of thoracotomies and therefore reduce risks when re-operations are necessary. However also transcatheter valves probably face the same limited lifespan as surgical valves, furthermore there are indications for increased risk of endocarditis with the use of transcatheter valves.⁴⁰ One of the promising developments for pulmonary valve replacement is the use of tissue engineered biological valves. As tissue engineered valves often use the patient's own cells, it is likely that the life expectancy of these valves will be much better as compared to current biological valves. However, more research is needed and clinical trials have to be performed, there is still a long way until (long term) these therapies will be available for patients.⁴¹ Until these new technologies have been further developed, surgical valves will be the most suitable options for patients

with congenital heart disease and the need for a prosthetic heart valve in the pulmonary position. Where transcatheter valves can be an option to delay further surgeries.

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Summary

Within the last decade the life expectancy of people with congenital heart disease has increased, resulting in more patients with congenital heart disease reaching adulthood. A large portion of these patients has had valve replacement, most common are aortic and pulmonary valve replacement. The aortic and pulmonary valve have a similar appearance; however, the hemodynamic circumstances differ between positions. Where the left ventricle is a high-pressure system the right ventricle is a low pressure system. The difference in hemodynamic circumstances given an explanation for the fact that pulmonary valves are larger as aortic valves.

There are several options for surgical replacement of the pulmonary valve. However, except for the Medtronic Contegra valve, which is only suitable for small sizes, all other surgical prosthetic valves have not been designed for the pulmonary position. Research has shown that prosthetic valve replacement in the pulmonary position has a higher risk for valve failure as in the aortic position. In this thesis we aim to give insight in to prevalence, mechanisms and effect of pulmonary valve replacement.

Chapter 1

In chapter 1 we describe the medium- to long-term results of mechanical pulmonary valve replacement, with valvar thrombosis as primary endpoint. Thrombolysis, reoperation and death were chosen as secondary endpoints

We retrospectively collected data from seven medical centers in Barcelona (Spain), Graz (Austria), Groningen (the Netherlands), Munich (Germany), Rochester (USA), Seoul (Republic of Korea), and Tehran (Iran). This resulted in data on 364 patients with mechanical valves implanted in the pulmonary position between 1965 and 2014.

Results of this study showed a median follow-up duration of 4.26 (range 0-27) years and a mean age at implantation of $27.16 \pm$ (SD 12.2) years. With a subgroup of 69.8 % Tetralogy of Fallot was the most common primary cardiac diagnosis. Absence of valvar thrombosis was 91% (95%CI 87%-94%) at 5 years and 86% (95% CI 81%-91%) at 10 years post PVR. With a success rate up to 88%, thrombolysis appeared to be a successful therapy. Absence of reoperation was 97% (95% CI 94%-99%) at 5 years post PVR and 91% (95%CI 85%-95%) at 10 years.

In conclusion, mechanical pulmonary valve replacement is associated with a risk of valvar thrombosis. Thrombolysis has shown to be an effective treatment for valvar thrombosis, but not for every patient.

Chapter 2

In chapter 2 we looked at the effect of a pressure difference in valvar hinge washing of mechanical bi-leaflet prosthetic heart valves, as hinge washing plays a crucial role in the prevention of prosthetic valve thrombosis. We performed an in-vitro study to evaluate the relationship between pressure difference and the amount of valvar leakage in closed

position. Based on similarity in inner diameter (range 20.5 – 21.4 mm) we tested Abbott SJM Regent size 23, Cryolife On-X size 23, LivaNova Carbomedics-R size 25, Medtronic Open Pivot-A size 25.

The results of the test show a logarithmic relationship between pressure difference and valvar leakage, where leakage increases with an increasing pressure difference. The Medtronic M-OP showed the lowest leakage volume under pulmonary conditions with 0.125 ± 0.014 (L/min), the highest leakage volume was shown by the On-x valve with 0.254 ± 0.01 (L/min). Results showed that leakage under pulmonary diastolic pressure condition (10mmHg) was between 23.3% and 29.3 % of the leakage under aortic diastolic pressure conditions (80mmHg).

From this study we concluded that the washing of the hinges of mechanical bileaflet prosthetic heart valves is related to the transvalvar pressure gradient in closed position. There was a significant difference in valve leakage between valve models.

Chapter 3

In chapter 3 the design of a new mechanical valve for the pulmonary position has been described. In general patients requiring a pulmonary valve replacement are young patients with a form of congenital heart disease. Due to their longer lifespan mechanical valves can be an excellent option for this patient population. However, the limitation for the off-label use of current mechanical valve prosthesis is the increased risk of valvar thrombosis when used in the pulmonary position.

Research has shown that thrombus formation in mechanical valves in most cases originates from the hinges of the valve. Due to the lower pressure conditions we have demonstrated in chapter 2 that the washing of the hinges that prevents thrombus formation is much lower under pulmonary than under aortic pressure conditions.

Our design strategy for this new design was to improve hinge washing of the existing valve model design to allow for more flow through the hinges, which in term should wash them free from micro-emboli. The final design consists out of two versions applicable to all bi-leaflet mechanical valves. In this design the housing of the valve stays intact, only changes are made to the leaflet to facilitate an easy production process. In the presence of a cavity pivot hinge design each leaflet will have two additional spaces on each ear of the leaflet, so four spaces will be added to each leaflet, making a combined total of 8 spacings in the entire valve design. For the open pivot hinge one cavity was added to the leaflet, positioned at the hinge region.

From the final design in the presence of a cavity pivot hinge a functional prototype was produced and tested in an in-vitro setting. The results of these in-vitro testing showed that we were able to reach the same level of valve leakage as under aortic conditions. Further research and development is needed to optimize the design.

Chapter 4

In chapter 4 the clinical results of the Carpentier-Edwards (CE) Perimount valve in pulmonary position have been described. The Perimount valve is originally designed for use in the aortic or mitral position, where the valve has demonstrated excellent long-term results and is one of the most implanted valves. In this study we evaluated the Perimount valve in the pulmonary position.

All patients that had a Perimount valve implanted between 2003 and 2013 at the University Medical Center Groningen were included into this study. Primary endpoint of the study was re-intervention, defined as transcatheter or surgical intervention. Secondary endpoint was the occurrence of valve failure, defined as significant valvular regurgitation or stenosis.

We included 45 patients with a median age of 27.8 years of which 55.6 % were women. The mean follow-up in this study was 5.8 ± 3.3 years. The results of this study showed 7 re-interventions of which 5 were surgical and 2 were transcatheter valve-in-valve interventions. Freedom from re-intervention was respectively 95% (SE 4%) and 83% (SE 8%) at 5- and 10- years follow-up. The morphological evaluation of the explanted valves showed a similar pattern for all valves of stiffened and retracted leaflets with extensive fibrous tissue overgrowth and the presence of myofibroblasts. Freedom from valve failure was 65% (SE 8%) at 5-year follow-up and 57% (SE 10%) at 10-year follow-up.

The CE Perimount valve has adequately functioned in the pulmonary valve position at 5 years follow-up, after 10-year follow-up valve failure and re-interventions are common. Explanted valves show retraction and stiffening of the leaflets due to a fibrotic layer on both sides of the leaflet.

Chapter 5

In chapter 5 we describe the hemodynamic properties of the Carpentier Edwards (CE) Magna Ease valve under pulmonary conditions in an in-vitro test setting. The CE Perimount Magna Ease has frequently been used off-label in the pulmonary position. This valve is one of the most frequently used and successful tissue prosthetic heart valves. Literature on the hemodynamic properties of this valve in the pulmonary position has not been available.

A pulse duplicator (Edwards valve analyzer) was used to evaluate the hydrodynamic characteristics of a 21 mm and 25 mm CE Magna Ease valve. Testing was performed under different pulmonic pressure conditions; 15/5 mmHg, 28/11 mmHg, 73/32 mmHg and normal aortic pressure, 120/80 mmHg, as a reference. To analyze the closing behavior of the valve moving images were obtained using a Phantom MIRO M320S high-speed camera at 600 frames per second.

Results of these experiments showed that under normal pulmonic conditions (28/11 mmHg) the leakage orifice area was 0.020 ± 0.012 mm² for the 21mm and 0.054 ± 0.041

mm² for the 25mm valve ($p=0.03$). This implies that the valve does not reach full closure. Hydrodynamic characteristics of the valves differed between pulmonary and aortic testing condition. Remarkable was the increased closing time and reduced leakage duration, meaning the valve closes slower and spends less time in closed position. Valvar closing volumes were significantly lower under hypotensive and normal pulmonary conditions than under normal aortic conditions ($P<0.05$), most likely due to the low diastolic pressures.

In conclusion under normal pulmonary pressure conditions, the hydrodynamic characteristics of the CE Magna Ease valves were significantly different compared to aortic conditions. Further research is needed to determine if these results are associated with prosthetic valve failure.

Chapter 6

In chapter 6 we evaluated the Quality of Life (QOL) of patients with congenital heart disease (CHD). With the increased life expectancy of patients with congenital heart disease (CHD) and more patients reaching adulthood, the QOL of life of these patients becomes more important. Historically the focus has been on surgical morbidity, mortality and the function of the valve in studies evaluating valve replacement in CHD. In chapter 6 we studied the QOL of adult CHD patients with a prosthetic heart valve in a multi-center cross-sectional observational study of adults. To measure QOL the RAND-36 questionnaire (a health-related QOL questionnaire, with eight domains scoring from 0 to 100, higher scores indicate a better QOL) was used. Besides QOL also functional status was measured with exercise capacity testing. We used Uni- and multivariable linear regression was used to find associations with QOL in this patient population.

We included 324 patients with CHD and a prosthetic heart valve in this study. Of these patients 127 patients had a single aortic valve replacement and 112 a single pulmonary valve replacement. Mean age at study inclusion was 40.6 ± 11.9 years and the majority of the patients was male (64.2%). We found that our population scored significantly lower than the general population on the general health, vitality, and social functioning domains ($p<0.05$). On the bodily pain domain, they scored significantly higher (less pain) ($p<0.001$). Furthermore, we found associations for age, gender, exercise capacity employment status and valve position to various aspect of QOL. For all domains of QOL NYHA class was associated with a lower score, reflecting the importance of functional capacity.

This study showed that adult patients with CHD and a prosthetic valve have lower scores on the QOL domains general health, vitality, and social functioning as compared to the general population. Furthermore, NYHA class was negatively associated with all QOL domains. We would advise health care professionals to be aware of these patterns in counseling patients.

General discussion

The results in this thesis demonstrate that there is a need for a suitable valve for the pulmonary position, tailored to the physiological circumstances of the right ventricle and the young age of this population. Currently available valve types each have its own limitation that tend to be more prone in the pulmonary position. We have demonstrated that a mechanical prosthetic valve can be a suitable option for pulmonary valve replacement. Furthermore, we have demonstrated that the hemodynamic conditions in which the valve is placed influence the functionality of valve. Our results showed that the quality of life of congenital heart disease patients with a prosthetic valve is comparable to the general population. Overall, we can conclude that the use of prosthetic valves in the pulmonary valve is suboptimal, while life expectancy increases and in particular the Quality of Life of patients with a pulmonary prosthetic valve does not seem to be affected.

NEDERLANDSE SAMENVATTING

In het voorbije decennium is de levensverwachting van mensen met aangeboren hartaandoeningen verder toegenomen, waardoor steeds meer patiënten de volwassen leeftijd bereiken. Een groot deel van deze patiënten heeft een klepoperatie ondergaan, waarbij de meest frequente vervangingen van aorta- en/of pulmonaal klep zijn. De aorta- en pulmonaal klep lijken in anatomische zin weliswaar veel op elkaar, maar de haemodynamiek waarin zij functioneren verschilt aanmerkelijk tussen beide kleppen. Het meest in het oog springende verschil bestaat uit de druk die in de linkerventrikel hoger is dan in de rechterventrikel. Dit drukverschil verklaart dat pulmonaalkleppen van nature een grotere diameter hebben dan aortakleppen (wet van Poiseuille).

Voor de chirurgische vervanging van de pulmonaal klep bestaat geen speciaal daarvoor ontworpen klepprothese, vanwege het veel geringere voorkomen van vervanging daarvan in vergelijking met de aortaklep. Menselijke donor-pulmonaalkleppen hebben de beste prognose op lange termijn, maar de beschikbaarheid daarvan is beperkt, waardoor er ook klepprothesen gebruikt moeten worden. De enige uitzondering daarop bestaat uit de Medtronic Contegra® klep, die wordt gemaakt van een klephoudende vena jugularis van een rund en die alleen beschikbaar zijn in kleinere afmetingen. Alle andere chirurgische klepprothesen die in de pulmonalis positie worden gebruikt zijn ontwikkeld voor de aorta of mitraal positie. Deze kleppen worden daarmee “off label” gebruikt voor pulmonaal klep vervanging, hetgeen wil zeggen dat de fabrikant daarvoor een beperkte verantwoordelijkheid neemt. Onderzoek heeft aangetoond dat klepvervanging in de pulmonaal positie een hoger risico geeft op falen dan in de aortapositie, hetgeen opgaat voor zowel mechanische als weefselkleppen. In dit proefschrift wordt inzicht gegeven in de prevalentie, mechanismen en het effect van pulmonaal klep vervanging.

Hoofdstuk 1

In hoofdstuk 1 wordt de middellange en lange termijn resultaten beschreven van mechanische pulmonaal klep vervanging met klep-trombose als primair eindpunt. Trombolysie, heroperatie en overlijden werden gekozen als secundaire eindpunten

We hebben retrospectief gegevens verzameld van zeven medische centra die daarover al gepubliceerd hadden: Barcelona (Spanje), Graz (Oostenrijk), Groningen (Nederland), München (Duitsland), Rochester (VS), Seoul (Republiek Korea) en Teheran (Iran). Dit resulteerde in gegevens over 364 patiënten met een mechanische klep geïmplantéerd in de pulmonaal positie tussen 1965 en 2014, hetgeen de grootste serie is tot nu toe.

Resultaten van deze studie toonden een mediane follow-up duur van 4,26 (van 0 tot 27) jaar en een gemiddelde leeftijd bij implantatie van $27,2 \pm 12,2$ jaar. Tetralogie van Fallot (69.8%) was de meest voorkomende primaire cardiale diagnose. Vrijheid

van klep-trombose was 91% (95% CI 87% -94%) na 5 jaar en 86% (95% CI 81% -91%) 10 jaar na mechanische pulmonaal klep vervanging. Met een slagingspercentage tot 88% lijkt trombolysen een succesvolle therapie voor mechanische pulmonaal klep-trombose. Vrijheid van reoperatie was 97% (95% CI 94% -99%) na 5 jaar en 91% (95% CI 85% -95%) 10 jaar na pulmonaal klep vervanging.

Concluderend, is mechanische pulmonaal klep vervanging geassocieerd met een hoger risico op klep-trombose dan in de aortapositie. Trombolysen is een effectieve behandeling gebleken voor pulmonaal klep-trombose, maar niet geschikt voor elke patiënt, vanwege de noodzakelijke anticoagulantia.

Hoofdstuk 2

In hoofdstuk 2 hebben we gekeken naar het effect van drukverschillen op het schoonspoelen van de scharnieren van mechanische “bi-leaflet” klepprothesen, omdat dit schoonspoelen van de scharnieren een cruciale rol speelt in de preventie van kleptrombose. Door middel van een in vitro test-opstelling is het verband tussen het drukverschil en de hoeveelheid klep lekkage in gesloten stand gemeten. Op basis van vergelijkbare binnendiameter (bereik 20,5 - 21,4 mm) hebben we de Abbott SJM Regent maat 23, Cryolife On-X maat 23, LivaNova Carbomedics-R maat 25, Medtronic Open Pivot – A maat 25 getest en vergeleken.

De resultaten van de studie laten een logaritmische relatie zien tussen drukverschil en klep-lekkage, waarbij lekkage toeneemt met een toenemend drukverschil. De Medtronic M-OP vertoonde het laagste lekvolume onder pulmonale druk omstandigheden met $0,125 \pm 0,014$ (L/ min), het hoogste lekvolume werd getoond door de On-X-klep met $0,254 \pm 0,01$ (L/ min). De resultaten toonden aan dat klep lekkage volume onder diastolische pulmonaal drukomstandigheden (10mmHg) tussen 23,3% en 29,3% was van het lekvolume onder diastolische aorta drukomstandigheden (80mmHg).

Uit deze studie concludeerden we dat het schoonspoelen van de scharnieren van mechanische bi-leaflet hartklep-prothesen gerelateerd is aan de drukgradiënt over de klep in gesloten positie. Daarnaast is er een significant verschil in kleplekkage tussen de verschillende klepmodellen.

Hoofdstuk 3

In hoofdstuk 3 is het ontwerp van een nieuwe mechanische klep voor de pulmonaal positie beschreven. Over het algemeen zijn patiënten die een pulmonaal klep vervanging nodig hebben jonge patiënten met een aangeboren hartafwijking. Vanwege hun langere levensduur kunnen mechanische kleppen een uitstekende optie zijn voor deze patiëntenpopulatie. De beperking voor het huidige off-label gebruik van mechanische klepprothese is het verhoogde risico op klep-trombose bij gebruik in de pulmonaal positie. Onderzoek heeft aangetoond dat thrombusvorming in mechanische kleppen in

de meeste gevallen ontstaat in de scharnieren van de klep. In hoofdstuk 2 hebben we aangetoond dat vanwege de lagere drukomstandigheden het schoonspoelen van de scharnieren ter voorkoming van thrombusvorming veel lager is onder pulmonale druk omstandigheden vergeleken met aorta drukomstandigheden.

Onze ontwerpstrategie voor dit nieuwe ontwerp was het verbeteren van het schoonspoelen van de scharnieren van de bestaande klep-modellen, dusdanig dat er meer stroming door de scharnieren mogelijk is en hiermee de vorming van micro-emboli voorkomen wordt. Het uiteindelijke ontwerp bestaat uit twee uitvoeringen voor alle bi-leaflet mechanische kleppen. In dit ontwerp blijft de behuizing van de klep intact, alleen worden wijzigingen in de klepbladen aangebracht om een eenvoudig productieproces te vergemakkelijken. Voor kleppen met een "cavity pivot" ontwerp wordt in het oor van elk blad twee extra uitsparingen gemaakt, in totaal worden er 4 uitsparingen per blad toegevoegd, dit resulteert in een totaal van 8 uitsparingen voor het gehele klepontwerp. Voor kleppen met een "open pivot scharnier" werd één holte toegevoegd aan het klepblad, gepositioneerd in het scharniergebied.

Van het uiteindelijke ontwerp in aanwezigheid van een cavity pivot scharnier is een functioneel prototype geproduceerd en getest in een in vitro omgeving. De resultaten van deze in-vitro test toonden aan dat we in staat waren om hetzelfde niveau van kleplekkage te bereiken als onder aorta-omstandigheden. Verder onderzoek en ontwikkeling zijn nodig om het ontwerp te optimaliseren.

Hoofdstuk 4

In hoofdstuk 4 zijn de klinische resultaten van de Carpentier-Edwards (CE) Perimount-klep in pulmonale positie beschreven. De Perimount klep is oorspronkelijk ontworpen voor gebruik in de aorta- of mitraal positie, waarbij de klep uitstekende lange termijn resultaten heeft laten zien en is een van de meest geïmplanteerde kleppen. In deze studie hebben we de Perimount-klep in de pulmonaal positie geëvalueerd.

Alle patiënten die een Perimount-klep hadden geïmplantiseerd gekregen tussen 2003 en 2013 in het Universitair Medisch Centrum Groningen werden opgenomen in deze studie. Het primaire eindpunt van de studie was her-interventie, gedefinieerd als transkatheter of een chirurgische ingreep. Secundair eindpunt was het optreden van klep falen, gedefinieerd als significante klep regurgitatie of stenose.

In de studie zijn 45 patiënten geïnccludeerd met een mediane leeftijd van 27,8 jaar, waarvan 55,6% vrouwen. De gemiddelde follow-up in deze studie was $5,8 \pm 3,3$ jaar. De resultaten van deze studie toonden 7 her-interventies waarvan 5 chirurgisch en 2 transkatheter klep-in-klep interventies. Vrijheid van her-interventie was respectievelijk 95% (SE 4%) en 83% (SE 8%) na een follow-up van 5 en 10 jaar. De morfologische beoordeling van de geëxplanteerde kleppen vertoonden een soortgelijk patroon voor alle kleppen, waarbij verstijfde en geschrompelde klepbladen te zien waren met uitgebreide

fibrotisch weefsel-overgroei en de aanwezigheid van myofibroblasten. Vrijheid van klep falen was 65% (SE 8%) na 5 jaar follow-up en 57% (SE 10%) na 10 jaar follow-up, hetgeen veel geringer is dan de resultaten in de aortapositie.

De CE Perimount functioneert naar behoren in de pulmonaal klep positie bij 5 jaar follow-up, na 10 jaar follow-up zijn klep falen en re-interventies gebruikelijk. Geëxplanteerde kleppen tonen terugtrekking en verstijving van de klep bladen door een fibrotische laag aan beide zijden van het blaadje.

Hoofdstuk 5

In hoofdstuk 5 beschrijven we de hemodynamische eigenschappen van de Carpentier Edwards (CE) Magna Ease-klep onder pulmonale omstandigheden in een in-vitro testomgeving. De CE Perimount Magna Ease wordt vaak off-label gebruikt in de pulmonaal positie. Deze klep is een van de meest gebruikte en succesvolle biologische hartklep protheses. Literatuur over de hemodynamische eigenschappen van deze klep in pulmonaal klep positie is niet gepubliceerd.

Een pulsuplicator (Edwards-klep-analysator) werd gebruikt om de hydrodynamische eigenschappen van CE Magna Ease-kleppen van 21 mm en van 25 mm te evalueren. Experimenten werden uitgevoerd onder verschillende pulmonaal druk omstandigheden; 15/5 mmHg, 28/11 mmHg, 73/32 mmHg en normale aortadruk, 120/80 mmHg, als referentie. Om het sluitgedrag van de klep te analyseren, werden bewegende beelden verkregen met een Phantom MIRO M320S hogesnelheidscamera met 600 frames per seconde.

De resultaten van deze experimenten toonden aan dat onder normale pulmonaal condities (28/11 mm Hg) de lekkage opening $0,020 \pm 0,012 \text{ mm}^2$ was voor de 21mm klep en $0,054 \pm 0,041 \text{ mm}^2$ voor de 25mm klep ($p = 0.03$). Dit impliceert dat de klep niet volledig wordt gesloten. Hydrodynamische kenmerken van de kleppen verschilden tussen pulmonaal- en aorta testomstandigheden. Opvallend was de langere sluitingstijd en kortere lekkage duur, wat betekent dat de klep langzamer sluit en minder tijd in gesloten positie doorbrengt. Klep sluit volumes waren significant lager onder hypotensieve en normale pulmonaal omstandigheden dan onder normale aorta omstandigheden ($P < 0,05$), waarschijnlijk vanwege de lage diastolische druk.

Concluderend waren de hydrodynamische eigenschappen van de CE Magna Ease-kleppen aanzienlijk anders onder normale pulmonale drukcondities dan onder normale aorta omstandigheden. Verder onderzoek is nodig om te bepalen of deze resultaten verband houden met het falen hartklep protheses in de pulmonaal positie.

Hoofdstuk 6

In hoofdstuk 6 hebben we de kwaliteit van leven van patiënten met aangeboren hartafwijkingen geëvalueerd. Met de hogere levensverwachting van patiënten met

congenitale hartziekte en meer patiënten die de volwassen leeftijd bereiken wordt de kwaliteit van leven van deze patiënten steeds belangrijker. Historisch gezien lag de nadruk op chirurgische morbiditeit, mortaliteit en de functie van de klep in onderzoek naar klepvervangings bij congenitale hartziekten. In hoofdstuk 6 hebben we de kwaliteit van leven bestudeerd van volwassen patiënten met een congenitale hartafwijking en een klepprothese in een multicenter cross-sectionele observationele studie van volwassenen. Kwaliteit van leven is gemeten met de RAND-36 vragenlijst (een gezondheid gerelateerde kwaliteit van leven vragenlijst met acht domeinen en scores tussen 0-100, hogere scores geven een betere kwaliteit van leven). Naast kwaliteit van leven werd ook de functionele status gemeten door middel van een inspanningstest. We gebruikten Uni- en multivariabele lineaire regressie om associaties met QOL te vinden in deze patiëntenpopulatie.

We namen 324 patiënten met CHZ en een prothetische hartklep in deze studie op. Van deze patiënten hadden 127 patiënten een enkele aortaklepvervangings en 112 een enkele pulmonaalklepvervangings. De gemiddelde leeftijd bij studie-inclusie was $40,6 \pm 11,9$ jaar en de meerderheid van de patiënten was man (64,2%). We vonden dat onze populatie significant lager scoorde dan de algemene populatie op de domeinen algemene gezondheid, vitaliteit en sociaal functioneren ($p < 0,05$). Op het lichaamsspijn domein scoorden ze significant hoger (minder pijn) ($p < 0,001$). Verder vonden we associaties voor geslacht, inspanningscapaciteit, arbeidsstatus en kleppositie bij verschillende aspecten van QOL. Voor alle domeinen van de QOL werd NYHA-klasse geassocieerd met een lagere score, wat het belang van functionele capaciteit weerspiegelt.

Deze studie toonde aan dat volwassen patiënten met een congenitale hartafwijking en een klepprothese lagere scores hebben op de kwaliteit van leven domeinen; algemene gezondheid, vitaliteit en sociaal functioneren in vergelijking met de algemene bevolking. Verder was de NYHA-klasse negatief geassocieerd met alle QOL-domeinen. Op Basis van deze resultaten wordt zorgverleners geadviseerd om zich bewust zijn van deze patronen bij de voorlichting en begeleiding van patiënten.

Algemene Discussie

De resultaten in dit proefschrift tonen aan dat er behoefte is aan een geschikte klep voor de pulmonaal positie, afgestemd op de fysiologische omstandigheden van de rechter hartkamer en de jonge leeftijd van deze populatie. Momenteel beschikbare kleptypen hebben elk hun eigen beperking die de neiging hebben meer prominent te zijn in de pulmonaal positie. We hebben aangetoond dat een mechanisch klepprothese een geschikte optie kan zijn voor vervanging van de pulmonaal klep, ondanks de hogere kans op klep-trombose, omdat deze goed behandeld kan worden met trombolytica. Verder hebben we laten zien dat de hemodynamische omstandigheden waarin de klep wordt geplaatst de functionaliteit van de klep beïnvloeden. Kleppen die ontworpen zijn voor

de aortapositie functioneren in de praktijk veel minder goed in de pulmonaal-positie. Onze resultaten toonden aan dat de kwaliteit van leven van patiënten met aangeboren hartafwijkingen met een klepprothese op sommige aspecten lager is vergeleken met de algemene bevolking. Al met al kunnen we concluderen dat het gebruik van prothese-kleppen in de pulmonaal-positie suboptimaal is, terwijl de levensverwachting toeneemt en met name de levenskwaliteit van patiënten met een pulmonaal klepprothese niet lijkt te worden beïnvloed.

CURRICULUM VITAE

Hanna Pragt was born on march 3th in Smallerland, The Netherlands. She finished secondary school in 2006 at the Drachtster Lyceum in Drachten. Hereafter she started the bachelor life science and technology, with a specialization in biomedical engineering at the University of Groningen. In 2013 she completed a senior internship was followed at LivaNova, Saluggia, Italy on the production of heart valve prosthesis and graduated from the master biomedical engineering at the University of Groningen.

In 2013 she started her PhD project at the thoracic surgery department of the University Medical Center Groningen, resulting in this thesis. In 2018 she started as a project coordinator for innovative project in medical device production at UMACOBV. Since April 2019 she works as medical technology coordinator for Treant care group advising the board of directors on the use of medical technology in both hospitals and care centers.

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Patent, mechanical heart valve for the right ventricle

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(54) **MECHANICAL HEART VALVE PROSTHESIS FOR THE RIGHT VENTRICLE**

MECHANISCHE HERZKLAPPENPROTHESE FÜR DAS RECHTE VENTRIKEL PROTHÈSE DE VALVE CARDIAQUE MÉCANIQUE POUR LE VENTRICULE DROIT

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DESCRIPTION

FIELD AND BACKGROUND OF THE INVENTION

- [0001] The present invention relates to mechanical heart valve prostheses. Mechanical heart valve prostheses generally operate hemodynamically, in conjunction with the pumping action of the heart, to take the place of a defective natural valve. These valves have generally been designed to function with one or more occluders each swiveling to open and close a passageway through a generally annular valve body within which the occluders are suspended.
- [0002] Pyrolytic carbon has been determined to be adequately non thrombogenic for use as a heart valve material. The problem of combatting thrombosis in mechanical valves is presently felt to lie in preventing excess turbulence, high shear stresses and local regions of stasis. Blood is a very delicate substance, and even minor abuses caused by turbulence and high shear stress can cause either thrombosis or emboli generation at local regions of stagnation. Regions of the valve that are particularly susceptible to the formation of thrombosis are the areas where the leaflets are pivotably suspended.
- [0003] U.S. patent 5,861,029 discloses a mechanical heart valve according to the introductory portion of claim 1 and according to the introductory portion of claim 2. The disclosed heart valve has two projections at each side of each leaflet, one projection of each pair of projections being located above a rim in the valve body passageway and the other one of each pair of projections being located below the rim, so that the rim between the projections of each pair holds the pivotable leaflets in the valve body passageway. Slots in the valve leaflets leave open passageways to the outside of the pivoting area of the leaflets when the leaflets are closed.
- [0004] U.S. patent 5,354,330 discloses a mechanical heart valve with a valve body having an interior wall surface with knobs cooperating with recesses in the side edge of said leaflet for keeping the leaflets in position, also during pivoting between the closed and open positions.
- [0005] A valve with particularly low propensity of causing thrombosis is disclosed in U.S. patent 5,641,324 (embodiments of this valve have been approved by the U.S. Food and Drug Administration for usage with particularly low dosages of anticoagulants in the aortic position). The valve has a pivot arrangement with two pairs of diametrically opposed pivot member sets each formed by an ear projecting laterally from the side edges of the leaflet and a cavity in the interior surface of its valve body, each ear projecting into one of the cavities. The ears are shaped to allow some regurgitant flow around the ears when the leaflets are closed.
- [0006] U.S. patent 6,296,663 discloses a mechanical bi-leaflet valve in which the leaflets each have ears projecting into mutually opposite recesses in the annular body. In this valve, the leaflets have notches allowing some regurgitant flow along the ears when the leaflets are closed.
- [0007] These mechanical valves are specifically designed for implantation in the left ventricle. Maximum pressure drops (pressure differences between locations immediately upstream and downstream of the valve or occluders thereof) over the closed cardiac valve in the right ventricle are typically about eight times smaller than over the closed cardiac valve in the left ventricle. Accordingly, when a mechanical heart valve prosthesis is implanted in the right ventricle the flow through the valve hinges when the valve leaflets are in the closed position is much smaller than when the same valve would have been implanted in the left ventricle. This lower flow through the valve hinges is a probable cause for a higher incidence of clots originating from the valve hinge areas in mechanical heart valve prostheses in the right ventricle than in mechanical heart valve

prostheses in the left ventricle. For this reason, mechanical prosthetic heart valves have not been popular for implantation in the right ventricle. However, the generally less thrombogenic alternatives of allograft (homograft) and biological heart valve prostheses have a much shorter lifetime than mechanical heart valve prostheses. This disadvantage is often exacerbated when the heart valve prosthesis is applied as a right ventricle heart valve prosthesis, because many diseases resulting in a need of a right ventricular heart valve prosthesis are innate diseases, so that patients receiving a first right ventricular heart valve prosthesis, often have a life expectancy that is a multiple of the lifetime of an implanted allograft (homograft) or biological heart valve prosthesis and therefore can expect to require multiple heart valve replacements, each involving heart surgery or delivery via a catheter and each preceded by a period of relatively poor performance of the heart valve prosthesis approaching its end of lifetime.

SUMMARY OF THE INVENTION

- [0008]** It is an object of the present invention to provide a mechanical heart valve prosthesis that is particularly suitable for use as a right ventricular heart valve prosthesis.
- [0009]** According to the invention, this object is achieved by providing a prosthetic heart valve according to claim 1 or 2.
- [0010]** The leaflet passageways through the ear or through the recess of each pivot member set allow flow through that ear and the associated cavity or through that recess when the leaflets are in the closed positions. Thus, a particularly effective flushing is concentrated in areas around the pivot axes of the leaflets, where the leaflets are suspended continuously and move relatively little as the leaflets move between open and closed positions, so the risk of formation of thrombosis would otherwise be relatively high. Moreover, this effect is of particular relevance at the low maximum pressure drops over a closed heart valve occurring in the right ventricle.
- [0011]** Further features, effects and details of the invention appear from the detailed description and the drawings. BRIEF DESCRIPTION OF THE DRAWINGS 5 [0012] Fig. 1 is a perspective view of an example of a heart valve according to the present invention with leaflets 10 in an open position; Fig. 2 is a sectional view along the line II-II of Fig. 1, but with a suture ring attached to the valve; Fig. 3 is a vertical sectional view along line III-III of Fig. 2, one leaflet half being of a first embodiment 15 and the other leaflet half being of a second embodiment; Fig. 4 is a view similar to Fig. 2, but with the leaflets in closed positions and the suture ring omitted; Fig. 5 is a fragmentary sectional view taken generally 20 along line V-V of Fig. 8; Figs. 6 and 7 are fragmentary horizontal sectional views taken respectively along the lines VI-VI and VII-VII of Fig. 2, the leaflets being omitted; Fig. 8 is a combination of fragmentary sectional views taken along the lines VII-VII of Fig. 2 (left half of Fig. 8) and Fig. 4 (right half of Fig. 8); Fig. 9 is a plan view of a leaflet, one half of which is of the first embodiment and the other half of which is of the second embodiment; 30 Fig. 10 is a perspective view of the leaflet embodiments of Fig. 9; Fig. 11 is a side elevation view of the leaflet embodiments of Figs. 9 and 10; Fig. 12 is sectional side view through line XII-XII in 35 Fig. 3, but with a right leaflet omitted and left leaflets in fully closed position; Fig. 13 is a cross-sectional side view of another example of a valve according to the invention; and Fig. 14 is a cross-sectional view along line XIV-XIV 40 in Fig. 13.

DETAILED DESCRIPTION

[0013] Figs. 1-12 show an example of a prosthetic heart valve 11 according to the present invention and a variant thereon, both examples being of a basic design as disclosed in U.S. patent 5,641,324, but with modifications. Heart valve 11 includes a generally annular valve body 13 which carries a pair of pivoting occluders or leaflets 15 that alternately open and close either to allow, when in open positions (Figs. 1-3 and the left half of Fig. 8), the smooth flow of blood in the downstream direction, as indicated by the arrow A in Fig. 2, or to prevent, when in the closed positions (Figs. 4, 5, and 12 and the right half of Fig. 8) substantial backflow of blood, i.e. regurgitation. The valve body 13 defines a valve body passage-way bounded by its generally arcuate, mostly cylindrical interior wall surface 17. The valve body 13 has a curved entrance region 19 at its upstream end, which has been found to substantially increase streamlined flow characteristics through the valve with low turbulence and substantially no generation of thrombosis. A pair of diametrically opposed, thickened wall sections 21 protrude inward from an otherwise circular cylindrical surface, creating what is referred to as a tabulated cylindrical surface as a result of the thickened sections 21 terminating in facing, parallel flat wall surfaces 23 in which cavities 25 are formed that each function as one-half of a pivot member set which pivot member sets guide the opening and closing movements of the leaflets 15. Otherwise, the interior surface downstream of the curved entrance region 19 is generally rectilinear in axial direction of the passageway through the valve body 13.

[0014] The exterior surface of the valve body 13 in the region downstream of the flared entrance section 19 is substantially that of a surface of a right circular cylinder except for a slightly thickened central portion wherein a shallow groove 29 is formed between a pair of raised bands 29a. A metal stiffening attachment ring 30 with a plurality of circumferentially spaced apart inwardly protruding fingers 30a is mated therewith to add stability and rigidity to the valve body. The valve body is preferably made of a suitable material, such as pyrocarbon or pyrocarbon-coated graphite, as is well known in this art, which has sufficient resiliency that it can be deformed so as to permit the insertion of the pair of leaflets 15 in their operative locations. The metal ring 30 is also used to support the sewing ring of appropriate design, as broadly known in this art.

[0015] In the present example, the leaflets 15 are identical in shape and size. Each leaflet has two rectilinear, flat, surfaces forming an inflow surface 31 and an outflow surface 33. With the leaflets in the closed position (see Fig. 4), the inflow surface 31 faces upstream and the outflow surface 33 faces downstream. Although the leaflets 15 are flat, other configurations, such as sections of hollow cylinders of circular or elliptical cross section, can alternatively be employed, for instance as described in U.S. patent 5,246,453.

[0016] The leaflets 15 each have a major arcuate edge surface 35, which is located at the downstream edge of the leaflet in the open position, and each has a minor mating edge surface 37 which is located at the opposite, upstream edge of the leaflet in the open position. The arcuate edge surface 35 abuts and is shaped to seat closely against the cylindrical sidewall interior surface 17 of the valve body 13 when the leaflet 15 is in the closed position. The minor edge surface 37 is formed at an angle so as to mate flush against the corresponding mating edge surface 37 of the opposing leaflet when both leaflets 15 are in the closed position, as best seen in Fig. 4. The minor edge surface 37 is accordingly oriented at an angle to the inflow surface 31 which is substantially the same as the downstream angle which the outflow surface 33 forms with the centerline plane 64 (see Fig. 8) in the closed position, preferably an angle between about 30° and about 60°. The centerline plane 64 is defined as a plane which includes the centerline of the

valve body passage- way and which is parallel to the pivot axes of the leaflets. In the illustrated embodiment, the centerline plane 64 is perpendicular to the flat wall surfaces 23 of the valve body passageway. The angle the outflow and inflow surfaces form with the centerline plane 64 preferably corresponds to the extent of the angular rotation that each leaflet 15 undergoes when moving from the fully open 10 position to the fully closed position or back.

[0017] As best seen in Figs. 9-11, the leaflets 15 each have two pairs of intermediate straight edge regions 39 located between the minor mating edge surface 37 and the major arcuate edge surface 35, the straight edge regions 39 of each pair being located on opposite sides of a laterally extending ear or tab 41. As can be seen in Figs. 10 and 11, the ears 41 are of the same thickness as the rest of the flat leaflets 15. The ears 41 are elongated in an upstream-downstream direction when 20 viewed in their open orientation. The ears 41 have lateral edge surfaces, which are rectilinear surfaces of generally shallow curvature as viewed looking at the leaflet from the side of the inflow surface 31. More specifically, as best seen in Figs. 10 and 11, they each have a shallow rounded upstream edge surface 43 and a generally similar downstream edge surface 45. The upstream edge surface 43 is the longer, extending generally laterally of the ear, and it meets and blends smoothly into the downstream surface 45. The major portion of the rectilinear upstream edge surface 43 is perpendicular to the flat inflow and outflow surfaces of the leaflets 15, which flat surfaces simply extend through the regions of the ears, so that the ears have inflow and outflow surfaces that are coplanar with the leaflet main body inflow and outflow surfaces 31, 33. A short arcuate transition edge section 47 is interposed between the major arcuate edge surface 35 and the flat section 39.

[0018] As is best seen in Figs. 3, 5 and 8-12, the ears 41 each bound two leaflet passageways 76, 77, in this embodiment designated as 'ear passageways' through that ear 41. In Figs. 3, 9 and 10, one of the ears 41' is shown in the form of an alternative embodiment with ear passageways 78, 79 of a different design. Although not necessary, it is generally preferred that all the ears are of the same design. The ear passageways 76, 77, 78, 79 are each located spaced from the upstream and downstream ends of the respective ear 41, 41' for allowing flow through that ear and the associated cavity when the leaflets 15 are in the closed positions. 50

[0019] The thickened wall sections 21 of the valve body 13 in the regions where the cavities 25 are located are formed with an upstream transition surface 49 and a downstream transition surface 51 which lead smoothly from the circular entrance region and the circular exit 55 region of the valve body 13 to the flat wall surfaces 23 wherein the cavities 25 are located.

[0020] Each thickened wall section 21 includes two side-by-side cavities which are mirror images of each other and which are located on opposite sides of the centerline plane 64. The depth of the cavities 25 is such that the apex of the curved upstream edge surface 43 of the ear does not quite touch the rear walls 54 of the cavities and a clearance of about 0.0254 - 0.1016 mm (1-4 mils/ 0.001 - 0.004 inch) is left. The flat wall surfaces 23 of the thickened regions serve as the primary bearing surfaces against which the straight edge surfaces 39 of the leaflets bear. The clearance between the shallow curved edge surface 43 of the ear and the rear wall of the cavity allows some flow along the outside of the leaflet ears 41, 41' while the leaflets are closed (Figs. 4 and 11 and left-hand portion of Fig. 8). This counteracts clotting in the pivot region. Because each of the ears 41, 41' of the leaflets 15 bounds at least one ear passageway 76, 77, 78, 79 through that ear 41, 41', the ear passageways 76, 77, 78, 79 being located spaced from the outer ends of the respective ear 41, 41', for allowing flow through that ear 41, 41' and the associated cavity 25 when the leaflets 15 are in the closed positions, a particularly effective flushing of the cavities 25 is achieved and ensured at the low maximum pressure drops over the closed heart valve occurring in the right

ventricle. In the present example, the flows through the ears 41, 41' also entrains flow along the outside of the ears 41, 41', so that such flushing is also enhanced. Because the maximum pressure drop over the closed heart valve in the right ventricle is relatively low, the ear passageways 76, 77, 78, 79 through the ear 41, 41' do not result in excessively high regurgitant flow rates or velocities through the closed heart valve.

- [0021] As best seen in Figs. 2, 4 and 12, the cavities 25 each have an upstream lobe 57 and a downstream lobe 59 on opposite sides of an intermediate throat section 61. The intermediate throat section 61 is bounded by a pair of curved fulcrums termed an outward fulcrum 63 and an inward fulcrum 65 with respect to their location having reference to the centerline plane 64. The outward fulcrum 63 is located substantially even with, but preferably slightly upstream of said inward fulcrum.
- [0022] The upstream lobe 57 is formed with an inclined, straight, camming wall section 67, which is elongated in a direction oriented at an angle of between about 5° and about 30°, preferably between about 15° and about 25°, to the centerline plane 64.
- [0023] The downstream lobe 59 includes a straight locator wall section 71 immediately below the inward fulcrum leading to the downstream end 75 of the cavity (Fig. 12). The flat wall section 71 is oriented parallel to the centerline plane 64 and thus provides a guide surface against which the outflow surfaces of the ears 41 bear in the full open position, as best seen in Fig. 2. As best seen in Fig. 11, the leaflet ears 41 preferably have their rounded downstream edge surfaces 45 oriented so as to be at an acute angle to the outflow surface 33 of the leaflet, thus presenting essentially a line of contact between the ear downstream edge surface 45 and the straight locator wall section 71, which tends to reduce friction and promote cleansing in this region.
- [0024] The leaflets 15 are installed in the valve body 13 by squeezing the body at diametrically opposite locations, as for example along a diameter which is perpendicular to the centerline plane 64. Squeezing causes the diametrically opposed flat wall sections 23 to separate farther from each other, permitting the ears 41 to be passed into the cavities 25. When the squeezing force is removed, the valve body 13 returns to its original annular configuration, leaving only the desired minimal clearance between the flat wall surfaces 23 of the valve body and the straight lateral edge surfaces 39 of the leaflets, in which positions the leaflets are slidably-pivotally mounted for travel between the open and closed positions. The metal stabilizing ring 30 can be installed by snapping into place or by shrink-fitting, in the exterior circumferential groove 29 following the installation of the leaflets or before installing the leaflets.
- [0025] With the heart valve operatively installed in a patient, when it is in the open position, the two leaflets 15 assume an open equilibrium position with respect to the high flow and the direction of blood downstream through the passageway, which may be an orientation where they are substantially parallel to the centerline plane 64, as illustrated in Figs. 1, 2 and the left half of Fig. 8. Should the dynamic blood forces within the valve body passageway change, the left or right hand leaflet can rotate slightly in closing sense so as to maintain such a low energy position either with or without some slight translation. In such an equilibrium position, the leaflets 15 provide very low obstruction to the downstream flow of blood. Yet, despite even such a substantially parallel, full open position, the pivot construction is such that any translational movement either downstream or upstream from this substantially parallel position causes the leaflets to rotate in the direction of closing. Furthermore, in the fully open position as shown in Fig. 2, the leaflets 15 are mounted so as to divide the valve body passageway into 3 sections, a center section located between the two leaflets 15 and two flanking sections. As best seen in Fig. 7, the arrangement is such that the cross-sectional area of each of the two flanking passageway

sections is preferably at least as large as the cross-sectional area of the center flow passageway section. 45

[0026] During conditions of high rate of flow of blood downstream through the valve body, both leaflets 15 can be oriented substantially parallel to the centerline of the valve with the outflow surfaces of the ears 41 in contact with the flat wall sections 71 of the downstream lobes of 50 the cavities 25 and with the ear upstream edge in juxtaposition with the camming wall 67 so that rotation past the parallel orientation is prohibited. The flow rate of blood through the valve during the pumping stroke of the associated chamber of the heart will generally exert sufficient force upon the inflow surfaces 31 of the leaflets such as to maintain the leaflets in this substantially parallel alignment. As the reverse flow of blood upstream through the valve begins, the leaflets 15 and the ears 41 immediately translate upstream. This upstream translation of the ears causes immediate camming engagement of the inflow surface edge of each upstream edge surface 43 against the adjacent straight camming wall section 67 of each cavity, while the outflow surfaces of the ears may slide along the rounded inward fulcrums 65. By camming engagement is meant contact wherein there is relative sliding movement along a surface which is inclined to the direction in which the net forces are attempting to move an object, i.e. upstream and parallel to the centerline of the valve body. This camming action causes the leaflet to very promptly pivot or swing toward its closed position while the translation movement continues until the upstream edges of the leaflet ears reach the top of the upstream lobes 57. Such initial pivoting is guided by the movement of the inflow surface edge of the ear upstream surface 43 along the camming surface 67 while the outflow ear surface generally slides along the inward fulcrum 65.

[0027] When the force of the backflowing blood against the outflow surface 33 of each leaflet has become significant, it causes the inflow surfaces of the ears to contact the outward fulcrums 63, and pivoting thereafter continues guided in part by sliding contact with the outward fulcrum 63. The leaflet has thus pivoted a significant amount as a result of the upstream translation and the shifting to contact with the outward fulcrum 63. Thereafter, the upstream edge surfaces of the ears are guided by movement along the arcuate wall section 69 while the ears simultaneously engage the outward fulcrums 63. Contact with the concave wall sections 69 and the fulcrums 63 remains substantially continuous for about the final one-half of the angular rotation of the ears, and the curvature of the wall 69 is designed so that substantially only rotational motion occurs as the upstream edge surfaces 43 slide therealong as the leaflets thereafter swing to the fully-closed position, illustrated in Figs. 4, 5, the right hand half of Fig. 8 and Fig. 12. In such position, mating edge surfaces 37 of the leaflets abut each other, and the downstream arcuate edge surfaces 35 of the leaflets abut and seat against the cylindrical interior surface 17 of the valve body. During a major portion of the closing movement and specifically during the final stages, this motion is almost pure rotational motion to avoid sliding of the ears along the fulcrums at this time when the upstream edges of the ears move slightly downstream as a result of this rotation. When the mating edges 37 of the two leaflets meet, the contact between the upstream edge of each ear and the arcuate wall 69 is broken, as seen in Fig. 12, thus avoiding the possibility of localized wear when the pressure across the valve is highest. When the leaflet reaches its nearly closed position, the liquid between the edge 35 of the leaflet and the orifice wall acts like a cushion, and the leaflet further decelerates just before it impacts the wall, reducing the noise and any propensity for cavitation.

[0028] In the fully closed valve, with the leaflets 15 oriented as illustrated in Fig. 4, wherein they are shown in elevation, the force of the blood against the outflow surface 33 of each leaflet is borne mainly by the downstream arcuate edge surfaces 35 seating against the interior valve body

surface and by the ears 41 bearing against 5 the outward fulcrums 63. At the instant complete closure is achieved, the pressure of the blood against the outflow surfaces of the leaflets is at its highest and results in regurgitant flow through the ear passageways 76, 77, 78, 79. This causes effective flushing of the central areas of 10 the cavities 25 that are most susceptible to the formation of thrombosis due to stagnation of blood in areas where blood cells are most likely to be subjected to stress and deformation. Flow through the cavities 25 in an upstream direction, is enhanced by the flushing through the ear 15 passageways 76, 77, 78, 79 in each cavity as can be seen from Figs. 5 and 12. The ear passageways through the ears tend to concentrate backflow in central regions of the pivot arrangements close to the pivot axes, where such cleansing flow serves to positively guard against 20 the occurrence of clotting at low maximum pressure drops over the closed valve leaflets as occurring in heart valve prostheses implanted in the right ventricle. Because the maximum pressure drop over the closed heart valve in the right ventricle is relatively low, regurgitant 25 flow rates or velocities through the ear passageways of the closed heart valve are not excessively high. Turbulence and shear stress caused by high local flow velocities are associated to increased risk of thrombosis formation and damage to blood cells. 30

[0029] If, as in the present example, the dimensioning of the ears and the cavities also leaves a pathway for backflow laterally past the edges of the leaflet ears, such backflow around and past the ears 41, 41' is to some extent entrained by the flushing through the passageways 76, 77, 78, 79. The average clearance between the edges of the ears 41 and the walls of the cavities 25 is preferably at least about 50 microns or about 0.002 inch, with the clearance being the least at the region of the apex of the curved upstream edge surface 43. There may 40 be slightly greater clearance adjacent to the edge surfaces 45 of the ears because of the translating design of the leaflets.

[0030] The first embodiment 41 of the leaflet ears differs from the second embodiment in that the ear passageways have an open side facing an associated one of the cavities 25. This is advantageous for providing a particularly effective flushing around the outside of in particular central portions of the ears 41. An advantage of circumferentially closed passageways 78, 79 in the ears 50 41' is that the positioning of the ear passageways 78, 79 can be selected more freely without interfering with the camming effect of the ears along edges of the cavities 25. **[0031]** While only one ear passageway may be provided in each ear, in the present example, each ear 41, 41' 55 bounds two ear passageways 76, 77, 78, 79. By providing two or more ear passageways through each ear, a relatively large and evenly distributed flushing of the cavities 25 is obtained, while the passageways 76, 77, 78, 79 have no or relatively little effect on the camming action between the edges of the cavities and the ears. In the first embodiment, one of the passageways 76 is oriented obliquely through the leaflet ear 41, so that it extends from one of the lobes 57 to the other one of the lobes 59 and edges of the passageway 76 do not contact the convex camming surfaces 63, 65 bounding the throat, i.e. the convex camming surfaces bounding the throat do not pass over edges of the passageway 76 when the leaflet moves from the closed position to the open position or back. Thus, a particularly effective flushing of the cavities 25 is achieved with no interference with the camming action between the camming surfaces 63, 65 and the ears 41.

[0032] The single or multiple ear passageways in each ear may for instance have a width of at least 0.2 mm and more preferably at least 0.4 mm and at most 0.8 mm and more preferably 0.6 mm and a length that is for instance equal to the width or up to 3, 4, 5, 6, 7 or 8 times the width. Thus, at the low maximum pressure drops occurring over the closed valve leaflets in the right ventricle, sufficient flow for flushing without too much or too fast regurgitant flow is obtained.

- [0033]** In the shown embodiments, of each pair of ear passageways of an ear, a first one of the ear passageways 76, 77, 78, 79 is located at least partially in a first one of the lobes 57 and the other one is located at least partially in a second one of the lobes 59 when the leaflets 15 are in the closed positions. Thus, the flushing is concentrated in the lobes 57, 59 of the cavities 25, so that the cavities are flushed particularly effectively, even at low maximum pressure drops over the closed leaflets.
- [0034]** A central portion of each ear 41, 41' projects into an associated one of the cavities 25 between the ear passageways 76, 77, 78, 79 of that ear 41, 41', so that the central portions of the ears are available for suspending the leaflet relative to the cavity.
- [0035]** Each ear 41, 41' extends into an associated one of the cavities 25 over a depth, a central portion of each ear 41, 41' extending into the associated one of the cavities over that depth. Thus, the central portions of the ears, where relative motion between the ears and the cavities is smallest, project furthest into the cavities, thus reducing the risk of damaging blood cells between mutually shifting surfaces.
- [0036]** Furthermore, the central portion of each ear 41, 41' is in the throat section of the associated cavity when the leaflets are in the closed positions, so that the central portions are available for the camming action relative to the fulcrums 63, 65 bounding the throat section at least when the leaflets are moving near the closed positions.
- [0037]** The passageways 76, 77, 78, 79 extend into leaflet portions adjacent to the ears 41, 41'. This is advantageous for achieving a substantial flow rate into and along the cavities 25 at low maximum pressure drops over the closed leaflets.
- [0038]** When blood flow again reverses, as for example when the pumping stroke of the associated chamber begins again, downstream displacement, i.e. translation, of the leaflets 15 initially occurs as a result of the force of the blood against the inflow surfaces 31. As is evident from Fig. 12, the outflow surfaces of the ears 41 will quickly come in contact with the inward fulcrums 65, causing opening pivoting motion to quickly begin with the major arcuate edge surface 35 swinging downstream. The downstream edge surfaces 45 of the ears will likely reach the lower arcuate ends 75 of the downstream lobes 59 10 prior to the ears rotating completely about their pivot points on the fulcrums 65 until the substantially parallel position shown in Fig. 2 is reached, with the ears abutting the flat wall section 71 in each downstream lobe.
- [0039]** Figs. 13 and 14 show another example of an application of the principle that the pivot arrangement of a heart valve is flushed effectively in its most thrombo-genic areas closely around the pivot axes of the leaflet, where movements of the leaflet between open and closed positions are smallest, by regurgitant flow 20 through leaflet passageways in that area, in particular at low pressure drops over the closed valve as occurring when a heart valve has been implanted in the right ventricle. The valve according to this example is based on a valve disclosed in U.S. patent 5,354,330. 25
- [0040]** As is best seen in Fig. 13, the valve according to this example has a generally annular valve body 113 having an interior wall surface 119 which defines a valve body passageway 117 for blood flow there through which is generally symmetrical about a longitudinal centerline. 30 A pair of cooperating leaflets 115 is mounted in the valve body 113 to alternate between an open position 115 (Figs. 13 and 14) where the flow of blood in a downstream direction is permitted and a closed position (Fig. 13 dash and dot lines 115') where flow of blood in the reverse 35 direction is substantially prevented. The pivot member sets each have a recess 141 in the side edge of the leaflet 115 and a knob 125 of the interior surface 119 of the valve body 113. Each knob 125

projects into one of the recesses 141. Furthermore, abutments 180, 181 are provided for stopping the leaflets 115 in the open and closed positions.

[0041] The recesses 141 each include a leaflet passageway 176 through the recess 141. The leaflet passageways 176 each form a leaflet passageway portion 45 of the recess 141 leaving a distance to the interior surface 119 of the valve body 113, which is larger than a clearance between the interior surface 119 of the valve body and portions of the side edge of the leaflet 115 adjacent to the passageway. This allows flow through that recess 141 when the leaflets 115 are in the closed positions 115'. The leaflet passageways of this embodiment ensure that regurgitant flow is concentrated along central portions of the knob 125 and the recesses 141 around the pivoting axes of the leaflets 115. Thus, the valve is most effectively flushed in an area around the most stationary zones of the leaflets 115 where risk of formation of a thrombosis is highest.

[0042] For ensuring that a regurgitant flow of sufficient magnitude is obtained, the leaflet passageways preferably each have an overall width in a direction perpendicular to a nearest portion of said surface of said valve body, that is larger than twice and preferably larger than, in order of increasing preference, three, five or ten times the clearance between the interior surface 119 of the valve body 113 and portions of the side edge of the leaflet 115 adjacent to the leaflet passageway 176.

[0043] For concentrating the regurgitant flow in the central areas around the pivot axes and leaving large bearing surfaces against the knobs 125, the leaflet passageways 176 are each located spaced from the ends of that recess 141 that are upstream and downstream when the leaflet 115 is in its open position. Also for this purpose, the leaflet passageways 176 each have a width, measured in a tangential direction of the interior wall surface 119, that is at least 20% and more preferably 30% smaller than a distance from the upstream end to the downstream end of that recess 141.

[0044] To ensure sufficient regurgitant flow for significantly reducing the formation of thromboses where the leaflets are hinged to the valve body and in particular in the area of the hinge axis, the cross-sectional surface area of the passages bounded by each of the ears or included in each of the recesses is preferably at least 0.2 mm² per ear or recess and more preferably at least 0.4 mm², 0.6 mm² or 0.7 mm² per ear or recess. On the other hand, to avoid more regurgitant flow than is useful for counteracting the formation of thromboses where the leaflets are hinged to the valve body and in particular in the area of the hinge axis, the cross-sectional surface area of the passages bounded by each of the ears or included in each of the recesses is preferably at most 2.5 mm² per ear or recess and more preferably at most 1.5 mm², 1.0 mm² or 0.9 mm² per ear or recess.

[0045] Although the invention has been described with respect to certain preferred embodiments, which include what the inventors presently consider to be the best mode for carrying out the invention, it should be understood that various changes and modifications that would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention which is defined by the claims appended hereto. For example, the invention can also be embodied in a valve of a different basic design. More in particular, as indicated, the invention is not limited to occluders in the form of leaflets having flat body sections but is considered to be also applicable to leaflets having curved body sections with substantially rectilinear surfaces. Also, the number of passageways bounded by each ear or included in each recess may be larger or smaller. For instance, a single passageway may extend obliquely through each ear from a first one of the lobes of the associated cavity to the other lobe of the associated cavity, the ends of the passageway being positioned such that, regardless the operational position of the leaflet, none of the edges of the passageway contacts the convex fulcrums bounding the throat area

between these lobes. Thus, a particularly effective flushing through the throat area of the cavity between the lobes is obtained without interfering with the camming action between the leaflet and the convex fulcrums bounding the throat area. Also, each recesses 5 may include for instance two or three passageways.

[0046] Several features have been described as part of the same or separate embodiments. However, it will be appreciated that the scope of the invention also includes embodiments having combinations of all or some 10 of these features other than the specific combinations of features embodied in the examples. **Claims 15**

1. A prosthetic heart valve including a generally annular valve body (13) having an interior, generally arcuate wall surface (17) which defines a valve body passageway for blood flow there- through which is generally symmetrical about a lon- gitudinal centerline, a pair of cooperating leaflets (15), said leaflets being mounted in said valve body (13) to alternate between an open position where the flow of blood in a down- 25 stream direction is permitted and a closed position where the flow of blood in the reverse direction is counteracted, and a pivot arrangement which guides said leaflets (15) in moving between said open and closed positions, 30 characterized in that said pivot arrangement comprises ears (41) respec- tively projecting laterally from opposite side edges of each of said leaflets (15) and two pairs of diamet- rically opposed cavities (25) in said interior surface 35 (17) of said valve body (13), each of said ears (41) projecting into an associated one of said cavities (25), said ears (41) each have opposite ends, the ends of each ear being located upstream and downstream 40 of that ear (41) when said leaflets (15) are in the open position, and each of said ears (41) bounds at least one ear pas- sageway (76, 77, 78, 79) through that ear, said at least one ear passageway being located spaced 45 from said upstream and downstream ends of that ear (41) for allowing flow through that ear and the associated one of said cavities (25) when said leaf- lets (15) are in said closed positions. 50
2. A prosthetic heart valve including a generally annular valve body (113) having an in- terior, generally arcuate wall surface (119) which de- fines a valve body passageway (117) for blood flow therethrough which is generally symmetrical about 55 a longitudinal centerline, a pair of cooperating leaflets (115), said leaflets be- ing mounted in said valve body (113) to alternate between an open position where the flow of blood in a downstream direction is permitted and a closed position where the flow of blood in the reverse direc- tion is counteracted, and a pivot ar- rangement with pivot member sets on dia- metrically opposite sides of each leaflet, which guides said leaflets (115) in moving between said open and closed positions, characterized in that said pivot member sets each comprise a recess (141) in the side edge of said leaflet (115) and a knob of said interior surface (119) of said valve body (113), said knob (125) projecting into said recess, each of said recesses (141) has opposite ends, the ends of each recess being located upstream and downstream of that recess when said leaflets (115) are in the open position, and each of said recesses (141) includes at least one leaflet passageway (176) through that recess, said at least one leaflet passageway (176) forms a leaflet passageway portion of said recess (141) leav- ing a distance to said interior surface (119) of said valve body (113), which is larger than a clearance between said interior surface (119) of said valve body (113) and portions of said side edge of said leaflet adjacent to said leaflet passageway (176), for allowing flow through that recess (141) when said leaflets (115) are in said closed positions.
3. A heart valve according to claim 1, wherein said at least one ear passageway (76, 77, 78, 79) has an open side facing an associated one of said cavities (25).
4. A heart valve according to any of the preceding claims, wherein the or each ear (41) or recess (141) bounds or, respectively, includes at least two of said ear or leaflet passageways (76, 77, 78, 79; 176).
5. A heart valve according to claim 1 and optionally claim 3 or 4, wherein said cavities (25) each have an upstream lobe (57) and a downstream lobe (59) which are separated by a throat section (61) defined by convex outward and inward fulcrums (63, 65), and wherein a first one of said at least two of said ear passageways (76, 77, 78, 79) is located at least par- tially in a first one of said lobes (57) and a second one of said at least two of said ear passageways is located at least partially in a second one of said lobes (59) when said leaflets (15) are in said closed posi- tions.

6. A heart valve according to claim 1 and according to claim 4 or 5, wherein a central portion of each ear (41) projects into an associated one of said cavities (25) between said at least two of said ear passage- ways (76, 77, 78, 79).
7. A heart valve according to claim 1 and optionally any of the claims 3-6, wherein each ear (41) extends into an associated one of said cavities (25) over a depth, a central portion of each ear (41) extending into the associated one of said cavities (25) over said depth. 5
8. A heart valve according to claim 1 and according to claim 6 or 7, wherein said cavities (25) each have an upstream lobe (57) and a downstream lobe (59) which are separated by a throat section (61) defined 10 by convex outward and inward fulcrums (63, 65) and wherein said central portion of each ear (41) is in said throat section (61) when said leaflets (15) are in said closed positions. 15
9. A heart valve according to claim 8, wherein at least one of the passageways is oriented obliquely through the leaflet, so that it extends from one of the lobes (57) to the other one of the lobes (59) of the associated cavity (25) and edges of said at least one 20 of the passageways do not contact any of the convex outward and inward fulcrums (63, 65) defining the throat (61) in any operational position of the leaflet.
10. A heart valve according to claim 1 and optionally any 25 of the claims 3-9, wherein said at least one ear pas- sageway (76, 77, 78, 79) extends into a leaf portion adjacent to said ear.
11. A heart valve according to any of the preceding 30 claims, wherein said ear or leaflet passageways (76, 77, 78, 79; 176) each have an overall width in a di- rection perpendicular to a nearest portion of said sur- face of said valve body (13; 113), that is larger than twice and preferably larger than, in order of increas- 35 ing preference, three, five or ten times said clearance between said interior surface (17; 119) of said valve body and portions of said side edge of said leaflet adjacent to said passageway. 40
12. A heart valve according to claim 2 and any of the claim 11, wherein said at least one leaflet passage- way (176) is located spaced from said upstream and downstream ends of that recess (141). 45
13. A heart valve according to claim 12, wherein said leaflet passageways (176) each have a width meas- ured in a tangential direction of said interior wall sur- face (119), that is at least 20% and more preferably at least 30% smaller than a distance from said up- 50 stream end to said downstream end of said recess (141).
14. A heart valve according to any of the preceding claims, wherein the passages bounded by each of 55 the ears (41) or included in each of the recesses (141) have a cross-sectional surface area of at least 0.2 mm² per ear or recess and more preferably at least 0.4 mm², 0.6 mm² or 0.7 mm² per ear or recess.
15. A heart valve according to any of the preceding claims, wherein the passages bounded by each of the ears (41) or included in each of the recesses (141) have a cross-sectional surface area of at most 2.5 mm² per ear or recess and more preferably at most 1.5 mm², 1.0 mm² or 0.9 mm² per ear or recess. Patentansprüche

1. Prothetische Herzklappe umfassend einen im Allgemeinen ringförmigen Ventilkörper (13) mit einer inneren, im Allgemeinen bogenförmigen Wandfläche (17), die einen Ventilkörperdurchgang für den Blutfluss definiert, der im Allgemeinen symmetrisch um eine Längsmittellinie herum ist, ein Paar zusammenwirkender Blättchen (15), die in dem Ventilkörper (13) angebracht sind, um zwischen einer offenen Position, in der der Blutfluss in stromabwärtiger Richtung zulässig ist, und einer geschlossenen Position, in der dem Blutfluss in umgekehrter Richtung entgegengewirkt wird, zu wechseln, und eine Schwenkanordnung, die die Blättchen (15) beim Bewegen zwischen den offenen und geschlossenen Positionen führt, dadurch gekennzeichnet, dass die Schwenkanordnung Ohren (41) aufweist, die jeweils seitlich von gegenüberliegenden Seitenkanten jedes der Blättchen (15) vorstehen und zwei Paare von diametral gegenüberliegenden Hohlräumen (25) in der Innenfläche (17) des Ventilkörpers (13), wobei die Ohren (41) jeweils in einen der zugehörigen Hohlräume (25) hineinragen, die Ohren (41) jeweils gegenüberliegende Enden haben, wobei sich die Enden jedes Ohrs stromaufwärts und stromabwärts von diesem Ohr (41) befinden, wenn sich die Blättchen (15) in der offenen Position befinden, und jedes der Ohren (41) wenigstens einen Ohrdurchgang (76, 77, 78, 79) durch dieses Ohr begrenzt, wobei der mindestens eine Ohrdurchgang im Abstand von den stromaufwärtigen und stromabwärtigen Enden dieses Ohrs (41) angeordnet ist, um einen Fluss durch dieses Ohr und den zugehörigen der Hohlräume (25) zu ermöglichen, wenn sich die Blättchen (15) in den geschlossenen Positionen befinden.
2. Prothetische Herzklappe umfassend einen im Allgemeinen ringförmigen Ventilkörper (113) mit einer inneren, im Allgemeinen bogenförmigen Wandfläche (119), die einen Ventilkörperdurchgang (117) für den Blutfluss durch diesen definiert, der im Allgemeinen symmetrisch um eine Längsmittellinie liegt, ein Paar zusammenwirkender Blättchen (115), wobei die Blättchen in dem Ventilkörper (113) montiert sind, um zwischen einer offenen Position, in der der Blutstrom in stromabwärtiger Richtung zulässig ist, und einer geschlossenen Position, in der dem Blutstrom, der in umgekehrter Richtung fließt, entgegengewirkt wird, zu wechseln, und eine Schwenkanordnung mit einem Schwenkelement, das an diametral gegenüberliegenden Seiten jedes Blättchens angeordnet ist und die Blättchen (115) bei der Bewegung zwischen der offenen und der geschlossenen Position führt, dadurch gekennzeichnet, dass die Schwenkelemente jeweils eine Aussparung (141) in der Seitenkante des Blättchens (115) und eine Noppe der Innenfläche (119) des Ventilkörpers (113) umfassen, wobei die Noppe (125) in die Aussparung hineinragt, jede der Aussparungen (141) gegenüberliegende Enden hat, wobei sich die Enden jeder Aussparung stromaufwärts und stromabwärts dieser Aussparung befinden, wenn sich die Blättchen (115) in der offenen Position befinden, und jede der Aussparungen (141) mindestens einen Blättchendurchgang (176) durch diese Aussparung umfasst, wobei der mindestens eine Blättchendurchgang (176) einen Blättchendurchgangsteil der Aussparung (141) bildet, der einen Abstand zu der Innenfläche (119) des Ventilkörpers (113) belässt, der größer ist als ein Abstand zwischen der Innenfläche (119) des Ventilkörpers (113) und von Abschnitten der Seitenkante des Blättchens neben dem Blättchendurchgang (176), um einen Fluss durch diese Aussparung (141) zu ermöglichen, wenn sich die Blättchen (115) in den geschlossenen Positionen befinden.
3. Herzklappe nach Anspruch 1, wobei der mindestens eine Ohrdurchgang (76, 77, 78, 79) eine offene Seite aufweist, die einem zugehörigen der Hohlräume (25) zugewandt ist.
4. Herzklappe nach einem der vorangehenden Ansprüche, wobei das oder jedes Ohr (41) oder die Aussparung (141) jeweils mindestens zwei der Ohr- oder Blättchendurchgänge (76, 77, 78, 79; 176) umfasst.

5. Herzklappe nach Anspruch 1 und optional nach Anspruch 3 oder 4, wobei die Hohlräume (25) jeweils einen stromaufwärtigen Flügel (57) und einen stromabwärtigen Flügel (59) aufweisen, die durch einen Halsabschnitt (61) getrennt sind, der durch konvex nach außen und nach innen gerichtete Drehpunkte (63, 65) definiert ist, und wobei ein erster der mindestens zwei Ohrdurchgänge (76, 77, 78, 79) mindestens teilweise in einem ersten der Flügel (57) angeordnet ist, und ein zweiter der mindestens zwei Ohrpassagen zumindest teilweise in einem zweiten der Flügel (59) angeordnet ist, wenn sich die Blättchen (15) in den geschlossenen Positionen befinden.
6. Herzklappe nach Anspruch 1 und nach Anspruch 4 oder 5, wobei ein zentraler Abschnitt jedes Ohrs (41) in einen zugehörigen Hohlraum (25) zwischen den mindestens zwei der Ohrdurchgänge (76, 77, 78, 79) hineinragt.
7. Herzklappe nach Anspruch 1 und optional nach einem der Ansprüche 3 bis 6, wobei sich jedes Ohr (41) über eine Tiefe in einen der zugehörigen Hohlräume (25) erstreckt, wobei sich ein zentraler Abschnitt jedes Ohrs (41) in einen der zugehörigen Hohlräume (25) über die Tiefe erstreckt.
8. Herzklappe nach Anspruch 1 und nach Anspruch 6 oder 7, wobei die Hohlräume (25) jeweils einen stromaufwärtigen Flügel (57) und einen stromabwärtigen Flügel (59) aufweisen, die durch einen Halsabschnitt (61) getrennt sind, der durch konvex nach außen und nach innen gerichtete Drehpunkte (63, 65) definiert ist, und wobei sich der zentrale Abschnitt jedes Ohrs (41) in dem Halsabschnitt (61) befindet, wenn sich die Blättchen (15) in den geschlossenen Positionen befinden.
9. Herzklappe nach Anspruch 8, wobei mindestens einer der Durchgänge schräg durch das Blättchen ausgerichtet ist, so dass es sich von einem der Flügel (57) zu dem anderen der Flügel (59) des zugehörigen Hohlraums (25) erstreckt und die Kanten des mindestens einen der Durchgänge keinen der konvexen nach außen und nach innen gerichteten Drehpunkte (63, 65) berühren, die den Hals (61) in einer beliebigen Betriebsstellung des Blättchens definieren.
10. Herzklappe nach Anspruch 1 und optional nach einem der Ansprüche 3 bis 9, wobei sich der mindestens eine Ohrdurchgang (76, 77, 78, 79) in einen an das Ohr angrenzenden Blättchenabschnitt erstreckt.
11. Herzklappe nach einem der vorangehenden Ansprüche, wobei die Ohr- oder Blättchendurchgänge (76, 77, 78, 79; 176) jeweils eine Gesamtbreite in einer Richtung senkrecht zu einem nächstgelegenen Abschnitt der Oberfläche des Ventilkörpers (13; 113) aufweisen, die größer ist als das Doppelte und, in der Reihenfolge der zunehmenden Bevorzugung, das Drei-, Fünf- oder Zehnfache des Hohlraums zwischen der Innenfläche (17; 119) des Ventilkörpers und Abschnitten der Seitenkante des Blättchens ist, das sich neben dem Durchgang befindet.
12. Herzklappe nach Anspruch 2 und einem der Ansprüche 11, wobei der mindestens eine Blättchendurchgang (176) im Abstand von den stromaufwärtigen und stromabwärtigen Enden dieser Aussparung (141) angeordnet ist.
13. Herzklappe nach Anspruch 12, wobei die Blättchendurchgänge (176) jeweils eine in tangentialer Richtung der Innenwandfläche (119) gemessene Breite haben, d. h. um mindestens 20% und bevorzugter um mindestens 30% kleiner als eine Entfernung von dem stromaufwärtigen Ende zu dem stromabwärtigen Ende der Aussparung (141).
14. Herzklappe nach einem der vorhergehenden Ansprüche, bei der die Durchgänge, die von jedem der Ohren (41) begrenzt oder in jeder der Aussparungen (141) enthalten sind,

eine Querschnittsfläche von mindestens 0,2 mm² pro Ohr oder Aussparung und bevorzugter mindestens 0,4 mm², 0,6 mm² oder 0,7 mm² pro Ohr oder Aussparung aufweisen. 20

- 15.** Herzklappe nach einem der vorhergehenden Ansprüche, bei der die Durchgänge, die von jedem der Ohren (41) begrenzt oder in jeder der Aussparungen (141) enthalten sind, eine Querschnittsfläche von höchstens 2,5 mm² pro Ohr oder Aussparung und 25 bevorzugter höchstens 1,5 mm², 1,0 mm² oder 0,9 mm² pro Ohr oder Aussparung aufweisen. Revendications **30**

1. Valve cardiaque prothétique comprenant : un corps de valve généralement annulaire (13) ayant une surface de paroi intérieure généralement arquée (17) qui définit une voie de passage de corps de valve pour l'écoulement de sang à travers cette dernière, qui est généralement symétrique autour d'une ligne centrale longitudinale, 40 une paire de feuillets (15) coopérants, lesdits feuillets étant montés dans ledit corps de valve (13) pour alterner entre une position ouverte dans laquelle l'écoulement de sang dans une direction en aval est autorisé et une position fermée dans laquelle l'écoulement de sang dans la direction inverse est contrecarré, et un agencement de pivot qui guide lesdits feuillets (15) en se déplaçant entre lesdites positions ouverte et fermée, 50 caractérisée en ce que : ledit agencement de pivot comprend des oreilles (41) faisant respectivement saillie à partir des bords latéraux opposés de chacun desdits feuillets (15) et deux paires de cavités (25) diamétralement opposées dans ladite surface intérieure (17) dudit corps de valve (13), chacune desdites oreilles (41) faisant saillie dans une cavité associée desdites cavités (25), lesdites oreilles (41) ont chacune des extrémités opposées, les extrémités de chaque oreille étant positionnées en amont et en aval de cette oreille (41) lorsque lesdits feuillets (15) sont dans la position ouverte, et chacune desdites oreilles (41) délimite au moins une voie de passage d'oreille (76, 77, 78, 79) à travers cette oreille, ladite au moins une voie de passage d'oreille étant positionnée à distance desdites extrémités en amont et en aval de cette oreille (41) pour permettre l'écoulement à travers cette oreille et la cavité associée desdites cavités (25) lorsque lesdits feuillets (15) sont dans lesdites positions fermées.
2. Valve cardiaque prothétique comprenant : un corps de valve généralement annulaire (113) ayant une surface de paroi intérieure (119) généralement arquée qui définit une voie de passage de corps de valve (117) pour l'écoulement du sang à travers cette dernière qui est généralement symétrique autour d'une ligne centrale longitudinale, une paire de feuillets coopérants (115), lesdits feuillets étant montés dans ledit corps de valve (113) pour alterner entre une position ouverte dans laquelle l'écoulement du sang dans une direction en aval est autorisé et une position fermée dans laquelle l'écoulement du sang dans la direction inverse est contrecarré, et un agencement de pivot avec des ensembles d'élément de pivot sur les côtés diamétralement opposés de chaque feuillet, qui guide lesdits feuillets (115) lors du déplacement entre lesdites positions ouverte et fermée, caractérisée en ce que : lesdits ensembles d'élément de pivot comprennent chacun un évidement (141) dans le bord latéral dudit feuillet (115) et un bouton de ladite surface intérieure (119) dudit corps de valve (113), ledit bouton (125) faisant saillie dans ledit évidement, chacun desdits évidements (141) a des extrémités opposées, les extrémités de chaque évidement étant positionnées en amont et en aval de cet évidement lorsque lesdits feuillets (115) sont dans la position ouverte, et chacun desdits évidements (141) comprend au moins une voie de passage de feuillet (176) à travers cet évidement, ladite au moins une voie de passage de feuillet (176) forme une partie de voie de passage de feuillet dudit évidement (141) laissant une distance jusqu'à ladite surface intérieure (119) dudit corps de valve (113), 5 qui est supérieure à un jeu entre ladite surface intérieure (119) dudit corps de valve (113) et des parties dudit bord latéral dudit feuillet adjacent à ladite voie de passage de feuillet (176), pour permettre l'écoulement 10 à travers cet évidement (141), lesdits feuillets (115) sont dans lesdites positions fermées.
3. Valve cardiaque prothétique selon la revendication 1⁵, dans laquelle ladite au moins une voie de passage d'oreille (76, 77, 78, 79) a un côté ouvert faisant face à une cavité associée desdites cavités (25).

4. Valve cardiaque prothétique selon l'une quelconque ²⁰ des revendications précédentes, dans laquelle la ou chaque oreille (41) ou évidemment (141) délimite ou comprend respectivement au moins deux parmi les- dites voies de passage d'oreille ou de feuillet (76, 77, 78, 79 ; 176).²⁵
5. Valve cardiaque prothétique selon la revendication 1 et facultativement la revendication 3 ou 4, dans laquelle lesdites cavités (25) ont chacune un lobe en amont (57) et un lobe en aval (59) qui sont séparés ³⁰ par une section de gorge (61) définie par des points d'appui convexes vers l'extérieur et vers l'intérieur (63, 65), et dans laquelle une première desdites au moins deux desdites voies de passage d'oreille (76, 77, 78, 79) est positionnée au moins partiellement ³⁵ dans un premier desdits lobes (57) et une seconde desdites au moins deux desdites voies de passage d'oreille est positionnée au moins partiellement dans un second desdits lobes (59) lorsque les feuillets (15) sont dans lesdites positions fermées. ⁴⁰
6. Valve cardiaque prothétique selon la revendication 1 et selon la revendication 4 ou 5, dans laquelle une partie centrale de chaque oreille (41) fait saillie dans une cavité associée desdites cavités (25) entre les- ⁴⁵ dites au moins deux desdites voies de passage d'oreille (76, 77, 78, 79).
7. Valve cardiaque prothétique selon la revendication 1 et facultativement l'une quelconque des revendications 3 à 6, dans laquelle chaque oreille (41) s'étend dans une cavité associée desdites cavités (25) sur une profondeur, une partie centrale de chaque oreille (41) s'étendant dans la cavité associée desdites cavités (25) sur ladite profondeur. ⁵⁵
8. Valve cardiaque prothétique selon la revendication 1 et selon la revendication 6 ou 7, dans laquelle les- dites cavités (25) ont chacune un lobe en amont (57) et un lobe en aval (59) qui sont séparés par une section de gorge (61) définie par des points d'appui convexes vers l'extérieur et vers l'intérieur (63,65) et dans laquelle ladite partie centrale de chaque oreille (41) est dans ladite section de gorge (61) lorsque lesdits feuillets (15) sont dans lesdites positions fermées.
9. Valve cardiaque prothétique selon la revendication 8, dans laquelle au moins l'une des voies de passage est orientée de manière oblique à travers les feuillets, de sorte qu'elle s'étend à partir de l'un des lobes (57) à l'autre des lobes (59) de la cavité (25) associée et des bords de ladite au moins une des voies de passage ne sont pas en contact avec l'un quelconque des points d'appui convexes vers l'ex- térieur et l'intérieur (63, 65) définissant la gorge (61) dans l'une quelconque des positions opérationnelles du feuillet.
10. Valve cardiaque prothétique selon la revendication 1 et facultativement selon l'une quelconque des re- vendications 3 à 9, dans laquelle ladite au moins une voie de passage d'oreille (76, 77, 78, 79) s'étend dans une partie de feuillet adjacente à ladite oreille.
11. Valve cardiaque prothétique selon l'une quelconque des revendications précédentes, dans laquelle les- dites voies de passage d'oreille ou de feuillet (76, 77, 78, 79 ; 176) ont chacune une largeur globale dans la direction perpendiculaire à la position la plus proche de ladite surface dudit corps de soupape (13 ; 113) qui est supérieure à deux fois et de préférence supérieure à, dans l'ordre de préférence croissant, trois, cinq ou dix fois ledit jeu entre ladite surface intérieure (17 ; 119) dudit corps de valve et des par- ties dudit bord latéral dudit feuillet adjacent à ladite voie de passage.
12. Valve cardiaque prothétique selon la revendication 2 et selon la revendication 11, dans laquelle ladite au moins une voie de passage de feuillet (176) est positionnée à distance desdites extrémités en amont et en aval de cet évidemment (141).
13. Valve cardiaque prothétique selon la revendication 12, dans laquelle lesdites voies de pas- sage de feuillet (176) ont chacune une largeur mesurée dans une direction tangentielle de ladite surface de paroi intérieure (119) qui est au moins 20 % et encore de préférence au

moins 30 % inférieure à une distance de ladite extrémité en amont à ladite extrémité en aval dudit évidement (141).

- 14. Valve cardiaque prothétique selon l'une quelconque des revendications précédentes, dans laquelle les passages délimités par chacune des oreilles (41) ou inclus dans chacun des évidements (141) ont une surface transversale d'au moins 0,2 mm² par oreille ou évidement et encore de préférence d'au moins 0,4 mm², 0,6 mm² ou 0,7 mm² par oreille ou évidement. 5
- 15. Valve cardiaque prothétique selon l'une quelconque des revendications précédentes, dans laquelle les passages délimités par chacune des oreilles (41) ou inclus dans chacun des évidements (141) ont une surface transversale de 2,5 mm² au maximum par oreille ou évidement et encore de préférence au maximum de 1,5 mm², 1,0 mm² ou 0,9 mm² par oreille ou évidement.

15 20 25 30 35 40 45 50 55

REFERENCES CITED IN THE DESCRIPTION

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Fig. 1

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Fig. 12

Fig. 13

Fig. 14