Prediction of Clinical Outcome after Right Ventricular Outflow Tract Intervention

Jamie Romeo

ISBN: 978-94-6361-415-3
Layout and printed by: Optima Grafische Communicatie (www.ogc.nl)

Prediction of Clinical Outcome after Right Ventricular Outflow Tract Intervention

Het voorspellen van uitkomsten na interventie in de rechter ventrikel uitstroombaan

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 9 september 2020 om 15:30 uur

door

Jamie Leslie Robin Romeo

geboren te Rotterdam

Erasmus University Rotterdam

DOCTORAL COMMITTEE

Promotor:	Prof. dr. J.J.M. Takkenberg
	Prof. dr. A.J.J.C. Bogers
Other members:	Prof. dr. M.G. Hazekamp
	Prof. dr. J.W. Roos-Hesselink
	Prof. dr. W.A. Helbing
Co-Promotor:	Dr. Mr. M.M. Mokhles

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Voor mijn Opa en Oma

TABLE OF CONTENTS

1

General introduction

The heart consists of two atria and two ventricles, which are serially connected, providing pulmonary circulation systemic circulation, respectively. This set up allows maintaining circulation of blood and nutrients to the heart itself through the coronary circulation and to the rest of the body. Ideally it directs blood unobstructedly from atria to ventricles to the great vessels through competent valves.

It has been estimated that 9 out of every 1,000 alive newborns have a structural developmental heart defect [1]. This roughly translates into 1,500 per year or 4 per day in the Netherlands. These defects are called congenital heart disease (CHD), as congenital refers to being born with it. The complete spectrum of congenital heart diseases is vast and complex in terms of affected structures, symptomatology, presentation and treatment.

SURGICAL/INTERVENTIONAL THERAPY

Although understanding of structural heart defects and associated symptomatology exists for many years, surgical correction is relatively new. Important inventions and discoveries have led to the first attempts of extra- and intracardiac surgery. The most important were the invention of the heart-lung machine (Max von Frey; 1885), heparin (Jay McLean; 1916), and antibiotics (Alexander Fleming; 1929). These enabled Alfred Blalock to place the first systemic-pulmonary shunt to treat severe cyanosis in tetralogy of Fallot in 1944, after which Sir Walton Lillehei performed the first open heart surgery in a young boy in 1954 [2, 3]. As many congenital heart diseases have a dismal natural course, these advancements have enabled enormous progress in both life expectancy and quality of life.

Patients who need right ventricular outflow tract (RVOT) reconstruction form a diverse population. Most often, these are patients with CHD as approximately 1 in 5 CHD involves the RVOT. Common diagnoses are tetralogy of Fallot, pulmonary atresia, transposition of the great arteries, double outlet right ventricle and truncus arteriosus. RVOT reconstruction can also be part of primary aortic valve repair, with or without congenital defects. This is the case in the Ross procedure during which the diseased aortic valve is replaced by the patients' own competent pulmonary valve, as pioneered by Donald Ross in 1967 [4].

Homografts

Besides efficient methods to sustain and protect circulation to the rest of the body during open heart surgery, prosthetic replacements of malformed cardiac structures have been a major challenge in the early days and still are in contemporary surgery. In 1966 Donald Ross first described the use of a human donor valve or 'homograft' to reconstruct the RVOT in a patient with pulmonary atresia [5]. Homografts have since then been

extensively used for both pulmonary and aortic valve replacement. Their independence from anticoagulation due to a negligible thrombosis risk, and low risk of endocarditis makes them attractive valve replacements [6]. The main shortcoming of homografts is their limited durability. Especially in small children durability is limited and structural valve deterioration leading to valve replacement within the first postoperative decade is frequently encountered [7-11]. Somatic outgrowth is one of the main determinants but blood group incompatibility, immunological factors and small diameters have been suggested as well [9-13].

Alternatives for RVOT reconstruction are bioprostheses, decellularized homografts, mechanical prostheses, and tissue engineered valves. The use of bioprostheses is sometimes preferred because they are readily available in a wide size range which is especially important in small children, for which small sized homografts are scarce. The Contegra valve, made from a bovine jugular vein, is probably the most used bioprosthesis. However, multiple comparisons between the Contegra valve and homografts have consistently indicated increased rates of endocarditis and deterioration of the former, questioning their equivalence [14-18]. In decellularized homografts, the cells of the donor are removed, hereby isolating the extracellular matrix. Decellularized homografts are expected to be more durable compared with untreated homografts, because of a reduced antigenicity of the former. Although initial results suggest that decellularized valves are not inferior in terms of replacement rates, long term performance is still unknown [19, 20]. Compared to mechanical valves, homografts have a major advantage given their independence from anti-coagulation. Mechanical valves inherently subject patients to permanent use of anti-coagulation which is associated with significant risks of severe bleeding [21, 22]. Lastly, the young field of tissue engineering has gained enormous interest and holds high expectations. The central concept is called 'endogenous tissue restoration' which entails the implantation of a scaffold which is supposed to be populated in vivo with circulating endothelial stem cells. Whether tissue engineered heart valves will meet expectations will become clear in the next. At the same time the XPLORE-2 study is being enrolled in the USA, aimed at determining the feasibility to implant bioabsorbable pulmonary valves. Despite these alternatives, homografts are currently still the preferred alternatives for right sided lesions, due to their extensive durability, low risk of endocarditis and anticoagulation independence [14, 16, 23-25].

Current Challenges in Surgical Care

Despite the excellent properties of homografts, durability is long but still limited. The valves gradually become stenotic due to progressive calcification, develop regurgitation or a combination of both. This this called structural valve deterioration, which is a common but poorly understood process. The resulting pressure and volumetric overload can lead to adverse ventricular remodeling, heart failure and rhythm disturbances which

may result in premature death [26-28]. Therefore, timely replacement before irreversible adverse changes have occurred seems rational. However, repeated surgical intervention becomes progressively hazardous and complex. This especially poses problems for patients who received their first homograft during infancy, with a freedom from valve replacement of only 28% after 15 years [6]. Furthermore, as demand permanently exceeds supply, homografts are scarce. Correct timing of reintervention thus entails a careful trade-off between preventing morbidity and mortality on one side (i.e. operating too late), versus preventing intervening too soon and hereby unnecessarily exposing patients to surgical risks. An additional difficulty is the unknown benefit of a competent valve in an adult heart which already has been chronically remodeling due to valve incompetence. The assumption thus far has been that timely pulmonary valve replacement might reverse right ventricular dysfunction and adverse remodeling. However, results in mainly tetralogy of Fallot are conflicting and describe relatively short term observations [29]. Therefore, many questions regarding valve selection, reintervention criteria, indication and timing are still relevant and unanswered.

The need for intervention in case of cardiac defects is undisputed, as for many CHD the natural course is depressing. However, as knowledge increased during the last decades, the exact timing, methods and indication have been fiercely debated. For instance, initial shunting has been completely replaced by complete single stage correction in an elective setting in patients with tetralogy of Fallot. Differences in opinion, beliefs, experience and 'gut feeling' have created vast differences between centers and even individual surgeons. For example, some centers have abandoned unifocalization of systemic pulmonary collateral arteries, as others deem it essential in patients with pulmonary atresia. And some surgeons believe in monocusp reconstruction when placing a transannular patch to reduce the amount of regurgitation, while others are very skeptical.

In this setting, a completely new population of patients has emerged, as roughly 85% of all children born today with CHD will survive into adulthood [30]. We are currently challenged by this entirely new group of patients, as our understanding of the 'natural course' after surgical correction is limited. Our current believes about the benefit and methods of reintervention in these grown-ups are a combination of extrapolations of knowledge about children and first-presenters, and experience. The problem is that these extrapolations might not be valid.

TETRALOGY OF FALLOT

Tetralogy of Fallot is the most common cyanotic congenital heart disease, estimated to be present in 34 per 100.000 live borns [1]. The anatomy was first described by Etienne Fallot in 1888 and consists of stenosis of RVOT mostly with pulmonary valve

involvement, a ventricular septal defect and an overriding aorta, associated with right ventricular hypertrophy [31]. Stenosis of the RVOT and pulmonary valve increases right ventricular systolic pressure and can induce right ventricular hypertrophy when present for extensive periods. Furthermore, the increased right ventricular pressure causes blood to shunt from the right to the left ventricle through the ventricular septal defect, causing systemic desaturation. Correction often entails surgical intervention in which pulmonary valve sparing surgery should be aimed for, but in which often the RVOT is widened with a transannular patch. The VSD is usually closed with a patch.

Although correction with a transannular patch immediately alleviates obstruction and allows more blood flow to the lungs, it renders the valve inherently incompetent. The resulting chronic regurgitation has long been regarded as unharmful, as patients often do not report any symptoms during the initial 20 years after surgery. However, several papers published in the early 2000's indicated that chronic regurgitation can lead to right ventricular dilatation, arrhythmia and heart failure, which substrates to premature death [26, 28, 32]. Since those publications, pulmonary valve replacement with a homograft or biological valve has widely been accepted as appropriate therapy in these patients. The exact timing of this procedure is not known, however, and has been heavily debated. Differences in insight about the clinical indication (whether to postpone the surgery till symptom development or not), and volumetric thresholds have led to differences in timing. Furthermore, some surgeons are openly starting to question whether PVR has any benefit at all [33]. The purely volumetric changes which were associated with the hazards of arrhythmia and death early 2000s, show a mixed response to PVR [29]. Till this date, no conclusive evidence has been published indicating a hazard reduction after PVR [33-35]. In a recent paper by Tal Geva, two important concepts were mentioned: an 'infliction point' and 'serial analysis of measurements' [35]. Both concepts can be demonstrated with a relatively underexposed and underused branch of biostatistics which will be repeatedly used throughout this thesis.

Special interest groups

Within the field of congenital heart disease and right sided valvular reconstruction, some groups of patients have been relatively underexposed. These are women, patients who have repeatedly undergone RVOT surgery and middle-aged adults who underwent the pulmonary autograft procedure. Possible reasons could be that these groups have only emerged relatively recently due to advancements of surgical care and possibilities. Accumulation of data and advancements in statistical methodology are now sufficient to effectively and precisely answer important clinical questions.

Women

Virtually no published literature exists about women who underwent RVOT reconstruction with a homograft. Extensive literature does however exist about women after aortic valve replacement with all available valvular alternatives [36-39]. Not much is known about the outcome of pregnancy of women after RVOT reconstruction, or about the potential effects on the durability of homografts. This is remarkable since pregnancy is a physically demanding period. Hemodynamically it can be characterized as a prolonged period of increased systolic blood pressures, circulating volumes and heart rate, which can extend long beyond the delivery [40, 41]. Pregnancy should be openly discussed and ideally be planned after counseling by both an obstetrician-gynecologist and cardiologist. Especially, women with CHD have an increased risk for pregnancy and labor related complications [42]. Careful follow up by both specialists is therefore warranted before, during and after pregnancy. In this thesis we will investigate the outcomes of pregnancy in women who underwent RVOT reconstruction with a homograft, and the effect of pregnancy on homograft durability.

Repeatedly operated patients

Experience had shown that repeated surgical interventions can become increasingly difficult and hazardous due to progressive adhesions and scarring. The perioperative hospital course is complex and recovery may be challenging and long. One method aimed at reducing the number of surgical interventions and therefore some of the interventional risks, is transcatheter valve implantation. Transcatheter pulmonary valve implantation (TPVI) with a bioprosthesis was introduced by Philipp Bonhoeffer in 2000 in a 12-year old boy [43]. The so called 'Melody valve' was initially introduced as a method to extend functionality of conduits in situ, and hereby delay surgical reintervention. Nowadays, it is estimated that over 13.000 patients have successfully undergone transcatheter pulmonary valve implantation. We now know that its effects on valve performance are good offering relieve from severe stenosis and regurgitation, and delay from surgery for at least 5 years [44-46]. Beyond this period, no current knowledge exists yet. However, the effects on ventricular function are to a large extent still unknown. Furthermore, its reintervention rate is substantial, and multiple comparisons with homografts have indicated an increased risk of endocarditis, comparable to the rate of surgical bioprostheses [15]. In this thesis, the first results of a Dutch multicenter experience with TPVI are presented.

Non-elderly Adults with aortic valve disease

After a spike in interest in the Ross procedure in a wide range of patients during the late 90'and early 2000', it made up only 0.09% of all aortic valve replacements in the USA in 2010 [47]. Disappointing results about autograft durability, primarily limited by dilatation of the neo-aortic root, have dampened enthusiasm [48]. The complexity of the

procedure and steep learning curve further limit eagerness of young surgeons to master the technique [49]. This has led to adult patients till roughly 65 years almost uniformly receiving a mechanical valve, despite the severe and exponentially increasing risks of stroke and major bleeding due to the inherent anti-coagulants dependence. Note that a linearized annual occurrence rate of major bleeding of only 1-2% in young adults with a life expectancy exceeding 20 years, translates into a significant life-time risk of at least 18.3-32.2%, with extensive impact on quality of life. It has been repeatedly shown that optimizing self-monitoring and lowering the therapeutic range of INR has a limited effect on reducing thromboembolic or bleeding events and the subsequent hazard of death [50, 51]. New long term reports indicate superior results after the Ross procedure compared to AVR with mechanical valves and bioprostheses in selected patients. This underlines major drawbacks namely increased risks of structural valve deterioration and endocarditis in bioprostheses, and severe bleeding and cerebral vascular accidents with mechanical valves [52-56]. Furthermore, these comparisons have also indicated that the Ross procedure has been the only aortic valve alternative enabling life-expectancy comparable to a matched general population [52, 53, 57]. A randomized controlled trial showed that survival after the Ross procedure is also better than in AVR with a homograft, despite the double number of valves at risk in the former [58]. Despite these data uniformly indicating superior results of the Ross procedure, popularity has been steadily declining [47]. Shared decision making by actively involving well informed patients by using a decision aid could be one of the answers to the lost opportunities [59, 60]. In addition to presenting extra treatment options that could benefit the patient in the long term, use of a decision aid improves knowledge of patients and reduces decisional conflict, anxiety and depression leading to a better mental well-being [60]. In this thesis the long term outcomes after the Ross procedure in young and middle aged patients will be investigated.

AIMS OF THIS THESIS

The aim of this thesis is to obtain a better insight into determinants of patient outcome after RVOT reconstruction with a homograft and optimization of the timing of (re-) intervention.

The following research topics will be addressed:

1. Outcome of contemporary surgical correction of tetralogy of Fallot. (Chapter 2)
2. Homograft durability and risk factors for accelerated homograft failure in patients with right sided congenital heart disease. (Chapters 3, 4, 6, 10, 11)

3. Quality of life after right ventricular outflow tract reconstruction with a homograft conduit. (Chapter 6)
4. Application of appropriate statistical methods for assessment of patient outcome after RVOT reconstruction. (Chapters 5, 6 and 8)
5. Optimal timing of reintervention in patients with corrected Tetralogy of Fallot. (Chapter 7)
6. The influence of pregnancy on patient outcome in women who have undergone RVOT reconstruction with a homograft conduit. (Chapter 9)
7. The influence of pregnancy on the durability of homografts. (Chapter 10)
8. Patient outcome after the Ross procedure in middle aged adults. (Chapter 11)
9. Patient outcome after transcatheter valve implantation in the RVOT. (Chapter 12)

OUTLINE

In **Chapter 2,** the available literature on contemporary surgical repair of Tetralogy of Fallot is reviewed, and key surgical aspects of the procedure are evaluated. Pooled estimates of key outcomes are presented for different age groups and per continent. Temporal trends of surgical approach will be provided as well, along with an in-depth discussion and evaluation of the outcome and evidence for current clinical and surgical decision making.

In **Chapter 3**, homograft durability in young patients with pulmonary atresia is investigated. Patients with pulmonary atresia often need valvular reconstruction during initial correction at a young age and are therefore especially prone to undergo repeated valvular interventions. The presence of systemic collateral arteries might be of importance to homograft durability given the influence of pulmonary vascular resistance on homograft performance. We compare patients with pulmonary atresia with and without systemic collateral arteries on homograft durability.

In **Chapter 4**, homograft durability in young children with CHD will be assessed. Scarcity in terms of right sized homografts forced surgeons to be creative. The effects of downsizing homografts will be analyzed with mixed effects modeling.

In **Chapter 5** we critically review recently published literature in the European Journal of Cardio-Thoracic Surgery and common statistical methodology which is in our opinion heavily flawed and outdated. Improvements and different methodological strategies to more efficiently exploit available data are suggested.

In **Chapter 6** the long term durability and clinical outcome will be determined in a consecutive cohort of patients who underwent RVOT reconstruction with a homograft at the Erasmus University Medical Center. Clinical endpoints will be analyzed with conventional Cox proportional hazards models and presented with Kaplan Meier plots.

Serial echocardiographic measurements of peak gradient and regurgitation grade are analyzed with mixed effects models and presented in an interactive application. Lastly, Quality of Life is assessed with the Short-Form 36.

In **Chapter 7** suggestions and nuances in the discussion regarding reintervention in Fallot are presented. By using mixed effects models we analyze serially collected QRS duration and present new insights regarding optimal timing of reintervention.

In **Chapter 8** recently published evidence in Circulation will be critically evaluated. Tetralogy of Fallot still is a highly debated topic with vastly diverging opinions. Valid and solid evaluation and interpretation of data is needed to answer important questions. It turns out that is not always the case.

In **Chapter 9 and 10** the outcome of pregnancy in women who underwent RVOT reconstruction with a homograft will be investigated. Homograft performance with pregnancy related complications and outcome. Furthermore, we analyze the association between the occurrence of pregnancy with the longitudinal gradient and regurgitation grade of homografts. By using mixed and joint modeling we determine whether the occurrence of pregnancy affects the hazard of valve replacement.

In **Chapter 11** we present the outcome of 1431 middle-aged patients who underwent the Ross procedure in one of five experienced high volume centers. We present challenging evidence supporting a more prominent place for the Ross procedure in todays' menu of AVR.

In **Chapter 12** the first report on the Dutch Experience with transcatheter pulmonary valve implantation will be presented by combining results of the Erasmus University Medical Center with the Radboud University Medical Center. Serial echocardiographic and electrocardiographic measurements will be analyzed with mixed models and clinical outcome up to 12 years will be presented with Kaplan-Meier plots.

The most important findings will be discussed along with our future perspectives in **Chapter 13**.

REFERENCES

1. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
2. Lillehei, C.W., et al., Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. Ann Surg, 1955. 142(3): p. 418-42.
3. Lillehei, C.W., Controlled cross circulation for direct-vision intracardiac surgery; correction of ventricular septal defects, atrioventricularis communis, and tetralogy of Fallot. Postgrad Med, 1955. 17(5): p. 388-96.
4. Ross, D.N., Replacement of aortic and mitral valves with a pulmonary autograft. Lancet, 1967. 2.
5. Ross, D.N. and J. Somerville, Correction of pulmonary atresia with a homograft aortic valve. Lancet, 1966. 2(7479): p. 1446-7.
6. Romeo, J.L.R., et al., Long-term clinical outcome and echocardiographic function of homografts in the right ventricular outflow tract†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy265-ezy265.
7. Stark, J., et al., Fate Of Subpulmonary Homograft Conduits: Determinants Of Latehomograft Failure. The Journal of Thoracic and Cardiovascular Surgery, 1997. 115(3): p. 506-516.
8. Troost, E., et al., Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration. Eur Heart J, 2007. 28(20): p. 2503-9.
9. Lund, A.M., et al., Early reintervention on the pulmonary arteries and right ventricular outflow tract after neonatal or early infant repair of truncus arteriosus using homograft conduits. Am J Cardiol, 2011. 108(1): p. 106-13.
10. Forbess, J.M., et al., Cryopreserved homografts in the pulmonary position: determinants of durability. Ann Thorac Surg, 2001. 71(1): p. 54-9; discussion 59-60.
11. Kalfa, D.M., et al., Pulmonary position cryopreserved homograft in non-Ross patients: how to improve the results?†. European Journal of Cardio-Thoracic Surgery, 2012. 42(6): p. 981-987.
12. Christenson, J.T., et al., Blood group incompatibility and accelerated homograft fibrocalcifications. J Thorac Cardiovasc Surg, 2004. 127(1): p. 242-50.
13. Tweddell, J.S., et al., Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation, 2000. 102(19 Suppl 3): p. III130-5.
14. Poinot, N., et al., Pulmonary valve replacement after right ventricular outflow tract reconstruction with homograft vs Contegra(R): a case control comparison of mortality and morbidity. J Cardiothorac Surg, 2018. 13(1): p. 8.
15. Sharma, A., et al., A Systematic Review of Infective Endocarditis in Patients With Bovine Jugular Vein Valves Compared With Other Valve Types. JACC Cardiovasc Interv, 2017. 10(14): p. 1449-1458.
16. Mery, C.M., et al., Risk factors for development of endocarditis and reintervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. J Thorac Cardiovasc Surg, 2016. 151(2): p. 432-9, 441 e1-2.

17. Ugaki, S., et al., An increased incidence of conduit endocarditis in patients receiving bovine jugular vein grafts compared to cryopreserved homograft for right ventricular outflow reconstruction. Ann Thorac Surg, 2015. 99(1): p. 140-6.
18. Albanesi, F., et al., Incidence and risk factors for Contegra graft infection following right ventricular outflow tract reconstruction: long-term results. Eur J Cardiothorac Surg, 2014. 45(6): p. 1070-4.
19. da Costa, F.D.A., et al., Decellularized Versus Standard Pulmonary Allografts in the Ross Procedure: Propensity-Matched Analysis. The Annals of Thoracic Surgery, 2018.
20. da Costa, F.D.A., et al., Decellularized Allografts for Right Ventricular Outflow Tract Reconstruction in Children. World J Pediatr Congenit Heart Surg, 2017. 8(5): p. 605-612.
21. Koertke, H., et al., Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J, 2007. 28(20): p. 2479-84.
22. Kulik, A., et al., Mechanical versus bioprosthetic valve replacement in middle-aged patients. Eur J Cardiothorac Surg, 2006. 30(3): p. 485-91.
23. Mercer, C.W., et al., Polytetrafluoroethylene conduits versus homografts for right ventricular outflow tract reconstruction in infants and young children: An institutional experience. J Thorac Cardiovasc Surg, 2018.
24. Vitanova, K., et al., Which type of conduit to choose for right ventricular outflow tract reconstruction in patients below 1 year of age?dagger. Eur J Cardiothorac Surg, 2014. 46(6): p. 961-6; discussion 966.
25. Urso, S., et al., The Contegra conduit in the right ventricular outflow tract is an independent risk factor for graft replacement. Eur J Cardiothorac Surg, 2011. 40(3): p. 603-9.
26. Gatzoulis, M.A., et al., Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. The Lancet, 2000. 356(9234): p. 975-981.
27. Gatzoulis, M.A., et al., Right and left ventricular systolic function late after repair of tetralogy of Fallot. Am J Cardiol, 2000. 86(12): p. 1352-7.
28. Therrien, J., et al., Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation, 2001. 103(20): p. 2489-94.
29. Ferraz Cavalcanti, P.E., et al., Pulmonary Valve Replacement After Operative Repair of Tetralogy of Fallot: Meta-Analysis and Meta-Regression of 3,118 Patients From 48 Studies. Journal of the American College of Cardiology, 2013. 62(23): p. 2227-2243.
30. van der Bom, T., et al., The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. Am Heart J, 2012. 164(4): p. 568-75.
31. Fallot, A., Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque), par le Dr. A. Fallot. 1888, Marseille: Impr. de Barlatier-Feissat.
32. Therrien, J., et al., Pulmonary valve replacement in adults late after repair of tetralogy of fallot: are we operating too late? J Am Coll Cardiol, 2000. 36(5): p. 1670-5.
33. Bokma, J.P., et al., A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart, 2018. 104(9): p. 738-744.
34. Heng, E.L., et al., Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Circulation, 2017. 136(18): p. 1703.

35. Geva, T., et al., Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients with Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort. Circulation, 2018.
36. Arabkhani, B., et al., Does Pregnancy Influence the Durability of Human Aortic Valve Substitutes? Journal of the American College of Cardiology, 2012. 60(19): p. 1991-1992.
37. Cleuziou, J., et al., Pregnancy does not accelerate biological valve degeneration. Int J Cardiol, 2010. 145(3): p. 418-21.
38. Avila, W.S., et al., Influence of pregnancy after bioprosthetic valve replacement in young women: a prospective five-year study. J Heart Valve Dis, 2002. 11(6): p. 864-9.
39. Sadler, L., et al., Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. Bjog, 2000. 107(2): p. 245-53.
40. Duvekot, J.J. and L.L. Peeters, Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv, 1994. 49(12 Suppl): p. S1-14.
41. Robson, S.C., W. Dunlop, and S. Hunter, Haemodynamic changes during the early puerperium. Br Med J (Clin Res Ed), 1987. 294(6579): p. 1065.
42. Elkayam, U., et al., High-Risk Cardiac Disease in Pregnancy: Part I. J Am Coll Cardiol, 2016. 68(4): p. 396-410.
43. Bonhoeffer, P., et al., Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet, 2000. 356(9239): p. 1403-5.
44. Chatterjee, A., et al., Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies. J Am Heart Assoc, 2017. 6(8).
45. Harrild, D.M., et al., Impact of transcatheter pulmonary valve replacement on biventricular strain and synchrony assessed by cardiac magnetic resonance feature tracking. Circ Cardiovasc Interv, 2013. 6(6): p. 680-7.
46. Borik, S., et al., Percutaneous pulmonary valve implantation: 5 years of follow-up: does age influence outcomes? Circ Cardiovasc Interv, 2015. 8(2): p. e001745.
47. Reece, T.B., et al., Rethinking the ross procedure in adults. Ann Thorac Surg, 2014. 97(1): p. 175-81.
48. Mokhles, M.M., et al., Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. Eur Heart J, 2012. 33(17): p. 2213-24.
49. Bouhout, I., et al., Impact of the Learning Curve on Early Outcomes Following the Ross Procedure. Can J Cardiol, 2017. 33(4): p. 493-500.
50. Heneghan, C., et al., Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. The Lancet, 2012. 379(9813): p. 322-334.
51. Matchar, D.B., et al., Effect of Home Testing of International Normalized Ratio on Clinical Events. New England Journal of Medicine, 2010. 363(17): p. 1608-1620.
52. Buratto, E., et al., Improved Survival After the Ross Procedure Compared With Mechanical Aortic Valve Replacement. J Am Coll Cardiol, 2018. 71(12): p. 1337-1344.
53. Sharabiani, M.T., et al., Aortic Valve Replacement and the Ross Operation in Children and Young Adults. J Am Coll Cardiol, 2016. 67(24): p. 2858-70.

54. Mazine, A., et al., Long-Term Outcomes of the Ross Procedure Versus Mechanical Aortic Valve Replacement: Propensity-Matched Cohort Study. Circulation, 2016. 134(8): p. 576-85.
55. Andreas, M., et al., The Ross procedure offers excellent survival compared with mechanical aortic valve replacement in a real-world setting. Eur J Cardiothorac Surg, 2014. 46(3): p. 409-13; discussion 413-4.
56. Alsoufi, B., et al., Mechanical valves versus the Ross procedure for aortic valve replacement in children: propensity-adjusted comparison of long-term outcomes. J Thorac Cardiovasc Surg, 2009. 137(2): p. 362-370 e9.
57. Mokhles, M.M., et al., Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation, 2011. 123(1): p. 31-8.
58. El-Hamamsy, I., et al., Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet, 2010. 376(9740): p. 524-31.
59. Korteland, N.M., et al., Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation. Eur Heart J, 2017. 38(45): p. 3370-3377.
60. Korteland, N.M., et al., Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection? A Multicenter Randomized Trial. Circ Cardiovasc Qual Outcomes, 2017. 10(2).

2

Outcome after Surgical Repair of Tetralogy of Fallot: a Systematic Review and Meta-Analysis

Jamie LR Romeo, Jonathan RG Etnel, Johanna JM Takkenberg, Jolien W Roos-Hesselink , Wim A Helbing, Pieter van de Woestijne, Ad JJC Bogers, M Mostafa Mokhles

Journal of Thoracic and Cardio-Vascular Surgery

ABSTRACT

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. Intracardiac correction was pioneered by Walton Lillehei in 1955 and has since then gone through major developments. The aim of this study was to provide a systematic literature review of published results on the long-term outcome of complete surgical correction of TOF.

Methods

Medline, Pubmed, Embase, Web of science, Cochrane and Google scholar were systematically searched for literature published between January 2000 and July 2018. Pooled estimates with a random effects model after log-transformation were calculated for mortality and reintervention. Potential heterogeneity was assessed by subgroup analyses and meta-regression.

Results

A total of 143 papers of 137 distinct cohorts comprising 21,427 patients and total follow-up duration of 147,430 patient-years were included. Overall mean age at correction was 3.7±5.6 years, but excluding papers exclusively focusing on correction in adults yielded a mean age of 0.5±2.5 years at correction. Prior palliative shunts (107 studies), a transventricular approach (81 studies) and a transannular patch (TAP) (124 studies) were used in 16% (range 0-78%), 39% (range 0-100%) and 49% (range 0-100%) of the patients, respectively. In case a TAP was used, monocusp reconstruction was applied in 15% (range 0-100%) (49 studies). The most common genetic abnormality was Down syndrome, with a pooled estimated prevalence of 4.6% (range: 0-12.3%). The pooled estimates of early and late mortality were 2.84% (95% CI 2.34–3.45) and 0.42%/year (95% CI 0.33-0.54), respectively. The pooled estimate of late cardiac mortality was 0.26%/year (95% CI 0.21-0.34). Valve related mortality and non-valve related mortality had pooled estimates of 0.20%/year (95% CI 0.15-0.26) and 0.17%/year (95% CI 0.12-0.22), respectively. The pooled estimate of reintervention was 2.26%/year (95% CI 1.86-2.75).

Conclusion

TOF can be surgically corrected at a young age with low perioperative and long term mortality. Life-long intensive follow-up and substantial reintervention rates characterize the clinical course.

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic heart defect presenting in 3.4 per 10,000 live births [1, 2]. After being described by Étienne Fallot in 1888, it is currently known that an anterior misalignment of the conoventricular septum causes a broad spectrum of cardiac malformations [3]. The central malformations are a pulmonary stenosis, ventricular septal defect (VSD), and overriding aorta, accompanied by right ventricular hypertrophy. Total correction was pioneered by Walton Lillehei in 1955 by way of cross circulation and involves relieving the right ventricular outflow tract (RVOT) obstruction and closure of the VSD. [4]. Correction can be delayed by creating a shunt as a palliative first step. The natural course without surgery is dismal with less than 50% surviving the first three years and very few reaching adulthood [5]. Nowadays surgery can be performed with low perioperative mortality [6]. However, residual structural lesions with hemodynamic consequences and therefore reintervention are common [7]. Chronic pulmonary regurgitation and volume overload can have significant adverse consequences such as diminished exercise tolerance, arrhythmia, heart failure and sudden cardiac death [8, 9]. As initial cohorts are now reaching late adulthood, it becomes increasingly clear that significantly increased morbidity and mortality mark the lives of patients [10, 11].

To the best of our knowledge, we present the first systematic literature review and meta-analysis of outcome in patients after correction of TOF, with attention to surgical approach and techniques throughout the years.

METHODS

The protocol for this study was reviewed and approved by the Medical Ethics Review Committee of the Erasmus University Medical Center (MEC 2016-265). Informed consent was waived. The systematic review and meta-analysis was performed in accordance with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) and registered in PROSPERO (CRD42016039670) [12, 13].

Literature search strategy

A systematic literature search was conducted on 4th of July 2018 in Pubmed, Embase, Web of Science, Cochrane, and Google Scholar by a biomedical information specialist (Appendix A). Retrospective and prospective observational studies or randomized controlled trials written in English reporting on outcome after complete repair of tetralogy of Fallot in human subjects were included. Studies had to report on at least 20 patients and be published after the 1st of January 2000.

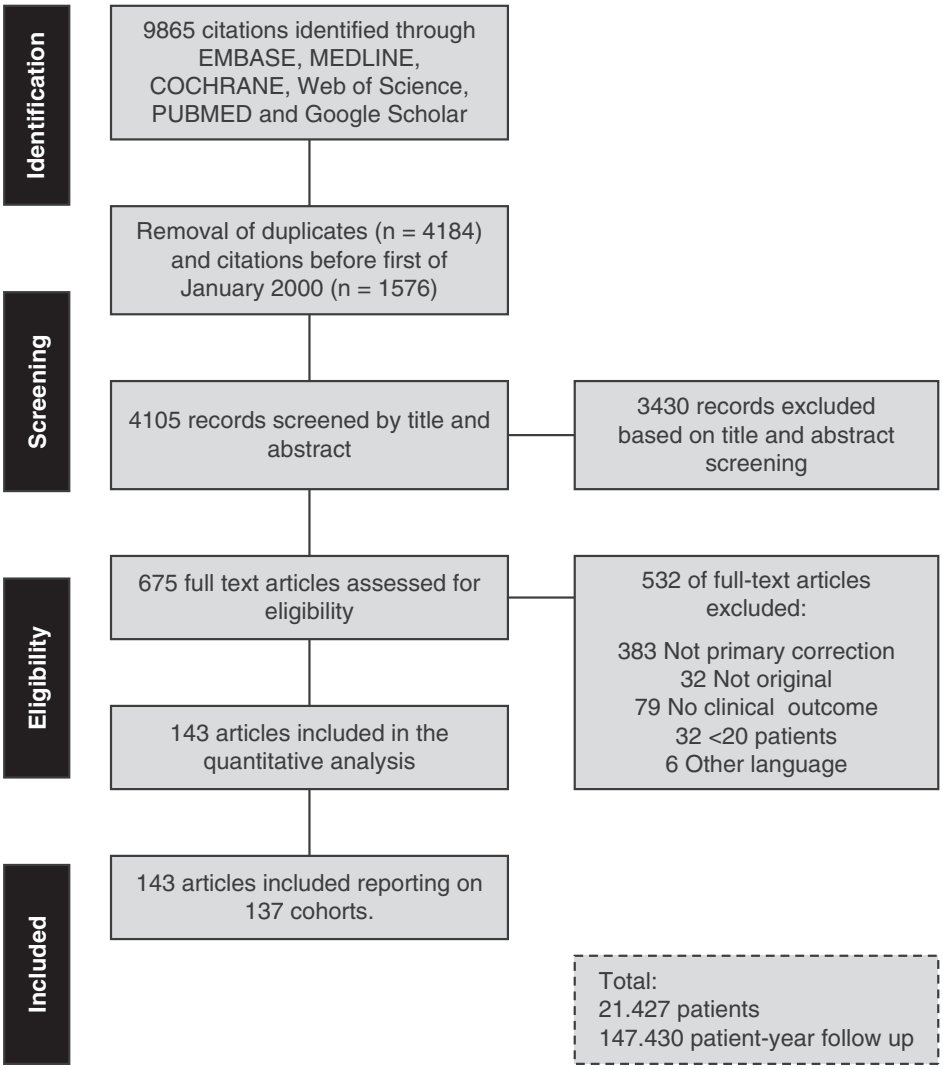


Figure 1 flow diagram of the search strategy

Exclusion criteria were non original articles, systematic reviews, case reports, meta-analyses, non-published work or studies not describing any of the outcome measures and studies including >10% patients with pulmonary atresia and/or major aortic pulmonary collateral arteries. In case of multiple publications on overlapping study populations, the publication with the greatest total follow-up in patient years and/or overall completeness of data was included for each outcome of interest separately.

Two authors (JLRR and JRGE) independently screened all titles and abstracts. A selection was made for full text screening after which full text assessment determined final

inclusion. The reference lists were manually screened for additional studies. In case of disagreement, an agreement was negotiated with a third independent reviewer (MMM).

Data extraction

Microsoft Office Excel 2010 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data was extracted independently by two reviewers (JLRR and JRGE) After data extraction, each reviewer verified the other reviewer's data entries. In case of discrepancies an agreement was negotiated. Recorded study characteristics, baseline patient and operative characteristics and outcome events are listed in the appendix.

Morbidity and mortality were documented according to the 2008 AATS/STS/EACTS guidelines [14]. The outcomes are early and late survival, and late reintervention. Early mortality was described separately as operative, within 30 days post-surgery and within initial hospital stay. Late mortality was any death beyond this period. Further detail on the variables is provided in the appendix. If total follow-up duration in patient-years was not reported, it was calculated by multiplying the number of patients with the mean follow-up duration of that study.

Statistical analysis

Continuous variables were reported as means ± standard deviations (SD) or median with range as appropriate. Categorical variables were reported as frequency with percentages. Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early risks of mortality and linearized occurrence rates of late morbidity and mortality were calculated for each individual study and pooled with the use of inverse variance weighting in a random-effects model according to the DerSimonian and Laird method. Outcomes were pooled on a logarithmic scale, as the Shapiro–Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. Inverse variance weighting was conducted according to the number of patients for early mortality and according to the number of patient-years of follow-up for late events. If variable means were not reported, medians were used instead. If variable standard deviations were not reported, this was estimated by dividing the standard deviation by 4 or the interquartile range by 1.35. Heterogeneity between studies was assessed with the Cochran Q and I^2-statistic and meta-regression was used to assess the potential effect on the primary outcomes [15]. Mean age, study size, inclusion type (consecutive or not), design (retrospective vs prospective), operational approach, and mean implantation year were tested as potential causes for heterogeneity using univariable random-effects meta-regression. Studies not reporting certain outcomes were excluded from the calculation of that pooled effect measure. In case of zero events for a certain outcome, 0.5 events were added for that study. P-values less than .05 were considered significant (2-tailed). The influence of potential publication bias on pooled outcome was investigated by conducting sensitivity

analyses by temporarily excluding the smallest quartile (by sample size) of included studies. Microsoft Excel (2010) and Comprehensive Meta-analysis (Version 2.0, Biostat, Englewood, USA) were used to perform the meta-analysis and meta-regression, respectively.

Table 1 Study Characteristics

First Author	Year of Publication	Inclusion period	Sample Size (N)	Male sex (%)	Mean age at repair ±SD	Prior palliative shunt (%)
D'Udekem [40]	2000	1964-1984	191	58,6	5,00±11,23	30,4
Dyamenahalli [30]	2000	1987-1994	89	73,0	1,08±0,36	23,6
Hirsch [21]	2000	1988-1999	31	71,0	0,06±0,03	6,5
Parry [19]	2000	1992-1999	42	NR	0,17±0,06	0,0
Pozzi [17]	2000	1993-1998	132	NR	1,28±1,38	18,9
Sohn [63]	2000	1984-1994	48	62,5	21,20±7,05	4,2
Boening* [16, 45]	2001	1975-1999	269	56,5	4,10±6,00	20,1
Bacha [22]	2001	1972-1977	57	70,2	0,67±0,49	0,0
Masuda [28]	2001	1975-1999	92	NR	0,51±0,26	5,4
Kaulitz [23]	2001	1987-1994	62	NR	0,49±0,28	0,0
Lange [80]	2001	1974-2000	197	60,0	0,66±0,24	11,2
Cobanoglu [20]	2002	1981-1995	63	63,5	0,54±0,03	27,0
Faidutti [81]	2002	1980-1999	501	NR	5,30±4,00	6,8
Alexiou [42]	2002	1974-2000	160	56,3	0,53±0,24	6,3
De Ruijter [82]	2002	1977-2000	171	62,0	1,90±2,50	19,3
Turrentine [57]	2002	1990-1999	84	39,3	2,38±2,44	44,0
Van Dongen [29]	2003	1997-1999	78	47,4	0,67±0,36	3,8
Ando [83]	2003	1978-2002	400	56,8	5,49±6,15	35,5
Atik [64]	2004	1982-2001	39	43,6	26,60±12,25	10,3
Lee [26]	2004	1990-2002	160	63,1	0,68±0,22	0,0
Nakazawa+ [84, 85]	2004	1970-1995	512	NR	4,40±6,00	NR
Henry [86]	2005	1998-2003	25	NR	NR	12,0
Erdoğan [65]	2005	1985-2002	64	56,3	20,60±7,50	3,1
Hörer [66]	2005	1974-2003	52	46,2	28,90±9,90	38,5
Kolcz [18]	2005	1998-2004	66	NR	0,09±0,14	0,0
Giannopoulos [87]	2005	1997-2004	163	45,4	1,50±3,40	8,0
Stewart [46]	2005	1997-2004	102	50,0	0,49±1,45	24,5
Airan [88]	2006	2000-2005	300	64,0	2,80±9,88	8,7
Michielon [89]	2006	1994-2004	306	57,2	0,53±0,44	13,1
Ge [90]	2006	1999-2003	115	NR	14,50±9,80	NR

RESULTS

Search

The search yielded 4,105 unique articles of which 143 matched our inclusion criteria (Figure 1). These reported on 137 different cohorts comprising 21,427 unique patients spanning operative cohorts from 1951 till 2017 (Table 1).

Transventriculair approach (%)	Transannular patch use (%)	30-Day mortality (%)	Late mortality (%/y)	Late Reinter-vention (%/y)	Total follow up dura-tion (patient-years)
99,0	51,8	0,0	0,40	0,85	3773
88,8	61,8	6,7	NR	NR	NR
6,5	93,5	0,0	0,62	6,24	160
14,3	23,8	0,0	0,38	2,26	133
31,8	65,2	0,0	0,13	0,13	390
91,7	35,4	0,0	0,45	2,72	221
51,3	38,3	10,8	0,27	2,54	1457
100,0	64,9	14,0	0,07	0,75	1340
NR	53,3	0,0	0,52	1,57	383
NR	59,7	4,8	0,12	1,93	415
NR	19,3	NR	NR	1,60	1503
98,4	84,1	4,8	0,57	0,29	699
NR	50,5	1,4	0,23	0,73	4810
56,9	60,0	1,9	0,12	2,49	1728
91,8	73,7	6,4	0,30	2,44	1642
NR	100,0	1,2	0,18	NR	282
11,5	35,9	1,3	NR	NR	NR
NR	49,5	0,5	0,06	0,31	3569
59,0	15,4	5,1	2,05	2,05	147
100,0	48,8	2,5	0,06	2,73	880
NR	20,3	NR	0,13	NR	5990
NR	NR	4,0	NR	NR	NR
NR	68,8	3,1	0,61	1,53	326
92,3	5,8	15,4	0,94	1,56	640
100,0	87,9	4,5	0,26	6,23	193
0,0	15,3	0,0	0,10	0,20	497
1,0	19,6	0,0	0,35	2,42	289
0,0	0,0	1,3	0,07	0,07	710
0,0	67,6	4,6	0,25	3,96	1188
100,0	26,1	0,9	0,33	NR	299

Table 1 Study Characteristics (*continued*)

First Author	Year of Publication	Inclusion period	Sample Size (N)	Male sex (%)	Mean age at repair ±SD	Prior palliative shunt (%)
Chittithavorn [91]	2006	2002-2004	31	51,6	7,70±5,10	45,2
Gang Liu [60]	2006	2003-2005	29	NR	7,20±4,70	0,0
Lu [67]	2006	1990-2004	57	36,8	24,80±8,40	0,0
Bisoi [68]	2007	1991-2001	284	68,7	19,40±2,50	15,8
Sadiq [69]	2007	1995-2004	58	63,8	22,50±5,00	3,4
Seddio [92]	2007	1995-2003	97	NR	0,63±2,62	28,9
Ghavidel [70]	2008	1995-2005	51	60,8	22,20±5,50	15,7
Kantorova [33]	2008	1996-2005	61	73,8	0,28±0,12	0,0
De Moraes Neto [93]	2008	1996-2004	67	53,7	0,60±0,21	0,0
Voges [47]	2008	1997-2006	216	NR	3,73±NR	NR
Tamesberger [34]	2008	1995-2006	90	63,3	0,13±0,08	0,0
Kaza [51]	2009	1990-2007	83	NR	0,03±0,02	NR
Li [94]	2009	2006-2008	99	60,6	8,11±7,35	0,0
Fraser [49]	2009	1995-2008	304	56,6	0,75±5,75	16,8
Gerling [25]	2009	1992-2003	124	60,5	4,06±8,25	10,5
Boni [55]	2009	2000-2008	24	54,2	0,68±1,78	0,0
Ma [95]	2009	2002-2007	76	64,5	5,60±2,10	0,0
Jost [96]	2010	1970-2007	52	57,7	50,00±8,00	51,9
Park [36]	2010	2000-2008	24	45,8	0,42±0,43	45,8
Park [59]	2010	1986-2007	734	60,5	1,43±6,86	21,0
Lim [97]	2010	1997-2008	90	61,1	0,79±14,24	16,7
François [98]	2010	1993-2008	88	61,4	0,81±0,62	21,6
Hashemzadeh [99]	2010	1995-2006	101	58,4	8,23±4,90	41,6
Kanter [35]	2010	2002-2008	36	NR	0,29±0,02	44,4
Tanveer [100]	2010	2008-2008	60	66,7	13,03±2,12	78,3
Pande [101]	2010	2005-2007	40	NR	9,60±8,90	NR
Ismail [62]	2010	2002-2007	83	67,5	1,51±1,90	NR
Arenz [102]	2011	2006-2009	63	NR	NR	0,0
Gnanappa [103]	2011	2003-2008	23	NR	32,30±NR	8,7
Lindberg [104]	2011	1951-2008	541	NR	2,34±NR	43,4
Tchoumi [105]	2011	2003-2009	22	63,6	9,18±6,50	NR
Robinson [106]	2011	1997-2008	140	NR	NR	0,0
Till [107]	2011	2004-2010	32	71,9	0,43±0,39	6,3
Hua [48]	2011	2006-2010	139	68,3	0,54±0,25	0,0
Van Der Hulst [56]	2012	NR	171	47,4	2,97±4,87	30,4
Jeewa [108]	2012	1991-2009	180	55,0	1,00±0,80	6,7
Yang [109]	2012	1970-2009	179	55,9	19,20±8,30	16,8

Transventricular approach (%)	Transannular patch use (%)	30-Day mortality (%)	Late mortality (%/y)	Late Reintervention (%/y)	Total follow up duration (patient-years)
0,0	54,8	0,0	3,23	3,23	16
0,0	100,0	3,4	NR	NR	NR
NR	73,7	7,0	0,97	0,32	309
78,2	70,4	9,9	0,54	0,46	1306
100,0	75,9	6,9	0,59	0,30	338
11,3	80,4	2,1	0,13	2,06	388
NR	64,7	2,0	0,56	2,24	179
NR	72,1	1,6	0,36	3,28	275
89,6	64,2	3,0	0,41	0,20	246
NR	32,3	NR	NR	1,54	586
93,3	65,6	0,0	0,48	6,90	420
NR	83,1	NR	NR	25,36	79
100,0	61,6	3,0	NR	NR	NR
1,0	73,0	0,3	0,57	1,14	877
NR	35,5	4,8	0,69	3,62	580
0,0	0,0	0,0	0,76	4,57	66
100,0	31,3	0,0	0,66	NR	76
NR	19,2	5,8	3,74	0,90	775
20,8	66,7	4,2	0,60	6,02	83
57,6	56,3	3,7	0,14	2,44	9187
17,8	20,0	0,0	0,34	NR	293
0,0	68,2	NR	NR	2,96	607
20,8	59,4	6,9	0,70	NR	287
0,0	83,3	0,0	1,42	4,26	141
90,0	73,3	3,3	5,52	NR	18
0,0	100,0	2,5	2,50	NR	40
0,0	77,1	0,0	NR	NR	NR
100,0	100,0	0,0	NR	NR	NR
8,7	13,0	4,3	1,09	1,09	46
75,8	24,0	5,7	0,35	NR	8548
NR	54,5	9,1	0,85	NR	59
NR	64,3	NR	NR	NR	444
6,3	75,0	0,0	0,40	4,80	125
0,0	5,0	0,7	0,32	0,32	313
34,5	41,5	NR	NR	NR	4138
NR	33,3	NR	NR	NR	1440
NR	37,4	2,2	0,33	0,87	2416

Table 1 Study Characteristics (*continued*)

First Author	Year of Publication	Inclusion period	Sample Size (N)	Male sex (%)	Mean age at repair ±SD	Prior palliative shunt (%)
Chiu [110]	2012	1970-2002	819	61,1	6,50±7,60	14,5
Bové [54]	2012	1994-2010	140	60,0	0,55±2,08	19,3
Arenz [37]	2013	2005-2012	87	64,4	0,29±0,14	0,0
Zheng [71]	2013	1995-2010	56	46,4	29,50±10,65	0,0
Bakhtiary [27]	2013	1998-2009	120	53,3	0,42±0,20	0,0
Sun [111]	2013	2008-2009	106	50,9	0,92±0,43	0,0
Kim [41]	2013	1991-2011	326	58,9	1,08±17,73	27,6
Sasson [58]	2013	2003-2009	163	58,3	2,32±4,71	9,2
Sfyridis [112]	2013	1997-2010	245	59,6	1,60±13,85	13,1
Amirnovin [113]	2013	2005-2009	25	64,0	0,33±0,25	NR
Zhang [114]	2013	2010-2011	89	57,3	4,30±1,66	0,0
Attanawanich [115]	2013	1990-2004	93	NR	4,60±2,25	32,3
Kim [116]	2013	1997-2007	340	NR	3,00±11,98	5,3
Waqar [117]	2013	2009-2012	129	68,2	14,90±6,48	3,1
Bautista-Hernandez [52]	2013	2009-2012	38	NR	0,46±2,44	NR
Egbe* [118-120]	2014	2001-2012	97	52,6	0,41±NR	0,0
Mimic [24]	2014	2003-2011	251	55,0	0,68±2,30	17,1
Kim [50]	2014	1989-2005	114	66,7	0,78±0,17	2,6
Yaliniz [121]	2014	2004-2010	112	NR	1,92±0,98	NR
François [122]	2014	2008-2010	31	61,3	0,49±0,41	12,9
Woldu [123]	2014	2004-2011	163	60,7	NR	5,7
Nakashima [124]	2014	NR	40	NR	0,68±0,72	52,5
Niu [125]	2014	1995-2008	298	56,7	0,81±0,61	16,8
Kirsch [31]	2014	1995-2009	277	57,0	0,28±0,13	0,0
Peer [126]	2014	2004-2011	155	62,6	0,20±0,04	0,0
Talwar [72]	2014	2002-2013	41	68,3	35,80±6,00	4,9
Hoashi [127]	2014	1989-2000	84	56,0	1,90±1,40	13,1
Vida [53]	2014	2007-2013	69	27,5	0,31±0,33	1,4
D'Udekem* [128, 129]	2014	1980-2005	675	62,2	1,31±NR	32,6
Luijten [130]	2015	1970-2012	453	63,1	0,58±4,90	12,8
Saygi [131]	2015	2010-2013	122	55,7	2,30±2,50	12,3
Ylitalo [44]	2015	1962-2007	600	60,0	3,90±4,10	24,8
Ji [132]	2015	2012-2012	113	69,0	1,38±0,47	14,2
Devendran [133]	2015	2005-2012	79	NR	6,00±10,33	6,3
Sen [134]	2016	2010-2014	80	NR	0,39±0,21	5,0
Bigdelian [135]	2016	2010-2013	40	42,5	0,71±0,19	0,0
Alassal [136]	2016	NR	183	45,9	NR	NR

Transventriculair approach (%)	Transannular patch use (%)	30-Day mortality (%)	Late mortality (%/y)	Late Reinter-vention (%/y)	Total follow up dura-tion (patient-years)
82,9	54,2	2,3	0,27	NR	13808
0,0	65,7	0,0	0,10	2,48	1050
80,5	65,5	0,0	0,19	6,44	264
100,0	76,8	3,6	0,42	1,68	476
100,0	50,8	0,0	0,09	2,81	570
50,0	NR	1,9	0,29	0,14	350
32,2	35,9	0,3	0,40	3,73	1983
0,0	57,7	2,5	NR	NR	NR
0,0	73,9	0,0	0,14	1,10	2083
NR	NR	4,0	4,00	16,00	13
NR	70,8	1,1	NR	NR	NR
100,0	100,0	5,4	NR	NR	763
NR	NR	0,6	NR	5,85	992
0,0	15,5	0,8	3,15	NR	32
100,0	73,7	0,0	0,72	NR	70
29,9	21,6	0,0	0,13	0,39	776
69,7	52,6	0,4	0,09	4,07	1130
13,2	50,0	0,0	0,22	1,44	1387
NR	NR	9,8	0,22	NR	224
0,0	61,3	0,0	0,81	NR	62
NR	65,0	0,0	0,36	19,29	140
NR	55,0	0,0	0,22	1,30	230
0,0	0,0	0,0	0,38	NR	2116
29,6	67,5	0,0	NR	NR	NR
93,5	32,9	0,6	NR	NR	NR
26,8	14,6	4,9	1,43	NR	140
0,0	0,0	0,0	0,08	0,23	1327
0,0	50,7	0,0	0,46	1,83	110
0,0	69,0	1,0	0,10	2,39	7898
0,0	64,9	1,1	0,18	2,59	6029
NR	79,5	7,4	NR	NR	NR
NR	31,7	6,7	0,40	1,15	10517
31,9	61,9	0,0	0,54	NR	367
0,0	74,7	2,5	0,39	2,34	128
NR	63,8	6,3	8,33	15,00	60
33,3	NR	5,8	1,25	NR	40
NR	24,6	1,6	NR	NR	NR

Table 1 Study Characteristics (*continued*)

First Author	Year of Publication	Inclusion period	Sample Size (N)	Male sex (%)	Mean age at repair ±SD	Prior palliative shunt (%)
Amir [137]	2018	2007-2016	41	NR	NR	NR
Amirghofran [138]	2016	2001-2010	349	57,9	4,00±4,17	NR
Arafat [139]	2018	2011-2016	46	67,4	1,09±0,40	17,4
Balasubramanya [140]	2018	2005-2015	43	53,5	0,05±0,05	0,0
Bhardwaj and Ladha * [141, 142]	2017	2013-2015	200	64,5	3,05±1,31	NR
Guevara [143]	2017	2010-2015	60	63,3	1±NR	NR
Jalili [144]	2017	1995-2010	92	52,2	7,30±8,40	NR
Jang [145]	2016	2000-2009	36	50,0	1,04±0,52	16,7
Khan [146]	2016	2012-2014	80	60,0	21±0,21	NR
Kim [147]	2016	2000-2005	43	60,5	1,17±0,54	23,3
Logoteta [148]	2018	1996-2006	87	64,4	14,20±13,80	19,5
Mercer-Rosa [149]	2017	2012-2017	151	62,9	0,30±0,30	13,9
Pande [150]	2018	2006-2010	70	80,0	11,00±15,50	NR
Raj [151]	2017	NR	50	52,0	6,00±2,87	NR
Wilder and Hickey * [152, 153]	2016	2000-2012	383	55,9	0,53±4,16	NR
Wilder and Hickey * [152, 153]	2017	2000-2012	42	61,9	0,13±0,14	NR
Wilder and Hickey * [152, 153]	2017	2000-2012	28	46,4	0,38±0,49	NR
Dharmapuram [154]	2017	2013-2015	52	NR	1,50±1,13	0,0
Sullivan [155]	2017	2000-2015	284	60,2	0,54±2,56	NR
An [156]	2017	2004-2014	23	NR	4.00±1,18	NR
Li [157]	2016	2008-2014	67	59,7	1.00±4,44	NR
Waqar [158]	2017	2012-2017	307	74,9	9,56±4,89	1,3
Caruana[159]	2017	1962-2000	103	60,2	6,31±13,97	37,9
Dobbels [160]	2017	1962-2015	273	57,9	1.00±2,96	NR
Dorobantu [161]	2018	2000-2013	1560	72,6	0,5±0	15,1
Lodin [162]	2017	2007-2015	115	59,1	0,35±0,13	NR
Sandoval [163]	2016	2000-2015	89	NR	0,32±0,20	0,0
Simon[164]	2017	2000-2010	94	61,7	0,34±0,20	0,0
Villemain [165]	2016	1992-2013	141	NR	NR	NR
Pathan [166]	2017	2015-2015	66	66,7	6,20±2,50	NR
Naik [167]	2017	2009-2012	21	66,7	0,25±0,36	0,0
Chira + Chira [168, 169]	2017	2001-2006	71	67,6	NR	0,0
Wallen [170]	2018	2008-2016	450	NR	NR	0,0

NR = not reported, * results of articles with considerable or undetermined overlapping cohorts are combined, + Erratum considered when analyzing data

Transventricular approach (%)	Transannular patch use (%)	30-Day mortality (%)	Late mortality (%/y)	Late Reintervention (%/y)	Total follow up duration (patient-years)
NR	NR	1,2	NR	NR	NR
NR	45,3	4,3	NR	NR	NR
NR	23,9	4,3	0,56	2,82	177
NR	55,8	2,3	0,33	16,61	151
NR	NR	5,5	NR	NR	NR
NR	NR	NR	NR	NR	NR
NR	NR	14,1	7,61	28,26	92
NR	100,0	# NR	NR	NR	342
NR	NR	8,8	NR	NR	NR
NR	NR	1,2	0,63	1,69	473
NR	32,2	1,1	0,04	1,07	1122
NR	58,3	3,3	NR	NR	NR
NR	NR	NR	0,89	NR	335
NR	NR	2,0	NR	NR	NR
NR	NR	0,3	NR	NR	1953
NR	NR	2,4	NR	NR	214
NR	NR	3,6	NR	NR	143
0,0	100,0	3,8	0,58	2,31	87
0,0	73,9	2,1	NR	0,04	1396
56,5	21,7	0,0	NR	NR	NR
NR	56,7	1,5	NR	NR	NR
0,0	NR	1,3	NR	NR	NR
NR	33,0	19,4	0,26	0,81	2716
NR	100,0	NR	0,31	0,01	6552
NR	45,7	2,1	NR	3,93	7332
NR	58,3	0,9	NR	NR	NR
NR	44,9	0,0	0,22	0,11	445
0,0	51,1	0,0	NR	NR	NR
NR	0,0	NR	NR	NR	NR -
NR	15,2	13,6	NR	NR	- NR
100,0	0,0	NR	NR	NR	67
0,0	64,8	NR	0,15	NR	338
NR	100,0	5,6	NR	NR	NR

Study and baseline characteristics

The pooled overall mean age at correction was 3.7±5.6 years and mean follow up time was 8.6±6.1 years (total follow-up 147,430 patient-years). Among studies with a mean age at correction less than one year, hereby excluding papers focusing on correction in adults, revealed a mean age was 0.5±2.5 years at correction.

Outcomes

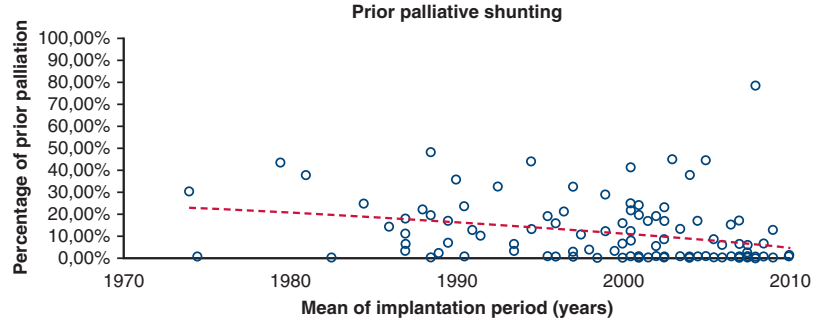
Pooled estimates of associated cardiac and genetic abnormalities are presented in Table 2. The most common genetic abnormality was down syndrome (25 studies), with a pooled estimated prevalence of 4.6% (range: 0-12.3%). Pooled estimates for all studies, per mean age group and studies with a mean follow up duration exceeding 10 years are presented in tables 3A and 3B. Funnel plots for all outcomes are presented in the supplementary files. Overall, early mortality is 2.84% (95% confidence interval [CI] 2.34-3.45%) after correction, after which the linearized probability of death is 0.42% per year (95% CI 0.33-0.54%). The yearly rate of reintervention is 2.26% (95% CI 1.86-2.28%), with reintervention due to severe pulmonary regurgitation of 0.42% per year (95% CI 0.28-0.62%) and reintervention due to severe obstruction of the RVOT of 0.76% per year (95% CI 0.60-0.97%). Pooled estimates of survival and reintervention grouped per continent are presented in the Central picture. Subgroup analyses of articles reporting predominant use of a transatrial-transpulmonary approach (i.e. >90% of the cases) and similar subgroup analyses of a transventricular approach are presented in table 3C.

Figures 2 through 4 present the temporal trends of transannular patch (TAP) use, prior palliation and a transventricular approach (as opposed to transatrial/transpulmonary approach) as a function of the mean year of surgery of each study, by absolute proportion and after log-odds-transformation. The proportion of TAP over time remained stable around 50%. The prevalence of prior palliation and a transventricular approach in the included cohorts declined over time to approximately 7% and 10%, respectively. Regression lines were fitted assuming a logarithmic association, indicating significant decline over time ($p<0.001$) of prior palliation and a transventricular approach, respectively. Figure 5 (central image) shows the global distribution of included articles with the pooled estimates of key outcomes.

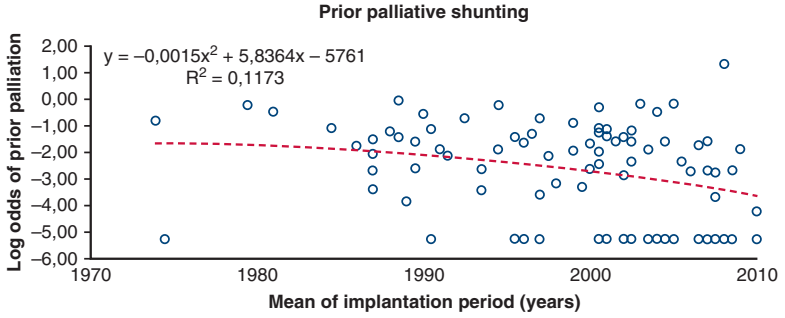
Table 2 Reported prevalence of associated abnormalities

	Pooled prevalence	Range (%)	Studies (n)
Associated cardiac abnormalities			
ASD (%)	18,49	0-79,25	29
PFO (%)	13,53	0-76,16	14
PDA (%)	12,36	0-35,94	23
Multiple VSDs (%)	2,28	0-6,86	18
LSVC (%)	5,61	0-13,64	22
Coronary Anomaly (%)	5,00	0-19,67	37
Subaortic Membrane (%)	0,32	0-1,33	10
Arteria Lusoria (%)	0,10	0-1,15	10
Right Sided Aortic Arch (%)	12,45	0-53,57	31
APVP (%)	1,62	0-8,50	17
Other (%)	14,33	0-56,73	27
Genetic abnormalities			
22q11.2 deletion (%)	4,00	0-16,67	25
Down syndrome (%)	4,62	0-12,32	25
Noonan syndrome (%)	0,31	0-1,59	12
VACTERL association (%)	1,56	0-3,92	14
CHARGE syndrome (%)	0,73	0-2,94	12
Goldenhar syndrome (%)	0,21	0-1,15	10
Arnold-Chiari malformation (%)	0,14	0-1,75	9
Other (%)	6,99	0-17,86	15

APVC = Abnormal Pulmonary Venous Circulation, ASD = Atrial Septal Defect, CHARGE = Coloboma Heart defects Choanal Atresia Retardation Genitourinary malformation and Ear abnormalities, LSVC = Left-sided Superior Vena Cava, PDA = Patent Ductus Arteriosus, PFO = Patent Foramen Ovale, VACTERL = vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities, VSD = Ventricular Septal Defect.

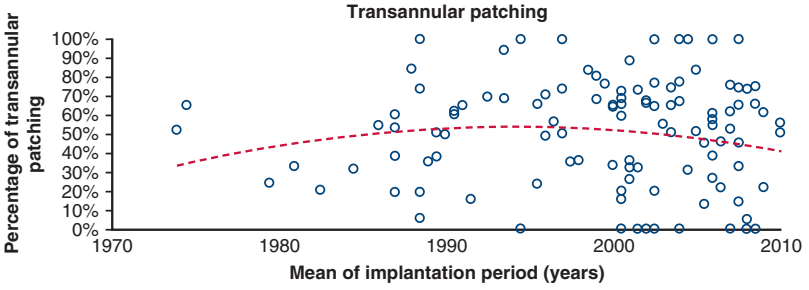


A

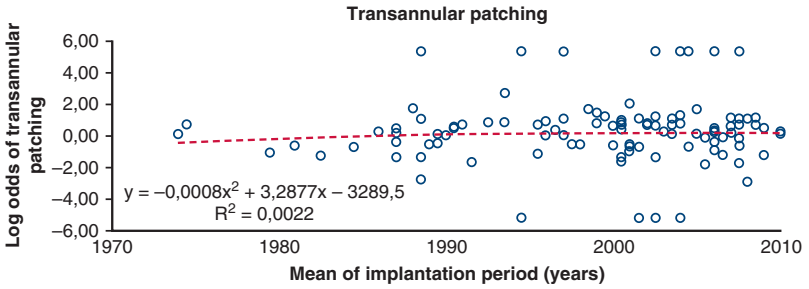


B

Figure 2 Prevalence of prior palliative shunting over time



A



B

Figure 3 Prevalence of transannular patching over time

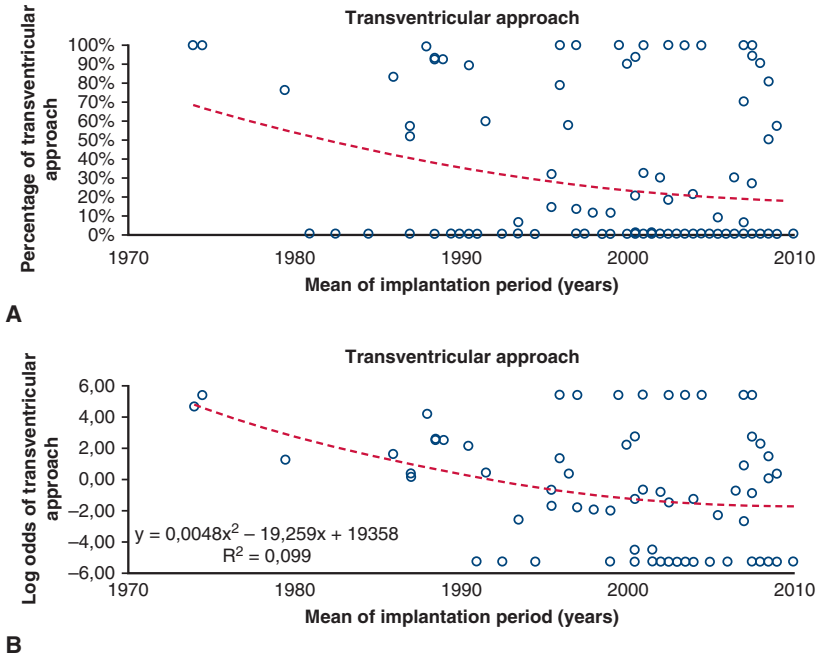


Figure 4 Prevalence of a transventricular approach over time

Meta-regression

There was evidence for substantial heterogeneity among some outcomes (table 3). Results of the univariable meta-regression are presented in Table 4, as potential explanation for heterogeneity. We found that studies with a higher age at correction (p<.001), earlier year of correction (p=.008), a higher rate of a trans ventricular approach (p<.001), and a higher rate of prior palliation reported an increased early mortality. Furthermore, studies with a higher age at correction (p<.001), later year of operation (p=.013) and smaller study size (p<.001) and larger proportions of TAP use (p<.001) or prior palliation (p<.001) reported increased late mortality.

Table 3A Pooled early mortality and late annualized mortality risks, late annualized operation and reintervention risks

	Overall		Average age ≤ 1 year	
	Pooled estimate (range)	N	Pooled estimate (range)	N
Age mean±sd (y)	3.7±5.6	128	0.5±2.5	56
Previous palliative shunt	16 (0-78)	107	11 (0-53)	47
Transventricular approach	39 (0-100)	81	30 (0-100)	39
Transatrial completely	58 (0-100)	75	65 (0-100)	35
Transannular patch (TAP)	49 (0-100)	124	50 (0-94)	53
TAP with Monocusp Reconstruction	15 (0-100)	49	10 (0-55)	18

	Estimate (95% CI)	N	I^2	P-value	Estimate (95% CI)	N	I^2	P-value
Early mortality (%)	2.84 (2.34-3.45)	123	76%	<.001	1.99 (1.49-2.64)	52	46%	<.001
Late mortality (%/y)	0.42 (0.33-0.54)	93	78%	<.001	0.35 (0.24-0.53)	41	54%	<.001
Cardiac mortality (%/y)	0.26 (0.21-0.34)	82	44%	<.001	0.19 (0.13-0.28)	36	0%	.934
Valve related mortality (%/y)	0.20 (0.15-0.26)	77	33%	.004	0.18 (0.12-0.27)	36	0%	.929
Death related to reintervention (%/y)	0.13 (0.10-0.18)	78	14%	.163	0.17 (0.11-0.27)	36	0%	.924
Non valve related mortality (%/y)	0.17 (0.12-0.22)	79	30%	.008	0.17 (0.11-0.26)	36	0%	.917
Non-cardiac mortality (%/y)	0.21 (0.16-0.27)	81	32%	.004	0.20 (0.13-0.31)	29	49%	.002
Reintervention (%/y)	2.26 (1.86-2.75)	81	94%	<.001	2.24 (1.74-2.89)	31	93%	<.001
Reoperation (%/y)	1.66 (1.35-2.04)	75	90%	<.001	1.55 (1.25-1.25)	30	79%	<.001
Reintervention for severe PR (%/y)	0.42 (0.28-0.62)	49	84%	<.001	0.56 (0.38-0.81)	25	33%	.059
Reintervention for severe RVOTO (%/y)	0.76 (0.60-0.97)	55	66%	<.001	1.12 (0.88-1.42)	30	63%	.003
Catheter based reintervention (%/y)	0.71 (0.51-1.00)	63	91%	<.001	0.69 (0.40-1.18)	25	94%	<.001
PM or ICD (%/y)	0.18 (0.14-0.23)	62	19%	<.001	0.11 (0.08-0.15)	24	0%	.784

Sd = Standard Deviations, N = number of studies reporting on the variable, PM = pacemaker, ICD = implantable cardioverter defibrillator, PR= Pulmonary regurgitation, RVOTO = right ventricular outflow tract obstruction, VRM = valve related mortality, TAP = transannular patch, NYHA = New York Heart Association.

Table 3B Pooled early mortality and late annualized mortality risks, late annualized operation and reintervention risks

	Average age > 1 year		Mean follow-up > 10 years	
	Pooled estimate (range)	N	Pooled estimate (range)	N
Age mean±sd (y)	5.7±7.1	72	4.0±6.4	21
Previous palliative shunt	19 (0-78)	55	24 (0-48)	19
Transventricular approach	46 (0-100)	40	49 (0-100)	13
Transatrial completely	54 (0-100)	39	51 (0-100)	10
Transannular patch (TAP)	49 (0-100)	65	49 (0-100)	21
TAP with Monocusp Reconstruction	19 (0-100)	28	18 (0-100)	6

	Estimate (95% CI)	N	I^2	P-value	Estimate (95% CI)	N	I^2	P-value
Early mortality (%)	3.78 (3.96-4.82)	65	80%	<.001	3.61 (2.28-5.73)	18	87%	<.001
Late mortality (%/y)	0.48 (0.34-0.67)	50	85%	<.001	0.29 (0.18-0.46)	20	92%	<.001
Cardiac mortality (%/y)	0.30 (0.22-0.42)	45	63%	<.001	0.17 (0.11-0.25)	15	69%	<.001
Valve related mortality (%/y)	0.21 (0.15-0.31)	40	56%	<.001	0.09 (0.05-0.14)	13	59%	.004
Death related to reintervention (%/y)	0.11 (0.07-0.18)	41	34%	.020	0.04 (0.03-0.07)	13	0%	.441
Non valve related mortality (%/y)	0.16 (0.11-0.25)	42	52%	<.001	0.07 (0.05-0.10)	13	12%	.329
Non-cardiac mortality (%/y)	0.24 (0.18-0.31)	47	5%	.375	0.26 (0.12-0.56)	12	49%	.027
Reintervention (%/y)	2.34 (1.71-3.21)	46	94%	<.001	2.21 (1.12-4.35)	13	95%	<.001
Reoperation (%/y)	1.81 (1.28-2.57)	43	93%	<.001	1.55 (0.98-2.47)	12	86%	<.001
Reintervention for severe PR (%/y)	0.36 (0.19-0.67)	24	91%	<.001	0.29 (0.14-0.59)	9	90%	<.001
Reintervention for severe RVOTO (%/y)	0.43 (0.28-0.64)	25	74%	<.001	0.54 (0.34-0.88)	8	72%	.001
Catheter based reintervention (%/y)	0.72 (0.45-1.16)	35	87%	<.001	0.46 (0.10-2.10)	9	94%	<.001
PM or ICD (%/y)	0.25 (0.19-0.33)	35	7%	.359	0.31 (0.17-0.55)	8	23%	.245

Sd = Standard Deviations, N = number of studies reporting on the variable, PM = pacemaker, ICD = implantable cardioverter defibrillator, VRM = valve related mortality, TAP = transannular patch, NYHA = New York Heart Association.

Table 3C Pooled early mortality and late annualized mortality risks, late annualized operation and reintervention risks

	Transatrial/transpulmonary approach >90% of cases		Transventricular approach >90% of cases	
	Pooled estimate (range)	N	Pooled estimate (range)	N
Age mean±sd (y)	2.5±5.8	30	6.2±5.7	20
Previous palliative shunt	14 (0-45)	28	12 (0-78)	19
Transventricular approach	0 (0-10)	29	97 (90-100)	21
Transatrial completely	99 (91-100)	30	3 (0-10)	18
Transannular patch (TAP)	50 (0-100)	29	58 (0-100)	21
TAP with Monocusp Reconstruction	10 (0-100)	21	25 (0-59)	3

	Estimate (95% CI)	N	I^2	P-value	Estimate (95% CI)	N	I^2	P-value
Early mortality (%)	1.53 (1.10-2.14)	29	21%	.152	3.56 (2.26-5.62)	20	61%	<.001
Late mortality (%/y)	0.35 (0.23-0.55)	23	48%	.006	0.46 (0.32-0.67)	16	19%	.241
Cardiac mortality (%/y)	0.23 (0.12-0.44)	20	42%	.025	0.29 (0.17-0.48)	16	23%	.192
Valve related mortality (%/y)	0.18 (0.10-0.34)	20	30%	.102	0.24 (0.16-0.37)	16	0%	.533
Death related to reintervention (%/y)	0.19 (0.09-0.38)	20	29%	.108	0.15 (0.08-0.29)	16	0%	.590
Non valve related mortality (%/y)	0.20 (0.10-0.40)	20	37%	.052	0.17 (0.08-0.34)	16	27%	.155
Non-cardiac mortality (%/y)	0.28 (0.17-0.48)	20	34%	.068	0.21 (0.13-0.32)	16	0%	.538
Reintervention (%/y)	2.64 (1.67-4.16)	20	92%	<.001	2.02 (1.42-2.86)	15	91%	<.001
Reoperation (%/y)	2.09 (1.50-2.91)	20	78%	<.001	1.51 (1.08-2.12)	14	81%	001
Reintervention for severe PR (%/y)	0.63 (0.35-1.13)	14	73%	<.001	0.42 (0.29-0.60)	10	0%	.442
Reintervention for severe RVOTO (%/y)	0.97 (0.66-1.43)	18	60%	.001	0.65 (0.33-1.27)	11	75%	001
Catheter based reintervention (%/y)	0.72 (0.28-1.90)	16	93%	<.001	0.40 (0.18-0.88)	12	91%	001
PM or ICD (%/y)	0.15 (0.07-0.30)	13	25%	.196	0.23 (0.14-0.35)	14	19%	.247

Sd = Standard Deviations, N = number of studies reporting on the variable, PM = pacemaker, ICD = implantable cardioverter defibrillator, VRM = valve related mortality, TAP = transannular patch, NYHA = New York Heart Association.

Table 4. Meta-regression for early and late death and late reintervention, respectively. Coefficients for the logit incidence and annual occurrence rates respectively, with 95% confidence intervals and p-values

	Coefficient	95% CI	*p*-value
Early mortality			
Age	0.026	0.015 – 0.038	<.001
Year of operation	-0.032	-0.059 – (-0.009)	0.008
Study size	-.001	-0.002 – 0.000	0.257
Study design (prospectively)	-0.236	-1.0.23 – 0.550	0.556
Gender (female)	0.453	-2.694 – 3.601	0.778
TAP	-0.002	-0.007 – 0.003	0.401
Transventricular approach	0.011	0.007 – 0.015	<.001
Staged approach	0.013	0.005 – 0.020	<.001
Monocusp reconstruction	-0.007	-0.015 – 0.001	0.226
Late mortality			
Age	0.049	0.041 – 0.057	<.001
Year of operation	0.033	0.007 – 0.059	0.013
Study size	-0.002	-0.003 – (-0.001)	<.001
Study design (prospective)	0.327	-0.711 – 1.364	0.537
Gender (female)	1.224	-2.232 – 4.680	0.488
TAP	-0.012	-0.017 –0.000	<.001
Transventricular approach	0.003	0.000 – 0.006	0.136
Staged approach	0.026	0.018 – 0.033	<.001
Monocusp reconstruction	0.003	-0.014 – 0.020	0.739
Late reintervention			
Age	-0.041	-0.050 – -0.032	<.001
Year of operation	0.048	0.022 – 0.075	<.001
Study size	-0.001	-0.002 – 0.001	0.263
Study design (prospective)	-0.021	-1.137 – 1.094	0.970
Gender (female)	-2.574	-6.264 – 1.115	0.171
TAP	0.016	0.013 – 0.019	<.001
Transventricular approach	0.000	-0.002 – 0.001	0.887
Staged approach	-0.022	-0.026 – -0.017	<.001
Monocusp reconstruction	0.009	0.000 – 0.018	0.0580

TAP = Transannular patch

DISCUSSION

This is the first systematic review and meta-analysis of outcome after complete repair of TOF. TOF can be corrected with low procedural mortality and good long term survival. Both the use of a transventricular approach and prior palliation with a shunt have declined during the last decades. Depending on anatomy and clinical status, complete single stage repair can be safely accomplished at an age of 6 months. However, the rate of reintervention is substantial and most if not all patients can be expected to undergo one or more reinterventions during their lifetime, highlighting the importance of lifelong follow up. Associated structural and genetic abnormalities are common and should be considered.

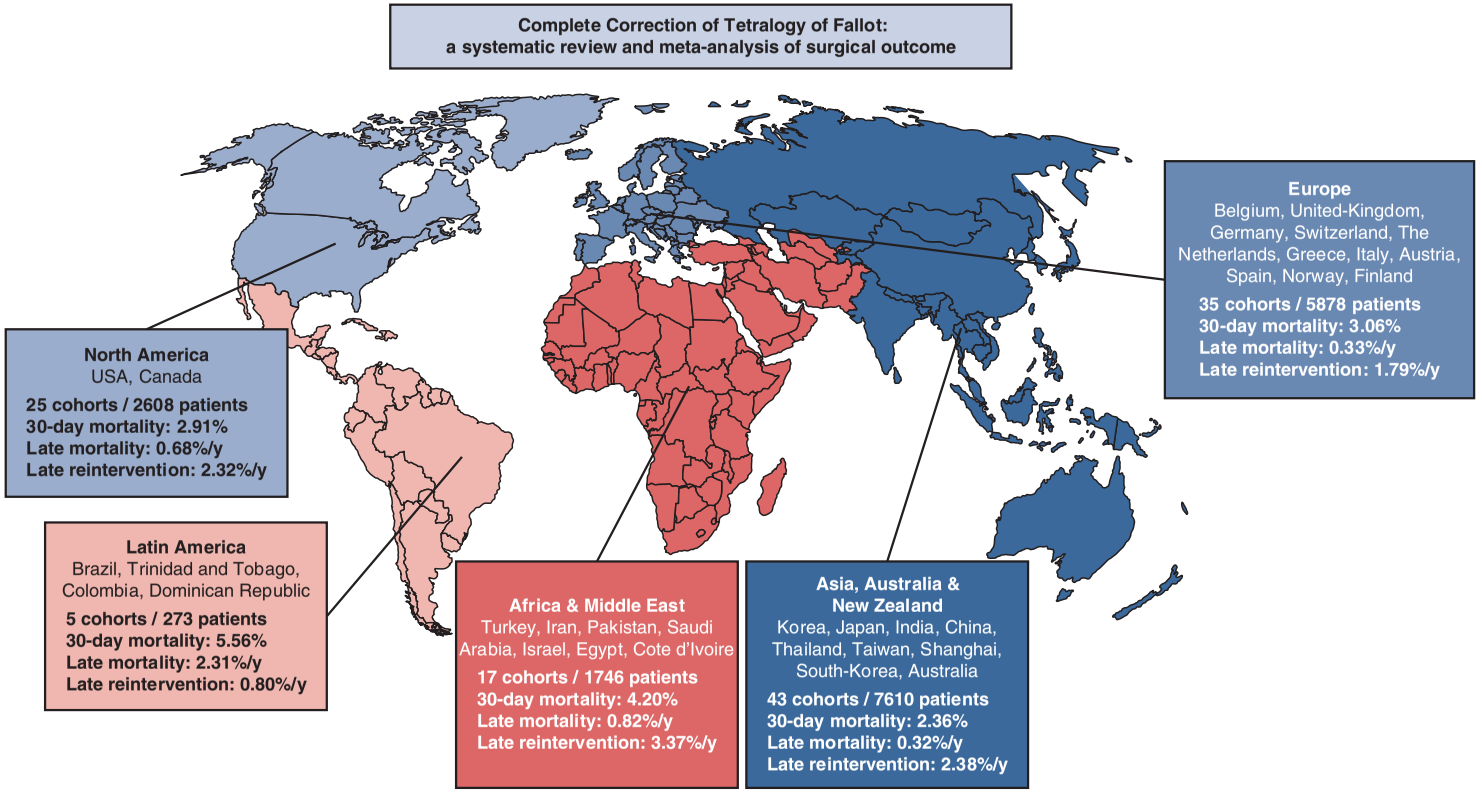


Figure 5 Global distribution of included literature with estimates of key outcomes

Pediatric outcomes

The subgroup analysis showed that repair in children below the age of 1 can be achieved with low early and late mortality and morbidity. Over the last decades a trend occurred towards complete repair in younger cyanotic as well as acyanotic patients [16-20], as also evidenced by our results. Complete repair before the age of 1 is generally associated with good short and long term outcome, with an acceptable reintervention risk [17, 18, 21-28], but occasionally prolonged intensive care unit stay [29] and prolonged overall hospital stay [30, 31]. The subgroup analysis indicated no differences in short and long term mortality when focusing on age groups. Substantial reintervention rates have been described however in symptomatic neonates undergoing complete single stage repair [21]. It also seems that patients under one year at time of repair show comparable normal development in pulmonary artery size regardless of symptomatology [23]. Overall, complete repair before the age of 1 can be achieved without compromising outcome, regardless of symptomatology.

Primary repair versus prior palliation

In 1945 Blalock and Taussig described the first 3 patients in which a shunt was used as palliation [32]. Since then, primary repair versus prior palliation has been debated, as it is interrelated with the shift towards earlier correction. Currently, the issue has remained relevant and continues to be debated. The results of this study show that palliation prior to correction has declined over time. Our subgroup analysis indicated that in studies with a mean age less than one, prior palliation was performed in only 11% of cases. Historically it was assumed that a hypoplastic pulmonary annulus and arteries were contra-indications for primary repair. Advocates of primary repair believed, however, that hypoplastic arteries reflect the lack of flow, and therefore would benefit from an early flow restoration. A review of 251 consecutive patients operated in the Great Ormond Street Hospital revealed no difference in late reintervention rate between primary and staged repair. Their policy preferred prior palliation in symptomatic patients and patients with additional genetic and anatomic abnormalities. In asymptomatic patients, elective primary repair was undertaken around 6 months with good results [24]. A uniform policy of elective primary repair in children under 6 months can also result in favorable outcome, despite a TAP being used more often [33]. Even in symptomatic neonates, early primary repair can be performed safely but has been associated with increased TAP use and more frequent late reinterventions [34, 35]. In 24 symptomatic patients under 3 months of age, Park and colleagues reported a TAP rate of 46.2% and a comparably favorable short term outcome [36]. In a uniform policy of primary repair in symptomatic children under the age of 6 months, Arenz and colleagues described 100% operative and late survival in 87 consecutive patients after 7 years and deemed shunting as obsolete [37]. The Leipzig Heart Centre reported outcome in 120 patients below 8

months of age after a similar policy of primary repair and reported an actuarial survival of 100% after 10 years [27]. In conclusion, a policy of early complete repair can be carried out safely by experienced centers.

Transannular patching

The overall temporal trend of the use of a TAP has remained stable around 50% during the last 50 years (Figure 3). During the early 2000's the detrimental nature of chronic PR became apparent leading to a more conscious use of TAP [9, 38, 39], because in young patients TAP had been associated with an increased rate of late adverse events [40, 41]. Repair of younger, asymptomatic patients does not always increase TAP rate however [19, 20, 23, 42]. Furthermore, in the reports mentioned earlier in which younger age was associated with an increased TAP rate, late outcome was not compromised.

It is however more likely that differences in TAP usage are the result of policy based on symptomatology and severity of RVOT obstruction, rather than age per se [43]. In case a TAP is needed, it has been associated with a lower incidence of RVOT restenosis and does not appear to influence long term survival and reintervention rate [20, 22, 44, 45]. However, one has to consider the fact that guidelines and consensus about reintervention for RVOT restenosis are more clear than for severe PR. Furthermore, only the rate of techniques could be assessed retrospectively from which we have to assume that the anatomy (i.e. severe stenosis) demanded aggressive relief. Therefore, it could also be argued that TAP is not a risk factor itself, but indicates a more difficult and hazardous anatomy to begin with. Vast technical differences in TAP like length and width of the patch, the resulting annulus, length of the ventriculotomy and additional infundibulectomy further limit inferences. Secondly, it is more likely that residual lesions regardless of the surgical approach eventually determine survival and reintervention.

Pulmonary valve preservation

Acknowledgement of the adverse consequences of chronic PR also raised interest in techniques and the indication of when the PV could be spared. The intention of operating pulmonary valve-sparingly often includes extensive subvalvular and infundibular resection, a transatrial-transpulmonary approach, and peri-annular patching with no or a limited RV incision. Safe execution with sufficient reduction in RV to LV pressure ratios has been described in patients with a PV annulus z-score >-4 [46, 47]. Introducing a strategy of restrictive annular enlargement in the University Hospital of Schlesweig-Holstein in Germany led to a lower TAP rate without an increase in residual RVOT obstruction or reintervention rate. No TAP was used in any pulmonary annulus with a z-score >-2 [47]. Hua and colleagues used a cut-off z-score of >-3 and successfully avoided a TAP in 95% of their patients [48]. The policy of the Texas Children's Hospital includes limiting the length of the transannular incision to a maximum of 5 mm into the infundibulum, which

could be followed in 99% of 301 consecutive patients. Significant RVOT obstruction was present in only 2 patients and freedom from reoperation was 96% after 7 years [49]. Kim and colleagues compared annulus preservation with TAP in two cohorts which were propensity score matched on pulmonary artery size and PV annulus diameter (z-score). Freedom from PVR was significantly lower in patients who received a TAP [50]. Kaza and colleagues preferred valve preservation to both TAP and conduits in any annulus with a z-score of >-2 [51]. Additional intraoperative balloon dilatation of the PV is potentially effective in relieving RVOT obstruction while retaining annular growth potential [52, 53]. In general, these policies allow safe execution with occasionally a modest increase in residual RVOT gradient but an overall reduction in PR [46-48, 54, 55]. Any resulting mild residual RVOT gradient without significant PR can be treated conservatively [56].

Monocusp reconstruction

In case a TAP is deemed unavoidable, monocusp reconstruction to limit PR can be an intuitively appealing alteration. In cohorts in which the use of monocusp reconstruction was described we found a comparable pooled annual early and late mortality incidence of 2.91% and 0.29%/year, respectively, to the overall population. Pooled annual late reintervention of 1.82% was also comparable to the overall population. Whether monocusp reconstruction reduces significant PR remains questionable however. Turrentine and colleagues found a significantly lower incidence of significant PR in patients after PTFE monocusp reconstruction after a 3.6 year follow up, with preserved leaflet mobility in 85%. However, a TAP was used relatively soon if annuli had a z-score < -1 [57]. Sasson and colleagues performed PTFE monocusp reconstruction in patients with an annulus z-score <-2, and also reported a lower incidence of significant PR at discharge [58]. More often however, monocusp reconstruction did not prevent the development of significant PR beyond the direct postoperative period [51]. Park and colleagues found no benefit in terms of early survival and reoperation [59]. Although it can be performed safely with a modest additional bypass time, often no clear and persistent benefit is reported on PR or reintervention rates beyond the immediate postoperative period [28, 42, 51, 59-62].

Outcome after correction at adult age

Several authors report outcome after elective correction of adolescents (>12 years) [63-72]. Pooled linearized occurrence rates of early and late mortality of these patients were 7.55% and 0.95%/year, respectively. These patients generally represent a specific subset of survivors with mild pulmonary stenosis that for diverse reasons did not undergo or require complete correction. Overall, these patients can also be corrected safely with good long term outcome [65] and substantial functional improvement [63, 70], but,

as our analysis shows, there is an increased early mortality warranting careful patient selection.

PVR after correction

Conclusive evidence that supports a survival benefit in patients that undergo PVR with severe PI after initial correction is still lacking [73, 74]. In the current paradigm PVR results in beneficial RV remodeling which should induce a reduction in the hazard of arrhythmia and heart failure; both potentially lethal. The rationale for PVR is based on the severe consequences of unrestrained PR and adverse RV remodeling, but reversibility of hazard is till this day still implied. Volumetric and hemodynamic improvements within the first year after PVR are evident and have led to a broad support for proactive intervention in asymptomatic patients [75, 76]. Nevertheless, a survival benefit has never been proven and the influence on QRS duration and risk of arrhythmia are conflicting [73, 74, 77-79]. The search continues towards finding the right biomarker, thresholds and treatment goals that could guide optimal timing of PVR.

Furthermore, long term reports into the fourth and fifth post-operative decade are extremely rare. Subtle variation in surgical technique, timing and policy could perhaps only come to expression as hazard differences in late adulthood. As we are currently entering the period in which the first patients will enter late adulthood after contemporary surgical correction, reports like the one by Cuypers and colleagues highlight the importance of long follow-up and are highly desirable [11].

STRENGTHS AND LIMITATIONS

We presented the first systematic review and meta-analysis on clinical outcome after complete correction of TOF. It represents an extensive review of all contemporary literature. The results presented here can be used in future guidelines and help members of congenital Heart Teams in making better decisions before, during and after surgical correction.

Our study has several limitations. It is a meta-analysis of mostly retrospective and observational studies with limited follow up and all limitation inherent to the pooling of observation data without access to individual patient data. Events are assumed to be evenly distributed across time which is a resulting limitation. The heterogeneous nature of TOF is evident and its highly complex set of anatomical anomalies, rarely seen in isolation, must be seen as a continuous spectrum of complexity. This was partly reflected by the overall heterogeneity among the outcomes which we could not completely explain. Developments over time have led to evolution of insights and contemporary practice. Presented associations between surgical approach and outcomes are therefore to be

interpreted with caution as they are always confounded by unobservable anatomic variation and constantly developing clinical judgement. The reported prevalence of associated genetic or cardiac abnormalities probably represents the bare minimum of the true prevalence. Differences in interest, resources and clinical capacity may have led to differences in detection and reporting rate. Lastly, surgical correction is a privilege common in modern western society but rare in most third-world and developing nations. Data from these countries is scarce. More data on outcome of developing countries and outcome during late adulthood is urgently required.

CONCLUSIONS

Advanced statistical analysis substantiates the clinical evidence that Tetralogy of Fallot can be surgically corrected at a young age with an early mortality of 2.84% and a linearized yearly occurrence rate of death of 0.42%. Patients that undergo correction often present with additional cardiac and genetic abnormalities. Substantial reintervention rates characterize clinical course, emphasizing the importance of life-long intensive follow-up and multidisciplinary care.

REFERENCE LIST

1. Hoffman, J.I. and S. Kaplan, The incidence of congenital heart disease. J Am Coll Cardiol, 2002. 39(12): p. 1890-900.
2. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
3. Fallot, A., Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque), par le Dr. A. Fallot. 1888, Marseille: Impr. de Barlatier-Feissat.
4. Lillehei, C.W., et al., Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. Ann Surg, 1955. 142(3): p. 418-42.
5. Bertranou, E.G., et al., Life expectancy without surgery in tetralogy of Fallot. Am J Cardiol, 1978. 42(3): p. 458-66.
6. Ferraz Cavalcanti, P.E., et al., Pulmonary valve replacement after operative repair of Tetralogy of Fallot: Meta-analysis and meta-regression of 3,118 patients from 48 studies. J Am Coll Cardiol, 2013. 62(23): p. 2227-2243.
7. Cuypers, J.A.A.E., et al., Unnatural history of tetralogy of fallot: Prospective follow-up of 40 years after surgical correction. Circulation, 2014. 130(22): p. 1944-1953.
8. Nollert, G.D.A., et al., Risk Factors for Sudden Death After Repair of Tetralogy of Fallot. Ann Thorac Surg, 2003. 76(6): p. 1901-1905.

9. Gatzoulis, M.A., et al., Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. The Lancet, 2000. 356(9234): p. 975-981.
10. Nollert, G., et al., Long-term results of total repair of tetralogy of Fallot in adulthood: 35 years follow-up in 104 patients corrected at the age of 18 or older. Thorac Cardiovasc Surg, 1997. 45(4): p. 178-81.
11. Cuypers, J.A., et al., Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. Circulation, 2014. 130(22): p. 1944-53.
12. Moher, D., et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg, 2010. 8(5): p. 336-41.
13. Stroup, D.F., et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama, 2000. 283(15): p. 2008-12.
14. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
15. Higgins, J.P., et al., Measuring inconsistency in meta-analyses. Bmj, 2003. 327(7414): p. 557-60.
16. Boening, A., et al., Correction of tetralogy of Fallot: Does the time period of surgery influence the outcome? Thorac Cardiovasc Surg, 2001. 49(4): p. 210-215.
17. Pozzi, M., et al., Tetralogy of Fallot: What operation, at which age. Eur J Cardio-thorac Surg, 2000. 17(6): p. 631-636.
18. Kolcz, J. and C. Pizarro, Neonatal repair of tetralogy of Fallot results in improved pulmonary artery development without increased need for reintervention. Eur J Cardio-thorac Surg, 2005. 28(3): p. 394-399.
19. Parry, A.J., et al., Elective primary repair of acyanotic tetralogy of Fallot in early infancy: overall outcome and impact on the pulmonary valve. J Am Coll Cardiol, 2000. 36(7): p. 2279-83.
20. Cobanoglu, A. and J.M. Schultz, Total correction of tetralogy of fallot in the first year of life: Late results. Ann Thorac Surg, 2002. 74(1): p. 133-138.
21. Hirsch, J.C., R.S. Mosca, and E.L. Bove, Complete repair of tetralogy of Fallot in the neonate: results in the modern era. Ann Surg, 2000. 232(4): p. 508-14.
22. Bacha, E.A., et al., Long-term results after early primary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg, 2001. 122(1): p. 154-161.
23. Kaulitz, R., et al., Primary repair of tetralogy of fallot in infancy--the effect on growth of the pulmonary arteries and the risk for late reinterventions. Cardiol Young, 2001. 11(4): p. 391-398.
24. Mimic, B., et al., Neither age at repair nor previous palliation affects outcome in tetralogy of fallot repair. Eur J Cardio-thorac Surg, 2014. 45(1): p. 92-99.
25. Gerling, C., et al., Do the age of patients with tetralogy of fallot at the time of surgery and the applied surgical technique influence the reoperation rate? a single-center experience. Herz, 2009. 34(2): p. 155-160.
26. Lee, J.R., et al., Complete repair of tetralogy of Fallot in infancy. Interact Cardiovasc Thorac Surg, 2004. 3(3): p. 470-474.
27. Bakhtiary, F., et al., Outcome and incidence of re-intervention after surgical repair of tetralogy of fallot. J Card Surg, 2013. 28(1): p. 59-63.

28. Masuda, M., et al., Early and late results of total correction of congenital cardiac anomalies in infancy. Jpn J Thorac Cardiovasc Surg, 2001. 49(8): p. 497-503.

29. Van Dongen, E.I., et al., The influence of perioperative factors on outcomes in children aged less than 18 months after repair of tetralogy of Fallot. J Thorac Cardiovasc Surg, 2003. 126(3): p. 703-710.

30. Dyamenahalli, U., et al., Influence of perioperative factors on outcomes in children younger than 18 months after repair of tetralogy of Fallot. Ann Thorac Surg, 2000. 69(4): p. 1236-1242.

31. Kirsch, R.E., et al., Results of elective repair at 6 months or younger in 277 patients with tetralogy of Fallot: A 14-year experience at a single center. J Thorac Cardiovasc Surg, 2014. 147(2): p. 713-717.

32. Blalock, A. and H.B. Taussig, The surgical treatment of malformations of the heart: In which there is pulmonary stenosis or pulmonary atresia. Journal of the American Medical Association, 1945. 128(3): p. 189-202.

33. Kantorova, A., et al., Primary early correction of tetralogy of Fallot irrespective of age. Cardiol Young, 2008. 18(2): p. 153-157.

34. Tamesberger, M.I., et al., Early primary repair of tetralogy of fallot in neonates and infants less than four months of age. Ann Thorac Surg, 2008. 86(6): p. 1928-35.

35. Kanter, K.R., et al., Symptomatic Neonatal Tetralogy of Fallot: Repair or Shunt? Ann Thorac Surg, 2010. 89(3): p. 858-863.

36. Park, C.S., et al., Symptomatic young infants with tetralogy of fallot: One-stage versus staged repair. J Card Surg, 2010. 25(4): p. 394-399.

37. Arenz, C., et al., Is there any need for a shunt in the treatment of tetralogy of fallot with one source of pulmonary blood flow? Eur J Cardio-thorac Surg, 2013. 44(4): p. 648-654.

38. Gatzoulis, M.A., et al., Right and left ventricular systolic function late after repair of tetralogy of Fallot. Am J Cardiol, 2000. 86(12): p. 1352-7.

39. Geva, T., et al., Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol, 2004. 43(6): p. 1068-1074.

40. D'Udekem, Y., et al., Tetralogy of Fallot: Transannular and right ventricular patching equally affect late functional status. Circulation, 2000. 102(19): p. III116-III122.

41. Kim, H., et al., Early and late outcomes of total repair of tetralogy of Fallot: Risk factors for late right ventricular dilatation. Interact Cardiovasc Thorac Surg, 2013. 17(6): p. 956-962.

42. Alexiou, C., et al., Repair of tetralogy of Fallot in infancy with a transventricular or a transatrial approach. Eur J Cardio-thorac Surg, 2002. 22(2): p. 174-183.

43. Lee, C., et al., Does limited right ventriculotomy prevent right ventricular dilatation and dysfunction in patients who undergo transannular repair of tetralogy of Fallot? Matched comparison of magnetic resonance imaging parameters with conventional right ventriculotomy long-term after repair. J Thorac Cardiovasc Surg, 2014. 147(3): p. 889-95.

44. Ylitalo, P., et al., Need of transannular patch in tetralogy of fallot surgery carries a higher risk of reoperation but has no impact on late survival: Results of fallot repair in Finland. Eur J Cardio-thorac Surg, 2015. 48(1): p. 91-97.

45. Boening, A., et al., Tetralogy of fallot: Influence of surgical technique on survival and reoperation rate. Thorac Cardiovasc Surg, 2001. 49(6): p. 355-360.
46. Stewart, R.D., et al., Tetralogy of Fallot: results of a pulmonary valve-sparing strategy. Ann Thorac Surg, 2005. 80(4): p. 1431-8; discussion 1438-9.
47. Voges, I., et al., Restrictive enlargement of the pulmonary annulus at surgical repair of tetralogy of Fallot: 10-year experience with a uniform surgical strategy. Eur J Cardio-thorac Surg, 2008. 34(5): p. 1041-1045.
48. Hua, Z., et al., A new pulmonary valve cusp plasty technique markedly decreases transannular patch rate and improves midterm outcomes of tetralogy of Fallot repair. Eur J Cardio-thorac Surg, 2011. 40(5): p. 1221-1226.
49. Fraser, C.D., et al., Right ventricular infundibulum sparing (RVIS) tetralogy of fallot repair: A review of over 300 patients. Ann Surg, 2009. 250(4): p. 611-617.
50. Kim, G.S., S. Han, and T.J. Yun, Pulmonary Annulus Preservation Lowers the Risk of Late Postoperative Pulmonary Valve Implantation After the Repair of Tetralogy of Fallot. Pediatr Cardiol, 2014. 0.
51. Kaza, A.K., et al., Long-term results of right ventricular outflow tract reconstruction in neonatal cardiac surgery: Options and outcomes. J Thorac Cardiovasc Surg, 2009. 138(4): p. 911-916.
52. Bautista-Hernandez, V., et al., Valve-sparing tetralogy of fallot repair with intraoperative dilation of the pulmonary valve. Pediatr Cardiol, 2013. 34(4): p. 918-923.
53. Vida, V.L., et al., Evolving strategies for preserving the pulmonary valve during early repair of tetralogy of Fallot: Mid-term results. J Thorac Cardiovasc Surg, 2014. 147(2): p. 687-696.
54. Bové, T., et al., Assessment of a right-ventricular infundibulum-sparing approach in transatrial-transpulmonary repair of tetralogy of Fallot. Eur J Cardio-thorac Surg, 2012. 41(1): p. 126-133.
55. Boni, L., et al., Current strategies in tetralogy of Fallot repair: pulmonary valve sparing and evolution of right ventricle/left ventricle pressures ratio. Eur J Cardio-thorac Surg, 2009. 35(5): p. 885-890.
56. Van Der Hulst, A.E., et al., Mild residual pulmonary stenosis in tetralogy of fallot reduces risk of pulmonary valve replacement. Ann Thorac Surg, 2012. 94(6): p. 2077-2082.
57. Turrentine, M.W., et al., PTFE monocusp valve reconstruction of the right ventricular outflow tract. Ann Thorac Surg, 2002. 73(3): p. 871-880.
58. Sasson, L., et al., Right ventricular outflow tract strategies for repair of tetralogy of Fallot: Effect of monocusp valve reconstruction. Eur J Cardio-thorac Surg, 2013. 43(4): p. 743-751.
59. Park, C.S., et al., The long-term result of total repair for tetralogy of Fallot. Eur J Cardio-thorac Surg, 2010. 38(3): p. 311-317.
60. Gang Liu, X., et al., Simultaneous Enlargement of the Pulmonary Annulus and the Pulmonary Cusp with Autologous Pericardium in Right Ventricular Outflow Tract Reconstruction. J Surg Res, 2006. 136(2): p. 320-324.
61. Anagnostopoulos, P., et al., Pulmonary valve cusp augmentation with autologous pericardium may improve early outcome for tetralogy of Fallot. J Thorac Cardiovasc Surg, 2007. 133(3): p. 640-647.
62. Ismail, S.R., et al., Early outcome of tetralogy of Fallot repair in the current era of management. J Saudi Heart Assoc, 2010. 22(2): p. 55-59.

63. Sohn, S. and Y.T. Lee, Outcome of adults with repaired tetralogy of Fallot. J Korean Med Sci, 2000. 15(1): p. 37-43.

64. Atik, F.A., et al., Long-term results of correction of tetralogy of Fallot in adulthood. Eur J Cardio-thorac Surg, 2004. 25(2): p. 250-255.

65. Erdogan, H.B., et al., Long-term outcome after total correction of tetralogy of Fallot in adolescent and adult age. J Card Surg, 2005. 20(2): p. 119-23.

66. Horer, J., et al., Correction of tetralogy of Fallot and of pulmonary atresia with ventricular septal defect in adults. Ann Thorac Surg, 2005. 80(6): p. 2285-91.

67. Lu, X., et al., Long-term results of surgical treatment of tetralogy of Fallot in adults. Thorac Cardiovasc Surg, 2006. 54(5): p. 295-9.

68. Bisoi, A.K., et al., Tetralogy of Fallot in teenagers and adults: Surgical experience and follow-up. Gen Thorac Cardiovasc Surg, 2007. 55(3): p. 105-112.

69. Sadiq, A., et al., Long-term functional assessment after correction of tetralogy of Fallot in adulthood. Ann Thorac Surg, 2007. 83(5): p. 1790-5.

70. Ghavidel, A.A., et al., Complete surgical repair of Tetralogy of Fallot in adults, is it ever too late? J Card Surg, 2008. 23(1): p. 23-6.

71. Zheng, D.W., et al., Long-term outcome of correction of tetralogy of Fallot in 56 adult patients. Chin Med J, 2013. 126(19): p. 3675-3679.

72. Talwar, S., et al., Repair of tetralogy of Fallot in or beyond the fourth decade of life. Congenit Heart Dis, 2014. 9(5): p. 424-32.

73. Heng, E.L., et al., Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Circulation, 2017. 136(18): p. 1703.

74. Bokma, J.P., et al., A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart, 2018. 104(9): p. 738-744.

75. Ferraz Cavalcanti, P.E., et al., Pulmonary valve replacement after operative repair of tetralogy of Fallot: meta-analysis and meta-regression of 3,118 patients from 48 studies. J Am Coll Cardiol, 2013. 62(23): p. 2227-43.

76. Cheung, E.W.Y., W.H.S. Wong, and Y.F. Cheung, Meta-analysis of pulmonary valve replacement after operative repair of tetralogy of fallot. Am J Cardiol, 2010. 106(4): p. 552-557.

77. Therrien, J., et al., Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation, 2001. 103(20): p. 2489-94.

78. Harrild, D.M., et al., Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. Circulation, 2009. 119(3): p. 445-51.

79. Gengsakul, A., et al., The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. European Journal of Cardio-thoracic Surgery, 2007. 32(3): p. 462-468.

80. Lange, R., et al., Results of biventricular repair of congenital cardiac malformations: Definitive corrective surgery? Eur J Cardio-thorac Surg, 2001. 20(6): p. 1207-1213.

81. Faidutti, B., et al., How to diminish reoperation rates after initial repair of tetralogy of Fallot? Ann Thorac Surg, 2002. 73(1): p. 96-101.

82. De Ruijter, F.T.H., et al., Right ventricular dysfunction and pulmonary valve replacement after correction of tetralogy of Fallot. Ann Thorac Surg, 2002. 73(6): p. 1794-1800.

83. Ando, M., et al., Tetralogy of Fallot with subarterial ventricular septal defect. Ann Thorac Surg, 2003. 76(4): p. 1059-1065.
84. Nakazawa, M., et al., Arrhythmias Late after Repair of Tetralogy of Fallot: A Japanese Multicenter Study. Circ J, 2004. 68(2): p. 126-130.
85. Nakazawa, M., et al., Erratum: Arrhythmias Late after Repair of Tetralogy of Fallot - A Japanese Multicenter Study (Circulation Journal (2004) 68 (126-130)). Circ J, 2004. 68(4): p. 403.
86. Henry, G., et al., Paediatric open heart surgery in Trinidad and Tobago: An example of collaborative care. West Indian Med J, 2005. 54(1): p. 9-13.
87. Giannopoulos, N.M., et al., Surgical results after total transatrial/transpulmonary correction of tetralogy of Fallot. Hell J Cardiol, 2005. 46(4): p. 273-282.
88. Airan, B., et al., Total Transatrial Correction of Tetralogy of Fallot: No Outflow Patch Technique. Ann Thorac Surg, 2006. 82(4): p. 1316-1321.
89. Michielon, G., et al., Genetic syndromes and outcome after surgical correction of tetralogy of fallot. Ann Thorac Surg, 2006. 81(3): p. 968-975.
90. Ge, J.J., et al., Right ventricular dysfunction due to right ventricular outflow tract patch. Asian Cardiovasc Thorac Ann, 2006. 14(3): p. 213-218.
91. Chittithavorn, V., et al., Predicted outcome after repair of tetralogy of fallot by postoperative pressure ratio between right and left ventricle. J Med Assoc Thailand, 2006. 89(1): p. 43-50.
92. Seddio, F., et al., Previous palliation in patients with tetralogy of Fallot does not influence the outcome of later repair. J Cardiovasc Med, 2007. 8(2): p. 119-122.
93. De Moraes Neto, F.R., et al., Intracardiac correction of Tetralogy of Fallot in the first year of life. Short-term and midium-term results. Braz J Cardiovasc Surg, 2008. 23(2): p. 216-223.
94. Li, B., et al., Clinical benefit of cardiac ischemic postconditioning in corrections of tetralogy of Fallot. Interact Cardiovasc Thorac Surg, 2009. 8(1): p. 17-21.
95. Ma, Z.S., et al., Effect of captopril on pulmonary artery pressure following corrective surgery for tetralogy of fallot. J Card Surg, 2009. 24(5): p. 553-557.
96. Jost, C.H.A., et al., Tetralogy of Fallot repair in patients 40 years or older. Mayo Clin Proc, 2010. 85(12): p. 1090-1094.
97. Lim, J.Y., et al., Tetralogy of Fallot without the infundibular septum-restricted growth of the pulmonary valve annulus after annulus preservation may render the right ventricular outflow tract obstructive. J Thorac Cardiovasc Surg, 2010. 0.
98. François, K., et al., The fate of the aortic root after early repair of tetralogy of Fallot. Eur J Cardiothorac Surg, 2010. 37(6): p. 1254-1258.
99. Hashemzadeh, K. and S. Hashemzadeh, Early and late results of total correction of tetralogy of fallot. Acta Med Iran, 2010. 48(2): p. 117-122.
100. Tanveer, R., et al., Continuous versus interrupted technique of ventricular septal defect (VSD) closure in total correction for tetrology of fallot pertaining to residal VSD. J Pak Med Assoc, 2010. 60(4): p. 253-256.
101. Pande, S., et al., Pericardial monocusp for pulmonary valve reconstruction: A new technique. Asian Cardiovasc Thorac Ann, 2010. 18(3): p. 279-284.

102. Arenz, C., et al., Congenital heart surgery: Surgical performance according to the Aristotle complexity score. Eur J Cardio-thorac Surg, 2011. 39(4): p. e33-e37.

103. Gnanappa, G.K., et al., Outcome of complex adult congenital heart surgery in the developing world. Congenit Heart Dis, 2011. 6(1): p. 2-8.

104. Lindberg, L., et al., How common is severe pulmonary hypertension after pediatric cardiac surgery? J Thorac Cardiovasc Surg, 2002. 123(6): p. 1155-1163.

105. Tchoumi, J.C.T., et al., Late surgical treatment of tetralogy of Fallot. Cardiovas J Afri, 2011. 22(4): p. 179-181.

106. Robinson, J.D., et al., The evolving role of intraoperative balloon pulmonary valvuloplasty in valve-sparing repair of tetralogy of Fallot. J Thorac Cardiovasc Surg, 2011. 142(6): p. 1367-1373.

107. Till, K., et al., Realignment of the ventricular septum using partial direct closure of the ventricular septal defect in Tetralogy of Fallot. Eur J Cardio-thorac Surg, 2011. 40(4): p. 1016-1019.

108. Jeewa, A., et al., Genetic determinants of right-ventricular remodeling after tetralogy of Fallot repair. Pediatr Res, 2012. 72(4): p. 407-413.

109. Yang, M.C., et al., Natural and unnatural history of tetralogy of Fallot repaired during adolescence and adulthood. Heart Vessels, 2012. 27(1): p. 65-70.

110. Chiu, S.N., et al., Long-Term survival and unnatural deaths of patients with repaired tetralogy of fallot in an asian cohort. Circ Cardiovasc Qual Outcomes, 2012. 5(1): p. 120-125.

111. Sun, G., et al., Primary repair of tetralogy of Fallot in infants: Transatrial/ transpulmonary or transventricular approach. Asian J Surg, 2013. 36(4): p. 137-143.

112. Sfyridis, P.G., et al., Preservation of right ventricular structure and function following transatrial-transpulmonary repair of tetralogy of fallot. Eur J Cardio-thorac Surg, 2013. 43(2): p. 336-342.

113. Amirnovin, R., et al., B-type natriuretic peptide levels predict outcomes in infants undergoing cardiac surgery in a lesion-dependent fashion. J Thorac Cardiovasc Surg, 2013. 145(5): p. 1279-1287.

114. Zhang, R., et al., Effect of morphine-induced postconditioning in corrections of tetralogy of fallot. J Cardiothorac Surg, 2013. 8: p. 76.

115. Attanawanich, S., et al., Pulmonary cusp augmentation in repair of tetralogy of Fallot. Asian Cardiovasc Thorac Ann, 2013. 21(1): p. 9-13.

116. Kim, S.J., et al., The role of transesophageal echocardiography during surgery for patients with tetralogy of fallot. Pediatr Cardiol, 2013. 34(2): p. 240-244.

117. Waqar, T., Y. Khan, and A. Jalal, Surgical repair of Tetralogy of Fallot in children and adult patients: A Retrospective analysis of early results. Pak J Med Health Sci, 2013. 7(1): p. 12-15.

118. Egbe, A., et al., Risk factors for morbidity in infants undergoing tetralogy of fallot repair. Ann Pediatr Cardiol, 2014. 7(1): p. 13-18.

119. Egbe, A.C., et al., Primary tetralogy of Fallot repair: Predictors of intensive care unit morbidity. Asian Cardiovasc Thorac Ann, 2014. 22(7): p. 794-799.

120. Egbe, A.C., et al., Predictors of Intensive Care Unit Morbidity and Midterm Follow-up after Primary Repair of Tetralogy of Fallot. Korean j. thorac. cardiovasc. surg., 2014. 47(3): p. 211-219.

121. Yaliniz, H., et al., Short-and mid-term results of xenograft-bovine pericardial patch in the repair of intracardiac defects: Final results of a single-centre study. Cardiol Young, 2014. 24(3): p. 510-514.

122. François, K., et al., Analysis of the aortic root in patients with tetralogy of Fallot undergoing early repair: Form follows function. J Thorac Cardiovasc Surg, 2014. 148(4): p. 1555-1559.

123. Woldu, K.L., et al., Impact of neonatal versus nonneonatal total repair of tetralogy of fallot on growth in the first year of life. Ann Thorac Surg, 2014. 98(4): p. 1399-1404.

124. Nakashima, K., et al., Pulmonary annulus growth after the modified Blalock-Taussig shunt in tetralogy of Fallot. Ann Thorac Surg, 2014. 98(3): p. 934-940.

125. Niu, M.C., et al., Low incidence of arrhythmias in the right ventricular infundibulum sparing approach to tetralogy of fallot repair. Pediatr Cardiol, 2014. 35(2): p. 261-269.

126. Peer, S.M., et al., Early primary repair of tetralogy of Fallot does not lead to increased postoperative resource utilization. Ann Thorac Surg, 2014. 98(6): p. 2173-2180.

127. Hoashi, T., et al., Long-term outcomes after definitive repair for tetralogy of Fallot with preservation of the pulmonary valve annulus. J Thorac Cardiovasc Surg, 2014. 148(3): p. 802-809.

128. D'Udekem, Y., et al., Low risk of pulmonary valve implantation after a policy of transatrial repair of tetralogy of fallot delayed beyond the neonatal period: The Melbourne experience over 25 years. J Am Coll Cardiol, 2014. 63(6): p. 563-568.

129. d'Udekem, Y., et al., Intersurgeon variability in long-term outcomes after transatrial repair of tetralogy of Fallot: 25 years' experience with 675 patients. J Thorac Cardiovasc Surg, 2014. 147(3): p. 880-6.

130. Luijten, L.W.G., et al., Long-term outcomes of transatrial-transpulmonary repair of tetralogy of Fallot. Eur J Cardio-thorac Surg, 2015. 47(3): p. 527-534.

131. Saygi, M., et al., Factors affecting perioperative mortality in tetralogy of Fallot. Pediatr Int, 2015. 57(5): p. 832-9.

132. Ji, Q., et al., Risk Factors for late right ventricular systolic dysfunction in pediatric patients with repaired tetralogy of fallot. Int Heart J, 2015. 56(1): p. 80-85.

133. Devendran, V., et al., Tetralogy of Fallot with subarterial ventricular septal defect: Surgical outcome in the current era. Ann Pediatr Cardiol, 2015. 8(1): p. 4-9.

134. Sen, D.G., et al., Aiming to Preserve Pulmonary Valve Function in Tetralogy of Fallot Repair: Comparing a New Approach to Traditional Management. Pediatr Cardiol, 2016.

135. Bigdelian, H. and M. Sedighi, Repair of Tetralogy of Fallot in Infancy via the Atrioventricular Approach. Korean j. thorac. cardiovasc. surg., 2016. 49(1): p. 9-14.

136. Alassal, M., et al., Total Correction of Tetralogy of Fallot at Early Age: A Study of 183 Cases. Heart Lung Circul, 2018. 27(2): p. 248-253.

137. Amir, G., et al., Neonatal cardiac surgery in the new era: Lessons learned from 1000 consecutive cases. Isr Med Assoc J, 2016. 18(11): p. 645-648.

138. Amirghofran, A.A., J. Badr, and M. Jannati, Investigation of associated factors with post-operative outcomes in patients undergoing Tetralogy of Fallot correction. BMC surg., 2018. 18(1): p. 17.

139. Arafat, A.A., et al., Surgical strategies protecting against right ventricular dilatation following tetralogy of Fallot repair. J Cardiothorac Surg, 2018. 13(1): p. 14.

140. Balasubramanya, S., et al., Right ventricular outflow tract reintervention after primary tetralogy of Fallot repair in neonates and young infants. J Thorac Cardiovasc Surg, 2017.

141. Bhardwaj, V., et al., Basic arterial blood gas biomarkers as a predictor of mortality in tetralogy of Fallot patients. Ann Card Anaesth, 2017. 20(1): p. 67-71.

142. Ladha, S., et al., The role of blood lactate clearance as a predictor of mortality in children undergoing surgery for tetralogy of Fallot. Ann Card Anaesth, 2016. 19(2): p. 217-224.

143. Guevara, J.H., A. Zorrilla-Vaca, and G.C. Silva-Gordillo, The utility of preoperative level of erythrocytosis in the prediction of postoperative blood loss and 30-day mortality in patients with tetralogy of fallot. Ann Card Anaesth, 2017. 20(2): p. 188-192.

144. Jalili, Z., C. Jalili, and E. Mahmoodzadeh, Outcomes of tetralogy of Fallot surgery in Kermanshah, Iran between 1995 and 2010. Acta Med Mediterr, 2016. 32: p. 1971-1975.

145. Jang, W.S., et al., Surgical Results of Monocusp Implantation with Transannular Patch Angioplasty in Tetralogy of Fallot Repair. Korean j. thorac. cardiovasc. surg., 2016. 49(5): p. 344-349.

146. Khan, I., et al., Surgery for Tetralogy of Fallot in Adults: Early Outcomes. Braz J Cardiovasc Surg, 2016. 31(4): p. 300-303.

147. Kim, H., et al., Long-term results of pulmonary valve annular enlargement with valve repair in tetralogy of Fallot. Eur J Cardio-thorac Surg, 2018. 53(6): p. 1223-1229.

148. Logoteta, J., et al., Restrictive enlargement of the pulmonary annulus at repair of tetralogy of Fallot: a comparative 10-year follow-up study. Eur J Cardiothorac Surg, 2017. 52(6): p. 1149-1154.

149. Mercer-Rosa, L., et al., Predictors of length of hospital stay after complete repair for tetralogy of fallot: A prospective cohort study. J Am Heart Assoc, 2018. 7(11).

150. Pande, S., et al., Fresh autologous pericardium to reconstruct the pulmonary valve at the annulus: When tetralogy of fallot requires a transannular patch at midterm. Tex Heart Inst J, 2016. 43(3): p. 207-213.

151. Raj, R., et al., Perioperative echocardiography-derived right ventricle function parameters and early outcomes after tetralogy of Fallot repair in mid-childhood: a single-center, prospective observational study. Echocardiography, 2016. 33(11): p. 1710-1717.

152. Hickey, E., et al., Annulus-Sparing Tetralogy of Fallot Repair: Low Risk and Benefits to Right Ventricular Geometry. The Annals of Thoracic Surgery, 2018.

153. Wilder, T.J., et al., Young infants with severe tetralogy of Fallot: Early primary surgery versus transcatheter palliation. J Thorac Cardiovasc Surg, 2017. 154(5): p. 1692-1700.e2.

154. Dharmapuram, A., et al., Preliminary Experience With the Use of an Extracellular Matrix to Augment the Native Pulmonary Valve During Repair of Tetralogy of Fallot. World J Pediatr Congenit Heart Surg, 2017. 8(2): p. 174-181.

155. Sullivan, R.T., P.C. Frommelt, and G.D. Hill, Earlier Pulmonary Valve Replacement in Down Syndrome Patients Following Tetralogy of Fallot Repair. Pediatr Cardiol, 2017. 38(6): p. 1251-1256.

156. An, G., et al., Mid-term Outcomes of Common Congenital Heart Defects Corrected Through a Right Subaxillary Thoracotomy. Heart Lung Circul, 2017. 26(4): p. 376-382.

157. Li, Y., et al., Impact of surgical correction of tetralogy of fallot on short-term right and left ventricular function as determined by 2-dimensional speckle tracking echocardiography. Medicine, 2016. 95(31).

158. Waqar, T., M.U. Riaz, and T. Mahar, Tetralogy of fallot repair in patients presenting after infancy: A single surgeon experience. Pak J Med Sci, 2017. 33(4): p. 984-987.

159. Caruana, M. and V. Grech, A first population-based long-term outcome study in adults with repaired tetralogy of Fallot in Malta. Congenit Heart Dis, 2017. 12(3): p. 301-308.

160. Dobbels, B., et al., Early versus late pulmonary valve replacement in patients with transannular patch-repaired tetralogy of Fallot. Interact Cardiovasc Thorac Surg, 2017. 25(3): p. 427-433.

161. Dorobantu, D.M., et al., Primary repair versus surgical and transcatheter palliation in infants with tetralogy of Fallot.

162. Lodin, D., et al., Revisiting the utility of technical performance scores following tetralogy of Fallot repair. J Thorac Cardiovasc Surg, 2017. 154(2): p. 585-595.e3.

163. Sandoval, J.P., et al., Right ventricular outflow tract stenting in tetralogy of fallot infants with risk factors for early primary repair. Circ Cardiovasc Interventions, 2016. 9(12).

164. Simon, B.V., et al., Use of a Dacron Annular Sparing Versus Limited Transannular Patch With Nominal Pulmonary Annular Expansion in Infants With Tetralogy of Fallot. Ann Thorac Surg, 2017. 103(1): p. 186-192.

165. Villemain, O., et al., Impact of anatomic characteristics and initial biventricular surgical strategy on outcomes in various forms of double-outlet right ventricle. J Thorac Cardiovasc Surg, 2016. 152(3): p. 698-706.

166. Pathan, I.H., S.K. Bangash, and A.M. Khawaja, Great Artery Ratio: Does It Really Matters in Total Correction of Tetralogy of Fallot? Pak. Heart J., 2017. 50(2): p. 100-104.

167. Naik, R., et al., Right ventricular function after repair of tetralogy of Fallot: A comparison between bovine pericardium and porcine small intestinal extracellular matrix. Cardiol Young, 2017. 27(8): p. 1522-1528.

168. Chira, M., et al., Behavioral Development is better after Early Repair of Tetralogy of Fallot. Rev. Cercet. Interv. Soc. 61: p. 256-266.

169. Chira, M., et al., Early Repair Benefits in Cognitive Development of Patients with Tetralogy of Fallot. Rev. Cercet. Interv. Soc. 57: p. 78-88.

170. Wallen, T.J., et al., Programmatic Changes to Reduce Mortality and Morbidity in Humanitarian Congenital Cardiac Surgery. World J Pediatr Congenit Heart Surg, 2018. 9(1): p. 47-53.

3

Homograft Durability after Correction of Pulmonary Atresia and Ventricular Septal Defect with or without Systemic Pulmonary Collateral Arteries

Pieter van de Woestijne, Jamie LR Romeo, Ingrid van Beynum, Maarten Witsenburg, M Mostafa Mokhles, Ad JJC Bogers

Submitted

ABSTRACT

Background

Pulmonary atresia and ventricular septal defect (PA-VSD), with or without systemic pulmonary collateral arteries (SPCAs), represent a complex anatomical and surgical spectrum of congenital heart disease. Currently, there is limited evidence about homograft durability after complete correction which are potentially affected by anatomical differences in pulmonary vasculature.

Material and Methods

A retrospective single center study was performed including all 70 consecutive PA-VSD patients (47 with SPCAs, 23 without SPCAs) operated between 1978 and 2018. Primary interest was homograft durability after complete repair. Longitudinal echocardiographic homograft function and right ventricular systolic pressure (RVSP) were analyzed with linear mixed effects models.

Results

The median follow-up time was 20 years. Of 46 patients with SPCAs, 37 (80.4%) underwent their biventricular correction at a median age of 2.7 years (inter quartile range 1.8-6.3 years). Two patients are currently awaiting unifocalization and correction. All 23 patients without SPCAs underwent successful complete correction at a median age of 1.6 years (inter quartile range 1.1-3.6 years). Freedom from any reintervention after 20 years was 15%. In case a homograft was inserted as part of correction, freedom from homograft replacement after 20 years was 32±11% in the SPCAs group, and 32±13% for patients without SPCAs. Indications for homograft replacement were isolated stenosis (n=7; 46.7%), isolated regurgitation (n=3; 20.0%) and mixed stenosis and regurgitation (n=5; 33.3%) in the SPCAs group. In patients without SPCAs, isolated stenosis was the indication in 8 (88.9%), and 1 (11.1%) patient had both stenosis and regurgitation. Peak homograft gradient was significantly (p=.0003) higher in patients without SPCAs, with a comparable rate of progression between the groups. The prevalence of severe pulmonary regurgitation was higher in patients with SPCAs, however, estimated at 35% at 10 years versus 15% in patients without SPCAs.

Conclusion

Homografts used for right ventricular outflow tract reconstruction in patients with PA-VSD, both with or without SPCAs, have limited durability. Repeated reintervention is common, and intensive follow up with attention to severe pulmonary regurgitation is warranted.

INTRODUCTION

Pulmonary atresia and ventricular septal defect (PA-VSD) with or without systemic pulmonary collateral arteries (SPCAs) are complex congenital cardiac defects. Without surgical intervention only 75% of patients survive the first year of life [1].

Varying sources of blood supply are present. In PA-VSD the pulmonary arterial system is essentially normal but initially duct-dependent and most often a first step in surgical treatment consists of creating an aorto-pulmonary shunt. In PA-VSD with SPCAs the pulmonary arterial system varies in each SPCA-supplied bronchopulmonary segment combined with varying presence of native pulmonary arteries (NPA) and single-stage or staged approach is an issue.

In both entities surgical approach and timing are important subjects. In PA-VSD without SPCAs the approach is aimed at preservation and inclusion of the complete NPA. In PA-VSD with SPCAs this is also the aim, but unifocalization and rehabilitation of the pulmonary arterial system is necessary. Regardless of surgical approach, right ventricular outflow tract on (RVOT) reconstruction with a valved conduit, often a homograft, is an essential part of biventricular correction. As patients with incorporated SPCA-segments may be expected to have a less compliant pulmonary arterial bed with higher pulmonary artery pressures, due to suture lines and increased pulmonary vacular resistence, homograft durability might be hampered in this regard. Homograft durability may be limited, manifesting as severe stenosis, regurgitation or a combination of both, and is associated with reintervention, morbidity and mortality [6, 7].

We therefore aimed to determine homograft durability during our 26-year experience with staged surgical repair of PA-VSD with or without SPCAs.

MATERIAL AND METHODS

All consecutive patients with PA-VSD with or without SPCAs who underwent correction between 1978 and 2018 in the Erasmus University Medical Center were included. Hospital records were retrospectively reviewed after the medical ethics commission reviewed and approved this study (MEC 12-477). Individual informed consent was waived.

Surgical technique

All patients were discussed in multidisciplinary meetings involving congenital cardiologists, cardiac surgeons and radiologists. Eligibility for biventricular complete repair was based on anatomical feasibility and invasive evaluation. Intracardiac anatomy was usually determined based on a combination of echocardiography, angiography and computed tomography. The Nakata index was calculated for most patients before and

after correction [8]. The right ventricular systolic pressure (RVSP) was obtained through cardiac catheterization or calculated with the simplified Bernoulli equation based on the systolic tricuspid regurgitation jet. A Nakata index of 150 was considered sufficient to be eligible for complete repair.

Complete single stage repair with concomitant unifocalization was performed in a minority of patients (N=4; 8.5%) operated between 1978 and 1992. Since then surgical policy has been a staged approach with RVOT reconstruction using a homograft conduit during final repair as early as clinically feasible. Depending on the presence and size of the confluent pulmonary and proximal arteries, a Melbourne shunt, as described by Mumtaz et al. has been used in x patients [9]. Trough separate lateral thoracotomies, unifocalization was intended, with intrapulmonary anastomosis if possible to avoid proximal segments of SPCAs to be include in the reconstructed pulmonary vascular bed. These procedures were most often completed with an ipsilateral modified Blalock Taussig (MBT) shunt. In case of a ductal dependent PA-VSD without SPCAs, neonatal palliation with a MBT shunt was applied in all patients, later followed by complete repair

Correction involved patch closure of the VSD baffling the left ventricle to the aorta and reconstruction of the RVOT with a cryopreserved homograft. No intraoperative flow studies were carried out and no VSD was deliberately left open. In all cases intra-operative echocardiography was used to check the adequacy of repair. Primary outcomes were homograft reintervention and replacement.

Statistical analysis

Categorical variables were presented as frequencies with percentages. Continuous variables were presented as means with standard deviation or medians with ranges, as appropriate. Time dependent outcomes were reported using Life-Tables methods for defined periods. Kaplan-Meier plots were made to visualize the occurrence of time-dependent outcomes. Serial echocardiographic measurements of the peak transvalvular homograft gradient and regurgitation grade were analyzed using linear mixed effects models. Statistical analyses were carried out with SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) and R statistical program, R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

Interstage results

Sixty-nine consecutive patients with (n=46) or without (n=23) SPCAs have been referred to our clinic (Table 1). Of 39 patients who underwent unifocalization, 29 (74.4%) under-

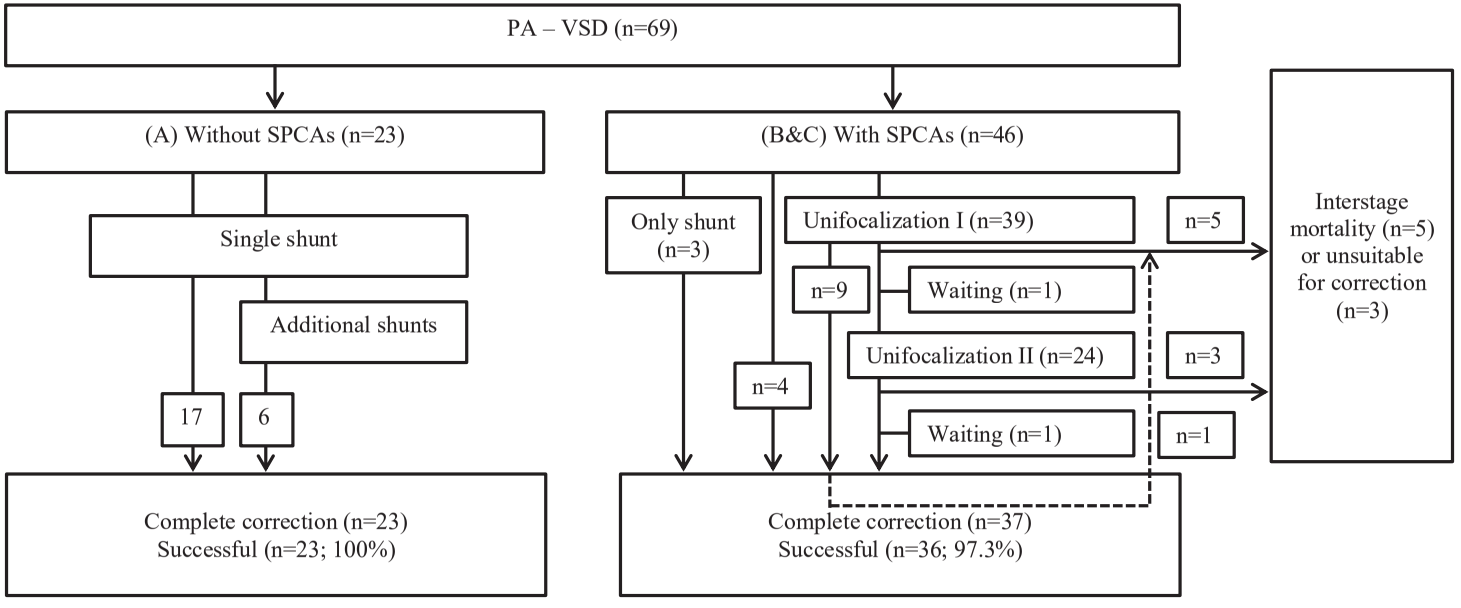
went successful correction at a median age of 2.6 (inter quartile range 1.8-5.8 years) (Figure 1).

Table 1 Baseline characteristics

Patients	PA – VSD with SPCAs (n=46)	PA-VSD without SPCAs (n=23)
Male (n)	22 (47.8)	12 (52.2)
Genetic abnormalities	12 (26.1)	2 (8.7)
22q11 deletion	12 (26.1)	0 (0)
16p11.2 deletion	0 (0)	1 (4.3)
5q22 duplication	0 (0)	1 (4.3)
Age first palliation (years)	0.58 (0.04-21.06)	0.04 (0.01-1.11)
Palliative shunts		
0	5 (10.9)	0 (0)
1	21 (45.7)	17 (73.9)
2	20 (43.5)	6 (26.1)
Palliative shunt	61 (100)	29 (100)
Blalock Taussig Shunt	47 (77.0)	22 (75.9)
Waterston shunt	1 (1.6)	5 (17.2)
Potts shunt	1 (1.6)	0 (0)
Central shunt	10 (16.4)	2 (6.9)
Melbourne shunt	2 (3.3)	0 (0)
Unifocalization		
Unifocalization	39 (84.8)	NA
Single stage complete correction	4 (8.7)	
Only shunting	3 (6.5)	
Interstage mortality (n)	5 (10.6)	0 (0)
Unsuitable for biventricular repair (n)	3 (6.5)	0 (0)
Interstage waiting (n)	2 (4.3)	0 (0)
Intention to perform complete correction (n)	36 (76.6)	23 (100)

PA = Pulmonary Atresia, VSD = Ventricular Septal Defect, SPCAs = Systemic Pulmonary Collateral Arteries

Two patients are currently alive and well and awaiting second unifocalization and complete correction, respectively. All patients without SPCAs reached correction at a median age of 1.6 years (IQR 1.1-3.6 years). Therefore, in total, 60 patients underwent complete repair at a median age of 2.2 years (IQR 1.3-6.1 years) of which 59 (98.3%) were surgically successful (Table 2).



A. Bronchopulmonary segments are only connected to native pulmonary arteries

B. Bronchopulmonary segments are connected to both native pulmonary arteries and through SPCAs

C. Bronchopulmonary segments are only connected through SPCAs

Figure 1 Surgical Flowdiagram

Table 2 Baseline characteristics of complete repair

Patients	PA – VSD with SPCAs (n=36)	PA-VSD without SPCAs (n=23)
Age (years)	5.3±2.7 2.7 (0.08-30.5)	2.8±2.8 1.6 (0.4-9.5)
Length (cm)	97±27	81±13
Weight (kg)	15.5±11.4	10±3.4
Creatinine	34±15	26±6.2
Hb (mmol/l)	10 (8-13)	10 (8-12)
Ht	0.38±0.47	0.39±0.50
CPB time (min)	186±70	171±46
Cross-clamp time (min)	106±35	111±21
Surgically successful	36 (97.3)	23 (100)
VSD closure	36 (97.3)	23 (100)
Valved conduit RVOT reconstruction		
Pulmonary homograft	31 (86.1)	16 (69.6)
Aortic homograft	4 (11.1)	3 (13.0)
Transannular patch	0 (0)	4 (17.4)
Other	1 (2.8)	0 (0)
Homograft diameter (mm)†	20 (12-25)	17 (11-24)
Postoperative complications		
Death	2 (5.6)	0 (0)
Rethoracotomy	6 (16.7)	1 (4.3)
for bleeding	4 (11.1)	0 (0)
for other reasons	2 (5.6)	1 (4.3)
Other	4 (11.1)	2 (8.7)

CPB = cardio pulmonary bypass time, RVOT = right ventricular outflow tract, RVSP = right ventricular systolic pressure, VSD = ventricular septal defect PA = Pulmonary Atresia, Defect, SPCAs = Systemic Pulmonary Collateral Arteries

†: if the homograft was bicuspidalized, the final diameter is reported.

OUTCOME

Two patients (5.6%) from the SPCAs group died in hospital shortly after correction. Follow up was complete for 56 (98.2%) hospital survivors after correction, after a median period of 20.6 years (range 0.12-38.3) and all within 2 years of study closing. One patient was lost to follow up immediately after correction due to emigration to her country of origin. There were 5 late deaths (8.9%) after a median 3.9 years (range 0.3-26.1 years) since correction at a median age of 25.8 years (range 5-43 years). All five late deaths occurred in the SPCA group, of which 4 cases of sudden unexplained unexpected death at 3 m onths, 5 months, 4 years and 20 years after correction. The fifth patient died 26 years since correction from pneumosepsis with right heart failure. Survival at 20 years

after correction was thus 100% in patients without SPCAs, and 86±6% in patients with SPCAs (Figure 2).

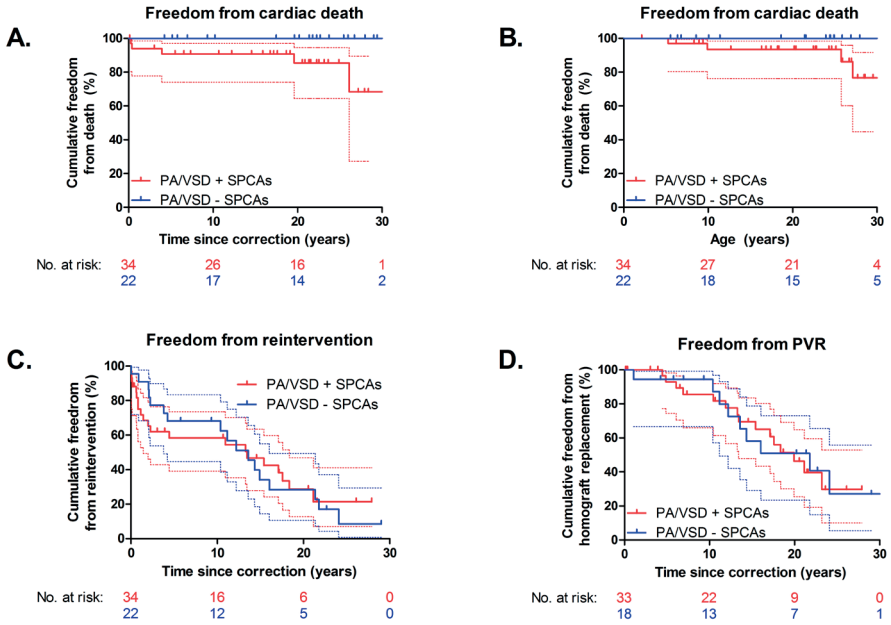


Figure 2 Freedom from valve related events since corection

Late events: reintervention

There were 63 reinterventions in 38 (67.9%) patients on the RVOT including 37 surgical and 26 transcatheter interventions after correction (Table 3).

Freedom from any intervention in patients with SPCAs after 10 and 20 years was 47±9% and 23±9%, respectively. In patients without SPCAs, this was 34±11% and 9±7%, respectively. In case a homograft was inserted as part of correction, freedom from homograft replacement after 20 years was 32±11% in the SPCA group, and 32±13% for patients without SPCAs. Indications for homograft replacement were isolated stenosis (n=7; 46.7%), isolated regurgitation (n=3; 20.0%) and mixed stenosis and regurgitation (n=5; 33.3%) in the SPCA group. In patients without SPCAs, isolated stenosis was the indication in 8 (88.9%) and 1 (11.1%) patient had a mixed hemodynamic profile. Peak homograft gradient was significantly higher (p=.0003) in patients without SPCAs, with a comparable rate of progression (Figure 3 & 4). The prevalence of severe PR was higher in patients with SPCAs however, estimated at 35% at 10 years versus 15% in patients without SPCAs (Figure 5).

Table 3 Reintervention in hospital survivors after correction

	PA – VSD with SPCAs (n=34)	PA-VSD without SPCAs (n=22)
	Number of events/LOR	Number of events/LOR
Reinterventions†		
Reintervention per patient	1 (0-8)	1 (0-3)
Patients with multiple	10	7
Surgical procedures§	22 (3.8%)	15 (3.4%)
PVR	14 (2.4%)	12 (2.7%)
Plasty confluens/branch PA	6 (1.0%)	8 (1.8%)
Residual VSD closure	6 (1.0%)	4 (0.9%)
Transcatheter procedures§	17 (2.9%)	9 (2.0%)
Balloon angioplasty	15 (2.6%)	9 (2.0%)
With stenting	13 (2.2%)	7 (1.6%)
Transcatheter PVR	3 (0.5%)	2 (0.5%)
Pacemaker or ICD placement	0 (0%)	0 (0%)
Reinterventions on†		
RVOT/MPA, including valve	20 (2.4%)	18 (4.1%)
Branch PA	19 (3.3%)	14 (3.2%)
Residual SPCAS	0 (0%)	NA
Residual VSD	6 (1.0%)	4 (0.9%)
Events		0 (0%)
Late death	5 (0.9%)	0 (0%)
Non Cardiac Death	1 (0.2%)	0 (0%)
Cardiac Death	4 (0.7%)	0 (0%)
Valve Related	0 (0%)	0 (0%)
SUUD	4(0.7%)	0 (0%)
Stroke	0 (0%)	0 (0%)
TIA	0 (0%)	0 (0%)
Bleeding	0 (0%)	0 (0%)
Endocarditis	2 (0.3%)	3 (0.7%)

LOR = Linearized Annual Occurrence Rate since correction, SUUD = Sudden Unexplained Unexpected Death, ICD = implantable cardioverter defibrillator, PVR = Pulmonary Valve Replacement, PA = Pulmonary Atresia, VSD = Ventricular Septal Defect, SPCA = Systemic Pulmonary Collateral Arteries, TIA = Transcient Ischemic Attack

§Concomitant procedures were reported separately.

†Reinterventions on different anatomical structures during the same session were reported separately.

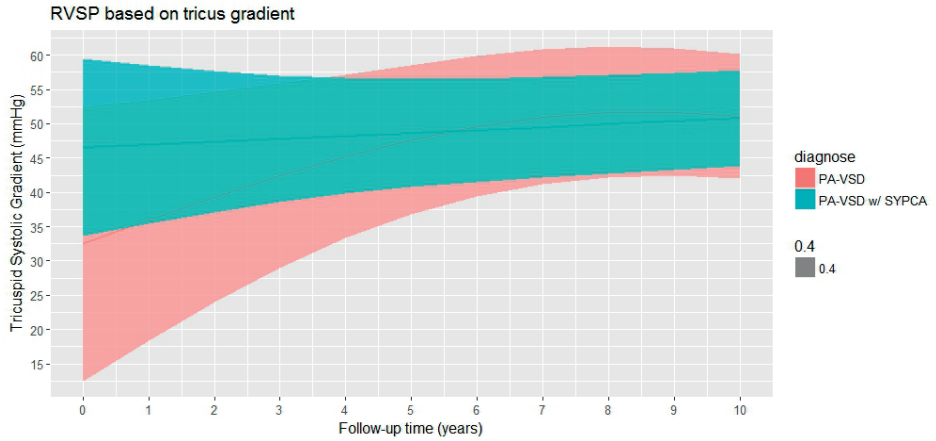


Figure 3 Right Ventricular Systolic Pressure

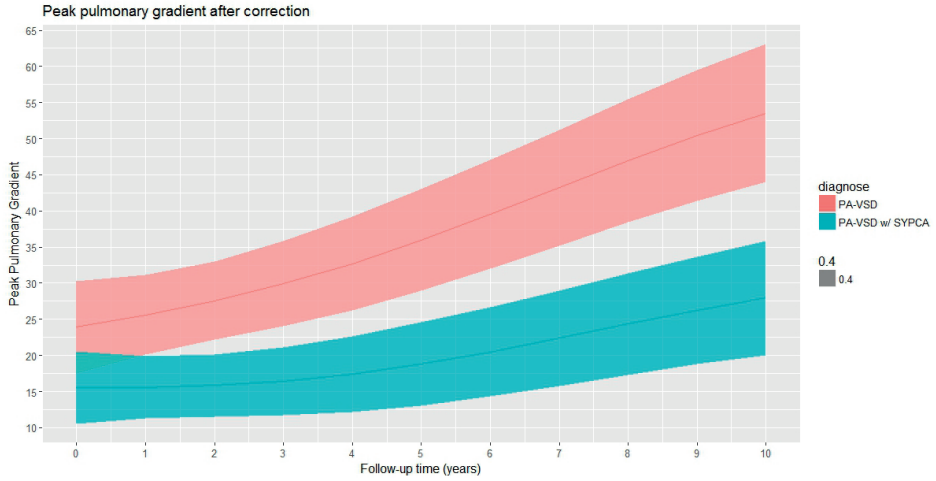


Figure 4 Peak Pulmonary Gradient in Homograft Recipients

All patients who underwent correction without an allograft (i.e. Hancock prosthesis [n=2] and TAP [n=3]), received a homograft at a later stage. Surgical reintervention due to restenosis of branch pulmonary arteries was performed in 11 (19.6%) patients. Closure of a residual VSD was performed in 10 (17.9%) patients. One left sided modified BTS was reinserted 9 months after correction in a 3 year old boy due to restenosis and hypoplasia of the left pulmonary artery with virtually no flow to the left lung. Of the four early patients who underwent single stage unifocalization and correction, 1 patient is still free from reintervention and in good clinical condition 27 years after correction. The other three all underwent reinterventions including PVR.

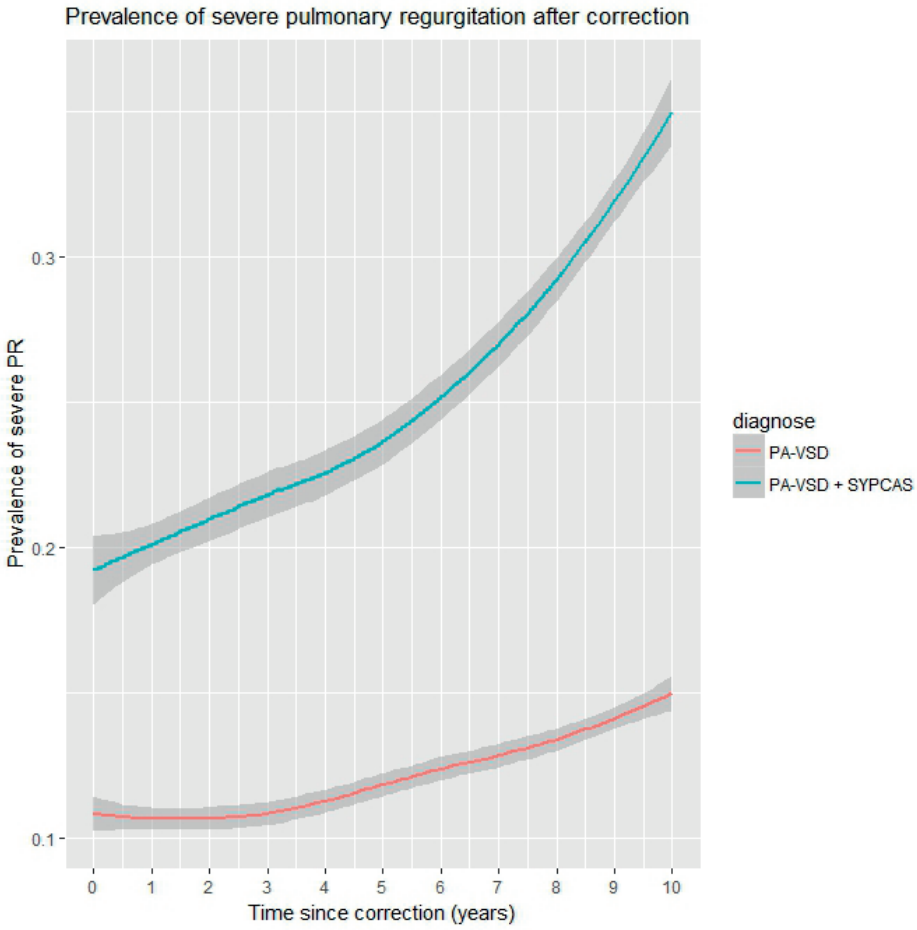


Figure 5 Prevalence of severe PR in homograft recipients

One patient who underwent correction at the age of 6 years, suddenly died at the age of 26 due to presumed rhythm disturbances. Another female patient who underwent single stage correction at the age of 9 with a Hancock prosthesis, underwent PVR with an aortic homograft 11 years later. Seventeen years later she underwent a Bentall procedure due to severe aortic regurgitation and RVOT reconstruction with a mechanical prosthesis due to severe stenosis and regurgitation of the homograft. She currently is in good clinical condition. The fourth patient underwent complete correction at the age of 1 month with an aortic homograft. The homograft was replaced 5 years later with concomitant reconstruction of the confluent pulmonary arteries.

DISCUSSION

Homografts used for right ventricular outflow tract reconstruction in patients with PA-VSD, both with or without SPCAs, have limited durability. In patients with PA-VSD and SPCAs durability is primarily limited by progressive regurgitation and in patients without SPCAs by progressive stenosis.

Homograft durability

The main shortcoming of homografts is durability which appears to be especially limited in young patients [10-12]. It is reasonable to expect most homografts to eventually fail due to severe stenosis, regurgitation or a combination of both. Reports on long term outcome after PA-VSD correction emphasizing homograft durability are sparse but similar high reintervention rates have been reported [13, 14]. In our series, the majority of patients in the SPCA group underwent at least one reintervention and almost halve of the patients underwent multiple reinterventions. In both groups, PVR was the most frequently performed surgical reintervention. Increased RV afterload, which is occasionally present in patients with unifocalized SPCAs, could further limit durability by exerting additional tissue stress. Mainwairing et al. reported a negative correlation between pulmonary artery pressure as directly measured by catheter postoperatively and aortic homograft durability [14]. Our results show that both RV systolic pressure and homograft replacement rate were comparable after correction between patients with or without SPCAs. Although the peak gradient was significantly higher in patients without SPCAs, a larger proportion of PVR was indicated by severe PR or mixed stenosis and regurgitation in patients with SPCAs, which equalized total PVR rates between the groups. This is remarkably similar to the results presented by Mainwaring et al. in which significant PR was present in the vast majority of failing homografts [14]. In a swine model, Petit et al. reported that a reduction of pulmonary artery pressure can lead to a reduced regurgitation fraction [15]. The exact nature of development of high RV systolic pressure over time since correction remains both a question and problem. Our results based on a staged approach indicate stable RV systolic pressure for at least 10 years after correction, while taking into account that 32% underwent at least one catheter intervention on the pulmonary vasculature since correction. Long term repeated analyses of RV systolic presuure are scarce, but the ones available generally report stable pressures [16]. It remains uncertain however to which extent the unifocalized pulmonary vasculature and RV systolic pressure in humans contributes to an increased prevalence of severe PR and homograft durability.

Surgical Policy

At both ends of the classification spectrum proposed by Castaneda et al. and the STS' Congenital Heart Surgery Nomenclature and Database Project, surgery is relatively straightforward [17, 18]. The surgical approach of patients with pulmonary segments exclusively connected to NPA is complete correction, sometimes in a single procedure with good short and long term results similar to our current findings [16, 19]. Similarly, if systemic collaterals are the only source of pulmonary blood flow, unifocalization is an essential part of correction. Carrillo et al. report acceptable reintervention rates in 28 patients without NPA who underwent single stage complete correction. Follow up was modest, however, and long term reliability on these SPCAs is still questionable [20]. Durability of SPCAs in patients with moderately matured NPA, which probably represent the majority of the population, is unclear. The value of unifocalization in this population has been questioned based on reportedly limited growth capacity and unpredictable durability of SPCAs [2, 21-23]. Our surgical policy is based om staged unifocalization, differing from others [5, 20, 24-26] in that we do not pursue single stage unifocalization and correction at the earliest onset, even in case of complete dual supply of pulmonary blood flow. Our strategy has combined elements of staged unilateral unifocalization with an ipsilateral or central shunt before complete correction, comparable to the policy employed at the Cleveland clinic [27]. Nevertheless, this approach results in more suturelines in the pulmonary arterial bed and possibly longer exposure of pulmonary arterial segments with increased pulmonary arterial pressure. In turn this may hamper longevity of homografts used in correction. This was however not observed in our study.

Study Strengths and Limitations

We presented the long term durability of homograft in patients with pulmonary atresia after a uniform strategy of correction with extensive centralized follow up. Advanced statistical techniques were used to analyze repeatedly assessed echocardiographic function of homografts and the RV systolic pressure. Limitations are inherent to the retrospective and single-center nature with a modest patient number, leading to some missing data and the potential for bias.

Conclusion

Homograft durability in patients with PA-VSD with or without SPCAs is comparable. Significant PR was more prevalent in patients with unifocalized SPCAs however. A multistage approach with staged unifocalization and concomitant shunting can lead to satisfactorily repair rates in patients with PA-VSD and SPCAs.

References

1. Leonard, H., et al., Natural and unnatural history of pulmonary atresia. Heart, 2000. 84(5): p. 499-503.
2. d'Udekem, Y., et al., Pulmonary atresia with ventricular septal defects and major aortopulmonary collateral arteries: Unifocalization brings no long-term benefits. The Journal of Thoracic and Cardiovascular Surgery, 2005. 130(6): p. 1496-1502.
3. Bauser-Heaton, H., et al., Programmatic Approach to Management of Tetralogy of Fallot With Major Aortopulmonary Collateral Arteries: A 15-Year Experience With 458 Patients. Circ Cardiovasc Interv, 2017. 10(4).
4. Carotti, A., et al., Determinants of outcome after surgical treatment of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. The Journal of Thoracic and Cardiovascular Surgery, 2010. 140(5): p. 1092-1103.
5. Reddy, V.M., et al., Early and Intermediate Outcomes After Repair of Pulmonary Atresia With Ventricular Septal Defect and Major Aortopulmonary Collateral Arteries. Circulation, 2000. 101(15): p. 1826.
6. Romeo, J.L.R., et al., Long-term clinical outcome and echocardiographic function of homografts in the right ventricular outflow tract†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy265-ezy265.
7. Mokhles, M.M., et al., Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg, 2011. 40(3): p. 571-8.
8. Nakata, S., et al., A new method for the quantitative standardization of cross-sectional areas of the pulmonary arteries in congenital heart diseases with decreased pulmonary blood flow. J Thorac Cardiovasc Surg, 1984. 88(4): p. 610-9.
9. Mumtaz, M.A., et al., Melbourne shunt promotes growth of diminutive central pulmonary arteries in patients with pulmonary atresia, ventricular septal defect, and systemic-to-pulmonary collateral arteries. Ann Thorac Surg, 2008. 85(6): p. 2079-83; discussion 2083-4.
10. Vitanova, K., et al., Which type of conduit to choose for right ventricular outflow tract reconstruction in patients below 1 year of age?dagger. Eur J Cardiothorac Surg, 2014. 46(6): p. 961-6; discussion 966.
11. Kalfa, D.M., et al., Pulmonary position cryopreserved homograft in non-Ross patients: how to improve the results?†. European Journal of Cardio-Thoracic Surgery, 2012. 42(6): p. 981-987.
12. Romeo, J.L.R., et al., Downsized cryopreserved and standard-sized allografts for right ventricular outflow tract reconstruction in children: long-term single-institutional experience. Interactive CardioVascular and Thoracic Surgery, 2018: p. ivy057-ivy057.
13. Bauser-Heaton, H., et al., Pulmonary reinterventions after complete unifocalization and repair in infants and young children with tetralogy of Fallot with major aortopulmonary collaterals. J Thorac Cardiovasc Surg, 2018. 155(4): p. 1696-1707.
14. Mainwaring, R.D., et al., Fate of right ventricle to pulmonary artery conduits after complete repair of pulmonary atresia and major aortopulmonary collaterals. Ann Thorac Surg, 2015. 99(5): p. 1685-91.

15. Petit, C.J., et al., Relief of branch pulmonary artery stenosis reduces pulmonary valve insufficiency in a swine model. The Journal of Thoracic and Cardiovascular Surgery, 2009. 138(2): p. 382-389.

16. Cho, J.M., et al., Early and long-term results of the surgical treatment of tetralogy of Fallot with pulmonary atresia, with or without major aortopulmonary collateral arteries. The Journal of Thoracic and Cardiovascular Surgery, 2002. 124(1): p. 70-81.

17. Tchervenkov, C.I. and N. Roy, Congenital Heart Surgery Nomenclature and Database Project: pulmonary atresia--ventricular septal defect. Ann Thorac Surg, 2000. 69(4 Suppl): p. S97-105.

18. Castaneda, A.R., R.A. Jonas, and J.E. Mayer, Tetralogy of Fallot. Cardiac Surgery of the Neonate and Infant, 1994: p. 215-234.

19. Amark, K.M., et al., Independent Factors Associated With Mortality, Reintervention, and Achievement of Complete Repair in Children With Pulmonary Atresia With Ventricular Septal Defect. Journal of the American College of Cardiology, 2006. 47(7): p. 1448-1456.

20. Carrillo, S.A., et al., Surgical Repair of Pulmonary Atresia With Ventricular Septal Defect and Major Aortopulmonary Collaterals With Absent Intrapericardial Pulmonary Arteries. Annals of Thoracic Surgery, 2015. 100(2): p. 606-613.

21. Liava'a, M., et al., Pulmonary atresia, ventricular septal defect, and major aortopulmonary collaterals: neonatal pulmonary artery rehabilitation without unifocalization. Ann Thorac Surg, 2012. 93(1): p. 185-91.

22. Brizard, C.P., M. Liava'a, and Y. d'Udekem, Pulmonary atresia, VSD and Mapcas: repair without unifocalization. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu, 2009: p. 139-44.

23. Norgaard, M.A., et al., Major aorto-pulmonary collateral arteries of patients with pulmonary atresia and ventricular septal defect are dilated bronchial arteries. Eur J Cardiothorac Surg, 2006. 29(5): p. 653-8.

24. Tchervenkov, C.I., et al., One-stage midline unifocalization and complete repair in infancy versus multiple-stage unifocalization followed by repair for complex heart disease with major aortopulmonary collaterals. The Journal of Thoracic and Cardiovascular Surgery, 1997. 114(5): p. 727-737.

25. Reddy, V.M., J.R. Liddicoat, and F.L. Hanley, Midline one-stage complete unifocalization and repair of pulmonary atresia with ventricular septal defect and major aortopulmonary collaterals. The Journal of Thoracic and Cardiovascular Surgery, 1995. 109(5): p. 832-845.

26. Murthy, K.S., et al., Evolving surgical management for ventricular septal defect, pulmonary atresia, and major aortopulmonary collateral arteries. Ann Thorac Surg, 1999. 67(3): p. 760-4.

27. Duncan, B.W., et al., Staged repair of tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries. The Journal of Thoracic and Cardiovascular Surgery, 2003. 126(3): p. 694-702.

28. Davies, B., et al., Unifocalization of major aortopulmonary collateral arteries in pulmonary atresia with ventricular septal defect is essential to achieve excellent outcomes irrespective of native pulmonary artery morphology. J Thorac Cardiovasc Surg, 2009. 138(6): p. 1269-75 e1.

29. DeCampli, W.M., et al., An institutional approach to, and results for, patient with tetralogy with pulmonary atresia and major systemic-to-pulmonary collateral arteries. Cardiol Young, 2010. 20 Suppl 3: p. 128-34.

30. Rome, J.J., et al., Tetralogy of Fallot with pulmonary atresia. Rehabilitation of diminutive pulmonary arteries. Circulation, 1993. 88(4 Pt 1): p. 1691-8.

31. Metras, D., et al., Pulmonary atresia with ventricular septal defect, extremely hypoplastic pulmonary arteries, major aorto-pulmonary collaterals. Eur J Cardiothorac Surg, 2001. 20(3): p. 590-6; discussion 596-7.
32. Lenoir, M., et al., Outcomes of palliative right ventricle to pulmonary artery connection for pulmonary atresia with ventricular septal defect. Eur J Cardiothorac Surg, 2017. 52(3): p. 590-598.
33. Chen, Q., et al., Multistage pulmonary artery rehabilitation in patients with pulmonary atresia, ventricular septal defect and hypoplastic pulmonary artery. Eur J Cardiothorac Surg, 2016. 50(1): p. 160-6.
34. Dragulescu, A., et al., Long-term results of pulmonary artery rehabilitation in patients with pulmonary atresia, ventricular septal defect, pulmonary artery hypoplasia, and major aortopulmonary collaterals. J Thorac Cardiovasc Surg, 2011. 142(6): p. 1374-80.
35. d'Udekem, Y., The Fuwai hospital experience with patients presenting late with pulmonary atresia, ventricular septal defect and hypoplastic pulmonary arteries. Eur J Cardiothorac Surg, 2014. 46(2): p. 304-5.

4

Down-sized cryopreserved and standard-sized allografts for right ventricular outflow tract reconstruction in children: long term single institution experience

Jamie LR Romeo, Grigorios Papageorgiou, Pieter C van de Woestijne, Johanna JM Takkenberg, Lauren EH Westenberg, Ingrid van Beynum, Ad JJC Bogers, M Mostafa Mokhles

Interactive CardioVascular and Thoracic Surgery

ABSTRACT

Background

The objective of this study was to determine long term results with bicuspidalised allografts compared to non-bicuspidalised allografts in children under two years undergoing primary correction of the right ventricular outflow tract.

Methods

Thirty-five consecutive bicuspidalised allografts were compared to 45 consecutive non-bicuspidalised allografts implanted during the same period. Valve related events were analyzed with Kaplan-Meier and Cox-regression techniques. Mixed-effects modeling was used to analyze serial echocardiographic measurements of pulmonary gradient. In addition, a systematic review with meta-analysis of published literature concerning implantation of bicuspidalised allografts was performed.

Results

Peri-operative characteristics and in hospital mortality (bicuspidalised 5 (14.3%), non-bicuspidalised 6 (13.3%)) were comparable (p=.902). Bicuspidalised allografts were smaller (14.7 vs 16.5 mm, p=0.023) and always (100%) of pulmonary origin compared to 26 (57.8%) of the standard-sized allografts There were no differences in late mortality between the bicuspidalised and non-bicuspidalised group (6.7% vs 7.7%, p=0.798) or freedom from allograft replacement at 10 years (82±10% and 71±8%, for bicuspidalised, and non-bicuspidalised allografts, respectively). Evolution of peak pulmonary gradient (p=0.273) was comparable between bicuspidalised and non-bicuspidalised allografts. Meta-analysis showed a pooled early and late mortality for bicuspidalised allograft patients of 10.72% (95% CI 6.13-18.75) and 1.6%/year (95% CI 0.99-2.79), respectively. Pooled estimated late reintervention and replacement rates were 5.94%/year (95% CI 3.42-10.30) and 3.78%/year (95% CI 2.69-5.32), respectively.

Conclusion

Bicuspidalisation seems a viable alternative to combat limited supply of small sized allografts with acceptable survival and reintervention rates comparable to non-bicuspidalised allografts.

INTRODUCTION

Since its introduction by Donald Ross in 1966 as possible and viable valve replacements, the use of cryopreserved allografts in pulmonary position has proven to be a good solution for right ventricular outflow tract (RVOT) reconstruction in congenital heart disease [1-3]. The rise of geographically dispersed valve and tissue banks has created an infrastructure in which supply can often meet demand in modern Western society. However, for the youngest and smallest patients there still exists a shortage of suitable allografts of adequate size.

Although some forms of congenital heart disease often allow delay in definite surgical repair by other means, others require surgery in the early childhood. Also, the trend towards early repair in infancy has driven demand for smaller diameter allografts. Michler and colleagues first described the technique of down-sizing tricuspid allografts to bicuspid valved conduits to combat the shortage of adequately sized allografts [4]. Since their introduction, a few other centers have adopted the technique and reported on their outcome [5-19].

This study is a retrospective analysis of our single-center consecutive experience with bicuspidalised allografts compared to non-bicuspidalised allografts for the reconstruction of the RVOT in children under two years including long term echocardiographic and clinical outcome. In addition we performed a systematic review and meta-analysis of outcome after implantation of bicuspidalised allograft.

MATERIALS AND METHODS

Patients and Methods

A retrospective database analysis was conducted in the Cardio-thoracic Surgery department of the Erasmus University Medical Center from 1994 till march 2016. The local ethics commission approved this study and waived individual informed consent (MEC 12-477). Clinical data was retrieved from medical records, surgery reports, and echocardiography reports. Echocardiographic volume and static measurements were obtained by M-mode. Evolution of pulmonary stenosis was assessed by Doppler measuring peak velocity across the pulmonary allograft transformed to gradient with the modified Bernoulli equation. All consecutive children under the age of two years at the time of allograft implantation were included. The Dutch Civil registry was consulted for every study participant to confirm life status.

All surgeries were performed by two attending surgeons. Two stage repair by means of a prior palliative shunt was reserved for those with sustained cyanosis or repeated cyanotic spells and ductus-dependent pulmonary circulation or those with unfavor-

able anatomy. Timing and indication of operation and reintervention was agreed upon during a weekly multidisciplinary heart team meeting with cardiologists and cardiac surgeons in line with current guidelines and contemporary practice. The decision to down-size was made by the attending surgeon when an adequately sized allograft was not readily available. Downsizing was accomplished through excising a longitudinal strip along the borders of one of the leaflets of a tricuspid allograft. The new borders were approximated to form a new bicuspid allograft.

Postoperative clinical data were collected from hospital records. Standardized transthoracic echocardiographic assessments were performed before hospital discharge and once every year when visiting the outpatient clinic. Hospital mortality was defined as mortality before hospital discharge after initial correction. Late mortality was any mortality after this period. Valve related events, reintervention and reoperation were reported according to the guidelines for reporting morbidity and mortality after cardiac valvular interventions [20]. Hospital survivors were followed through regular outpatient clinic visits at 2 week, 6 months and 1 year after surgery and yearly thereafter or on individual indication.

Statistical analysis

Continuous data are expressed as means with standard deviation, or median with range when appropriate. Categorical data are displayed as proportions and counts. Normality was tested with the Kolmogorov-Smirnov test. Comparison of continuous data was done with the two–tailed, unpaired Student's t-test or the Mann-Whitney U-test when appropriate. Categorical data were compared with the two-tailed Pearson Chi-square test or the Fisher's exact test. Potential risk factors for clinical and hemodynamic performance were assessed with the Cox proportional hazards test. Time-dependent event analysis was performed with the Kaplan-Meier method and Tarone-Ware test was applied to compare groups. Echocardiographic measurements of pulmonary gradient were analyzed using mixed-effects models, accounting for the correlation between the repeated measurements in each patient. To allow for more flexibility in the shape of the subject-specific trajectories over time, we used natural cubic splines with one knot, placed at the median follow-up time both in the fixed- and random-effects parts of the model. Moreover, we allowed for different slopes between bicuspidalised and non-bicuspidalised allografts while correcting for baseline clinical characteristics such as age, allograft size, type of allograft and type of congenital heart disease. The models' assumptions were validated with residual plots. Missing echocardiographic measurements were assumed to be missing at random and occurred in less than 1% and was therefore not imputed. Differences in the evolution of pulmonary gradient between bicuspidalised and non-bicuspidalised allografts were assessed using a likelihood ratio test. F-tests were used in evaluating which risk factors were most associated with the echocardiographic measurements and

were, thus, retained in the multivariable analysis. Statistical significance was defined by a P-value less than 0.05. Statistical analysis was performed with SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) and R (R Core Team (2016). URL https://www.R-project.org/).

Systematic review and meta-analysis

A review of the literature on bicuspidalised allografts in pulmonary position was performed (Supplementary document A). Two independent authors (JR & LW) screened titles and abstracts. A selection was made after which full text assessment determined eligibility and final inclusion in the meta-analysis. In case of disagreement a third independent reviewer decided. The reference lists of the included articles were screened for additional articles. Pooled estimates of the assumed linearized occurrence rates were calculated with log transformation for events within a random effects model [21]. Between study heterogeneity was assessed with the Chi-square statistic of Higgins [22]. Funnel plots were studied to access publication bias.

Table 1 Demographic and perioperative characteristics

Total: n=80 patients	Bicuspidalised (n=35)	Non-bicuspidalised (n=45)	P Value
Male gender (%)	19 (54)	28 (62)	.47
Age in days (range)	202±177 (20–660)	278±245 (7–717)	.11
Weight (kg)	5.95±2.28	6.09±2.93	.82
Length (cm)	62.61±10.65	63.20±13.11	.83
Diagnose n(%)			
Truncus Arteriosus	12 (34)	14 (31)	
TGA+PS	3 (9)	3 (7)	
PA+VSD	5 (14)	14 (31)	
Tetralogy of Fallot	3 (9)	4 (9)	
Ross	12 (34)	10 (22)	
Previous heart operations (%)	13 (37)	20(44)	.51
Previous Shunt (%)	8 (23)	16(36)	.22
Previous correction (%)s	3 (9)	0(0)	NA
Final diameter (mm)	14.71±0.98	16.49±3.12	0.002
Z-score	2.54±0.98	3.20±1.41	0.023
Allograft type n(%)			NA
Pulmonary	35 (100)	26 (58)	
Aortic		19 (42)	
Perfusion-time (min)	161.12±57.33	172.74±87.76	0.51
Cross-clamp time (min)	105.29±34.28	100.74±29.60	0.53
Hospital reoperation n(%)	8 (23)	7 (16)	0.41
Hospital mortality n(%)	5 (14)	6 (13)	0.90
Hospital stay median(range)	11 (7-108)	14 (4-213)	0.27

RESULTS

Early results

Eighty consecutive patients aged <2 years received a bicuspidalised (n=35) and normal-sized (n=45) allograft in RVOT position. Forty patients were included in a previous report [17]. Baseline and operative characteristics were comparable (Table 1). In both groups truncus arteriosus was the most commonW diagnosis (12; 34% and 14; 31%, respectively). In the bicuspidalised group exclusively pulmonary allografts were implanted. In the non-bicuspidalised group 19 (42%) aortic and 26(58%) pulmonary allografts were used. The final diameter of the bicuspidalised allografts was smaller (14.7 vs 16.5 mm, (p=0.002). The postoperative clinical course was comparable (Table 1). Hospital mortality was 14% (n=5) and 13% (n=6) for the bicuspidalised and standard-sized group, respectively (p=.90). All patients who died before discharge presented with multiple complex cardiac malformations (Table 2).

Table 2 Characteristics of in hospital mortality with cause of death

Diagnose	Age (months)	Gender	Valve	Allograft type	Cause of death
AS, AI, MS, MI	3.6	F	Bicuspidalised	Pulmonary	Heart failure
TAC, VSD, PFO, HOCM	2.1	M	Bicuspidalised	Pulmonary	Heart failure
TAC, PFO, bronchomalacia	4.7	F	Bicuspidalised	Pulmonary	Atelectasis, pneumonia, UTI
TAC, VSD	1.1	M	Bicuspidalised	Pulmonary	Heart failure
TAC, VSD	3.0	M	Bicuspidalised	Pulmonary	Rhythm disturbance
DORV, PA, AVSD, PDA	3.0	F	Standard-sized	Pulmonary	Intestinal ischemia
Aortic Atresia, VSD	1.6	F	Standard-sized	Aortic	Heart failure
TOF, PA	0.2	M	Standard-sized	Aortic	Respiratory insufficiency
PA, VSD, PFO	9.2	M	Standard-sized	Aortic	Heart failure
TAC, VSD, IAA	0.3	M	Standard-sized	Aortic	Heart failure
TAC, CoA, HOCM, VSD, PFO	1.0	M	Standard-sized	Pulmonary	Heart failure

AI=Aortic Insufficiency, AS=Aortic Stenosis, CoA=Coarctatio Aortae, DORV=Double Outlet Right Ventricle, F=Female, HOCM=Hypertrophic Cardiomyopathy, IAA=Interrupted Aortic Arch, M=Male, MI=Mitral Insufficiency, MS=Mitral Stenosis, PDA = Persistent Ductus Arteriosus, PFO=Persistent Foramen Ovale, TAC=Truncus Arteriosus Communis, VSD=Ventricle Septal Defect

Late results

Median follow-up was 6.5 years (range 1.3-16.5 years, total patient-years 216) and 11.8 years (range 0.1-20.1 years, total patient-years 413) for bicuspidalised and non-bicuspidalised allografts, respectively. One patient (2%) with a normal sized allograft was lost to follow up shortly after initial repair due to emigration. Follow-up was 98.6% complete.

There were two (7%) late deaths in the bicuspidalised group. The first death was 1.3 years after correction and attributed to septic shock following gastro-enteritis. The other patient died due to a cardiac but non-valve related cause 11.6 years after initial surgical correction. This child was known to have severe chronic heart failure, diastolic dysfunction and pulmonary hypertension, irresponsive to treatment. In the non-bicuspidalised group there were three (8%) late deaths. The first patient was readmitted five days after initial discharge with a candida sepsis and endocarditis and eventually succumbed to a severe pulmonary hypertensive crisis 0.14 years after operation. The cause of death of the second patient was heart failure with severe pulmonary regurgitation without surgical options four months after initial discharge. The third patient underwent correction of a pulmonary atresia with VSD but also had 22Q11-deletion syndrome and nephroblastoma and died 4 years after surgery. Exact cause of death remained unknown despite autopsy, however heart and lungs showed no plausible cause. There was no difference in late mortality (p=0.80) (figure 1). All five late deaths occurred in patients who received a pulmonary allograft.

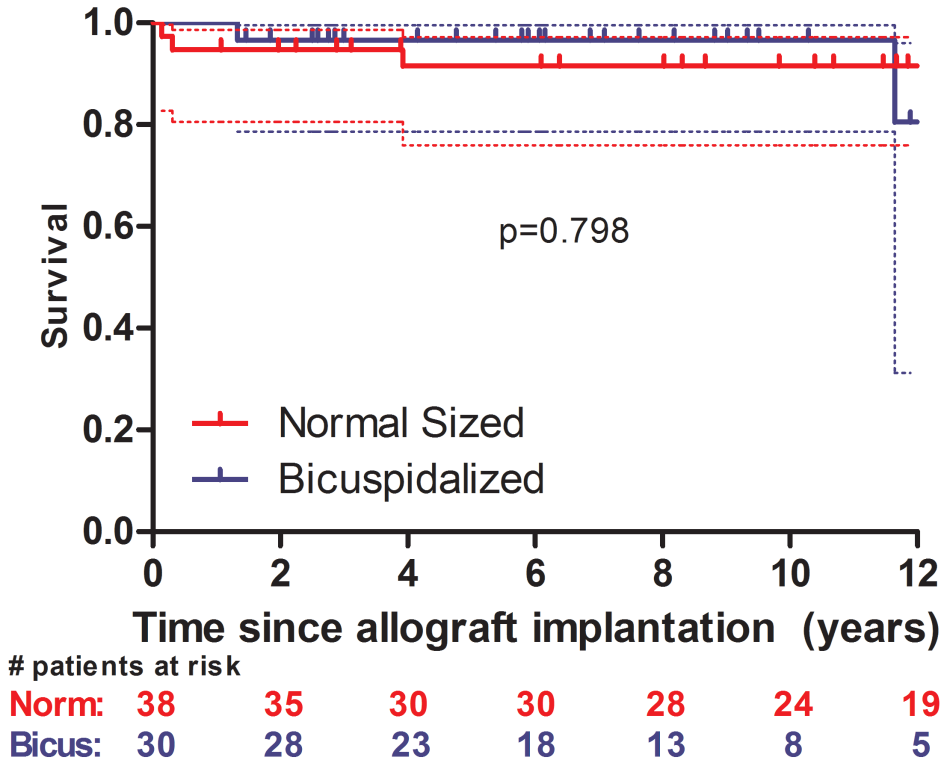


Figure 1 Kaplan-Meier plot of survival after allograft placement

There were 9 valve related events in 9(30%) patients with a bicuspidalised allograft, of which 8 cases of structural valve deterioration (SVD) and 1 case of endocarditis (Strepto-

coccus Pyogenes) (table 3). In the non-bicuspidalised group there were 24 valve related events in 19 (50%) patients, of which 23 cases of SVD and 1 case of endocarditis (Candida Albicans). Two of these patients presented repeatedly with severe allograft stenosis, subsequently treated twice with percutaneous balloon dilatation (figure 2).

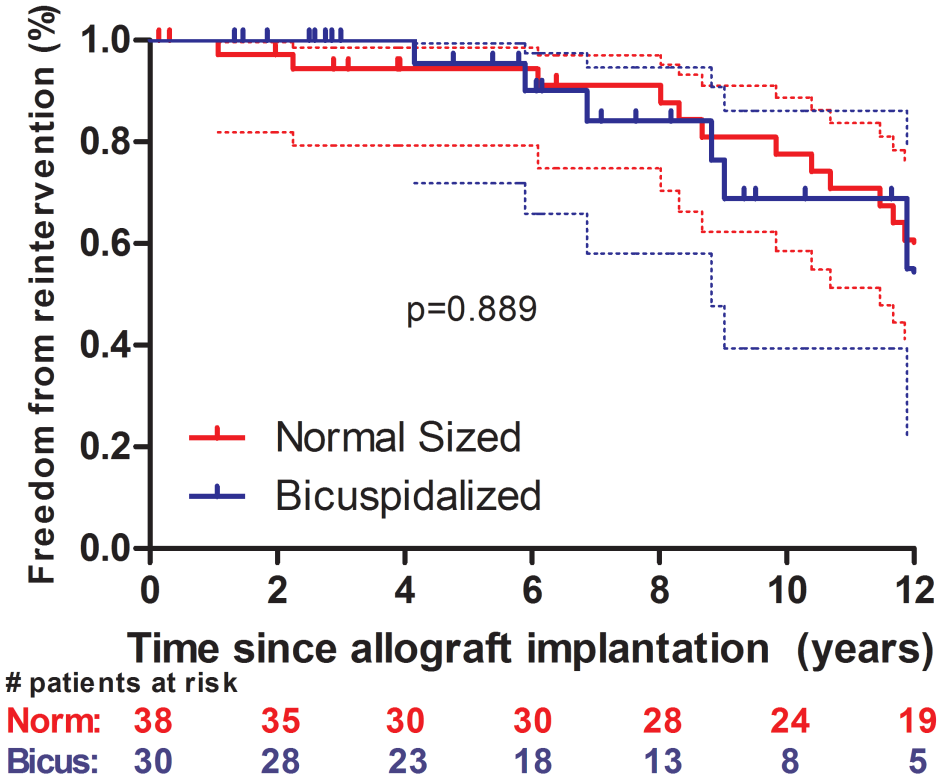


Figure 2 Kaplan-Meier plot of freedom from allograft reintervention

Five patients from the bicuspidalised and 19 from the non-bicuspidalised group underwent valve replacement after a comparable (p=0.57) median period of 8.8 years (range 4.2–14 years) and 11.5 years (range 1.1–16.6 years), respectively. All five conduits that required replacement in the bicuspidalised group were due to stenosis. One patient underwent additional infundibular resection 1.4 years after correction without valve replacement. Indications for replacement in the non-bicuspidalised group were conduit stenosis (n=13), insufficiency (n=2), and combined stenosis and insufficiency (n=2). No percutaneous valve implantations were conducted in bicuspidalised allografts. Three percutaneous valves (Melody®) were successfully placed in non-bicuspidalised patients. Freedom from allograft replacement at 1, 5, and 10 years was 100±0, 95±5 and 82±10% for bicuspidalised and 97±3, 94±4 and 71±8% for non-bicuspidalised allografts, respectively (p=0.57) (figure 3).

Table 3 Valve related events after allograft implantation

	Bicuspidalised	Non-bicuspidalised
Valve related events n(LOR)	9 (0.042/y)	24 (0.058/y)
SVD	8 (0.037/y)	23 (0.056/y)
NSVD	0	0
Valve thrombosis	0	0
Bleeding	0	0
Stroke/TIA	0	0
Non-cerebral embolic	0	0
Endocarditis	1 (0.0046/y)	1 (0.0024/y)
Reintervention	7 (0.032/y)	23 (0.056/y)
Indication	Stenosis 6 (0.028/y) Other 1 (0.0046/y)	Stenosis 17 (0.041/y) Regurgitation 2 (0.0048/y) Combined 4 (0.0097/y)
Surgical	Replacement 5 (0.023/y) Alteration* 1 (0.0046/y)	Replacement 16 (0.039/y)
Percutaneous	Melody (0) Balloon-dilatation 1 (0.0046/y)	Melody 3 (0.0074/y) Balloon-dilatation 4 (0.0097/y)

LOR=Linearized yearly Occurrence Rate, (N)SVD=(Non) Structural Valve Deterioration, pts=patients
*additional RVOT infundibulectomy

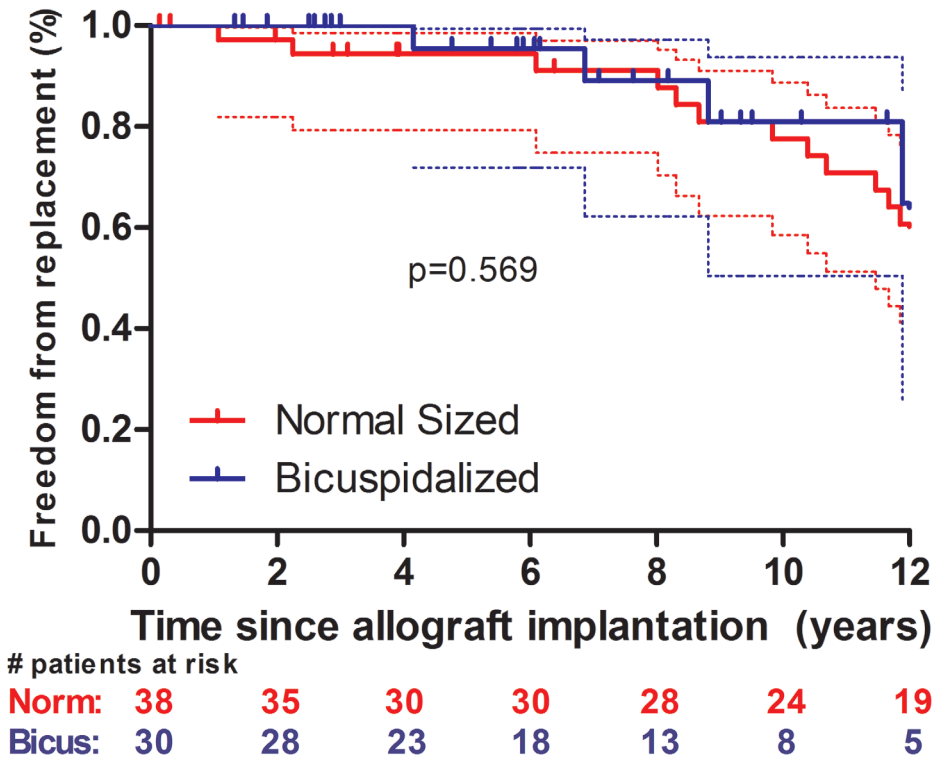


Figure 3 Kaplan-Meier plot of freedom from allograft replacement

A subgroup analysis including only pulmonary allografts, again indicated no difference in time to allograft replacement (p=0.72). Multivariable analysis including bicuspidalization, allograft origin and final allograft z-score confirmed the negligible importance of bicuspidalization in freedom from replacement (HR 1.264, 95% CI 0.403-3.965, p=0.69) (table 4).

Mixed models of echocardiographic outcome

During follow up 240 and 308 serial echocardiograms were completed (median number of measurements 9, range 1 to 22; median echocardiographic follow-up 7,6 years, range 0 to 19.1 years) for 30 (100%) hospital survivors of the bicuspidalised and 35 (90%) non-bicuspidalised patients, respectively. Overall echocardiographic follow up was therefore 95.7% complete. No difference in allograft gradient was observed during the follow-up between the groups (p=0.24) (figure 4).

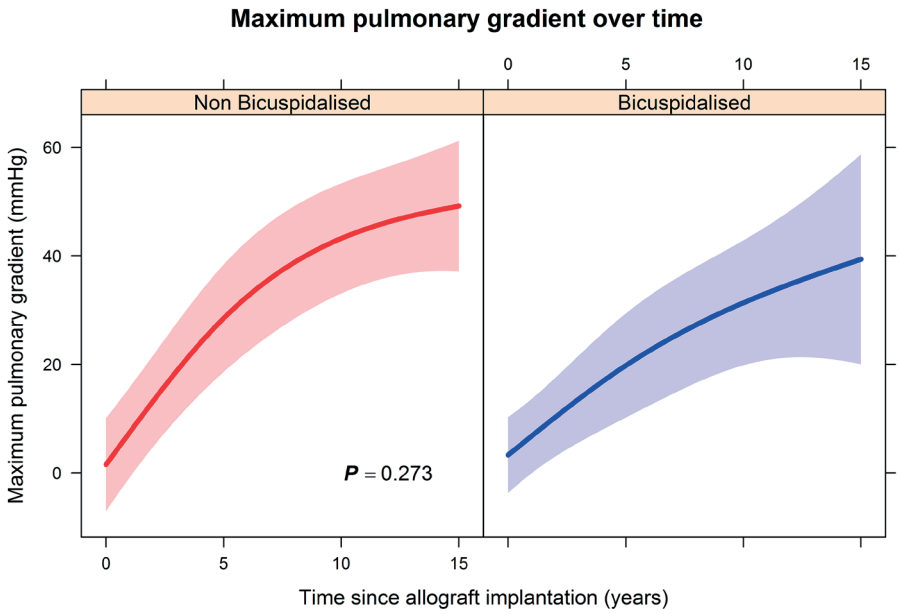


Figure 4 Average evolution of peak pulmonary gradient (mmHg) over time after allograft implantation

Systematic review and meta-analysis

The final search resulted in 17 articles (Supplementary figure B) written in English reporting on 14 unique patient populations eligible for analysis (Supplementary table C). The 17 articles describe a total of 324 patients with a bicuspidalised allograft in pulmonary position [4, 7, 10-19, 23, 24]. Total follow up duration for all early survivors (13 studies) is 1459 patient-years. The pooled estimate of early mortality is 10.72% (95% CI 6.13-18.75,

I2 = 50.0%, p = 0.017). There were 12 late deaths reported (12 studies) which results in a pooled estimate for late mortality of 1.6%/year (95% CI 0.99-2.79, I2 = 58.0%, p = 0.44). No late deaths were valve related. Reintervention defined as reoperation with replacement or catheter-based balloon dilatation with or without stenting (13 studies), resulted in a pooled estimate of 5.94%/year (95% CI 3.42-10.30). The pooled estimate of late replacement was 3.78%/year (95% CI 2.69-5.32) with low study heterogeneity (I2 = 8.4%, p = 0.36).

COMMENT

This study shows that both the long term clinical outcome and valve related event rate and the evolution of peak pulmonary gradient of bicuspidalised allografts are comparable to non-bicuspidalised valves. The results of our bicuspidalised cohort seem to be better compared to the results of the meta-analysis, with comparable early and late mortality rates but longer freedom from valve replacement.

Since Ross and Somerville introduced the practice of allografts used as conduits in RVOT position over fifty years ago, many potential alternatives have been proposed [3]. However, a cryopreserved allograft has remained the preferred conduit in RVOT reconstruction. In an attempt to overcome the issue of limited supply bicuspidalization was introduced in 1995 [4]. Since Michler et al. presented their favorable short term outcomes, many authors adopted their technique with success and showed durability similar to standard-sized valves [4, 12-15, 18, 24]. At the time, Michler et al. already questioned the possibility of accelerated stenosis after bicuspidalization and the lack of growth potential [4]. By using mixed-effects modeling we have shown that the hemodynamic evolution is comparable to non-bicuspidalised allografts, resulting in a comparable reintervention rate.

In a study by Urso et al. size developments expressed as Z-scores of 17 bicuspidalised allografts were compared to an equal size, age-matched cohort of standard sized allografts [18]. There was no difference found in outcome. Combined with the lower bleeding risks compared to synthetic grafts in infants this supports the use of this type of conduit when supply is limited. The only possible alternative conduit in the population below one year is the bovine jugular vein (BJV) graft [23]. Bove and colleagues are the only ones to directly compare bicuspidalised allografts in RVOT position to BJV conduits (Contegra®) [23]. Early postoperative outcome and mortality were comparable without differences in regurgitation rate. Bicuspidalised graft recipients did show significantly more often mild (10-15mmHg) stenosis compared to the Contegra group at the level of the distal anastomosis. However, a more severe pulmonary gradient exceeding 30mmHg was only found in two patients from the Contegra group and no gradient was found at

the valvular level in either of the two groups. Koirala et al. were the first to compare bicuspidalised allografts with non-bicuspidalised allografts [12]. They found no differences in freedom from reintervention and development of functional deterioration between the groups after comparing with a matched cohort of standard-sized allografts, comparable to the results of the present study. Overall freedom from reintervention at five years was 47% and comparable between both groups [12]. Although we report a better freedom from reintervention, we have to consider the effect of time and surgical improvements in contemporary surgical practice.

Compared with standard-sized allografts, bicuspidalised allografts seem equivalent in terms of survival and valve related reintervention [12-15, 18, 19, 24]. Studies on potential risk factors for bicuspidalised allograft failure are scarce. Truncus arteriosus [16, 19], age <1 [19], Z-score <1 [19], and extension with a polytetrafluorethylene (PTFE) patch [19] were proposed as significant risk factors for graft failure. We were unable to replicate the finding that truncus arteriosus, graft size or age are independent risk factors for graft dysfunction (Table 4). However, larger patient groups and longer follow up are needed to reveal any subtle difference in valve related outcome or hemodynamic burden. However, our results indicate that for both valve related outcome and hemodynamic evolution, the clinical course is comparable.

Baseline patient and perioperative characteristics are by themselves of limited value as risk factors for late events after valve replacement. During the last decades, more innovative statistical methods have become available which allow more precise prediction of valve function and patient outcome [25]. In this study, we have used mixed-effects models to predict longitudinal valve function adjusted for baseline characteristics. Assessment of valve function by longitudinal analysis of echocardiographic measurements while correcting for baseline characteristics accounts for both within- and between-patient variability. It also allows for flexibility in the specification of subject-specific trajectories, easily integrating the nonlinear nature of the evolution of pulmonary gradient over time. Adjusting for the correlation among the measurements within each patient as well as for the fact that the serial echocardiographic measurements are subject to measurement error, results in reduced bias and enhanced inferential power. As illustrated in this study, mixed-effects models constitute a framework which can aid in the analysis and prediction of valve function over time and should ideally replace currently used methods to explain valve function and dimensions over time, as these carry severe limitations [19, 23].

Study limitations

This is a retrospective single-center study of a diverse range of CHD with long term follow up. The limited number of patients and subsequent number of events limit the analysis of potential risk factors for valve function and outcome. Furthermore, the

greater proportion of pulmonary allografts in the bicuspidalised group might have favored their results.

CONCLUSION

The results of this study and the outcome of the review demonstrate good viability of the bicuspidalised valves in the first decade, and suggest that bicuspidalization can be a very well suited alternative in the absence of small size allografts.

REFERENCES

1. Mokhles, M.M., et al., Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg, 2011. 40(3): p. 571-8.
2. van de Woestijne, P.C., et al., Right ventricular outflow tract reconstruction with an allograft conduit in patients after tetralogy of Fallot correction: long-term follow-up. Ann Thorac Surg, 2011. 92(1): p. 161-6.
3. Ross, D.N. and J. Somerville, Correction of pulmonary atresia with a homograft aortic valve. Lancet, 1966. 2(7479): p. 1446-7.
4. Michler, R.E., J.M. Chen, and J.M. Quaegebeur, Novel technique for extending the use of allografts in cardiac operations. Ann Thorac Surg, 1994. 57(1): p. 83-7.
5. Hiramatsu, T., et al., Downsizing of valve allografts for use as right heart conduits. Ann Thorac Surg, 1994. 58(2): p. 339-42; discussion 342-3.
6. Kitamura, S., et al., Size-reduced cryopreserved pulmonary valve allograft for an RV-PA conduit: technical modification and functional evaluation. J Card Surg, 1995. 10(1): p. 14-20.
7. Monro, J.L., et al., Downsizing of valve allografts for use as right heart conduits. Ann Thorac Surg, 1995. 59(3): p. 789.
8. Santini, F. and A. Mazzucco, Bicuspid homograft reconstruction of the right ventricular outflow tract in infants. Ann Thorac Surg, 1995. 60(6 Suppl): p. S624-5.
9. Santini, F., et al., Use of oversized homografts for right ventricular outflow tract reconstruction in infants. J Heart Valve Dis, 1995. 4(2): p. 192-5.
10. Santini, F., et al., Usefulness of bicuspid homograft reconstruction of the right ventricular outflow tract in infants with complex congenital heart disease. Am J Cardiol, 1997. 80(10): p. 1377-9.
11. Yoshikawa, Y., et al., Pulmonary ventricular outflow reconstruction with a size-reduced cryopreserved pulmonary valve allograft: mid-term follow-up. Jpn Circ J, 2000. 64(1): p. 23-6.
12. Koirala, B., et al., Extending the usable size range of homografts in the pulmonary circulation: outcome of bicuspid homografts. Ann Thorac Surg, 2002. 73(3): p. 866-9; discussion 869-70.
13. McMullan, D.M., et al., Evaluation of downsized homograft conduits for right ventricle-to-pulmonary artery reconstruction. J Thorac Cardiovasc Surg, 2006. 132(1): p. 66-71.
14. Benjacholamas, V., et al., Bicuspidized pulmonary homograft for truncus arteriosus repair. Asian Cardiovasc Thorac Ann, 2008. 16(3): p. 189-93.
15. Shih, T., et al., Performance of bicuspidized pulmonary allografts compared with standard trileaflet allografts. Ann Thorac Surg, 2010. 90(2): p. 610-3.
16. Yang, J.H., et al., Midterm Results of Size-Reduced Cryopreserved Homografts for Right Ventricular Outflow Tract Reconstruction. Ann Thorac Surg, 2010. 89(6): p. 1821-1826.
17. Bramer, S., et al., Long-term outcome of right ventricular outflow tract reconstruction with bicuspidalized homografts. Eur J Cardiothorac Surg, 2011. 40(6): p. 1392-5.
18. Urso, S., et al., Evolution of the Z-score in size-reduced bicuspid homografts. J Heart Valve Dis, 2012. 21(4): p. 521-526.

19. Cleuziou, J., et al., Durability of down-sized homografts for the reconstruction of the right ventricular outflow tractdagger. Eur J Cardiothorac Surg, 2015.
20. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
21. Barron, S.J., M.T. Del Vecchio, and S.C. Aronoff, Intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies. Int J Dermatol, 2015. 54(1): p. 108-15.
22. Higgins, J.P., et al., Measuring inconsistency in meta-analyses. Bmj, 2003. 327(7414): p. 557-60.
23. Bove, T., et al., Early results of valved bovine jugular vein conduit versus bicuspid homograft for right ventricular outflow tract reconstruction. Ann Thorac Surg, 2002. 74(2): p. 536-41; discussion 541.
24. Perri, G., et al., Outcome of Standard and Bicuspidalized Cryopreserved Homografts for Primary Right Ventricular Outflow Tract Reconstruction. J Heart Valve Dis, 2015. 24(1): p. 83-88.
25. Andrinopoulou, E.R., et al., An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg, 2012. 93(6): p. 1765-72.

5

Time Dependent Right Statistics: This is the moment.

Jamie LR Romeo, Grigorios Papageorgiou, Johanna JM Takkenberg, M Mostafa Mokhles

European Journal of Cardio-Thoracic Surgery

DEAR EDITOR,

With great interest we read the recent article titled 'Long-term results of pulmonary valve annular enlargement with valve repair in tetralogy of Fallot' published in the European Journal of Cardio-Thoracic Surgery [1]. Kim and colleagues presented the results of 43 patients who underwent a thoroughly explained valvular repair technique during complete correction of tetralogy of Fallot. All patients survived and directly post-operative echocardiographically assessed pulmonary regurgitation (PR) grades and gradient (PG) were satisfactorily. After a mean follow-up duration of 131.9 months, only one reoperation took place which was not valve related. Despite huge improvements in the surgical repair of tetralogy of Fallot, severe regurgitation continuous to have detrimental effects on mortality and morbidity, often indicating reintervention. Therefore, we respect every effort directed at alleviating some of this well-known burden.

However, we found some major pitfalls in the subsequent statistical analyses.

The severity of PR is assessed qualitatively as also recommended by the guidelines [2]. Except for a rough categorization of severity, the numbers 0 to 4 contain no quantitative information about PR, and hold little relation amongst each other. Therefore, the arithmetic mean value of PR which the authors report does not convey any meaningful information. Any subsequent statistical test designed for continuous measurements is thereafter non-interpretable. Furthermore, the authors choose to report and analyze only the last known echocardiographic measurements. Hereby they effectively treated continuous processes as independent events without any regard for time by reporting and comparing the incidence of PR with Chi-Square test and gradients with Student's t-test. Unequal timing of echocardiographic assessment always needs to be accounted for. This is important because the implicit but fundamental assumption is that valve function develops and not happens.

An ideal approach towards repeatedly measured outcomes is the use of linear (gradient in mmHg) and generalized (ordinal PR) mixed effects modeling, nicely introduced by Andrinopoulos et. al. [3] and demonstrated by Mokhles et. al [4]. Correlation between repeated measurements in the same patient and disbalances in timing and number of observations can be accounted for by including random effects. Patient' characteristics (e.g. operative technique) can be related to changes in individual temporal evolutions. Furthermore, we feel that general reservations towards its complexity are unnecessary. Nowadays, even well-known statistical software packages (e.g. SPSS) provide elaborate possibilities and documentation without the need for extensive coding skills.

Imbalance in baseline covariates is a common phenomenon in nonrandomized observational studies and prohibit direct comparison, as acknowledged by the authors. Propensity score matching can then be the next best thing if a randomized controlled trial cannot be conducted because of practical and/or ethical reasons [5]. However, we

question the quality of the matching procedure in this study as the authors neglected to explain why a mere 25 of 43 (58%) patients was matched. After matching important (near) statistically significant imbalances in baseline covariates still remained, potentially confounding late PR. Most notably, echocardiographic follow up time was included which is fundamentally erroneous as it is highly likely to correlate with severity of PR.

We again like to compliment the authors on their efforts to reduce chronic PR with innovative surgical procedure. However, we do believe that potential positive results are unnecessarily obscured by a poor statistical approach and could merit significantly from linear and mixed effects models.

REFERENCES

1. Kim, H., et al., Long-term results of pulmonary valve annular enlargement with valve repair in tetralogy of Fallot. European Journal of Cardio-Thoracic Surgery, 2018: p. ezx497-ezx497.
2. Lancellotti, P., et al., Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging, 2013. 14(7): p. 611-44.
3. Andrinopoulou, E.R., et al., An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg, 2012. 93(6): p. 1765-72.
4. Mokhles, M.M., et al., Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. Eur Heart J, 2012. 33(17): p. 2213-24.
5. Blackstone, E.H., Comparing apples and oranges. J Thorac Cardiovasc Surg, 2002. 123(1): p. 8-15.

6

Long Term Clinical Outcome and Echocardiographic Function of Homografts in the Right Ventricular Outflow Tract

Jamie LR Romeo, M Mostafa Mokhles , Pieter van de Woestijne, Peter de Jong, Annemien van den Bosch, Ingrid M van Beynum, Johanna JM Takkenberg, Ad JJC Bogers

European Journal of Cardio-Thoracic Surgery

ABSTRACT

Objective

Although homografts are often the preferred valved conduits for right ventricular outflow tract reconstruction, data on long-term homograft related outcome, durability and impact on quality of life (QoL) are scarce. The aim was therefore to describe the long-term homograft function, clinical outcome and QoL after RVOT reconstruction.

Methods

We performed a single-center retrospective analysis of all consecutive patients who underwent RVOT reconstruction with a homograft. Multiple subsequent allografts in the same patients were regarded as separate subjects. Valve-related events were analyzed by Kaplan Meier and Life Table methods. Serial echocardiographic measurements were analyzed with mixed effects models. In addition, QoL was repeatedly assessed and compared with a matched general population.

Results

In total, 701 consecutive homografts were implanted in 604 patients (59.6% males, mean age at operation 19.5±15.2 (standard deviation)). Hospital mortality was 3.3%. After 25 years follow up, survival and freedom from valve replacement were 84±4% and 56±6%, respectively. Freedom from valve replacement after 15 years for patients under one year of age was 28±14% years, for those between 1 and 18, 59±8%, and for those older than 18, 82±5%. The peak gradient increased predominantly in the first postoperative decade in infants and pediatric patients from 19 to 54 mmHg. In adults, the average gradient increased from 9 to 31 mmHg after 14 years. Compared to a gender and age matched Dutch population, patients reported lower vitality and general health but less bodily pain. Patients in whom QoL was repeatedly assessed, reported lower scores on physical functioning and vitality after a 5-year follow up period. However, we found no differences in any of the subscales in patients who underwent valve replacement during the 5 year interval.

Conclusion

Homografts are a durable valve alternative for RVOT reconstruction. Especially, adults show extensive freedom from valve replacement and report a quality of life comparable with healthy subjects. Our online interactive application can be used to assess patient outcome after RVOT reconstruction with a homograft for different patient profiles.

INTRODUCTION

Right ventricular outflow tract (RVOT) reconstruction is often necessary in patients with a broad variety of congenital heart disease. The homograft is a well-known and accepted valved conduit. Its independence of anticoagulation and good hemodynamic behavior generally allow an unrestricted lifestyle [1]. Compared to biological alternatives (e.g. bovine jugular vein, BJV), mechanical prostheses and more novel advancements (e.g. decellularized valves), it has proven long term durability and a low risk for thromboembolic events and endocarditis [2, 3]. However, homografts are subjective to structural valve deterioration (SVD), eventually leading to replacement. Data on long term follow up in large cohorts of cryopreserved homografts in RVOT position is scarce. Furthermore, self-reported Quality-of-Life (QoL) has become increasingly important in assessing and comparing outcome after cardiac surgery. Repeatedly assessed QoL during follow-up of patients with RVOT reconstruction has not yet been reported.

The aim of this study is to present the long term clinical and functional outcome after RVOT reconstruction with a homograft by including serial echocardiographic measurements and repeatedly assessed quality of life.

METHODS

All consecutive patients who underwent RVOT reconstruction between April 1986 and November 2017 using a homograft in the Erasmus Medical Center Rotterdam were included in this retrospective cohort analysis. The Erasmus Medical Center is a tertiary referral center specialized in congenital cardiac surgery. The medical ethics commission reviewed and approved this study prior to its onset and waived individual informed consent (MEC 12-477).

Operative characteristics

Patients were preoperatively discussed in a regular heart team meeting including congenital and pediatric cardiologists, cardiac surgeons and radiologists. In our center only pulmonary homografts are currently being used as valved conduits for RVOT reconstruction. Implantation involved standard cardiopulmonary bypass on a beating heart with moderate hypothermia. When aortic crossclamping was applied, crystalloid cardioplegia (St. Thomas Hospital Solution) was used for myocardial protection. Running polypropylene sutures were used to interpose the homograft between the right ventricle and pulmonary stem.

Clinical outcome

Patients were seen postoperatively at regular outpatient visits at one month, six months and annually thereafter. Visits included physical examination, standardized echocardiography and electrocardiography. Valve related events and morbidity were classified according to the guidelines for reporting mortality and morbidity after cardiac valve interventions [4]. Multiple subsequent allografts in the same patients were regarded as separate subjects. The national civil registry was consulted in January 2017 to confirm life status of all patients discharged alive.

Echocardiographic follow up

Repeated standardized transthoracic echocardiograms were performed during outpatient clinical visits. Pressure gradients were calculated using the simplified Bernoulli equation based on the maximum transvalvular velocity from multiple acoustic windows with Continuous-wave Doppler. Regurgitation was assessed using color flow Doppler and graded as none, trace,-mild, moderate, or severe [5]. Significant regurgitation was defined as moderate and/or severe regurgitation.

Statistical methods

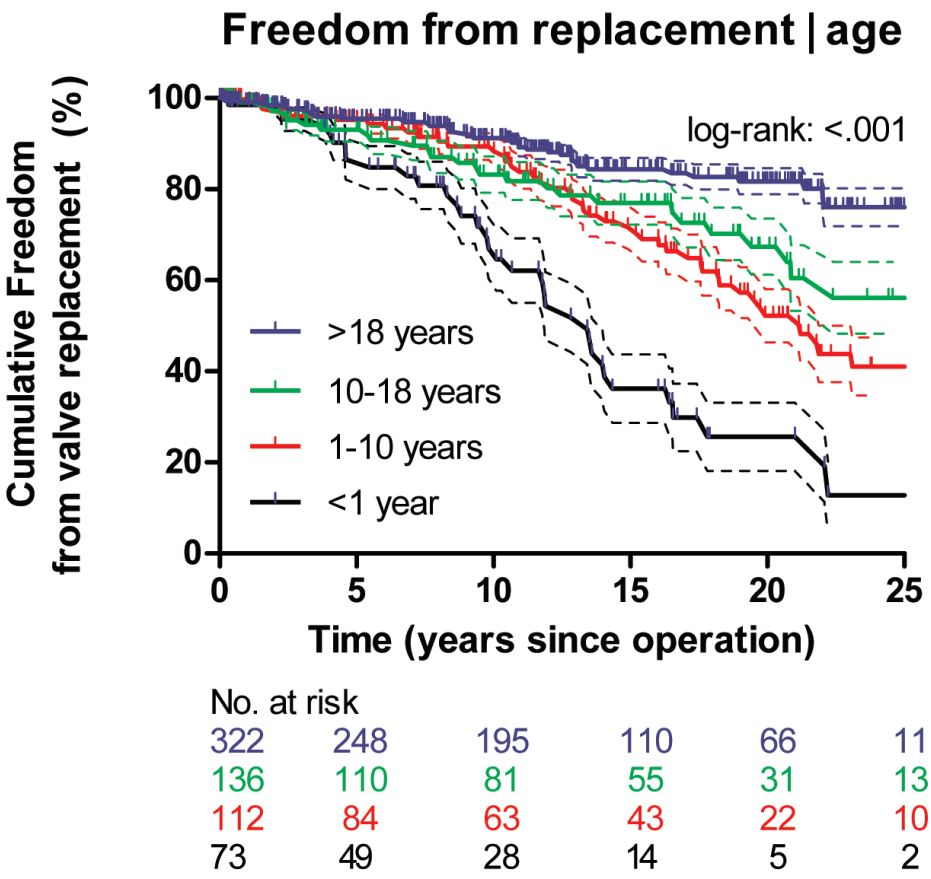
Normality was assessed using the Kolmogorov-Smirnov analysis. Continuous data were presented as mean±standard deviation (SD) or median (range), as appropriate. Comparisons between patients were performed with independent t-tests, the Mann-Whitney U test, Kruskal-Wallis 1-way ANOVA or Chi-square test, as appropriate. Time-dependent events were visualized by Kaplan-Meier plots and summarized with the life-tables technique. Univariable assessment of potential risk factors for survival, freedom from valve replacement and valve related events was performed with the log-rank test. Cox proportional hazards models using a backward stepwise elimination method were used to identify independent risk factors of valve replacement. A p-value criterion of >0.10 was used for elimination from the model, and <0.05 for retention. The proportionality assumption was tested by using a time dependent Cox model that included an interaction term of the risk factor with time.

Serial longitudinal measurements of the transvalvular gradient were analyzed with linear mixed effects models (LMM) as recommended by the guidelines for reporting mortality and morbidity after cardiac valve interventions [4]. The ordinal serial measurements of regurgitation were analyzed with a generalized mixed effect continuation ratio model. Random effects were included to account for the correlation among repeated measurements within patients and irregular timed and number of measurements. Natural cubic splines with three internal knots were used to account for the non-linear association with time. F-tests were used to assess the predictive value of each covariate on echocardiographic outcome. Model assumptions were checked by inspection of

residual plots, and transformations of the outcome variable were applied when appropriate.

Marginal models were constructed to determine the mean response, i.e. the average evolution of our sample population. In addition, effect plots of subject specific predictions were made for patients with median characteristics from each age category for illustrational purposes. Effect plots denoting the median and marginal probabilities were provided for the temporal likelihood trend of significant regurgitation. All resulting models are accessible through our interactive online application.

Self-reported Quality of life (QoL) was assessed in Dutch speaking patients older than 18 years at moment of assessment in a cross-sectional design using the standard short-form 36 (SF-36) [6]. Scores were compared to those of a gender and age matched general Dutch population using the Wilcoxon rank-sum test [7]. For each of the eight subscales of the SF-36, an univariable generalized linear model was employed to com-



Central image Cumulative freedom from homograft replacement per age category

Table 1. Baseline and Surgical characteristics

	Mean ± SD or median (range) or frequency (%)				
	All patients	**<1 year**	**1-10 years**	**>10-18 years**	**>18 years**
Patients (n=701)	701	86 (12.3)	149 (21.3)	118 (16.8)	348 (49.6)
Age (years) (n=701)	19.5 ± 15.2	0.35 ± 0.28	5.00 ± 2.90	14.23 ± 2.22	32.1 ± 10.6
Weight (kg) (n=701)	53 (2.3-111.0)	4.3 (2.3-9.3)	16 (4.0-47.0)	48 (23.0-87.1)	68.0 (34.5-111.0)
Length (cm) (n=701)	161 (40-200)	56 (40-75)	105 (48-147)	161 (132-190)	172 (135-200)
Male (n=701)	418 (59.6)	53 (61.6)	91 (61.1)	77 (65.3)	197 (56.6)
Number homograft (n=701)					
First	601 (85.7)	85 (98.8)	128 (85.9)	84 (71.2)	304 (87.4)
Second	88 (12.6)	1 (1.2)	20 (13.4)	32 (27.1)	35 (10.1)
Third	9 (1.3)	0 (0)	1 (0.7)	2 (1.7)	6 (1.7)
Fourth	3 (0.4)	0 (0)	0 (0)	0 (0)	3 (0.9)
Diagnosis (n=701)					
Tetralogy of Fallot	231 (33.0)	6 (7.0)	24 (16.1)	25 (21.2)	176 (50.6)
Ross procedure	189 (27.0)	18 (20.9)	30 (20.1)	38 (32.2)	103 (29.6)
PA with VSD	86 (12.3)	7 (8.1)	47 (31.5)	17 (14.4)	15 (4.3)
PA without VSD	12 (1.7)	0 (0)	5 (3.4)	2 (1.7)	5 (1.4)
TGA	50 (7.1)	8 (9.3)	22 (14.8)	13 (11.0)	7 (2.0)
TAC	63 (9.0)	41 (47.7)	8 (5.4)	10 (8.5)	4 (1.1)
Tricuspid Atresia	13 (1.9)	2 (2.3)	5 (3.4)	2 (1.7)	4 (1.1)
Isolated PS	28 (4.0)	0 (0)	1 (0.7)	7 (5.9)	20 (5.7)
Other	29 (4.1)	4 (4.7)	7 (4.7)	4 (3.4)	14 (4.0)
Previous Correction (n=701)	359 (51.2)	3 (3.5)	53 (35.6)	75 (63.6)	228 (65.5)
Previous shunt (n=701)	214 (30.5)	9 (10.5)	81 (54.4)	35 (29.7)	89 (25.6)
Bypass-time (min) (n=642)	153 ± 78	173 ± 77	152 ± 62	142 ± 80	150 ± 83
Cross-clamp use (n=631)	429 (68.0)	80 (96.4)	117 (82.4)	61 (59.8)	171 (56.3)
Cross-clamp time (min)	114 ± 42	102 ± 34	105 ± 32	117 ± 48	125 ± 47
Circulatory-arrest (n=701)	30 (4.3)	14 (16.3)	4 (2.7)	5 (4.2)	7 (2.0)
Circulation-arrest time (min)	35 ± 21.4	43 ± 18	21 ± 20	32 ± 19	31 ± 28
Diameter allograft (mm) (n=690)	22 (10-31)	15 (10-21)	21 (11-28)	23 (15-28)	24 (19-31)
Cryopreserved (n=670)	654 (93.3)	79 (91.9)	134 (89.9)	110 (93.2)	331 (100)
Donor type (n=629)					
Heart-beating	265 (41.5)	42 (53.8)	68 (49.6)	42 (38.9)	113 (35.8)
Non-heart-beating	355 (55.6)	34 (43.6)	66 (48.2)	62 (57.4)	193 (61.1)
Domino-heart	19 (3.0)	2 (2.6)	3 (2.0)	4 (3.7)	10 (3.2)
Male donor (n=632)	327 (51.7)	37 (46.8)	56 (41.5)	56 (52.8)	178 (57.1)
Hospital mortality (n=701)	23 (3.3)	11 (12.8)	3 (2.0)	0 (0.0)	9 (2.6)

DORV = Double Outlet Right Ventricle, n = number of cases for which data was available, PA = Pulmonary Atresia, PS = Pulmonary Stenosis, TAC = Truncus Arteriosus Communis, TGA = Transposition of the Great Arteries, VSD = Ventricular Septal Defect

pare subgroups and estimate effect sizes. Repeatedly assessed QoL measurements were compared using the Wilcoxon signed rank-test.

A p-value less than 0.05 was considered significant throughout the analyses. A Bonferroni correction was applied during the interpretation of results on the different subscales of the SF-36. Statistical analyses were performed with SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) and R statistical program, R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

During the study period, 701 homografts were implanted in 603 patients in RVOT position. Baseline clinical and surgical characteristics are summarized, per age category, in Table 1. In-hospital mortality was 3.3% (n=23) and predominantly occurred in patients aged less than one year (p<0.001). Last follow up was known of 435 (88.5%) patients within a year of study closing. Median FUP duration was 10.7 years (range 0.01-30.0 years, mean 11.4 years, total 7729 patient-years). Late mortality was observed in 57 (9.5%) patients and was due to a cardiac cause in 49 (86%) patients of which 16 cases (32.7%) of sudden cardiac death and 28 cases (57.1%) of end stage heart failure. Freedom from mortality of hospital survivors was 89% (95% confidence interval (CI) 85-93%)) at 10 years and 84% (95% CI 80-88%)) at 20 years.

Homograft durability

Homograft related reintervention (n=178; 25.4%) consisted out of surgical PVR (n=104; 14.8%), transcatheter PVR (n=42, 6.0%), surgical), surgery on the homograft without replacement (n=4, 0.6%), transcatheter balloon dilatation (n=22, 3.1%), conversion to total cavo-pulmonary connections (n=4, 0.6%), and one combined heart-lung transplantation (Table 2). Thirteen PVR procedures (9.0%) were preceded by balloon dilatation. Freedom from valve replacement (surgically or percutaneously) at 10 and 20 years were 76% (95% 72-80%) and 56% (95% CI 50-62%), respectively. Freedom from replacement (surgically or percutaneously) at 20 years was 16% (95% CI 8-24%), 48±5% and 76% (95% CI 72-80%) for patients under one, between 1 and 18 and older than 18, respectively (Figure 1A-F). Indications for replacement were severe stenosis (n=98; 67.1%), severe regurgitation (n=19; 13.0%), mixed stenosis and regurgitation (n=27; 18.5%) and endocarditis (n=2; 1.4%). Twenty-nine cases of endocarditis occurred in 27 patients (0.38%/patient-year) with a homograft, of which 2 cases eventually led to PVR. Zero cases of valve thrombosis and 6 (0.08%/patient-year) cases of stroke (4 major, 2 minor) were reported. Independent risk factors for valve replacement were younger age (p=0.022),

male gender (p=0.001), a smaller homograft diameter (in millimeters) (p=0.020) and use of an aortic homograft (p<0.001) (Supplementary Material, Table S1).

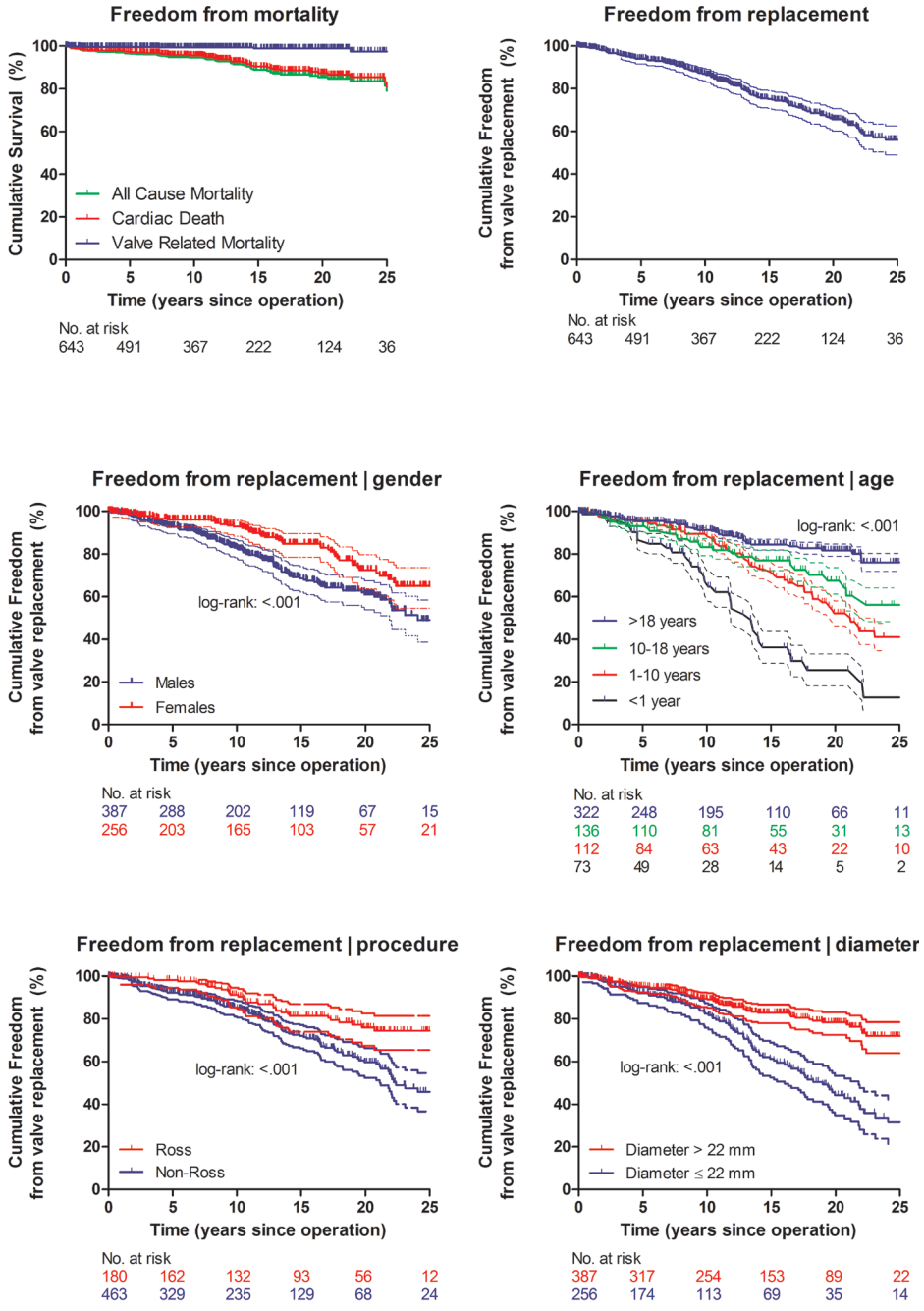


Figure 1 Survival and freedom from valve replacement with subgroup analyses

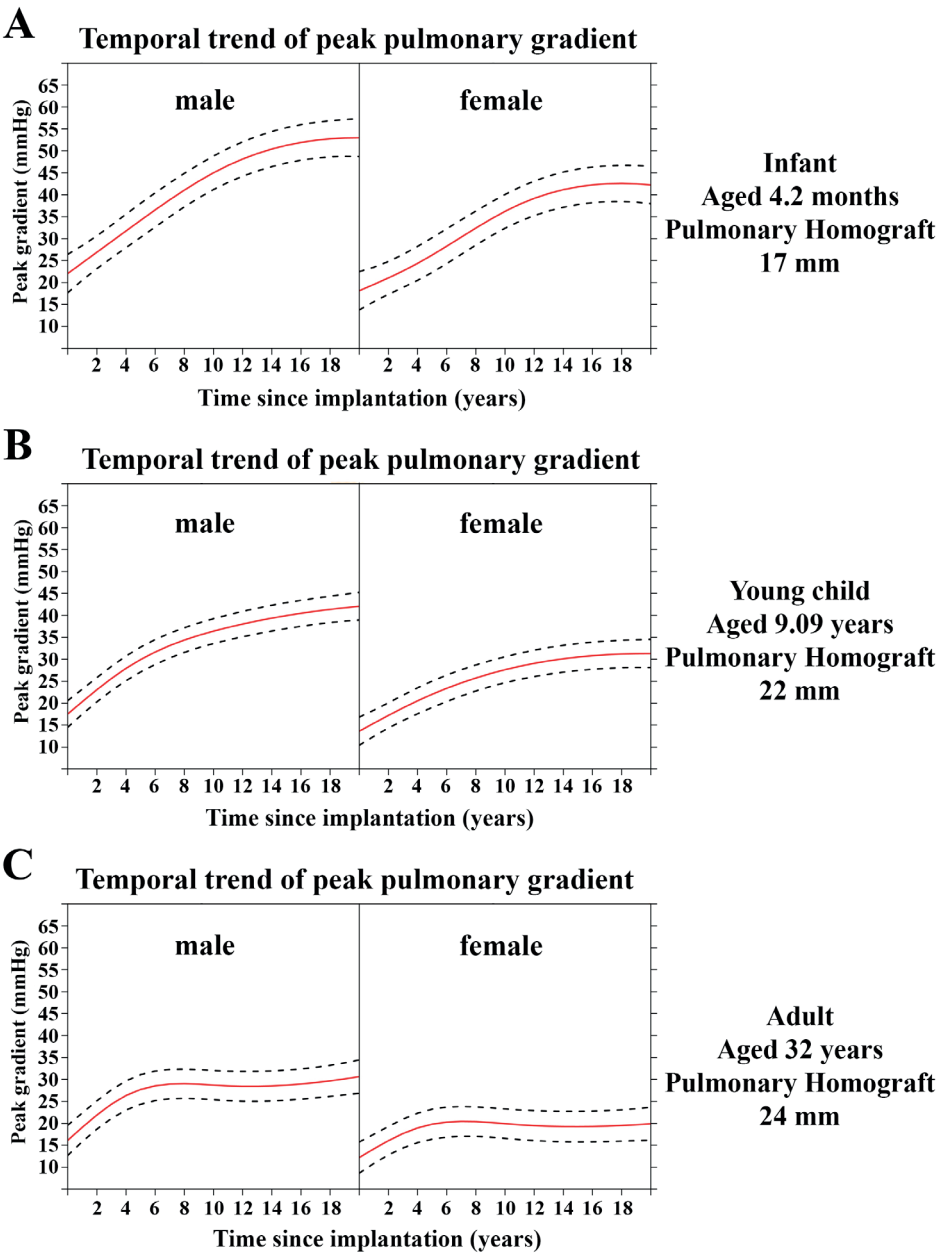


Figure 2 Transvalvular peak gradient (mmHg) per age group and per sex

Echocardiographic performance

A total of 6085 postoperative echocardiograms of 635 homografts (93.7% of hospital survivors) were available for longitudinal analyses. Figures 2A-C and 3A-C depict effectplots for marginal pulmonary gradient and regurgitation per age group and gender,

Table 2. Clinical long term outcome of hospital survivors

	All		<1 year		1-10 years		>10-18 years		>18 years	
Grafts (patient-years followed)	678 (7729)	LOR	75 (673)	LOR	146 (1769)	LOR	118 (1343)	LOR	339 (3944)	LOR
Valve related events (n)										
SVD	163	2.11%	39	5.79%	53	3.00%	27	2.01%	44	1.12%
NSVD	8	0.10%	1	0.15%	2	0.11%	4	0.30%	4	0.10%
Endocarditis	29	0.38%	0	0.00%	8	0.45%	8	0.60%	13	0.33%
Valve thrombosis	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Major bleeding	2	0.03%	0	0.00%	0	0.00%	0	0.00%	2	0.05%
Stroke	6	0.08%	0	0.00%	0	0.00%	2	0.15%	4	0.10%
Mortality (n)	57	0.74%	8	1.19%	8	0.45%	3	0.22%	38	0.96%
Cardiac-death	49	0.63%	6	0.89%	6	0.34%	3	0.22%	34	0.86%
Valve-related	5	0.06%	1	0.15%	3	0.17%	0	0.10%	1	0.03%
Sudden Unexplained	16	0.21%	1	0.15%	0	0.00%	1	0.01%	14	0.35%
Non-valve related	28	0.36%	4	0.59%	3	0.17%	2	0.01%	19	0.48%
Non-cardiac death	8	0.10%	2	0.30%	2	0.11%	0	0.00%	4	0.10%
Allograft-related reintervention (n)										
Balloon-dilatation	22	0.28%	7	1.04%	7	0.40%	2	0.01%	6	0.15%
PVR	146	1.89%	34	5.05%	45	2.54%	26	1.94%	41	1.04%
SPVR	104	1.35%	32	4.75%	33	1.87%	18	0.60%	21	0.53%
TPVR	42	0.54%	2	0.30%	12	0.68%	8	0.56%	20	0.51%
Other¥	9	0.12%	0	0.00%	5	0.28%	1	0.01%	3	0.08%
Replacement (n)	146	1.89%	34	5.05%	45	2.54%	26	1.93%	41	1.04%
Severe stenosis	98	1.27%	27	4.01%	31	1.75%	19	1.41%	21	0.53%
Severe regurgitation	19	0.25%	1	0.15%	3	0.17%	4	0.30%	11	0.28%
Mixed	27	0.35%	6	0.89%	10	0.57%	4	0.30%	8	0.20%
Endocarditis	2	0.03%	0	0.00%	1	0.01%	0	0.00%	1	0.03%
Pacemaker/ICD	35	0.45%	0	0.00%	5	0.29%	4	0.30%	26	0.66%

LOR = linearized occurrence rate per patient-year of follow up, (N)SVD = (Non) Structural Valve Deterioration, (S/T)PVR = (Surgical/Transcatheter) Pulmonary Valve Replacement, ICD = Implantable cardioverter-defibrillator

¥ Other: four surgical alterations without replacement of the homograft in children between 1 and 18, four conversions to total cavo-pulmonary connections, and one combined heart-lung-transplantation.

respectively. A younger age at implantation (p<.001), aortic grafts (p<.001), a smaller diameter (in millimeters) (p<.001), a non-Ross diagnosis (p=0.033) and male gender (p<.001) were independently associated with higher gradient. A larger diameter (in millimeters) (p<.001) and higher age (p=0.001) at implantation were associated with a decreased probability of a higher regurgitation grade.

Quality of life

Quality of life could be assessed in 244 patients (59.2% of patients who received the questionnaire). Respondents were on average older (p<.001) than patients that did not return the questionnaire. Other baseline characteristics were comparable (Supplementary Material, Table S2). Baseline characteristics of respondents are shown in Supplementary Material, Table S3 and overall scores in Supplementary Material, Table S4. Compared to an age and gender matched Dutch population, male and female patients rated vitality (p<.001) and general health (p<.001) significantly lower, but reported less bodily pain (p<0.001) (Supplementary Material, Table S4). Women scored significantly lower than men on the subscales physical functioning (p<.001), social functioning (p<.001), vitality (p<.001) and bodily pain (p<.001) (Supplementary Material, Table S5). No differences in QoL were reported based on diagnoses (Supplementary Material, Table S5).

Of 244 respondents, 125 patients had also completed the questionnaire 5 years earlier (Supplementary Material, Table S6). Of the 196 respondents in 2012, 71 (36.2%) did not complete the questionnaire this year due to death (n=12) and unknown reasons (n=59). Patients who still had the same homograft (n=112) showed lower scores on physical functioning (p=0.004), vitality (p=0.003) and general health (p=0.011). No differences in any of the SF-36 subscales were found in repeatedly measured patients who underwent re-PVR (n=13) during the five year period (Supplementary Material, Table S6). Comparing patients with the same homograft to those who underwent re-PVR yielded no significant differences in any of the subscales in 2012 (Supplementary Material, Table S6).

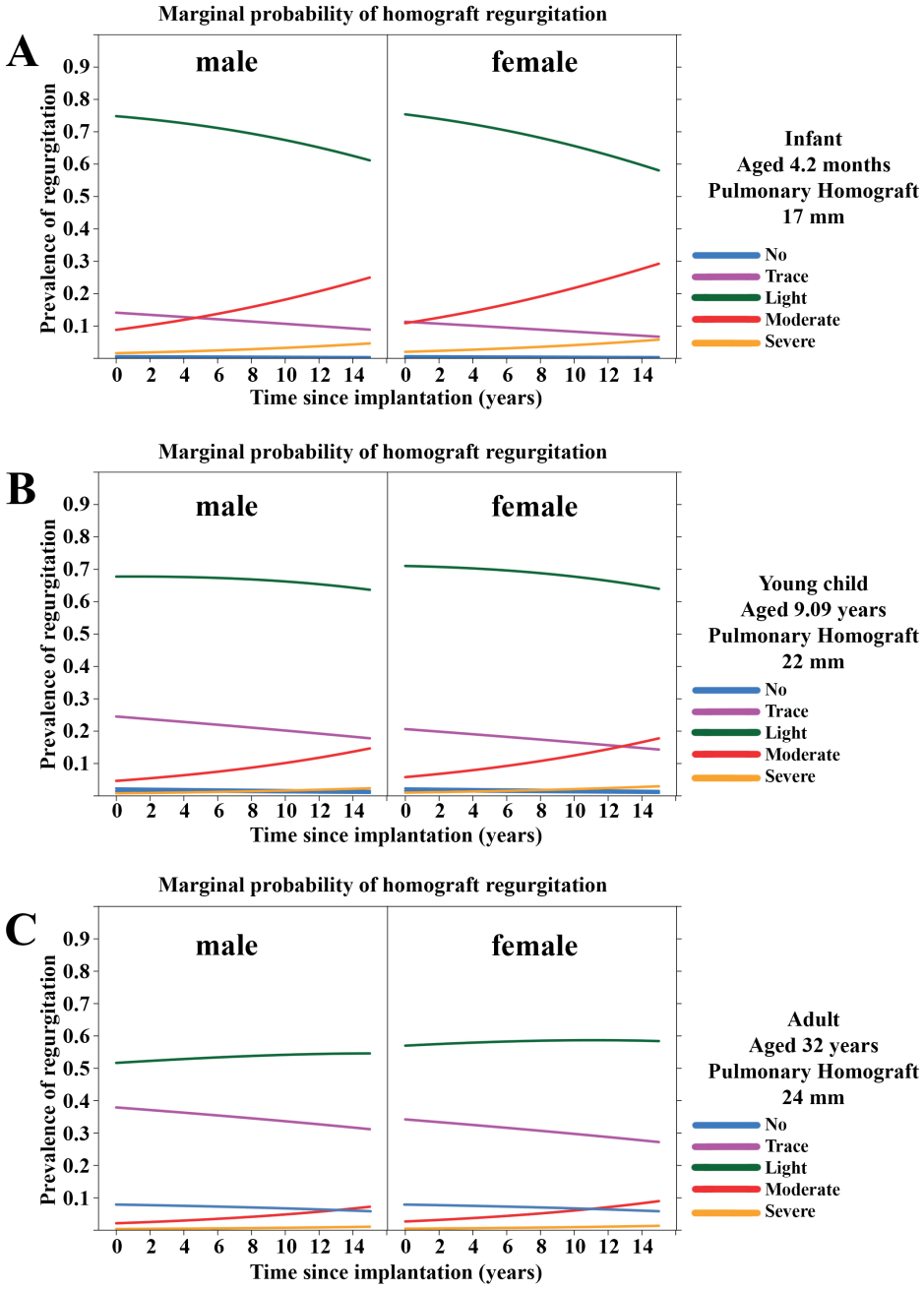


Figure 3 Probabilities of pulmonary regurgitation per age group and gender

DISCUSSION

This study shows that RVOT reconstruction with a homograft can be performed safely and can result in long term valve durability. A relatively low risk of valve related events and morbidity after 30 years of follow up is observed. Specifically women, Ross patients and adult patients show longest freedom from valve related reintervention and mortality. Homograft durability in infants is lowest, often caused by restenosis. Self-reported QoL is lower than a gender and age matched general population and remained stable in patients who underwent re-PVR. Based on data from this study an interactive online application was created which can be used to explore average and subject-specific temporal evolutions of gradient and regurgitation grade.

Survival and graft durability

Survival of 89% at 10 years and 84% at 20 years in our cohort is satisfactorily and comparable to similar reports on cryopreserved homograft [8, 9]. Early nor late mortality has ever been the predominant subject of debate however. In general, late mortality after RVOT reconstruction with a homograft is sporadically directly valve related but often pertains to the poor cardiac and general health of this complex population. Limited homograft durability has been the main concern and has been predominantly reported by early reports which included mixed diagnoses, aortic homografts and non-cryopreserved homografts [10, 11]. The risk factors for limited homograft durability that have been reported in the literature are non-Ross diagnosis, younger age at implantation, smaller grafts and aortic grafts which also were confirmed by multivariable analysis in our study [9, 12-14]. A potential explanation for a durability advantage in women is a different humoral and cellular immulogic response [15]. Furthermore, Ross patients are in general a carefully selected patient populations with excellent right ventricular function and no pulmonary hypertension. These optimal circumstances could be responsible for their durability advantage. These risk factors were confirmed by both the results of our survival analyses of allograft durability and longitudinal analyses of echocardiographic allograft function over time.

Early reintervention in children remains a well-known problem [14, 16, 17]. Although small sized valves and somatic outgrowth have been regarded as risk factors in children, different authors have made nuances to the practice of unrestricted oversizing of conduits [18-20]. In a report by Wells et al, only 3 of the 40 patients who underwent graft explantation showed somatic outgrowth. Shrinkage was the most common finding associated with fibro-intimal proliferation leading to narrowing of the lumen [18]. Bicuspidalization did not affected homograft durability and patient survival in our cohort of patients [21]. Furthermore, during the '90s it became evident that cryopreservation preserves the antigenic potential of the homograft. Cryopreserved homografts induce

an anti-HLA antibodies response shortly after implantation, which is persistent and more pronounced in children [22]. The effects of HLA-matched homografts on durability is still ambiguous however. Therefore, HLA-matching is currently not pursued, both in general as well as in our center and pulmonary homografts are actively preferred.

Limited availability of size-matched homografts has given way to alternatives. Downsizing larger homografts to bicuspid smaller ones is a good alternative which has not affected durability nor survival in our series [21]. Probably the most common alternative to the homograft in western society is the Contegra (Medtronic) valve made from a bovine jugular vein. However, multiple studies indicated the Contegra as independent risk factor for reintervention [19, 23]. In a propensity matched comparison with homografts by Urso et al., the Contegra conduit had an independent HR of 3.7 for graft replacement [23]. In children operated under one year, Vitanova et al. showed an earlier development of stenosis and regurgitation in Contegra valves, compared to homografts, despite a remarkable 48% of the homografts being of aortic origin [19]. In line with our series, valve related events in cohorts of homografts are rare [8, 24]. No valve thrombosis occurred in the entire cohort, and overall endocarditis and stroke rates were low and comparable with data reported by other studies. A higher incidence of endocarditis in bioprostheses has been consistently reported ranging from 7 to 11% [24-27]. An increased endocarditis rate is also observed in patients undergoing transcatheter bioprosthetic valve implantation which compares poorly to the less than 1% generally reported in homografts [2]. Moreover, most of the cases of endocarditis in our cohort could be managed conservatively without surgical reintervention.

Decellularized homografts have been developed which assumingly lack the antigenicity preserved in standard cryopreserved homografts. The first mid-term results on decellularized valves in human have been promising [28, 29]. Sarikouch et al. performed a matched comparison of decellularized valves with standard homografts and BJV. After 10 years, freedom from explantation was 100% for decellularized valves, compared to 84.2% (p=0.01) for standard cryopreserved homografts and 84.3% for BJV (p=0.01). All explantations were indicated by structural valve deterioration [29]. In a propensity matched comparison, decellularized valves were non-inferior to standard homografts during the first 5 postoperative years in Ross patients. However, both the mean gradient and regurgitation grade of decellularized valves appeared to increase in a more progressive pace towards the end of the 5 year period, warranting studies of longer follow up [28]. Currently, prospective European multicenter trials have been started which will shed more light on the potential of decellularized valves.

Quality of life

To the best of our knowledge, we presented the first results of repeatedly measured QoL in this population. The lower reported experience of bodily pain in patients compared

to the general population could potentially be explained by different coping mechanisms, which have been described extensively for a diversity of diseases [30]. Significant declines over time in physical functioning and vitality were reported by patients still with their first homograft in place along with a trend towards decline in general health. Although limited in number, patients who underwent re-PVR during the 5 year period reported comparable QoL on all subsets of the SF-36. This could suggest preservation or even improvement of QoL through homograft replacement. However, the number of patients is too small to derive any conclusions.

Clinical Implications

Predictions of our fitted mixed effect models are accessible through an online application. Physicians can study the influence of various combinations of patient and graft characteristics on long term homograft durability. Furthermore, differences in age and primary diagnosis, and the use of aortic and/or non-cryopreserved homografts are predominant in early studies. New studies including a larger proportion of recent patients could be more representative for current practice and provide valuable new perspectives on homograft durability.

STUDY STRENGTH AND LIMITATIONS

Limitations are inherently due to the retrospective and observational nature inevitably leading to missing data. This limitation was confined by focusing on hard clinical endpoints, less susceptible to bias. In conclusion, this study presents one of the largest single-center cohorts of consecutive patients with follow up exceeding 30 years. Advanced analyses of serial echocardiographic measurements are presented along with an online application presenting different patient and valve characteristics with long term subject-specific homograft function. Furthermore, this is the first time quality of life was repeatedly assessed in this population. However, these results should interpreted with caution given the limited number of repeated respondents.

CONCLUSION

Right ventricular outflow tract reconstruction with a homograft can result in excellent long term survival and freedom from valve related events and reintervention, especially in adult patients. Valve related events are rare and can generally be treated without surgical reintervention or mortality. An online application is available to predict subject-specific homograft function over time.

REFERENCES

1. Mokhles, M.M., et al., Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg, 2011. 40(3): p. 571-8.
2. Sharma, A., et al., A Systematic Review of Infective Endocarditis in Patients With Bovine Jugular Vein Valves Compared With Other Valve Types. JACC Cardiovasc Interv, 2017. 10(14): p. 1449-1458.
3. Boethig, D., et al., Mid term course after pediatric right ventricular outflow tract reconstruction: a comparison of homografts, porcine xenografts and Contegras. Eur J Cardiothorac Surg, 2005. 27(1): p. 58-66.
4. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
5. Baumgartner, H., et al., Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice. Journal of the American Society of Echocardiography, 2009. 22(1): p. 1-23.
6. Ware, J.E., Jr. and C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care, 1992. 30(6): p. 473-83.
7. Aaronson, N.K., et al., Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol, 1998. 51(11): p. 1055-68.
8. Kalfa, D.M., et al., Pulmonary position cryopreserved homograft in non-Ross patients: how to improve the results?†. European Journal of Cardio-Thoracic Surgery, 2012. 42(6): p. 981-987.
9. Troost, E., et al., Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration. Eur Heart J, 2007. 28(20): p. 2503-9.
10. LeBlanc, J.G., et al., Intermediate follow-up of right ventricular outflow tract reconstruction with allograft conduits. Ann Thorac Surg, 1998. 66(6 Suppl): p. S174-8.
11. Stark, J., et al., Fate Of Subpulmonary Homograft Conduits: Determinants Of Latehomograft Failure. The Journal of Thoracic and Cardiovascular Surgery, 1997. 115(3): p. 506-516.
12. Daenen, W. and M. Gewillig, Factors influencing medium-term performance of right-sided cryopreserved homografts. J Heart Valve Dis, 1997. 6(4): p. 347-53; discussion 353-4.
13. Bando, K., et al., Outcome of pulmonary and aortic homografts for right ventricular outflow tract reconstruction. J Thorac Cardiovasc Surg, 1995. 109(3): p. 509-17; discussion 517-8.
14. Kalfa, D., et al., How to choose the best available homograft to reconstruct the right ventricular outflow tract. The Journal of Thoracic and Cardiovascular Surgery, 2011. 142(4): p. 950-953.
15. Koolbergen, D.R., et al., The pathology of fresh and cryopreserved homograft heart valves: An analysis of forty explanted homograft valves. The Journal of Thoracic and Cardiovascular Surgery, 2002. 124(4): p. 689-697.
16. Askovich, B., et al., Right ventricle-to-pulmonary artery conduit longevity: is it related to allograft size? Ann Thorac Surg, 2007. 84(3): p. 907-11; discussion 911-2.
17. Tweddell, J.S., et al., Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation, 2000. 102(19 Suppl 3): p. III130-5.

18. Wells, W.J., et al., Homograft conduit failure in infants is not due to somatic outgrowth. The Journal of Thoracic and Cardiovascular Surgery. 124(1): p. 88-96.

19. Vitanova, K., et al., Which type of conduit to choose for right ventricular outflow tract reconstruction in patients below 1 year of age?dagger. Eur J Cardiothorac Surg, 2014. 46(6): p. 961-6; discussion 966.

20. Karamlou, T., et al., Oversizing pulmonary homograft conduits does not significantly decrease allograft failure in children☆. European Journal of Cardio-Thoracic Surgery, 2005. 27(4): p. 548-553.

21. Romeo, J.L.R., et al., Downsized cryopreserved and standard-sized allografts for right ventricular outflow tract reconstruction in children: long-term single-institutional experience. Interactive CardioVascular and Thoracic Surgery, 2018: p. ivy057-ivy057.

22. Hawkins, J.A., et al., Class I and class II anti-HLA antibodies after implantation of cryopreserved allograft material in pediatric patients. J Thorac Cardiovasc Surg, 2000. 119(2): p. 324-30.

23. Urso, S., et al., The Contegra conduit in the right ventricular outflow tract is an independent risk factor for graft replacement. Eur J Cardiothorac Surg, 2011. 40(3): p. 603-9.

24. Malekzadeh-Milani, S., et al., Incidence and outcomes of right-sided endocarditis in patients with congenital heart disease after surgical or transcatheter pulmonary valve implantation. J Thorac Cardiovasc Surg, 2014. 148(5): p. 2253-9.

25. Ugaki, S., et al., An increased incidence of conduit endocarditis in patients receiving bovine jugular vein grafts compared to cryopreserved homograft for right ventricular outflow reconstruction. Ann Thorac Surg, 2015. 99(1): p. 140-6.

26. Van Dijck, I., et al., Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. Heart, 2015. 101(10): p. 788-793.

27. Mery, C.M., et al., Risk factors for development of endocarditis and reintervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. J Thorac Cardiovasc Surg, 2016. 151(2): p. 432-9, 441 e1-2.

28. da Costa, F.D.A., et al., Decellularized Versus Standard Pulmonary Allografts in the Ross Procedure: Propensity-Matched Analysis. The Annals of Thoracic Surgery, 2018.

29. Sarikouch, S., et al., Decellularized fresh homografts for pulmonary valve replacement: a decade of clinical experience. Eur J Cardiothorac Surg, 2016. 50(2): p. 281-90.

30. Rinaldi, S., et al., Influence of coping skills on health-related quality of life in patients with systemic lupus erythematosus. Arthritis Rheum, 2006. 55(3): p. 427-33.

7

Timing of Pulmonary Valve Replacement in Patients with Corrected Fallot to Prevent QRS Prolongation

Jamie LR Romeo, Johanna JM Takkenberg, Judith AAE Cuypers, Natasha MS de Groot, Pieter van de Woestijne, Nico Bruining, Ad JJC Bogers, M Mostafa Mokhles

European Journal of Cardio-Thoracic Surgery

ABSTRACT

Background

Timing of pulmonary valve replacement (PVR) remains one of the most heavily debated topics in congenital cardiac surgery. Progressive We aimed to analyze the temporal evolution of QRS duration before and after PVR.

Methods

We included 158 consecutive patients wo underwent PVR after previous correction with transannular patch. All 3549 available serial standard 12-lead surface QRS measurements of 158 (100%) patients were analyzed with linear mixed effect modeling.

Results

PVR was performed at a mean age of 28.0±10.7 years, 23.4±8.4 years after correction. Hospital survival was 98.1%. A longer time interval between ToF correction and PVR ($p<0.001$), and an older age at correction ($p=0.015$) were predictive of progressive QRS prolongation after PVR. Women on average had a shorter QRS duration ($p=0.0047$) after PVR. The model predicted that in patients corrected early (model age 0.5 years), PVR within 17 years after correction leads to narrowing or stabilization of QRS width. PVR beyond 17 years was associated with prolongation of QRS duration. In a patient corrected late (model age 5 years) PVR has to be performed within 15 years after correction to prevent prolongation. Finally, a longer time period between correction and PVR was associated with an increased hazard of cardiac death (Hazard Ratio: 1.097, 95% confidence interval 1.002-1.200).

Conclusions

Prolongation of QRS duration after PVR was associated with a longer time between correction and PVR, older age at correction and male sex. Prevention of progressive QRS prolongation by earlier PVR can potentially reduce the hazard of adverse events after PVR.

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease in life births and can be repaired safely at a young age [1]. However, long term survival and freedom from reintervention are limited by the presence of ventricular arrhythmia, sudden death and heart failure [2, 3]. Ventricular tachyarrhythmia in repaired TOF patients is presumed to be the primary cause of sudden death. In the current paradigm it is believed that chronic volume overload, caused by residual pulmonary regurgitation (PR), leads to right ventricular (RV) dilatation. This ultimately predisposes for electromechanical dissociation and heart failure [3-5]. Pulmonary valve replacement (PVR) treats pulmonary regurgitation and results in RV remodeling during the first post-operative years [6]. However, RV reverse remodeling does not occur in every patient and adverse events still occur frequently after PVR [7]. It is currently unknown how to define and determine the optimal timeframe within which PVR should be performed.

QRS duration assessed through standardized 12-lead electrocardiogram may potentially be an prognostic biomarker for adverse cardiac events. A QRS duration exceeding 170-180 ms has repeatedly been indicated as independent predictor for malignant ventricular arrhythmia and sudden cardiac death [3, 8]. Furthermore, prolonged QRS duration is associated with regional wall motion abnormalities [9], RV dilatation [5], increased biventricular wall mass [10], and decreased left ventricular ejection fraction [10]. QRS duration can, therefore, be a potentially meaningful surrogate marker reflecting the impact of chronic severe PR and RV dilatation. A better understanding of the temporal evolution of QRS duration in patients with corrected TOF before and after PVR could improve timing of PVR.

We determined the temporal evolution of QRS duration before and after PVR in a consecutive cohort of corrected TOF patients.

METHODS

All consecutive patients (N=158) who underwent surgical PVR in the Erasmus University Medical Center Rotterdam between August 1987 and November 2017 after complete correction of ToF with a transannular patch (TAP) were included retrospectively. Patients with pulmonary atresia, ventricular septal defects and systemic collateral arteries were excluded. The institutional review board approved this study and waived individual informed consent (MEC 12-477).

Indication and Surgical technique

All patients were discussed in structured multidisciplinary meetings (congenital heart team meeting) including congenital cardiologists, congenital cardiac surgeons, and radiologist, prior to interventions. All indications for PVR were severe PR with signs of progressive RV dilatation or reduced function with or without cardiac related symptoms. PVR was generally performed through median sternotomy, using standard cardiopulmonary bypass as previously described. Cryopreserved homografts were used in all patients for right ventricular outflow tract reconstruction.

Study design

After discharge, patients were followed though our outpatient clinic at one week, 6 weeks, 6 months and annually thereafter. Standardized 12 lead (25 mm/s, 10 mm/mV) surface ECGs are acquired during every visit to our out-patient clinic regardless of symptomatology. Valve related events and mortality were reported according to the guidelines for reporting valve related mortality and morbidity [11]. Follow up within two years of study closing (February 2018) was available for 151 (97.4%) patients discharged alive after PVR. Four patients were lost to follow up after PVR due to emigration (n=3) and unknown reasons (n=1). QRS duration as marker of ventricular depolarization was extracted from computerized calculations based on the VERITAS^{TM} ECG algorithm (Mortara Instrument, 2018, Milwaukee, Wisconsin). Paced rhythms were excluded from the analysis and ECGs were censored in case of re-PVR. Sixteen (10.1%) patients underwent PM implantation 22.0±10.8 years after correction of which 4 before PVR, 10 after PVR and 2 concomitantly to PVR. An integrated assessment of the severity and physiology of pulmonary regurgitation was based on a multi-window perspective using transthoracic color flow and pulsed-wave Doppler echocardiography and qualitatively graded from none, light, moderate and severe. Significant regurgitation was defined as moderate or severe regurgitation [12].

Statistics

Continuous outcomes are reported as means±standard deviations (SD) or medians with range, as appropriate. Continuous variables between groups are compared using independent samples t-tests, one-way ANOVA analysis, or Kruskal-Wallis tests, as appropriate. Frequencies were presented with percentages and compared using chi-square tests. Correlations between continuous baseline variables were calculated using Pearson correlation, and reported with two-tailed significance levels. Time dependent outcomes were analyzed using life tables and visualized with Kaplan-Meier plots as a function of time to or since PVR. Sex, age at correction, time interval between correction and PVR, age at PVR, length at PVR, weight at PVR, creatinine (mmol/L) at PVR and QRS duration at PVR were studied as potential risk factors by uni- and multivariate cox proportional hazards models, using a backward stepwise elimination process. Missing values were

considered missing at random and not imputed due to the very small amount of missing values.

Continuous repeated measurements of QRS duration were analyzed using linear mixed effects modeling (LMM) [13]. A random effects structure with time was used to account for correlations between repeated measurements in the same patient and irregularly timed measurements. QRS duration was modeled as a function of time to PVR, including fixed effects for sex and age at correction. Time in relation to PVR was entered as a natural cubic spline with 2 internal knots. Furthermore, potential interaction effects between age at correction, sex, and time between correction and PVR, were explored. Effect plots were provided to illustrate the temporal evolution of QRS duration of an average patient. Given a significant trend towards earlier repair in our practice as well as contemporary surgical practice, early and late repair were defined as correction at the age of 6 months and 5 years, respectively.

Statistical analyses were performed with SPSS (IBM Corp. Released 2012. Version 24.0.) and R (LME4 package) (R Core Team (2016)).

RESULTS

Baseline patients and surgical characteristics

A total of 158 consecutive patients underwent surgical PVR after previous ToF correction with a TAP. Median age at correction was 2.0 years (range 5 days - 29.5 years) and 90 (57%) were males (Table 1). Mean time between correction and PVR was 23.4±8.2 years (range 1.93-44.) at a mean age of 28.0±10.7 years (range 2.1-66.4). Moderate or severe regurgitation were present in 155 (98.1%) patients before PVR. Figures 1A-C show the trend during the study period of age at ToF correction, at PVR and the time between correction and PVR. The figures indicate an increasingly younger age at correction and a relatively stable time interval between correction and subsequent PVR.

Clinical outcome

Hospital survival was 98.1% (n=155). Three patients (1.9%) died shortly after PVR due to sudden cardiac death presumably based on arrhythmia (n=1), severe esophageal bleeding and pulmonary infection after concomitant tracheal resection (n=1) and repeated rhythm disturbances with severe biventricular heart failure (n=1). All three patients had severe PR with RV dilatation and symptoms. Mean follow up time after PVR was 10.0±7.0 years (median 9.3, range 0.3-28.7 years, total 1555 patient years), during which 18 patients underwent a second PVR (6 surgically, 12 percutaneously), after a mean period of 7.9±5.5 years. Freedom from re-PVR after 10 and 15 years was 84±4% and 81±5%, respectively.

Table 1 Baseline, surgical, diagnostic characteristics

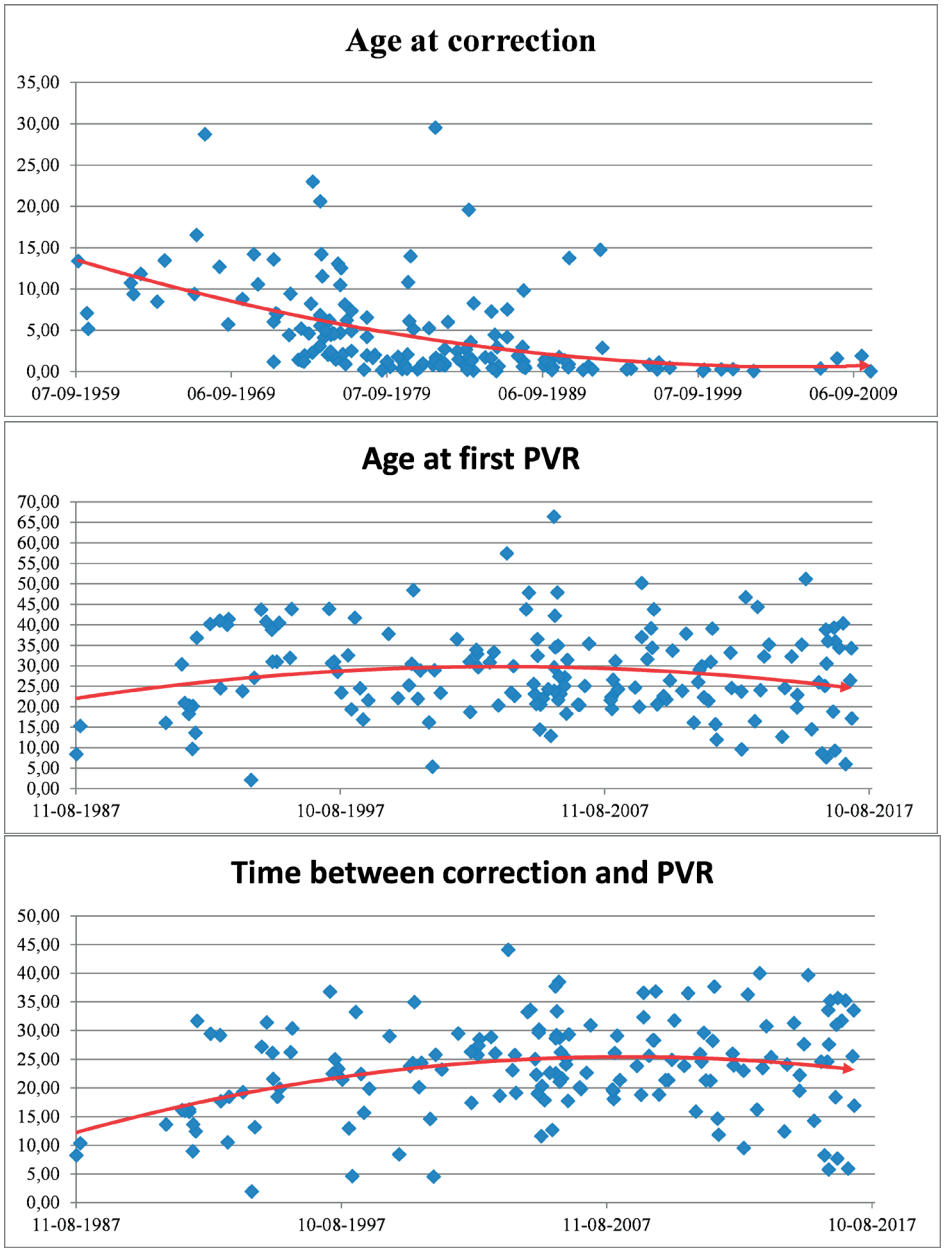
	Overall	interval <10 y	interval 10-20 y	interval 20-30 y	interval >30 y	p-value
Patients (n)	158 (100)	11 (7.0)	42 (26.6)	73 (46.2)	32 (20.3)	
Male sex (n)	90 (57.0)	7 (63.6)	19 (45.2)	41 (56.2)	23 (71.9)	0.140
Shunt before correction (n)	43 (27.2)	3 (27.3)	15 (35.7)	15 (20.5)	10 (31.3)	0.330
Age at correction (years)	4.6±5.5	3.1±5.5	4.9±7.0	3.7±3.8	6.9±6.0	0.035
Time correction-PVR (years)	23.4±8.2	6.7±2.3	16.3±2.9	25.0±2.8	34.5±3.3	<.001
Age at PVR (years)	28.0±10.7	9.8±5.9	21.1±7.2	28.8±5.7	41.5±7.8	<.001
Hemodynamic Indication						
Severe regurgitation	137 (86.7)	7 (63.6)	38 (90.5)	64 (87.7)	28 (87.5)	0.264
Severe stenosis	3 (1.9)	1 (9.1)	1 (2.4)	1 (1.4)	0 (0)	
Mixed	18 (11.4)	3 (27.3	3 (7.1)	8 (11.)	4 (12.5)	
RVOT Peak gradient (mmHg) (n=145)	18.1±20.7	46.1±53.3	20.0±17.5	14.9±13.7	13.7±11.0	<.001
Height (cm) (n=154)	170±14	139±21	168±11	173±10	175±11	<.001
Weight (kg) (n=141)	67±16	33±15	56±12	71±13	76±12	<.001
Previous heart operations* (%)						
1	101 (63.9)	7 (63.6)	24 (57.1)	48 (65.8)	22 (68.8)	0.640
2	46 (29.1)	3 (27.3)	13 (31.0)	22 (30.1)	8 (25.0)	
3	9 (5.9)	1 (9.1)	3 (7.1)	3 (4.1)	2 (6.3)	
4	2 (1.3)	0 (0)	2 (4.8)	0 (0)	0 (0)	
Pre-PVR QRS duration † (n=132)	150±31	141±32	147±31	150±30	155±35	0.674
Elective (>24 hours)	147 (93.0)	10 (90.9)	38 (90.5)	69 (94.5)	30 (93.8)	0.855
Diuretics use (n=156)	15 (9.6)	1 (9.1)	4 (9.8)	8 (11.1)	2 (6.3)	0.895
Sinus Rhythm (n=156)	137 (87.8)	11 (100)	38 (92.7)	63 (87.5)	25 (78.1)	0.154
Creatinine (mmol/l) (n=153)	70±19	43±16	63±17	74±14	79±20	<.001
Cross clamp time (n=141)	22±43	47±34	29±42	17±41	31±48	0.101
Perfusion time (n=147)	111±63	106±50	125±62	101±66	115±58	0.296
Pulmonary allograft‡ (n=154)	154 (97.5)	11 (100)	40 (95.2)	72 (98.6)	31 (96.9)	0.665
Diameter allograft (mm) (n=157)	24 (15-28)	22 (15-25)	24 (21-28)	24 (21-28)	24 (21-28)	0.440
Hospital mortality	3 (1.9)	0 (0)	1 (2.4)	1 (1.4)	1 (3.1)	0.889
ECG						
Total number available	3549	137	809	1816	787	
Pre-PVR (%)	323 (9.1)	11 (8.0)	49 (6.1)	185 (10.2)	78 (9.9)	0.242
Unique patients (n)	157 (99.4)	11 (100)	41 (97.6)	73 (100)	32 (100)	
ECGs/patient	22.5	12.5	19.7	24.9	24.6	0.142
Echocardiography						
Total number available	1747	130	472	821	324	
Pre-PVR (%)	533 (30.5)	29 (22.3)	85 (18.0)	282 (34.3)	137 (42.3)	0.151
Unique patients (n)	156 (98.7)	11 (100)	41 (97.6)	73 (100)	31 (96.9)	
Echos/patient	11.1	11.8	11.5	11.2	10.1	0.242
Follow up duration (years)	9.6±9.6	12.3±10.8	12.3±8.0	9.3±5.3	7.3±6.2	0.010
Max Post PVR QRS duration	158±37	142±35	153±34	159±32	168±48	NA

PVR = Pulmonary Valve Replacement, PR = Pulmonary Regurgitation, RVOT = Right Ventricular Outflow Tract

* = All previous open heart surgeries, including complete correction

† = QRS duration nearest in time but within one year prior to PVR.

‡ = Pulmonary allograft or Aortic allograft.



Figures 1A-C

Late cardiac death was observed in 9 patients, of which 3 (33%) also classified as having an extreme QRS duration (>230 ms) post PVR (Table 3). The relative risk of cardiac death in patients with an extreme QRS duration was 7.25 (95% CI 2.48-8.74; p=.002). The 9 patients that died through cardiac causes were corrected at an average age of

12.4±5.4 years (median 12.7, 4.5-23.0), and underwent PVR 28.6±5.6 years later (median 29.2, range 18.4-36.8). They died 11.0±4.2 years after PVR, at an average age of 52.0±8.9 years. Cumulative freedom from cardiac death of all hospital survivors after 10 and 15 years post PVR was 90±4% and 83±6%, respectively (Figure 3).

QRS duration over time

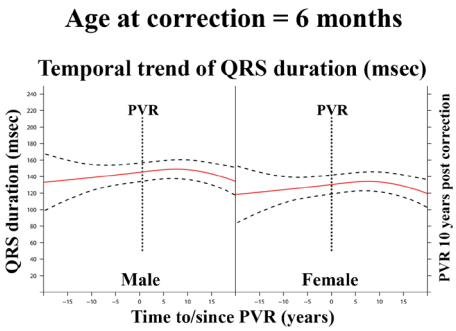
In total, 3549 ECGs were available for 157 (99.4%) patients, averaging 22.9 measurements per patient (Table 1). One patient underwent correction in 1976 and subsequent PVR in 1991 after which he died 14 days later due to severe rhythm disturbances. No ECG's could be retrieved from this patient.

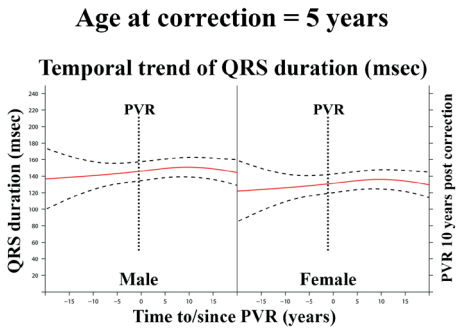
Patients are presented in different groups based on the time interval between ToF correction and PVR (interval between ToF correction and PVR <10 years vs 10-20 vs 20-30 vs > 30 years) (Table 1). The QRS duration prior to PVR was not associated with the time interval between correction and PVR (r=0.089, p=.311), and was comparable between the four groups (p=.674). However, the time interval between correction and PVR showed significant correlations with other baseline factors. A longer time interval between correction and PVR was correlated with older age at correction (r=.189, p=.017), older age at PVR (r=.864, p<.001), higher creatinine (r=.487, p<.001), greater diameter of allograft (r=.207, p=.009), greater height at PVR (r=.443, p<.001) and higher weight at PVR (r= .603, p<.001).

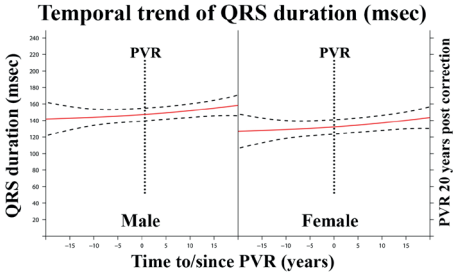
Figures 2A-B provide a panel of effect plots of QRS duration over time before and after PVR. Temporal trends are depicted for male and female patients corrected early (Figure 2A) and late (Figure 2B). Different time intervals between correction and PVR are vertically depicted (10, 20, 30 and 40 years after correction, respectively). Our online application (https://cts-erasmusmc.shinyapps.io/fallotqrs/) provides results for any combination of choice. The figure illustrates that no major changes occur in QRS duration before PVR, and QRS duration is comparable right before PVR, regardless of duration since correction. However, important changes in the overall slope of the evolution of QRS duration can be observed in patients who undergo PVR beyond a certain period. After PVR, a longer time period between correction and PVR (p<0.001), and an older age at correction (p=0.0185) were both significantly and independently associated with progression of QRS duration.

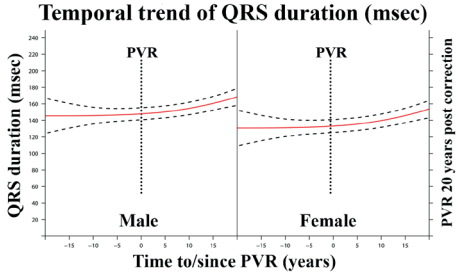
Pacemaker and ICD

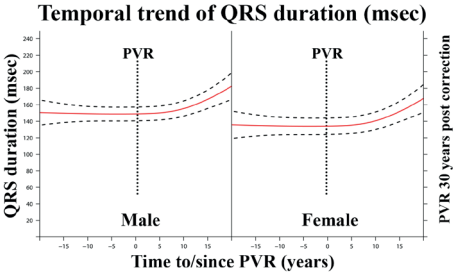
Among hospital survivors without a PM, the time interval between correction and PVR was not associated with the hazard of late PM implantation (HR1.035, 95% CI 0.958-1.118, p=0.383). A longer time interval between correction and PVR was however associated with an increased hazard of late ICD implantation (HR 1.137, 95% CI 1.039-1.244, p=0.005).

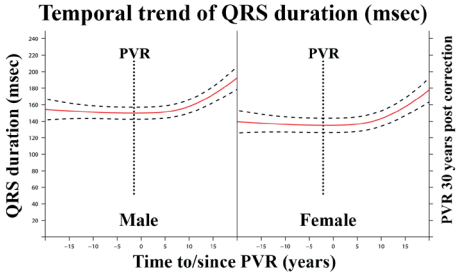


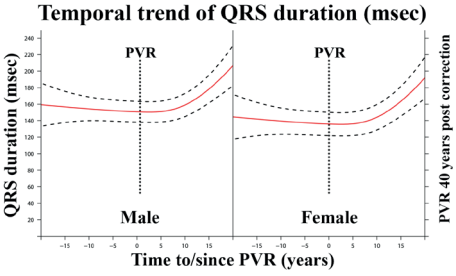












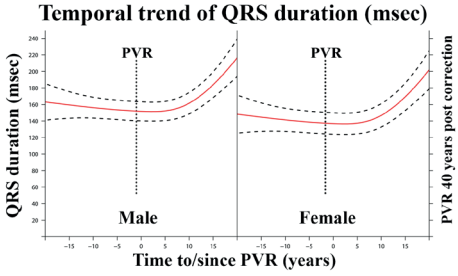


Figure 2A

Figure 2B

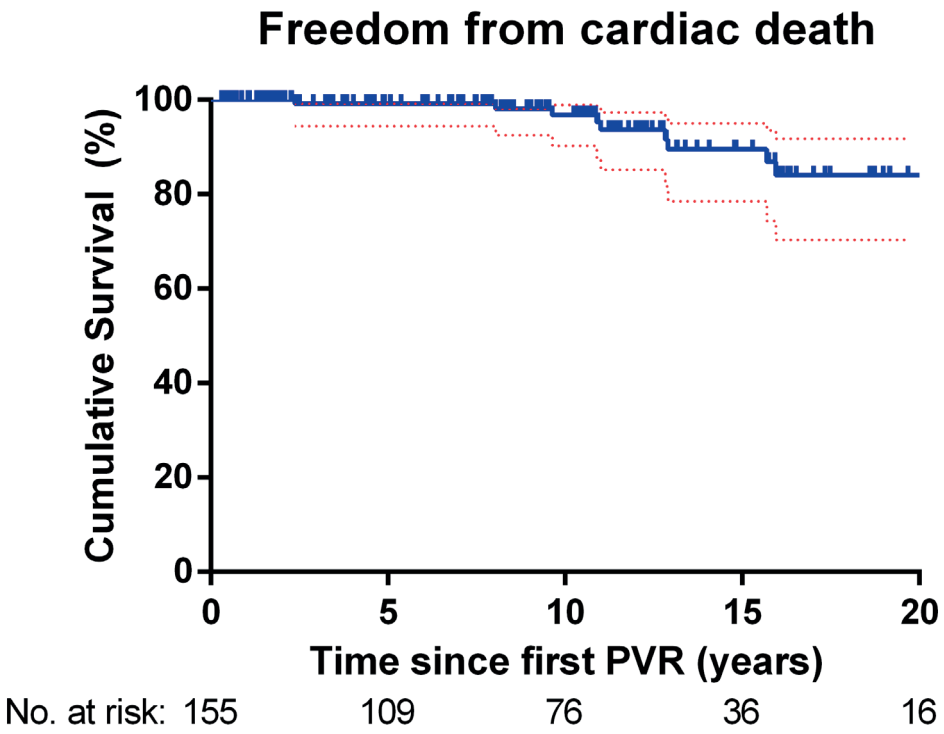


Figure 3. Kaplan-Meier curve of freedom from cardiac death

Table 2. Cox proportional hazards model for cardiac death

	Univariable		Multivariable	
Variable	HR	p-value	HR†	p-value
Cardiac death				
Sex	0.204 (0.042-0.989)	0.048	0.130 (0.016-1.085)	0.058
Age at correction	1.111 (1.030-1.198)	0.006		
Time correction-PVR	1.119 (1.034-1.211)	0.005	1.097 (1.002-1.200)	0.005
Age at PVR	1.095 (1.043-1.150)	<.001		
Length at PVR	1.058 (0.996-1.123)	0.069		
Weight at PVR	1.053 (1.009-1.098)	0.017		
Creatinine (mmol/L)	1.032 (0.988-1.079)	0.160		
QRS-duration pre PVR	1.004 (0.981-1.027)	0.733		

HR = Hazard Ratio, PVR = Pulmonary Valve Replacement

† = Because of the correlations between the covariates and linear dependency between age at correction, time-between correction and PVR, age at PVR, length and weight at PVR, only one (i.e. Time between correction and PVR) was entered in the multivariable part of the analysis.

Table 3. Characteristics of patients with extreme QRS (>230) and/or late cardiac death

Gender	Age at correction	Age at PVR	Time correction-PVR	Age last follow up/ death	Late cardiac death	Extreme QRS	PM	Max QRS	PM	Max QRS before PM
Male	9.3	40.7	31.4	48.8	Heart Failure	Yes	After PVR	336	After PVR	206
Male	13.4	48.4	35.0	64.3	Heart Failure	Yes	Never	260	Never	260
Male	13.0	42.2	29.2	53.2	SUUD	Yes	Never	260	Never	260
Female	11.8	41.0	29.2	56.7	SUUD	No	Never	174	Never	174
Male	16.5	43.7	27.2	53.3	Heart Failure	No	Never	142	Never	142
Female	12.7	38.8	26.1	51.6	Heart Failure	No	Never	222	Never	222
Male	7.0	43.8	36.8	54.7	Heart Failure	No	Never	194	Never	194
Male	4.5	28.9	24.3	31.2	SUUD	No	Never	178	Never	178
Male	23.0	41.4	18.4	54.3	Heart Failure	No	Never	186	Never	186
Male	4.4	44.4	40.0	47.8	Alive	Yes	Never	250	Never	250
Male	8.4	41.7	33.2	60.8	Alive	Yes	Never	252	Never	252
Female	2.0	24.5	22.4	43.4	Alive	Yes	At PVR	299	At PVR	NA
Male	8.8	37.8	29.0	50.6	Alive	Yes	After Correction	292	After Correction	NA
Female	0.2	23.4	23.2	39.1	Alive	Yes	After PVR	226	After PVR	226
Male	10.5	43.8	33.2	56.4	Alive	Yes	After PVR	239	After PVR	234
Male	2.3	32.4	30.2	41.5	Alive	Yes	After PVR	233	After PVR	176

PM = Pacemaker, SUUD = Sudden Unexplained Unexpected Death

DISCUSSION

This study is the first to show an association between timing of PVR and QRS duration using innovative and advanced statistics to model the individual long-term evolution of QRS duration before and after PVR in a homogenous group of corrected ToF patients. QRS duration after PVR is significantly associated with a longer time interval between initial correction and PVR, a higher age at correction and sex. In patients that undergo early ToF correction, progressive QRS prolongation after PVR can be prevented by intervening within approximately 17 years after correction. In patients with ToF correction at a later age, progressive QRS prolongation after PVR can be prevented by intervening within approximately 15 years after correction. The time interval between ToF correction and PVR is therefore associated with post-operative QRS duration, cardiac death and the hazard of postoperative ICD implantation. QRS duration is an important risk factor before and after PVR in corrected ToF patients, and prevention of prolongation might improve the outcome of these patients.

Central image

PVR and QRS duration

Few published studies have investigated the relation between PVR and QRS duration [14-29]. However, the results are heterogeneous with some authors reporting a stable QRS duration [17, 19, 20, 22, 28], some an increase [16], and some a decrease [6, 15, 18, 21, 25, 27] after PVR in corrected ToF patients. Therrien et al. were the first to report a stabilization in QRS duration after PVR in corrected ToF patients compared to a control group who had not undergone PVR [28]. Van Huysduynen et al. were the first to report a decline in QRS duration following PVR in 26 patients with corrected ToF with at least moderate regurgitation [29]. Oosterhof et al. studied 99 corrected TOF patients who underwent a first PVR and reported an initial decline in mean QRS duration directly post-surgery. QRS duration increased however during a median follow up of 5 years in patients with pre-operative QRS >120 msec. In patients with a preoperative QRS <120 ms, no increase was reported [30]. The mixed results of QRS duration could potentially also be explained by undisclosed differences in time interval between correction and PVR. Mixed effect modeling enabled us to model the variability that is inherent to and only observable in a longitudinal design that considers irregularly scheduled and collected measurements and accepts a non-linear evolution.

QRS prolongation as risk factor

Prolongation of QRS duration has been reported despite successful PVR and is predictive of adverse outcome [16, 25, 29]. As multiple studies have demonstrated the malignant nature of QRS progression as a substrate for cardiac dysfunction and increasing depolar-

ization disturbances, preventing this post-operative prolongation seems imperative [25, 29]. Scherptong et al reported that a post PVR QRS duration exceeding 180 msec was associated with a reduced freedom from a composite endpoint including death, re-PVR, ventricular tachyarrhythmia and symptomatic heart failure after 5 years [25]. Stabilization of QRS duration after PVR has occasionally been associated with a reduced frequency of ventricular tachycardia [18]. Harrild et al. studied 98 corrected ToF patients who underwent PVR 20 years after correction at a mean age of 5 years. In a later study, QRS duration did not change after PVR, and matched controls with significant PR and RV dilatation who did not undergo PVR showed no differences in reported ventricular tachycardia or death [17]. The average delay till PVR of 19.7 years is close to the timeframe proposed by this study with regard to prolongation prevention. Similarly, the change rate of QRS prolongation and older age at correction have been associated with an increased incidence of ventricular tachyarrhythmia and sudden death [5]. These findings underline the clinical importance of QRS duration after PVR and the relevance of preventing progression.

CONCLUSION

The decision whether to intervene in corrected ToF patients should ideally depend on the combination of multiple biomarkers with the clinical state of the patient. QRS duration is an easily obtainable biomarker with extensive prognostic capabilities in ToF patients suffering from chronic PR who undergo PVR. QRS prolongation after PVR might be prevented by not delaying PVR too long.

REFERENCES

1. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
2. Cuypers, J.A., et al., Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. Circulation, 2014. 130(22): p. 1944-53.
3. Gatzoulis, M.A., et al., Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. The Lancet, 2000. 356(9234): p. 975-981.
4. Abd El Rahman, M.Y., et al., Relation between right ventricular enlargement, QRS duration, and right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation after surgical repair. Heart, 2000. 84(4): p. 416-20.
5. Knauth, A.L., et al., Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart, 2008. 94(2): p. 211-216.
6. Ferraz Cavalcanti, P.E., et al., Pulmonary Valve Replacement After Operative Repair of Tetralogy of Fallot: Meta-Analysis and Meta-Regression of 3,118 Patients From 48 Studies. Journal of the American College of Cardiology, 2013. 62(23): p. 2227-2243.
7. Heng, E.L., et al., Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Circulation, 2017. 136(18): p. 1703.
8. Muller, J., et al., Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. Int J Cardiol, 2015. 196: p. 158-64.
9. Vogel, M., et al., Regional wall motion and abnormalities of electrical depolarization and repolarization in patients after surgical repair of tetralogy of Fallot. Circulation, 2001. 103(12): p. 1669-73.
10. Tzemos, N., et al., Adverse left ventricular mechanics in adults with repaired tetralogy of Fallot. Am J Cardiol, 2009. 103(3): p. 420-5.
11. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
12. Lancellotti, P., et al., European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr, 2010. 11(3): p. 223-44.
13. Andrinopoulou, E.R., et al., An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg, 2012. 93(6): p. 1765-72.
14. Chalard, A., et al., Effect of Pulmonary Valve Replacement on Left Ventricular Function in Patients With Tetralogy of Fallot. The American Journal of Cardiology, 2012. 110(12): p. 1828-1835.
15. Doughan, A.R., et al., Effects of pulmonary valve replacement on QRS duration and right ventricular cavity size late after repair of right ventricular outflow tract obstruction. Am J Cardiol, 2005. 95(12): p. 1511-4.
16. Gengsakul, A., et al., The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. European Journal of Cardio-thoracic Surgery, 2007. 32(3): p. 462-468.
17. Harrild, D.M., et al., Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. Circulation, 2009. 119(3): p. 445-51.

18. Hooft van Huysduynen, B., et al., Pulmonary valve replacement in tetralogy of Fallot improves the repolarization. Int J Cardiol, 2008. 124(3): p. 301-6.

19. Jang, W., et al., Mid-term results of bioprosthetic pulmonary valve replacement in pulmonary regurgitation after tetralogy of Fallot repair. European Journal of Cardio-Thoracic Surgery, 2012. 42(1): p. e1-e8.

20. Kleinveld, G., et al., Hemodynamic and Electrocardiographic Effects of Early Pulmonary Valve Replacement in Pediatric Patients After Transannular Complete Repair of Tetralogy of Fallot. Pediatric Cardiology, 2006. 27(3): p. 329-335.

21. Lee, C., et al., Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement. J Am Coll Cardiol, 2012. 60(11): p. 1005-14.

22. Lim, C., et al., Early replacement of pulmonary valve after repair of tetralogy: is it really beneficial? European Journal of Cardio-Thoracic Surgery, 2004. 25(5): p. 728-734.

23. Meijboom, F.J., et al., Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. J Thorac Cardiovasc Surg, 2008. 135(1): p. 50-5.

24. Oosterhof, T., et al., Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation, 2007. 116(5): p. 545-51.

25. Scherptong, R.W.C., et al., Follow-Up After Pulmonary Valve Replacement in Adults With Tetralogy of Fallot: Association Between QRS Duration and Outcome. Journal of the American College of Cardiology, 2010. 56(18): p. 1486-1492.

26. Shinkawa, T., et al., Performance of Bovine Pericardial Valves in the Pulmonary Position. The Annals of Thoracic Surgery, 2010. 90(4): p. 1295-1300.

27. Shiokawa, Y., et al., Pulmonary valve replacement long after repair of tetralogy of Fallot. Gen Thorac Cardiovasc Surg, 2012. 60(6): p. 341-4.

28. Therrien, J., et al., Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation, 2001. 103(20): p. 2489-94.

29. van Huysduynen, B.H., et al., Reduction of QRS duration after pulmonary valve replacement in adult Fallot patients is related to reduction of right ventricular volume. Eur Heart J, 2005. 26(9): p. 928-32.

30. Oosterhof, T., et al., Long-term effect of pulmonary valve replacement on QRS duration in patients with corrected tetralogy of Fallot. Heart, 2007. 93(4): p. 506-509.

8

Letter by Romeo et al Regarding Article,

"Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot: A Prospective Cardiovascular Magnetic Resonance and Clinical Study"

Jamie LR Romeo, Ad JJC Bogers, M Mostafa Mokhles

Circulation

TO THE EDITOR

We read with great interest the recent article by Heng and colleagues describing the follow-up of 57 repaired tetralogy of Fallot patients who underwent pulmonary valve replacement (PVR) with cardiac magnetic resonance (CMR) imaging.[1] They conclude that significant right heart structural reverse remodeling takes place immediately after PVR, followed by gradual further biological remodeling during follow-up.

The analysis concerned 57 relatively healthy individuals given their absence of contraindications to CMR, good kidney function and the elective setting. The authors did, however, not disclose the selection criteria that left them with only 57 of a potentially larger cohort (PVR and redo sternotomy; n=257) suggested by a recent overview of consecutive patients undergoing surgery in their center.[2] We are eager to learn about the distribution of clinically relevant covariates of these 57 compared to the entire cohort. Additionally, during the same time period specific volumetric thresholds as intervention criteria were adopted. It can be assumed that patients at the far ends of the volumetric spectrum will thus be less prevalent, as well as the subsequent 'extreme' hazards they may endure during follow up. What is the authors' opinion on how this influences the strength of the inferred causality?

Furthermore, prediction of right ventricle (RV) volume normalization was optimal with a preoperative RV end diastolic indexed volume of 158 mL/m2 and a preoperative RV end systolic indexed volume of 82 mL/m2. Although the discriminative qualities were demonstrated by an area under the curve of 0.88 and 0.90, respectively, model calibration was not mentioned at all. A model intended for prognostic capabilities demands good calibration to be clinically useful. Nonetheless, the relationship between reverse RV remodeling and adverse clinical outcome remains elusive. Applying this knowledge to individualized timing of PVR is even harder. Ideally, the current and future risk of adverse outcome should be continuously available given patient-specific characteristics, for example gender, age, etiology of the disease, type of graft used. Mixed and Joint modeling, an area of biostatistics that has received a lot of attention lately, carries these capabilities.[3-5] Using these methods, the temporal pattern of repeatedly gathered biomarkers like echocardiographic measurements can be analyzed and used to predict mortality and reintervention. Volumetric measurements can be associated with the risk of heartfailure, reoperation and mortality in a statistically robust manner. These dynamic prediction models are patient specific and enable visualization of current and future risks. Moreover, these risk estimates are updated instantaneously with new measurements and can thus be of direct value in clinical decision making.

This study represents an important contribution to our understanding of right ventricular reverse remodeling after PVR. However, we still question its predictive value for adverse clinical outcome which leaves us unsure how to use this information in optimiz-

ing timing of PVR. The application of joint models is advised as they are an excellent method for subject-specific prediction and individualized timing of PVR using repeatedly measured biomarkers.

ACKNOWLEDGEMENTS

We thank professor Johanna JM Takkenberg for her excellent and significant suggestions to this letter.

REFERENCES

1. Heng, E.L., et al., Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Circulation, 2017. 136(18): p. 1703.
2. Beurtheret, S., et al., Contemporary cardiac surgery for adults with congenital heart disease. Heart, 2017. 103(15): p. 1194-1202.
3. Andrinopoulou, E.R., et al., Combined dynamic predictions using joint models of two longitudinal outcomes and competing risk data. Stat Methods Med Res, 2015.
4. Andrinopoulou, E.R., et al., An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg, 2012. 93(6): p. 1765-72.
5. Rizopoulos, D., Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. Biometrics, 2011. 67(3): p. 819-29.

9

Maternal complications and pregnancy outcome after right ventricular outflow tract reconstruction with an allograft conduit

Jamie LR Romeo, Johanna JM Takkenberg, Jolien W Roos-Hesselink, Milad Hanif, Jerome MJ Cornette, Wouter Van Leeuwen, Arie van Dijk, Ad JJC Bogers, M Mostafa Mokhles

Journal of American College of Cardiology (JACC)

ABSTRACT

Background

There is no published evidence on pregnancy after RVOT reconstruction with an allograft.

Objectives

To describe pregnancy outcome in women with an allograft in RVOT position.

Methods

A retrospective cohort study of consecutive female patients who received an allograft in RVOT position was conducted. All patients between 18 and 50 years were screened for cardiac, obstetric and fetal outcomes of completed (≥20 week of gestation) pregnancies.

Results

In total, 196 women met the inclusion criteria, of which 56 had 89 completed pregnancies. Information could be retrieved in 84 (94.4%) cases. Mean maternal age was 29.6±4.3 years, with 80 (95.2%) patients in NYHA class I/II. The most common diagnosis was Tetralogy of Fallot. All women survived pregnancy. There were two (2.4%) cases of heart failure (arrhythmic and diastolic dysfunction), one case (1.2%) of infection (chorioamnionitis) and three cases (3.6%) of pre-eclampsia. No other cardiac or obstetric events were reported. All children were born alive after a median gestational age (GA) of 38.4 weeks (interquartile range(IQR) 36.9-39.6 weeks), with a median birthweight of 2930 grams (IQR 2535-3385 grams). Seventeen (20.2%) were small for gestational age (SGA) and 20 (23.8%) premature. Neonatal death was reported in two (2.5%) children. Preconception pulmonary regurgitation was associated with an increased probability of pre-term labor (OR 2.610, 95% CI 1.318–5.172). Compared to the general Dutch population, preterm delivery (25.0 vs 7.4%, $p<0.001$) and children with SGA (20.2 vs 10.0% $p=0.002$) were more common.

Conclusion

Women in good cardiac health after RVOT reconstruction with an allograft can safely experience pregnancy and labor. The higher incidence of preterm delivery and children small for gestational age warrants special attention.

INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of mortality among women [1]. More women die as a result of CVD including congenital heart diseases (CHD), than cancer, chronic lower respiratory disease, diabetes mellitus or Alzheimer disease, or than men with the same disease by absolute count [2]. Due to vast improvements in surgical and cardiac care, women with CHD often survive well beyond the childbearing age[3]. However, lifelong active care and follow up characterize their clinical path. This is especially important given the fact that in modern western countries, heart disease is the most important cause of maternal mortality [4]. The desire to safely bear children requires careful cardiac management and must, therefore, be considered and openly discussed well in advance[5]. This counseling should be performed well before pregnancy and is an essential aspect of informed- and shared decision making.

Some CHD require reconstruction of the right ventricular outflow tract (RVOT) either during initial surgical correction or during reintervention. An allograft is often the preferred valved conduit. Its excellent hemodynamic properties and lack of need for anticoagulants often permit an unrestricted life style with good quality of life [3, 6]. Especially the lack of need for life-long anticoagulation therapy is regarded as the main benefit for women with a child whish as they are a major concern with mechanical valves[7, 8]. Another reason why pregnancy is clinically important in women with CHD, is the increase in hemodynamic stress, expressed by an increase of circulating volume, cardiac output and heartrate during pregnancy, labor and puerperium[9-13]. Although the influence of this hemodynamic stress has been described for aortic valve replacement (AVR) with allografts and autografts[14, 15], little is known about allografts in RVOT position and there is no published evidence on the function of allografts in pulmonary position during and after pregnancy. Informing women before they even consider pregnancy on the potential risks of cardiac as well as obstetric events, complications and perinatal outcome is important and requires additional study.

To the best of our knowledge we will present the first study on patients with completed pregnancies after RVOT reconstruction with an allograft conduit.

METHODS

Study-design

All 280 female patients who received an allograft in RVOT position at the Cardio-Thoracic Surgery department of the Erasmus Medical Centre from April 1986 till February 2017 were screened. The institutional review board reviewed and approved this study prior to its onset (MEC 2012-477 and MEC 2017-158).

Study-population

All subjects alive that had not reached the age of 50 at the time of surgery and were 18 years or older at the time of this study were included (n=196). Information was collected through the hospital information system and a standardized questionnaire supplemented by a telephone interview. In case checkups during pregnancy by the cardiologist or gynecologist were performed elsewhere, the data was requested.

Outcomes

Completed pregnancy was defined as >20 weeks gestation and confirmed by a positive human chorion gonadotropin test or findings of a live fetus on obstetric ultrasound. In case no pregnancy had taken place, reasons for its absence were documented. A history of infertility (more than 2 years of unsuccessful documented regular attempts) and miscarriage (spontaneous fetal loss before 20 weeks of gestation) were documented for women with completed pregnancies. Cardiac and valve related events were classified according to the appropriate guidelines [16]. The New York Health Association (NYHA) classification was used to assess general cardiac status at the onset of pregnancy. Obstetric events were recorded as pregnancy induced hypertension (PIH, new onset of a systolic blood pressure >140 mmHg or diastolic >90 mmHg); hemolysis elevated liver enzymes low platelets (HELLP) syndrome; pre-eclampsia (PIH with >300 mg/l proteinuria per 24 hour sample); eclampsia (symptomatic pre-eclampsia with major seizures); gestational diabetes; mode of delivery (spontaneous, assisted); and preterm rupture of membranes (PROM); postpartum hemorrhage or fluxus (vaginal delivery >500ml, caesarean section >1000ml, or requiring infusion), and maternal death. Fetal or neonatal complications comprised intra-uterine death (death >20 weeks gestational age), premature birth (<37 week gestational age), small for gestational age (SGA, birthweight <10th percentile), perinatal death (death within 30 days postpartum), and congenital (heart) defects. The Netherlands Perinatal Registry (Perined, Utrecht, 2015) was used for calculation of appropriate birthweight and subsequent SGA based on gender, gestational age and para (i.e. primipara or multipara) [17]. Outcomes were compared to those of the general Dutch population in 2015 [17]. Pulmonary regurgitation (PR: no regurgitation, trace, mild, moderate, severe), and pulmonary stenosis (continuously measured as peak gradient over the pulmonary valve) at or within a two year period prior to conception were assessed by continuous echo Doppler[18].

Statistical analyses

Continuous data is presented as means with standard deviation (SD) or medians with inter quartile range (IQR) in case of non-normal distribution. Continuous variables were compared with unpaired Student t-tests or the Wilcoxon signed-rank test as appropriate. Categorical data is presented as absolute count and percentages. Binary outcomes were

compared with a Pearson's chi-square test. An One-Sample Chi-square Test was used to compare pregnancy related outcome to the incidence in the general Dutch population. Univariate linear and logistic regression were used to identify risk factors for pregnancy related outcomes. Throughout the analysis multiple pregnancies in the same patient were regarded as independent observations as well as multiple allografts in the same patient, not accounting for multilevel relationships. Statistical significance was defined by a P-value less than 0.05. Statistical analysis were performed with SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

RESULTS

All 280 females who received a RVOT allograft in our institution were screened, of which 196 allografts were eligible for inclusion (Figure 1). Follow up and pregnancy information was complete of 187 (95.4%) subjects (Appendix A). Informed consent was obtained from study participants or their legal representatives for subjects alive during April 2017. In total 89 completed pregnancies in 56 different patients with 56 allografts were confirmed by patients and hospital records. Informed consent was obtained from 52 (92.9%) patients, representing 84 (94.4%) of the 89 completed pregnancies. None of the women that underwent repeated PVR, had multiple pregnancies during the follow up time of different allografts. Of the 140 cases without pregnancy, 2 cases could be identified that had explicit cardiac contra-indications.

Baseline characteristics at pregnancy

Median age at allograft implantation was 21.8 years (IQR 15.7-25.0 years) (Table 1). The most common diagnosis was Tetralogy of Fallot (TOF) (n=23; 44.2%). Median age at the start of pregnancy and time since allograft-implantation were 29.0 years (IQR 26.4-32.8 years) and 6.7 years (IQR 3.3-11.6 years), respectively (Table 2). Clinical status at the onset of pregnancy was good with most patients in NYHA I or II (n=80; 95.2%). There was 1 (1.2%) patient with NYHA IV who despite explicit negative preconception advice on cardiac grounds became pregnant and refused termination. Nine (17.3%) patients reported a history of at least one miscarriage. Eighty (95.2%) pregnancies were conceived spontaneously without assistance. The median peak pulmonary gradient across the RVOT was 16 mmHg (range 3–58) with 15 (17.9%) >30mmHg, and 1 (1.2%) >50mmHg. Thirteen (15.5%) women had significant regurgitation. Anti-coagulation was used during 8 (9.5%) pregnancies for an aortic mechanical prosthesis (n=5), protein C deficiency (n=1), protein S deficiency (n=1) and a sustained arrhythmia (n=1).

Table 1 Maternal baseline characteristics

	N (%) or mean ± SD (range)
Patients (n)	52
Completed Pregnancies (>20 weeks)	84
Age at surgery (years)	21.2 ± 6.7 (2.3–32.0)
Diagnosis (n, %)	
TOF	23 (44.2)
Aortic Valve*	16 (30.8)
Isolated PS	5 (9.6)
PA + VSD	4 (7.7)
PA – VSD	1 (1.9)
TGA PS/PA	1 (1.9)
Tricuspid Atresia	1 (1.9)
Truncus Arteriosus	1 (1.9)
Previous heart operation (yes)	41 (78.8)
Previous shunt operation (yes)	14 (26.9)
Allograft type (pulmonary)	49 (94.2)
Allograft size (mm)	23.8 ± 2.3 (16–28)
Perfusion time (min)	148 ± 65.2 (39–295)

PA = Pulmonary Atresia, PS = Pulmonary Stenosis, SD = Standard Deviation, TGA = Transposition of the Great Arteries, TOF = Tetralogy of Fallot, VSD = Ventricle Septal Defect

* = Primary aortic valve lesion for which a pulmonary autograft (Ross) procedure was employed.

Complications during pregnancy

There was one case of infection which was a chorioamnionitis and funiculitis in a mother (G4P2A1) corrected for TOF at age 5.2 with subsequent PVR at the age of 28.5 (Table 3). Before her PVR she gave birth to a healthy child after an uncomplicated pregnancy and underwent an elective abortion for social reasons. At last menstruation she was in good cardiac status (NYHA I) with low pulmonary and aortic gradients (29 and 6 mmHg, respectively), no PR and only a trace of TR 1.8 years after allograft placement. After $22^{1/7th}$ weeks she developed a fever irresponsive to Augmentin intravenously, with CRP elevation and a left shift in the leukocyte differentiation. Under the suspicion of an intra-amniotic infection and subsequently high risk of developing an endocarditis and poor fetal prognosis, labor was induced at 23 weeks of gestation. The diagnosis was histopathologically confirmed postpartum. The child died shortly thereafter. The first of the two cases with heart failure was a patient (NYHA II) with mild PR and AR, and a peak pulmonary gradient of 3 mmHg at onset of pregnancy after PA with VSD correction 9.6 years earlier. She was successfully treated for a newly developed tachycardia with adenosine and metoprolol. After $39^{4/7th}$ weeks of gestation she gave birth to a healthy child and recovered well. The other case of heart failure occurred in a Ross patient (NYHA II), known with mild AS, PS and AR, and a badly functioning severely dilated left ventricle (LV). She was subsequently induced into labor after $33^{1/7th}$ weeks on maternal indication and recovered uneventfully. No cases of endocarditis, thrombo-embolic events,

and HELLP-syndrome occurred. Pre-eclampsia was reported in 3 (3.6%) cases but never progressed to eclampsia. One uncomplicated elective transcatheter intervention with balloon dilation and stenting of a symptomatic severe stenosis of the left pulmonary artery was performed. She was a primigravida in her fifth week of gestation and not known to be pregnant at the time.

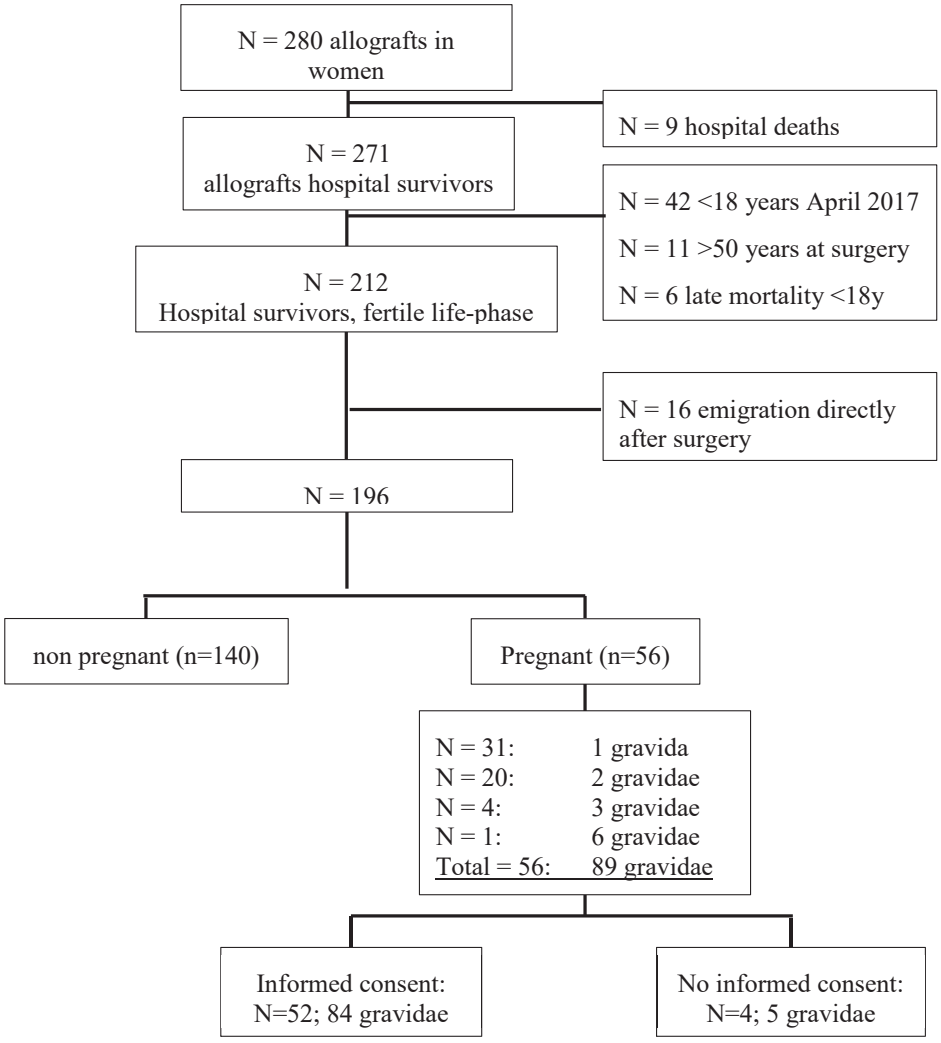


Figure 1 Flowchart of allograft patient selection process

Table 2 Completed pregnancies Baseline Characteristics

	N (%) or means ± SD (range)
Age at last menstruation (years)	29.6 ± 4.3 (21.2–39.7)
Time post operation (years)	8.6 ± 6.6 (0.72–26.9)
Pregnancy method (n, %)	
Spontaneous	80 (95.2)
OI	2 (2.4)
IUI	1 (1.2)
ICSI	1 (1.2)
IVF	0 (0)
Gravida (n, %)	
Primigravida	32 (38.1)
Multigravida	52 (61.9)
Para (n, %)	
Primipara	40 (47.6)
Multipara	44 (52.4)
History of miscarriages (n, %)	15 (17.9)
History of terminations (n, %)	15 (17.9)
NYHA classification prior (n, %)	
I	70 (83.3)
II	10 (11.9)
III	3 (3.6)
IV	1 (1.2)
PM or ICD in situ	6 (7.1)
Anticoagulants during pregnancy	8 (9.5)
Pulmonary valve gradient (mmHg) (n=82)	19.4 ± 12.4 (3–58)
Aortic valve gradient (mmHg) (n=77)	7.1 ± 4.1 (1–23)
Tricuspid Regurgitation grade (0-4) (n=69)	
None	0 (0)
Trace	21 (25.0)
Light	43 (51.2)
Moderate	5 (6.0)
Severe	0 (0)
Pulmonary Regurgitation grade (0-4) (n=83)	
None	6 (7.1)
Trace	15 (17.9)
Light	49 (58.3)
Moderate	8 (9.5)
Severe	5 (6.0)
Aortic Regurgitation grade (0-4) (n=72)	
None	13 (15.5)
Trace	14 (16.7)
Light	37 (44.0)
Moderate	7 (8.3)
Severe	1 (1.2)

ICD = Implantable Cardioverter Defibrillator, ICSI = Intra Cytoplasmic Semen Injection,
IUI = Intra Uterine Insemination, IVF = In Vitro Fertilization, NYHA = New York Heart Association, OI = Ovulation Induction, PM = Pacemaker, RVOT = right ventricular outflow tract, WHO = World Health Organization, modified WHO classification of maternal cardiovascular risk

Table 3 Maternal complications during pregnancy

	Overall (% of total)
Maternal Death	0 (0)
Loss of pregnancy	0 (0)
Heart failure	1 (1.2)
CVA/TIA	0 (0)
New onset arrhythmia	5 (6.0)
Exacerbation arrhythmia	1 (1.2)
PROM	1 (1.2)
ICD shock	0 (0)
Endocarditis	0 (0)
Thrombo-embolic event	0 (0)
PIH	7 (8.3)
HELLP syndrome	0 (0)
Gestational diabetes	1 (1.2)
Pre-eclampsia	3 (3.6)
Eclampsia	0 (0)
Infection	1 (1.2)

CVA = Cerebral Vascular Accident, HELLP = Hemolysis Elevated Liver Enzymes Low Platelet count (syndrome), PIH = Pregnancy Induced Hypertension, PROM = Prelabor Rupture of Membranes, TIA = Transient Ischemic Attack.

Fetal, obstetric and neonatal outcome

There were 84 completed pregnancies (all singletons) in 52 patients after a median gestational age of 38.4 weeks (IQR 36.9-39.6 weeks) (Table 4). Preterm birth was reported in 21 (25%) cases, with 15 (17.9%) and 6 (7.1%) cases of moderate (32–$36^{6/7th}$ weeks) and very (<32 weeks) preterm birth, respectively. Of the 21 preterm births, 18 were spontaneous and 3 were induced. Indication for these 3 induced labors were severe pulmonary hypertension (PHT) (n=1, induction at $26^{1/7th}$ weeks), confirmed chorioamnionitis and funiculitis, and prevention of endocarditis (n=1, induction at $23^{4/7th}$ weeks) and left sided heart failure (n=1, induction at $33^{1/7th}$ weeks). The severe PHT was already present before conception and repeatedly discussed during interdisciplinary meetings. Consensus was that she was WHO class IV and pregnancy was explicitly contraindicated, as discussed with the patient. Of the 18 cases of spontaneous preterm delivery, 2 women presented with placental abruption and 16 women had idiopathic preterm deliveries. All cases of arrhythmia, PIH, gestational diabetes and pre-eclampsia occurred in women delivering at term.

Median birthweight was 2930 grams (IQR 2635-3385 grams) with 17 (20.2%) infants born SGA (Appendix B). Of the infants born SGA, 13 (76.5%) were born at term. No mater-

nal mortality occurred. Fetal demise was not reported, however postnatal death occurred in 2 (2.4%) pregnancies. The first infant was born from a mother (G2P1) who underwent a Ross procedure at the age of 20.4 for a congenital aortic stenosis and previously gave

Table 4 Delivery outcome of mother and child

	N (%) or means ± SD (range)
Completed pregnancies (n, %)	84
Gestational age (weeks)	37.6 ± 3.6 (23.4–42.4)
A term (37 – $41^{6/7th}$ weeks)	61 (72.6)
Overall Post-term (>42 weeks)	2 (2.4)
Overall Pre-term (<37 weeks)	21 (25.0)
Moderately preterm (32 – $36^{6/7th}$ weeks)	15 (17.9)
Very preterm (<32 weeks)	6 (7.1)
Induction of labor (n, %)	37 (44.0)
Maternal indication	25 (67.6)
Fetal indication	10 (27.0)
Unknown reason	2 (5.4)
Right ventricular Function (n=70)	
Normal (EF > 50%)	28 (40.0)
Mild-moderate (EF 30-50%)	42 (60.0)
Severe (EF <30%)	0 (0)
Left ventricular Function (n=74)	
Normal (EF > 50%)	50 (67.6)
Mild-moderate (EF 30-50%)	24 (32.4)
Severe (EF <30%)	0 (0)
Mode of delivery (n, %)	
Vaginally	65 (77.4)
Cesarean section	19
Primary/prelabor	11
Maternal medically indicated	6
Fetal medically indicated	4
Unknown	1
Secondary/intrapartum	
Failure to progress during labor	8
Non-reassuring fetal status	2
Fetal malpresentation	4
Placental problems	1
	2
APGAR score (n=78)	
Post 5 minutes (8–10)	74 (94.9)
Post 10 minutes (8–10)	71 (97.5)
Birthweight (gram)	2887 ± 806 (520–4655)
SGA <10 percentile (n, %)*	17 (20.2)
Navel cord pH (n=57)	7.29 ± 0.28 (7.0–9.3)

Table 4 Delivery outcome of mother and child (*continued*)

	N (%) or means ± SD (range)
Base excess	-3.8 ± 3.2 (-13.8–1)
Blood loss (estimated, ml) (n=58)	457 ± 460 (50–3000)
Fluxus (≥1000 ml)	5 (8.8%)
Maternal death (n, %)	0 (0)
Perinatal death (n, %)	2 (2.4)
Fetal death (n, %)	0 (0)
Neonatal death (n, %)	2 (2.4)
ICU/CCU admission mother (n, %)	1 (1.2)
Health of perinatal survivors (n=82)	
Healthy child	76 (92.7)
Cardiac malformation	1 (1.2)
Wet lung disease	1 (1.2)
Retinopathy of premature	1 (1.2)
Phenylketonuria	1 (1.2)
Pyelectasia	1 (1.2)
Broncho pulmonary dysplasia	1 (1.2)

APGAR score = combined score of heart rate, respiratory effort, muscle tone, reflex irritability and color; CCU = cardiac care unit, EF = Ejection Fraction, ICU = intensive care unit, SGA = Small for Gestational Age.
* Adjusted for gestational age, fetal gender and parity

birth to a healthy child 3.9 years later after an uncomplicated pregnancy. At onset of her second pregnancy 7.3 years after the Ross procedure she was in good cardiac condition (NYHA I) with no residual pulmonary or aortic stenosis (9 and 2 mmHg, respectively) and only light aortic, pulmonary and tricuspid regurgitation. After 19 weeks of gestation she had prematurely ruptured membranes and ultrasound examinations thereafter showed anhydramnios with severe fetal growth delay. After $29^{4/7th}$ weeks of gestation she developed spontaneous contractions and gave birth to a boy (birthweight: 600 grams; <P 2,3) who succumbed one day later. The second case of neonatal death occurred in the previously mentioned patient who developed a chorioamnionitis and funiculitis.

One case of congenital cardiac anomaly (isolated VSD) was reported in another child. The mother was previously corrected for her PA/VSD. Other reported disorders were phenylketonuria (n=1), wet lung disease (n=1), bronchopulmonary dysplasia (n=1) and retinopathy of prematurity (n=1). At late follow up 4 children reportedly had developed ADHD and 2 developed autism.

Risk factor analysis

Figure 2 shows the incidence of obstetric and fetal outcomes compared to the Dutch population. Compared to the general Dutch population, pregnancies in our study were more often conceived spontaneously (95.2% vs 69.3%, p=.001), women more often had

pre-eclampsia (3.6% vs 0.3%, p <.001), children were less often delivered at term (72.6% vs 89.9%, p<.001) and more often SGA (20.2% vs 10.0%, p=.002), perinatal was more common (2.4% vs 0.3%, p<.001) and labor was more often induced (44.0% vs 21.3%, p<.001). No difference between diagnoses could be found.

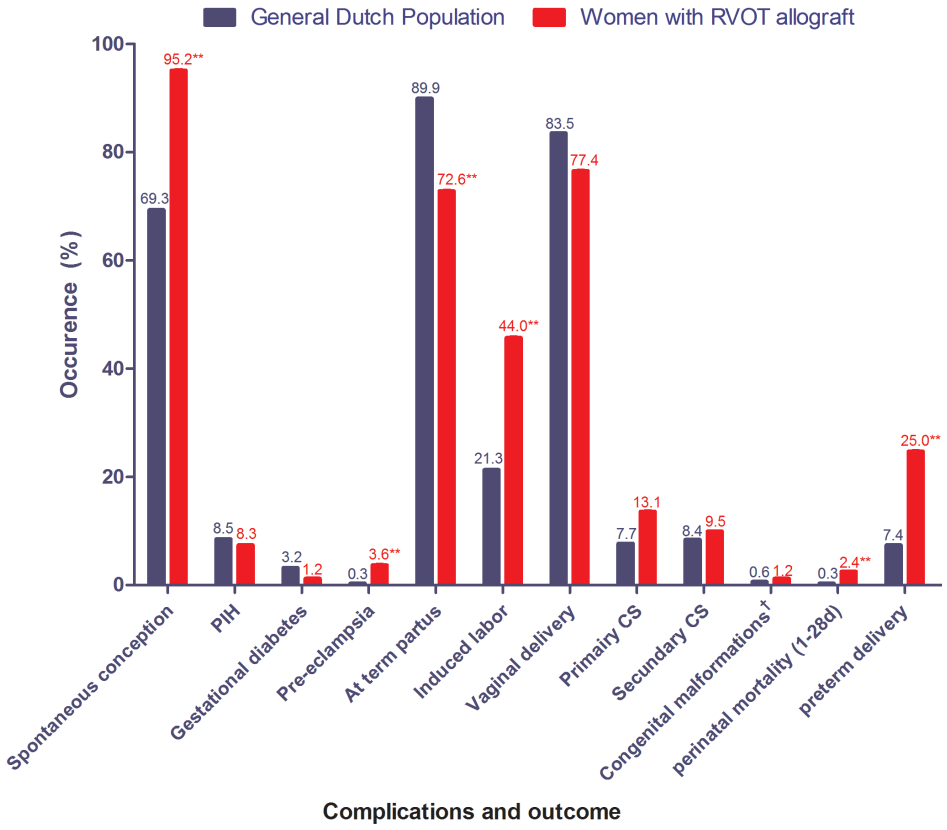


Figure 2

Older age at onset of pregnancy was associated with a lower probability of pre-term labor (OR 0.864, p=.037) (Table 5). Pulmonary regurgitation at onset of pregnancy was associated with an increased probability of pre-term labor (OR 2.610, p=.006) and a decrease in gestational age (p=.003). This association was only significant for TOF patients (OR 5.907, p=0.029) and other diagnoses (OR 4.688, p=0.037), but not for Ross patients (OR 0.840, p=0.759). After exclusion of the three patients with induced preterm labor, higher PR grade was still associated with a higher probability of preterm labor (OR 2.212, 95% CI 1.099-4.450). A higher pulmonary gradient at onset of pregnancy was associated with a lower probability of having a SGA neonate (OR 0.915, p=.014), even when cor-

recting for regurgitation grade (OR 0.894, p=.008). A diminished right or left ventricle function could not be associated with any the outcomes. Use of anticoagulant medication during pregnancy was also not a risk factor for preterm labor (OR 0.429, p=.442) or experiencing at least one of the complications during pregnancy (OR 3.545, p=0.114).

Table 5 Univariable risk factor analysis

Outcomes	Gestational age (weeks) Beta (95% CI)	Pre-term labor OR (95% CI)	Δ (Birthweight and SGA) (grams)† Beta (95% CI)	SGA OR (95% CI)
Predictors				
Age at operation (years)	.008 (-.111 – .126)	.977 (.905 – 1.054)	-.486 (-17.678 – 16.706)	1.083 (.984 – 1.192)
Time since operation (years)	.040 (-.078 - .159)	.967 (.890 – 1.051)	-.6.512 (-23.467 – 10.442)	.930 (.839 – 1.032)
Age at last menstruation (years)	.113 (-0.068 – 0.294)	.864 (.753 – .991)*	-16.668 (-42.680 – 9.343)	1.027 (.905 – 1.166)
Pulmonary gradient (mmHg)	.042 (-.021 – .106)	.967 (.920 – 1.016)	9.737 (-0.845 – 18.629)	.894 (.823 – 0.972)*
Pulmonary regurgitation (grade)	-1.285 (-2.113 – -.456)*	2.610 (1.318 – 5.172)*	47.530 (-80.984 – 176.044)	0.915 (.487 – 1.722)
Right ventricular function (grade)	0.954 (-0.733 – 2.641)	0.588 (0.191 – 1.812)	90.559 (-81.710 - 262.827)	0.417 (0.127 – 1.371)
Left ventricular function (grade)	-0.273 (-2.094 – 1.549)	1.182 (0.378 – 3.698)	-25.960 (-219.781 – 167.860)	0.833 (0.256 – 2.711)
Diameter of allograft (mm)	.145 (-.199 – 0.489)	.946 (.746 – 1.200)	-30.238 (-82.489 – 22.013)	1.269 (.942 – 1.710)
Aortic regurgitation (grade)	-.207 (-1.133 - .719)	1.607 (.845 – 3.057)	-17.509 (-139.634 – 104.616)	1.011 (.545 – 1.878)
Anticoagulance use (yes)	1.104 (-1.526 – 3.7353)	.429 (.049 – 3.711)	-365.931 (-731.180 – 0.682)	2.862 (.607 – 13.498)
Ross versus TOF	0.333 (-1.383 – 2.050)	0.349 (0.095 – 1.286)	195.520 (-68.035 - 459.074)	1.143 (0.358 – 3.651)

B = beta coefficient of univariable predictor, CI = Confidence Interval, OR = Odds Ratio, SGA = Small for Gestational Age of tenth percentile, TOF = Tetralogy of Fallot

†: The difference (Δ) between actual birthweight and indexed birthweight at the tenth percentile for gestational age, gender and para was calculated. A positive difference indicates a birthweight above the tenth percentile, and therefore not SGA

DISCUSSION

In our cohort, women with good cardiac function after RVOT reconstruction with an allograft conduit endured pregnancy safely with low prevalence of cardiac and obstetric adverse events. Pulmonary regurgitation at onset of pregnancy increased the probability of pre-term labor but was not associated with the risk of having a SGA neonate.

Higher pulmonary gradient at onset of pregnancy, however, was associated with a lower probability of having a SGA neonate and not with pre-term labor.

Shared and informed decision making during the lifelong follow up of female patients with congenital heart disease needs solid research, especially since this population of patients is growing significantly. Currently, the allograft is the preferred valve alternative for RVOT reconstruction which is performed at an increasingly younger age[3]. This increases the probability of becoming pregnant during an 'allograft lifetime'. Although the allograft allows patients to avoid using anticoagulant medication, it is subjective to structural valve deterioration and multiple allografts are often needed during a lifespan[3]. This continuous process potentially influences pregnancy outcome and vice versa and could be a consideration in the discussion regarding the optimal timing of valve reintervention. In our cohort, relatively few cardiac and obstetric events were reported in line with other studies describing pregnancies in patients with other types of CHD[15, 19-21]. All complications during pregnancy and labor were adequately managed without surgical reintervention and led to zero maternal mortality. Furthermore, the only intervention was a transcatheter balloon dilatation with stenting which was performed uneventfully after which a health child was born at term. However, the intervention would have been postponed if pregnancy was known prior. NYHA classification III or IV and/or a severe RV or LV dysfunction at onset of pregnancy have been associated with adverse maternal cardiac events during and post pregnancy before however, no increased risk was found in our cohort [22-25].

The risks of pregnancy seems to vary along with the exact cardiac diagnosis and surgical approach[19, 26-31]. The incidence of cardiac and obstetric events after total correction of TOF exceeds the average of the general population[27, 30, 32], with medication usage before pregnancy as independent risk factor for both cardiac and offspring events[27]. Also, pulmonary regurgitation and a diminished right ventricular function have been described as risk factors for cardiac events during pregnancy in a more heterogeneous cohort of CHD[22, 27, 30, 33]. In our series, higher pulmonary regurgitation at baseline was associated with an increased probability of spontaneous pre-term delivery. Reintervention in TOF often involves RVOT reconstruction with an allograft due to chronic regurgitation. Of the 32 patients with previously corrected TOF in our cohort, 6 (18.8%) entered pregnancy with moderate or severe regurgitation. These patients more often had preterm delivery. The exact role of PVR in case of significant regurgitation in repaired TOF is still unclear. Pulmonary gradient on the other hand was associated with a lower probability of having a child SGA. Fetal growth restriction as a consequence of maternal inability to increase cardiac output (CO) and maintain normal oxygen uptake has been suggested, and intuitively should be more prominent with severe regurgitation[32, 34, 35]. However, in our cohort pulmonary regurgitation was only associated with an increased probability of preterm labor but not with having a SGA neonate.

Significant chronic regurgitation and subsequent decrease in cardiac output might have led to maternal stress associated with premature labor. No indications for inflammation, infection, placental abruption or uterine pathology were apparent that otherwise could potentially explain spontaneous preterm labor. However, the exact causal pathway will most likely be multifactorial and needs further investigation.

Balci et al. indicated prior PVR as potential risk factor for obstetric events (OR 0.5, 95% CI 0.2-0.99) and reported a higher incidence of arrhythmia[27]. However, prior PVR was strongly correlated with use of cardiac medication and did not remain significant in the multivariate analysis. Dependency on cardiac medication might suggest a diminished ventricular function that could have existed prior to PVR which becomes more plausible if PVR is performed relatively late in the clinical course and reversal of ventricular dysfunction is limited[36]. Our results could suggest an argument to postpone pregnancy until after PVR to reduce regurgitation, which was associated with premature labor, especially in patients with corrected TOF.

Uebing et al. studied the influence of pregnancy on long term ventricular function in women with heart disease through echocardiographic measurements[37]. No significant deterioration in function and regurgitation grade of the pulmonary valve during follow-up were reported. A tendency towards a ventricular size increase was reported, compared to controls without a pregnancy. They also found TOF to be an independent risk-factor for ventricular size[37]. Baseline pulmonary gradient in our cohort was relatively low and could be associated with a lower probability of a SGA child. A (residual) pulmonary stenosis is usually well tolerated during pregnancy with very few reported cardiac complications even when severe[38, 39]. Spontaneous first trimester pregnancy loss has been described in women with moderate to severe RVOT obstruction and subsequent right ventricular dysfunction[30]. In our cohort, no pregnancy losses were reported and higher pulmonary gradient was even associated with improved pregnancy outcome. However, there were only a few patients with moderate or severe RVOT obstruction.

Neonatal outcome

Although little is known about the exact pathogenetic cause of CHD, a genetic factor is very plausible given the above average observed prevalence in offspring[40-43]. The expected recurrence rate depends on the CHD and its genetic mode of transmission [43]. In our modest cohort one child was reported having a CHD. We could not identify any pregnancy terminations based on findings of (expected) syndromic or cardiac malformation either during SEO or GUO.

The limited number of events in our cohort could indicate an optimally selected population of females in a tertiary specialized CHD clinic setting that well-considered and consciously planned pregnancy given the current and expected clinical course. Precon-

ception counseling of these women should include at the least the effects of pregnancy on the current but also on the future maternal cardiac function, for timing of pregnancy can potentially have a two-way causal relationship with the timing of intervention. It also demands a long term perspective involving the prevalence of valve related cardiac events, reoperation and reintervention. A specific population that might deserve more attention are women with corrected TOF. They are very often burdened with chronic regurgitation, which was identified as a risk factor during pregnancy, hereby potentially creating gender specific considerations in the timing discussion of PVR. The knowledge gained from our study can be used for the development of future treatment guidelines, as little attention is devoted towards allografts in pulmonary position in the current guidelines on the management of cardiovascular diseases during pregnancy [44].

STRENGTHS AND LIMITATIONS

We have presented the first study dedicated to pregnancy in women after RVOT reconstruction with an allograft. It provides information and insights into this steadily growing population. Limitations of the current study are its relatively small sample size and inherent retrospective nature inevitably leading to missing data and recall bias. Unfortunately, quantitative volumetric assessment by cardiac MRI within a clinically meaningful time frame to pregnancy was unavailable for many patients. Furthermore, the low number of events did not allow for extensive multivariate analyses. Lastly, the tertiary care setting might have induced some selection bias. More research is needed to evaluate the long term effects of pregnancy on valve durability and cardiac condition.

CONCLUSION

Women with allografts in RVOT position who are monitored in a tertiary dedicated CHD care setting can go through pregnancy safely with low risk of cardiac and obstetric events. Women with an active child whish should be counselled about the increased potential of preterm labor and should be regularly seen by a gynecologist and cardiologist before, during and after pregnancy.

CLINICAL PERSPECTIVES

Core Clinical Competencies in patient care: Women who underwent right ventricular outflow tract reconstruction can experience pregnancy safely. The incidence of preterm

labor and children small for their gestation age are higher compared to the general population.

Translational Outlook: The effects of pregnancy on long term durability of allografts in right ventricular outflow tract are virtually unknown. Future research should include statistical methods capable of efficiently analyzing repeated measurements. Optimizing valve function preconception might improve pregnancy outcome but requires additional research.

REFERENCES

1. Lozano, R., et al., Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 2012. 380(9859): p. 2095-128.
2. Mortality, G.B.D. and C. Causes of Death, Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2015. 385(9963): p. 117-171.
3. Mokhles, M.M., et al., Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg, 2011. 40(3): p. 571-8.
4. Cantwell, R., et al., Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. Bjog, 2011. 118 Suppl 1: p. 1-203.
5. Stout, K., Pregnancy in women with congenital heart disease: the importance of evaluation and counselling. Heart, 2005. 91(6): p. 713-4.
6. van de Woestijne, P.C., et al., Right ventricular outflow tract reconstruction with an allograft conduit in patients after tetralogy of Fallot correction: long-term follow-up. Ann Thorac Surg, 2011. 92(1): p. 161-6.
7. Steinberg, Z.L., et al., Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves. Journal of the American College of Cardiology, 2017. 69(22): p. 2681.
8. van Hagen, I.M., et al., Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation, 2015. 132(2): p. 132-42.
9. Stout, K.K. and C.M. Otto, Pregnancy in women with valvular heart disease. Heart, 2007. 93(5): p. 552-558.
10. Robson, S.C., et al., Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol, 1989. 256(4 Pt 2): p. H1060-5.
11. Robson, S.C., W. Dunlop, and S. Hunter, Haemodynamic changes during the early puerperium. Br Med J (Clin Res Ed), 1987. 294(6579): p. 1065.
12. Robson, S.C., et al., Cardiac output during labour. Br Med J (Clin Res Ed), 1987. 295(6607): p. 1169-72.
13. Adams, J.Q. and A.M. Alexander, Jr., Alterations in cardiovascular physiology during labor. Obstet Gynecol, 1958. 12(5): p. 542-9.
14. Arabkhani, B., et al., Does Pregnancy Influence the Durability of Human Aortic Valve Substitutes? Journal of the American College of Cardiology, 2012. 60(19): p. 1991-1992.
15. Heuvelman, H.J., et al., Pregnancy outcomes in women with aortic valve substitutes. Am J Cardiol, 2013. 111(3): p. 382-7.
16. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
17. Perined, Perinatale Zorg in Nederland 2015. 2015, Perined: Utrecht. p. 77.

18. Lancellotti, P., et al., European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr, 2010. 11(3): p. 223-44.
19. Yap, S.C., et al., Outcome of pregnancy in women after pulmonary autograft valve replacement for congenital aortic valve disease. J Heart Valve Dis, 2007. 16(4): p. 398-403.
20. Kampman, M.A., et al., Uteroplacental Doppler flow and pregnancy outcome in women with tetralogy of Fallot. Ultrasound Obstet Gynecol, 2017. 49(2): p. 231-239.
21. Goland, S., et al., Pregnancy in women with hypertrophic cardiomyopathy: data from the European Society of Cardiology initiated Registry of Pregnancy and Cardiac disease (ROPAC). Eur Heart J, 2017. 38(35): p. 2683-2690.
22. Khairy, P., et al., Pregnancy outcomes in women with congenital heart disease. Circulation, 2006. 113(4): p. 517-24.
23. Siu, S.C., et al., Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. Circulation, 2002. 105(18): p. 2179-84.
24. Siu, S.C., et al., Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation, 2001. 104(5): p. 515-21.
25. van Hagen, I.M., et al., Global cardiac risk assessment in the Registry Of Pregnancy And Cardiac disease: results of a registry from the European Society of Cardiology. Eur J Heart Fail, 2016. 18(5): p. 523-33.
26. Trigas, V., et al., Pregnancy-related obstetric and cardiologic problems in women after atrial switch operation for transposition of the great arteries. Circ J, 2014. 78(2): p. 443-9.
27. Balci, A., et al., Pregnancy in women with corrected tetralogy of Fallot: occurrence and predictors of adverse events. Am Heart J, 2011. 161(2): p. 307-13.
28. Yap, S.C., et al., Pregnancy outcome in women with repaired versus unrepaired isolated ventricular septal defect. Bjog, 2010. 117(6): p. 683-9.
29. Vriend, J.W., et al., Outcome of pregnancy in patients after repair of aortic coarctation. Eur Heart J, 2005. 26(20): p. 2173-8.
30. Veldtman, G.R., et al., Outcomes of pregnancy in women with tetralogy of Fallot. J Am Coll Cardiol, 2004. 44(1): p. 174-80.
31. Silversides, C.K., et al., Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. Am J Cardiol, 2003. 91(11): p. 1386-9.
32. Gelson, E., et al., Tetralogy of Fallot: maternal and neonatal outcomes. Bjog, 2008. 115(3): p. 398-402.
33. Greutmann, M., et al., Pregnancy outcome in women with congenital heart disease and residual haemodynamic lesions of the right ventricular outflow tract. Eur Heart J, 2010. 31(14): p. 1764-70.
34. Carvalho, J.S., et al., Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J, 1992. 67(6): p. 470-3.
35. van der Zee, E.N., et al., Targeting urine output and 30-day mortality in goal-directed therapy: a systematic review with meta-analysis and meta-regression. BMC Anesthesiol, 2017. 17(1): p. 22.
36. Ruys, T.P., et al., Cardiac medication during pregnancy, data from the ROPAC. Int J Cardiol, 2014. 177(1): p. 124-8.

37. Uebing, A., et al., Effect of pregnancy on clinical status and ventricular function in women with heart disease. Int J Cardiol, 2010. 139(1): p. 50-9.
38. Hameed, A.B., T.M. Goodwin, and U. Elkayam, Effect of pulmonary stenosis on pregnancy outcomes--a case-control study. Am Heart J, 2007. 154(5): p. 852-4.
39. Drenthen, W., et al., Non-cardiac complications during pregnancy in women with isolated congenital pulmonary valvar stenosis. Heart, 2006. 92(12): p. 1838-43.
40. Burn, J., et al., Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. Lancet, 1998. 351(9099): p. 311-6.
41. Marelli, A.J., et al., Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation, 2014. 130(9): p. 749-56.
42. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
43. Hoffman, J.I. and S. Kaplan, The incidence of congenital heart disease. J Am Coll Cardiol, 2002. 39(12): p. 1890-900.
44. European Society of, G., et al., ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J, 2011. 32(24): p. 3147-97.

10

Influence of Pregnancy on Long Term Durability of Allografts in Right Ventricular Outflow Tract

Jamie LR Romeo, Grigorios Papageorgiou, Johanna JM Takkenberg, Jolien W Roos-Hesselink, Wouter J van Leeuwen, Jerome MJ Cornette, Dimitris Rizopoulos, Ad JJC Bogers & M Mostafa Mokhles

Journal of Thoracic and Cardio-Vascular Surgery

ABSTRACT

Background

There is very limited published evidence about the influence of pregnancy on allograft durability in right ventricular outflow tract (RVOT) position. We present the first study using mixed and joint modeling.

Methods

This retrospective study compared clinical and valve related outcomes of all consecutive female hospital survivors in their fertile life phase (18–50 years) based on pregnancy. Serial echocardiographic measurements of pulmonary gradient and regurgitation were analyzed for their association with valve replacement using joint models for longitudinal and time-to-event data. Occurrence of first pregnancy was included as a time-dependent intermediate event in both the longitudinal and survival analyses of the joint model in order to assess its impact on the hemodynamic and clinical outcome.

Results

In total, 196 consecutive women in their fertile life-phase with an allograft were included. Complete information of 176 (90%) allografts in 165 women was available including 1395 echocardiograms. Of these women, 51 (30.9%) women had 84 completed pregnancies at an average age of 29.1±3.9 (SD) years; 8.1±6.1 years since allograft implantation. Tetralogy of Fallot was the most common diagnosis in both groups. After a mean follow up of 15.2 years (range 0.1-30), 7 (13.7%) parous underwent valve replacement, versus 20 (17.5%) nulliparous. During this follow up, the mean allograft gradient in parous (24.2 mmHg) and nulliparous (21.0 mmHg) was comparable (p=.225). One mmHg increase in pulmonary gradient increased the instantaneous risk of pulmonary valve replacement (PVR) by a ratio of 1.051 (p<.001), regardless of pregnancy. Similarly, development of moderate or severe regurgitation increased the risk of PVR (p=.038), regardless of pregnancy. Pregnancy was not associated with a change in the allograft gradient (p=.258), regurgitation grade (p=.774) or hazard of PVR (p=.796) during follow-up.

Conclusions

Pregnancy is not associated with impaired allograft durability in women with good cardiac health.

INTRODUCTION

Congenital heart disease (CHD) is present in 8-10 per 10.000 live births and often predisposes towards increased morbidity and earlier mortality, compared to the normal population [1-4]. The prevalence of CHD in young adulthood is expected to increase due to constantly improving surgical and clinical treatment options enabling patients to reach their fertile life phase [1, 2, 5]. In this regard, clinicians are confronted with a growing population of adults with congenital heart disease (ACHD).

Approximately 20% of all CHD involves the right ventricular outflow tract (RVOT). Pulmonary valve replacement (PVR) has, therefore, become the most frequently performed procedure in ACHD comprising approximately 10% of all procedures[6]. Suitable valve alternatives for RVOT reconstruction, however, are still scarce. The allograft is generally preferred over biological or mechanical prostheses for its excellent hemodynamic capabilities, durability and independence from anticoagulance which could be especially beneficial for childbearing women[7-10]. Structural valve deterioration (SVD) remains the main caveat of the allograft however, ultimately indicating repeated valve intervention [11]. As pregnancy induces hormonal changes and an important hemodynamic burden by increasing circulating volume, heart rate and bloodpressure[12, 13], it could potentially affect allograft durability. During the life long care and follow up of female ACHD, the wish and possibilities of pregnancy along with potential risks and long term outcome must be considered and actively addressed; ideally prior to pregnancy[14]. This information could also be used in pregnancy heart team meetings on women considering pregnancy and requiring valve surgery, as recommended by the most recent guidelines (Class 1 recommendation) [15].

This is the first report about the influence of pregnancy on long term function and durability of allograft conduits in RVOT position in women of childbearing age, using repeated measurement analysis.

METHODS

Study design

All consecutive patients who underwent RVOT reconstruction between April 1986 and January 2018 with an allograft at the Cardio-Thoracic Surgery department of the Erasmus Medical Center were included and screened for pregnancies. The Erasmus Medical Center is a tertiary referral center specialized in (congenital) cardiac surgery. All female patients older than 18 years at the time of this study and younger than 50 years at moment of surgery were retrospectively included. A detailed questionnaire was sent out to all women who confirmed pregnancy and gave informed consent. A supplementary

telephone interview was conducted for additional information. The Medical Ethics Commission reviewed and approved this study (MEC 17-158) after which written informed consent was acquired prior to onset of this study.

Operation technique

Allograft implantation was performed with standard cardiopulmonary bypass with moderate- or normothermia on a beating heart after median sternotomy. In case of concomitant intracardiac procedures the aorta was cross-clamped after which myocardial protection was achieved with crystalloid cardioplegia (St. Thomas' solution). Allografts were interposed between the right ventricle and pulmonary artery with running polypropylene 5.0 sutures. Our center exclusively uses cryopreserved allografts for RVOT reconstruction, preferring pulmonary allografts over aortic ones. Our institutional policy does not indicate any anticoagulation for homografts postoperatively after adequate mobilization.

Definitions

For this study, pregnancies were considered when reaching beyond >20 weeks of gestation. Parous and nulliparous women were thus defined as respectively having or having not experienced a pregnancy and delivery beyond 20 weeks of gestation. Gestational age was based on first trimester ultrasound and last menstrual period.

After pulmonary valve replacement, follow up by a cardiologist was regularly performed in all women during outpatient visits after one and six months and annually thereafter. Cardiac and valve related outcomes were reported according to the guidelines for reporting mortality and morbidity after cardiac valvular interventions[16]. All interventions were discussed during weekly multidisciplinary meetings involving (congenital) cardiologist, cardiac surgeons and radiologists. The primary endpoint of this study was pulmonary valve replacement (PVR) either surgically or percutaneously.

Echocardiographic

Allograft function was repeatedly assessed using standardized transthoracic echocardiograms during outpatient visits. Peak pulmonary gradient (mmHg) and regurgitation grade were assessed from a multi-window perspective according to the guidelines for the assessment of valve stenosis and regurgitation [17-19]. Peak pulmonary gradient was calculated with the modified Bernoulli equation from the peak transvalvular speed (m/s) and pulmonary regurgitation was graded qualitatively as non-significant (i.e. no regurgitation, trace or mild) or significant (moderate or severe).

Statistics

Baseline characteristics and measurements are summarized using descriptive statistics. Continuous measurements are summarized using means ± standard deviations or

medians with range. Qualitative measurements are summarized as absolute counts with percentages. All statistical tests were two-sided with a p-value lower than 0.05 considered as significant. Kaplan-Meier plots were used to describe cumulative freedom from valve replacement and mortality.

Serial echocardiographic measurements of pulmonary gradient and regurgitation were analyzed using a bivariate non-linear mixed-effects model, with a linear mixed-effects regression sub-model for the pulmonary gradient, and a mixed-effects logistic regression sub-model for pulmonary regurgitation. Both longitudinal sub-models were adjusted for the effects of age, donor sex, allograft diameter and type of allograft (i.e. aortic or pulmonary). The effect of pregnancy was determined by including a nonlinear effect of time using natural cubic splines from the onset of pregnancy in the sub-models of both pulmonary gradient and regurgitation grade. For the random effects structure we used a nonlinear effect of time as well as a nonlinear effect of time from the onset of pregnancy using natural cubic splines.

A time-dependent Cox model was used for the instantaneous risk of valve replacement. The value of both the pulmonary gradient and regurgitation, as estimated by the joint mixed-effects model, were included in the Cox model in order to determine their association with the instantaneous risk for valve replacement. The occurrence of a first pregnancy was entered in the model as a binary time-varying variate. Furthermore, interaction terms between the current value of the longitudinal trajectories of pulmonary gradient and regurgitation were included to investigate potential changes in the magnitude of the association between the hemodynamic outcomes and the instantaneous risk for valve replacement due to the occurrence of first pregnancy. More detailed information about the statistical models used in this study can be found in Appendix A.

The effect pregnancy on allograft function over time was thus assessed in three manners:

1. The effect of pregnancy on the longitudinal evolution of pulmonary gradient and regurgitation grade.
2. The effect of pregnancy as an independent covariate in a conventional proportional hazards model.
3. The interaction effect of pregnancy and the evolutions of both pulmonary gradient and the regurgitation grade in the joint model. I.e. does the occurrence of pregnancy alter the relationship between both markers and PVR?

Statistical analyses were performed with SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) and R (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

During the study period, 280 consecutive female patients underwent allograft implantation. Overall hospital mortality was 3.2% (n=9). We excluded 11 (3.9%) patients who were over 50 years at the time of surgery, 48 (17.4%) patients who had not reached 18 years and 16 (5.7%) patients who were lost to follow up due to return to their country of origin immediately post-surgery. Of the 196 allografts eligible for inclusion, 176 (90%) had complete clinical and echocardiographic follow-up (Table 1). None of the patients

Table 1. Perioperative characteristics of 176 female allograft recipients

	Total	Nulliparous	Parous	P-value
Allografts n(%)	176	125 (71)	51 (29)	
Aortic allograft	18 (10)	16 (13)	2 (4)	.078
Pulmonary allograft	158 (90)	109 (87)	49 (96)	
Pregnancies n(%)		0	84	NA
1			26	
2			20	
≥3			5	
Age at valve replacement (years)	22.2±12.5	22.7±14.1	21.4±7.3	.467
Age at first pregnancy (years)		NA	29.1±3.9	NA
Time of pregnancy since PVR (years)		NA	8.1±6.1	NA
Height at valve replacement (m)	151±31	147±34	159±17	.016
Weight at valve replacement (kg)	56±18	56±19	56±15	.925
Creatinine	59±18	58±19	61±15	.341
Right ventricular hypertrophy n(%)	38 (22)	32 (26)	6 (12)	.046
Left ventricular hypertrophy n(%)	27 (15)	22 (18)	5 (10)	.251
Diagnosis n(%)				
TOF	72 (41)	49 (39)	23 (45)	.235
Aortic Pathology*	42 (24)	27 (22)	15 (29)	
PA+VSD	19 (11)	16 (13)	3 (6)	
TA	12 (7)	11 (9)	1 (2)	
TGA+PA/PS	5 (3)	4 (3)	1 (2)	
PA–VSD	5 (3)	3 (2)	2 (4)	
Discordant	5 (3)	5 (4)	0 (0)	
Tricuspid Atresia	1 (1)	0 (0)	1 (2)	
Other	15 (9)	10 (8)	5 (10)	
Donor gender (male) n (%)	89 (51)	65 (52)	24 (47)	.619
Allograft size (mm)	23 (11-30)	23 (11-30)	24 (16-28)	.206
Perfusion time (min) (n=161)	145 (35-465)	143 (35-465)	151 (39-295)	.691
Pulmonary valve replacement	27	20 (16)	7 (14)	.332
Severe stenosis	14	12 (60)	2 (29)	
Severe regurgitation	6	4 (20)	2 (29)	
Mixed stenosis and regurgitation	7	4 (20)	3 (43)	

NYHA=New York Heart Association, PA=Pulmonary Atresia, PS=Pulmonary Stenosis, TA=Truncus Arteriosus, TGA=Transposition of the Great Arteries, TOF=Tetralogy of Fallot, VSD=Ventricular Septal Defect

* Primary aortic valve pathology for which a pulmonary autograft ('Ross') procedure was performed

who underwent repeated PVR had multiple pregnancies during the follow-up time of different allografts. Compared to nulliparous women, parous women had less often right ventricular hypertrophy (12% vs 26%, p=.046) at time of surgery. Other baseline characteristics were comparable (Table 1).

Pregnancy outcome

The cardiac and obstetric course and fetal outcomes of all pregnancies have been extensively described previously [20]. In short, parous women were in overall good cardiac and clinical health prior to pregnancy with an average pulmonary gradient of 19 mmHg, non-significant regurgitation in 83.3% and significant regurgitation in 16.7%. Mean age at last menstruation was 29.6±4.3 years, which was 8.6±6.6 years after allograft implantation. Two women were identified who became pregnant despite explicit contraindications on cardiac grounds. The first had a severely dilated and dysfunctioning left ventricle and the second had severe pulmonary hypertension. They were induced into premature labor but recovered uneventfully. Both still have their homograft in situ without signs of valve deterioration. No woman died during pregnancy or within the first year postpartum.

Long term clinical outcome

Median follow-up length from operation to last follow-up was 18.0 years (mean 17.4 years; range 2.0-30.0 years, total patient-years 887) and 13.7 years (mean 14.3 years; range 0.01-28.6 years, total patient-years 1784) for parous and nulliparous women, respectively. Thirteen women died during follow up (0.73%/patient-year), all nulliparous, with 10 (0.56%/patient-year) cases of cardiac death and 3 cases (0.17%/patient-year) of non-cardiac related death. Among the cardiac related deaths there was 1 (0.06%/patient-year) case of valve related death, 4 (0.22%/patient-year) cases of sudden unexplained death and 5 (0.28%/patient-year) cases of non-valve related cardiac death all comprising end-stage heart failure. One nulliparous woman died during an attempt to percutaneously implant a Melody valve indicated by severe stenosis 23.0 years after initial allograft implantation. All other reinterventions were performed successfully.

Following allograft implantation, there were 4 (3.2%) percutaneous balloon dilatation in the nulliparous, and 2 (3.9%) in the parous women. In the parous group there were 7 (0.8%/patient-year) PVR after 14.3±4.9 years after initial surgery. Six were surgically (4 allografts, 1 mechanical valve, 1 bioprosthesis (Medtronic Freestyle® valve)) and 1 was percutaneously (Melody® valve). Among the nulliparous 20 (1.24%/patient-year) underwent PVR after 14.1±5.5 years of which 13 surgically (all allografts) and 7 transcatheter Melody® valve implantations. All PVR were indicated by structural valve deterioration. Freedom from valve replacement after 20 years was 78±16% for parous and 66±14% for nulliparous women (Figures 1A-B).

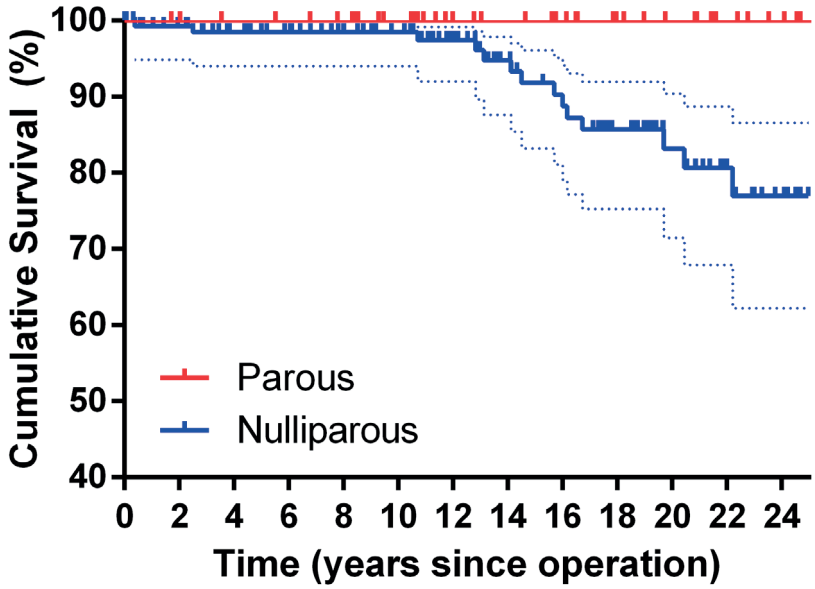


Figure 1A Kaplan-Meier curves of overall survival after allograft replacement

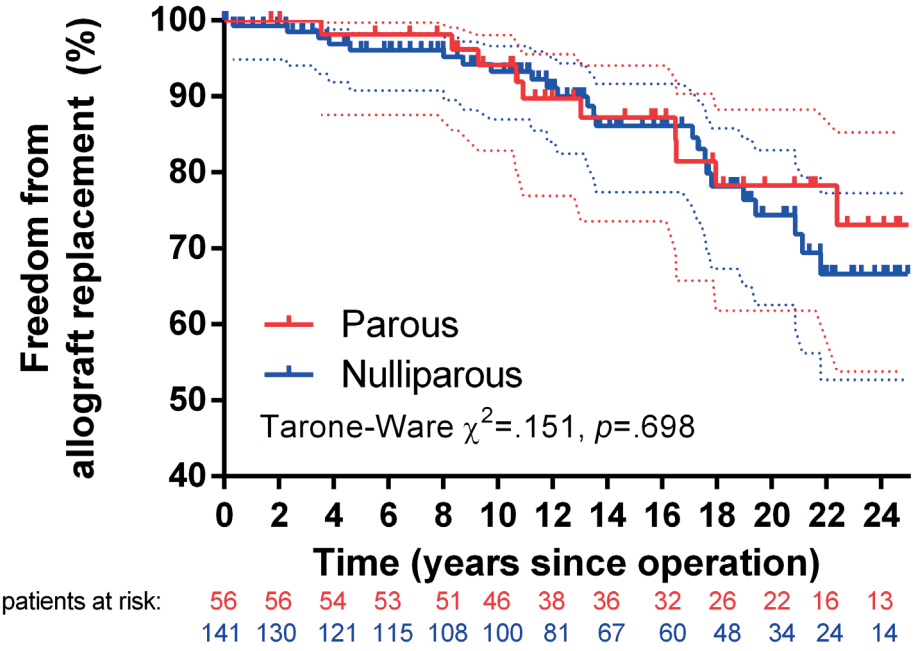


Figure 1B Kaplan-Meier curves of freedom from allograft replacement

Echocardiographic outcome

There were 1395 serial echocardiograms available for all included patients (mean 7, range 1-26) serial echocardiograms/patient). For women with multiple pregnancies, only the effect of the first pregnancy on the allograft hemodynamics were analyzed. Measurements in those cases were censored from the onset of the second pregnancy. The median time for women to have their first pregnancy after allograft implantation was 8 years. Figures 2A-B present the longitudinal evolutions of pulmonary gradient and regurgitation for scenarios with and without pregnancy. Figures 3A-B present both longitudinal evolutions along with the influence of pregnancy on the hazard of PVR.

The analyses of the association between both gradient and regurgitation, and the hazard of PVR showed that an 1 mmHg increase in the pulmonary gradient, increases the instantaneous risk of PVR by a ratio of 1.051 (p<.001). Similarly, an increase in the probability of significant regurgitation increases the instantaneous risk of PVR by a ratio of 1.209 (p=0.038). Pregnancy was, however, not associated with an increased hazard of PVR (p=0.796, Table 2).

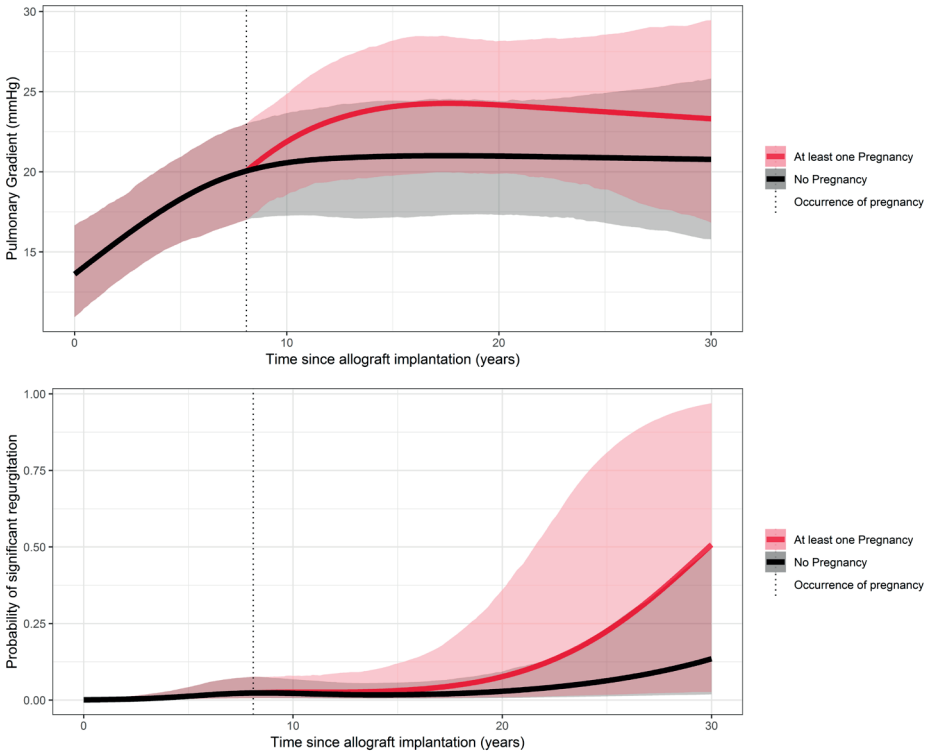


Figure 2A-B Mixed-effects models of transpulmonary peak gradient (mmHg) and moderate-severe regurgitation

Table 2 Joint model estimates of the association with pulmonary valve replacement

	HR	95% CI	p-value
Occurrence of first pregnancy	0.726	(0.049 - 4.482)	0.796
Age	1.000	(0.951 - 1.030)	0.890
Current value of gradient	1.051	(1.030 - 1.062)	< 0.001
Current value of regurgitation	1.209	(1.010 - 1.537)	0.038
Interaction with occurrence of first pregnancy:			
Current value of gradient	1.030	(0.980 - 1.105)	0.258
Current value of regurgitation	1.030	(0.844 - 1.391)	0.774

CI = Confidence Interval, HR = Hazard Ratio

The interaction between the longitudinal pulmonary gradient and regurgitation grade with pregnancy was non-significant (p=0.258 and p=0.774, respectively), indicating that pregnancy did not change the association between the hemodynamic outcomes and the hazard of valve replacement.

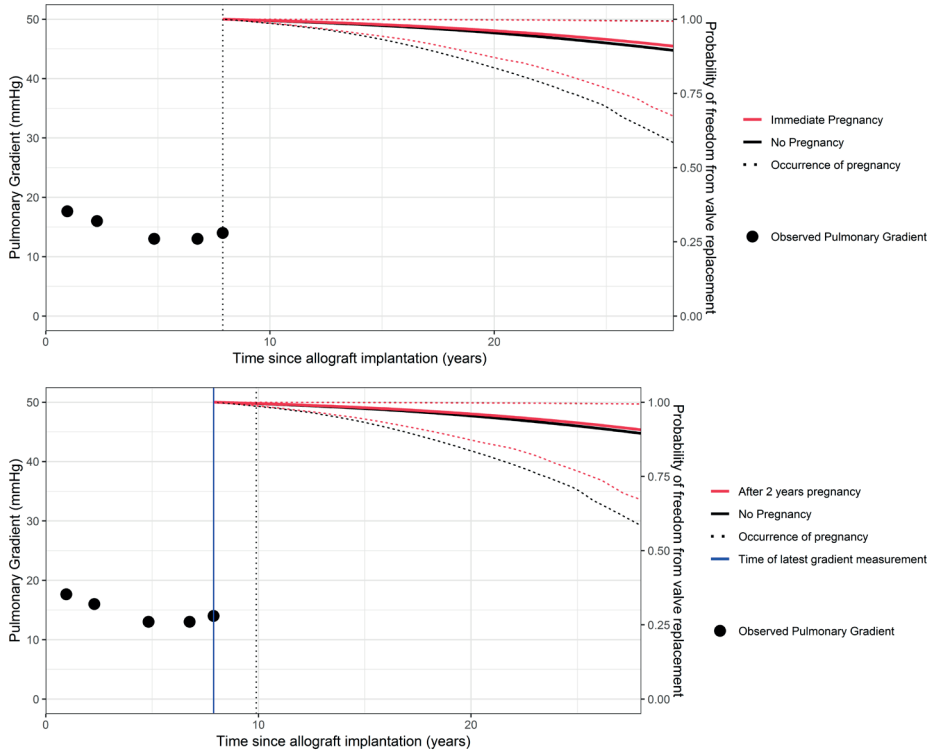


Figure 3A-B. Influence of pregnancy on freedom from valve replacement

DISCUSSION

We described the long term effect of pregnancy on the clinical and longitudinal echocardiographic outcome of allografts in RVOT position. The results show that the occurrence of pregnancy at any moment after allograft implantation is not associated with an increased hazard of PVR. Therefore, there is no evidence to support that pregnancy negatively influences allograft function over time.

Increased rates of complications during pregnancy like premature labor, fetal demise, severe bleeding and heart failure have been reported among a wide spectrum of corrected CHD, compared to the general population [20-25]. Much less is known about cardiac outcome late after pregnancy and impact of pregnancy on cardiac function. As life expectancy among practically all ACHD has substantially improved during the last decades, the number of pregnancies will likely increase as well [2, 3]. Multiple studies have demonstrated mechanical prostheses to carry extensive risks of pregnancy related complications [9, 10, 26]. Previous studies on pregnancy have mainly focused on bioprostheses and mechanical prostheses in the aortic position [27-30]. In their study on allografts and autografts in the aortic position, Arabkhani et al. described the influence of pregnancy on the longitudinal evolution of gradient, sino-tubular junction diameter, annulus diameter and regurgitation grade. They reported no significant influence of pregnancy on all mentioned evolutions with a comparable freedom from valve reoperation between parous and nulliparous [27]. In another report on allografts in aortic position North et al. reported a 10 year freedom from valve loss defined as allograft replacement or valve-related death of 72%, an no influence of pregnancy[29].

Although allografts and bioprostheses are less thrombogenic and therefore independent from anticoagulation, they suffer from structural deterioration [11, 31]. The outcome of parous women with RVOT allograft conduits has been reported earlier in smaller cohorts[32-35]. However, these studies only focused on complications during or directly after pregnancy without reporting the longitudinal allograft function over time and the effect of pregnancy on this outcome. These studies have generally reported positive clinical outcomes [32-35]. Cleuziou et al. studied the rate of degeneration of 45 bioprostheses and 42 allografts, of which 40 in RVOT position. Pregnancy was not a risk factor for accelerated valve failure with freedom from valve replacement at 10 years of 73% and 52% (p=0.2) for patients with and without pregnancy, respectively [33]. Oosterhof et al. studied the risk of allograft failure and dysfunction after repair of Tetralogy of Fallot. Data from the Zahara study were included and indicated no effect of pregnancy on allograft durability [36]. Metz et al. were the only authors to report a negative influence of pregnancy on general cardiac health in patients after pulmonary valve surgery. Among women who underwent PVR or pulmonary repair, 33 women with 95 completed pregnancies were compared to 20 nulliparous. A higher incidence rate

of the composite outcome of unanticipated cardiac surgery, heart failure and death was reported in the parous group compared to nulliparous women. However, when the authors looked closely at this group of patients the found that adverse cardiac outcome after pregnancy was more prevalent in patients with pulmonary valve surgery (not replacement) compared to those did had undergone PVR. [37]. The mixed cohort of Metz et al. including a modest proportion of patients with replaced valves can potentially explain their findings. In general however, research about the influence of pregnancy on prosthetic valve durability is limited and even though in line with our results, often lack statistically robust methodology [27, 32-36, 38].

In our cohort, parous women differed in baseline characteristics only with regard to right ventricular hypertrophy. Other baseline characteristics were comparable. However, cardiac and general health, other than allograft function alone, might have influenced the desire, ability and advise from consulting cardiologists to become pregnant. In parous women, pregnancy did not influence allograft function and hazard of PVR. However, the results and, therefore, conclusions are restricted to parous women and are therefore more likely to be in better cardiac health. Only two women could be identified who became pregnant despite explicit contraindications on cardiac grounds.

This study shows that longitudinal allograft function over time is unaffected by the occurrence of pregnancy. Therefore, pregnancy does not influence durability of allografts as demonstrated by using a novel and advanced biostatistical framework [39]. The use of mixed and joint modelling has been limited in Cardio-Thoracic research even though it has been recommended by the 2008 guidelines for reporting mortality and morbidity after cardiac valve interventions [16, 27, 40]. Combining serial measurements of any biomarker with a time dependent event is a statistically robust method to test the potential influence of the latter, by more optimally utilizing available data.

STRENGTH AND LIMITATIONS

We assessed the effect of pregnancy on RVOT allograft durability was longitudinally assessed using innovative statistical methods. Furthermore, follow-up completeness was high and a large number of standardized echocardiograms were available for the analyses. In contrast to earlier studies, innovative statistical methods were used to analyze the data. Because pregnancy is ethically and practically impossible to randomize, future research should combine these type of innovative statistics with data from prospectively followed cohorts.

The exact potential mechanism through which pregnancy could influence long term allograft function is largely unknown. As the change in hemodynamics are transitory during pregnancy, it would be more clinically accurate to model a temporary effect of

pregnancy which fades of after labor. However, this approach would require an extensive amount of measurements before, during and after pregnancy to reliably estimate the temporal effect and was therefore impossible in the current analysis. Furthermore, while the effect of pregnancy on pulmonary gradient and pulmonary regurgitation was not found to substantially alter their evolutions, a small change was detected. Taking into account that only 13.7% of the subjects experienced pregnancy, results should be interpreted with care since power is low.

CONCLUSION

The occurrence of pregnancy at any moment during at least the first 15 years after RVOT reconstruction with an allograft conduit does not influence allograft durability.

REFERENCES

1. van der Bom, T., et al., The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. Am Heart J, 2012. 164(4): p. 568-75.
2. Gilboa, S.M., et al., Congenital Heart Defects in the United States: Estimating the Magnitude of the Affected Population in 2010. Circulation, 2016. 134(2): p. 101-9.
3. O'Leary, J.M., et al., The Changing Demographics of Congenital Heart Disease Hospitalizations in the United States, 1998 Through 2010. Jama, 2013. 309(10): p. 984-986.
4. Hoffman, J.I. and S. Kaplan, The incidence of congenital heart disease. J Am Coll Cardiol, 2002. 39(12): p. 1890-900.
5. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
6. (STS), T.S.o.T.S., Adults - Spring 2017 Harvest. 2017.
7. Mokhles, M.M., et al., Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg, 2011. 40(3): p. 571-8.
8. Wong, V., C.H. Cheng, and K.C. Chan, Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. Am J Med Genet, 1993. 45(1): p. 17-21.
9. Steinberg, Z.L., et al., Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves. Journal of the American College of Cardiology, 2017. 69(22): p. 2681.
10. van Hagen, I.M., et al., Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation, 2015. 132(2): p. 132-42.
11. Romeo, J.L.R., et al., Long-term clinical outcome and echocardiographic function of homografts in the right ventricular outflow tract†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy265-ezy265.
12. Stout, K.K. and C.M. Otto, Pregnancy in women with valvular heart disease. Heart, 2007. 93(5): p. 552-558.
13. Basquin, A., et al., Transcatheter valve insertion in a model of enlarged right ventricular outflow tracts. J. Thorac. Cardiovasc. Surg., 2010. 139(1): p. 198-208.
14. Stout, K., Pregnancy in women with congenital heart disease: the importance of evaluation and counselling. Heart, 2005. 91(6): p. 713-4.
15. Regitz-Zagrosek, V., et al., 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. European Heart Journal, 2018. 39(34): p. 3165-3241.
16. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
17. Baumgartner, H., et al., Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice. Journal of the American Society of Echocardiography, 2009. 22(1): p. 1-23.
18. Lancellotti, P., et al., European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr, 2010. 11(3): p. 223-44.

19. Cleuziou, J., et al., Durability of down-sized homografts for the reconstruction of the right ventricular outflow tractdagger. Eur J Cardiothorac Surg, 2015.
20. Romeo, J.L.R., et al., Outcomes of Pregnancy After Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit. Journal of the American College of Cardiology, 2018. 71(23): p. 2656-2665.
21. Trigas, V., et al., Pregnancy-related obstetric and cardiologic problems in women after atrial switch operation for transposition of the great arteries. Circ J, 2014. 78(2): p. 443-9.
22. Balci, A., et al., Pregnancy in women with corrected tetralogy of Fallot: occurrence and predictors of adverse events. Am Heart J, 2011. 161(2): p. 307-13.
23. Bedard, E., K. Dimopoulos, and M.A. Gatzoulis, Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J, 2009. 30(3): p. 256-65.
24. Yap, S.C., et al., Pregnancy outcome in women with repaired versus unrepaired isolated ventricular septal defect. Bjog, 2010. 117(6): p. 683-9.
25. Grewal, J., et al., Pregnancy outcomes in women with dilated cardiomyopathy. J Am Coll Cardiol, 2009. 55(1): p. 45-52.
26. Ayad, S.W., et al., Maternal and Fetal Outcomes in Pregnant Women with a Prosthetic Mechanical Heart Valve. Clin Med Insights Cardiol, 2016. 10: p. 11-7.
27. Arabkhani, B., et al., Does Pregnancy Influence the Durability of Human Aortic Valve Substitutes? Journal of the American College of Cardiology, 2012. 60(19): p. 1991-1992.
28. Dore, A. and J. Somerville, Pregnancy in patients with pulmonary autograft valve replacement. Eur Heart J, 1997. 18(10): p. 1659-62.
29. North, R.A., et al., Long-term survival and valve-related complications in young women with cardiac valve replacements. Circulation, 1999. 99(20): p. 2669-76.
30. Basude, S., et al., Pregnancy outcome and follow-up cardiac outcome in women with aortic valve replacement. Obstet Med, 2014. 7(1): p. 29-33.
31. Christenson, J.T., et al., Homografts and xenografts for right ventricular outflow tract reconstruction: long-term results. Ann Thorac Surg, 2010. 90(4): p. 1287-93.
32. Avila, W.S., et al., Influence of pregnancy after bioprosthetic valve replacement in young women: a prospective five-year study. J Heart Valve Dis, 2002. 11(6): p. 864-9.
33. Cleuziou, J., et al., Pregnancy does not accelerate biological valve degeneration. Int J Cardiol, 2010. 145(3): p. 418-21.
34. Jamieson, W.R., et al., Pregnancy and bioprostheses: influence on structural valve deterioration. Ann Thorac Surg, 1995. 60(2 Suppl): p. S282-6; discussion S287.
35. Sadler, L., et al., Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. Bjog, 2000. 107(2): p. 245-53.
36. Oosterhof, T., et al., Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. Eur Heart J, 2006. 27(12): p. 1478-84.
37. Metz, T.D., et al., Impact of pregnancy on the cardiac health of women with prior surgeries for pulmonary valve anomalies. Am J Obstet Gynecol, 2013. 209(4): p. 370.e1-6.

38. Heuvelman, H.J., et al., Pregnancy outcomes in women with aortic valve substitutes. Am J Cardiol, 2013. 111(3): p. 382-7.
39. Papageorgiou, G., et al., An Overview of Joint Modeling of Time-to-Event and Longitudinal Outcomes. Annual Review of Statistics and Its Application, 2018.
40. Mokhles, M.M., et al., Capturing echocardiographic allograft valve function over time after allograft aortic valve or root replacement. The Journal of Thoracic and Cardiovascular Surgery, 2014. 148(5): p. 1921-1928.e3.

11

Long term clinical and echocardiographic outcome in young and middle aged adults undergoing the Ross procedure

Jamie Romeo, Grigorios Papageorgiou, Francisco da Costa, Hans Sievers, Ad Bogers, Ismail el-Hamamsy, Peter Skillington, Rochelle Wynne, Stefano Mastrobuoni, Gebrine El Khoury, Johanna Takkenberg & Mostafa Mokhles

Jama Cardiology

ABSTRACT

Background

Surgical options for aortic valve replacement in middle aged adults are limited and suboptimal. The Ross (pulmonary autograft) procedure is potentially a good alternative in this patient population. We aimed to describe the long term clinical and echocardiographic outcome in middle aged adults who underwent the Ross procedure.

Methods

An international multicenter study was conducted including consecutive patients of 18 to 65 years who underwent the Ross procedure between 1990 and 2016. Serial echocardiographic measurements of valve function were analyzed using mixed effects modeling. Mortality rate was compared to that of an age, sex and country matched general population.

Results

During the study period, 1431 patients (74.3% males; n=1063) were operated at a median age of 47.7 years (SD=9.5; range 18.1-70.5), of which 76.1% (n=778) had a bicuspid aortic valve. Implantation techniques were root inclusion in 355 (24.9%), root replacement in 485 (34.0%) and subcoronary implantation in 587 (41.1%). Right ventricular outflow tract reconstruction was performed with homografts in 98.6% (n=1189) and bioprostheses in 1.4% (n=17). In hospital mortality concerned 10 patients (0.7%). Median follow up was 9.2 years (13015 total patient years). Survival after 10 and 15 years was 95.1% (95% CI 93.8–96.5%) and 88.5% (95% CI 85.9-91.1%), respectively. Survival of patients was comparable to that of a sex, age and country matched general population (p=0.18). Freedom from autograft and allograft reintervention after 15 years was 92.0% and 97.2%, respectively. Late events were autograft endocarditis in 14 patients (0.11%/patient-year), homograft endocarditis in 11 patients (0.08%/patient-year) and stroke in 37 patients (0.3%/patient-year).

Conclusions

Given the excellent short and long term outcome in young and middle aged adults, the Ross procedure should be considered in young and middle aged adults who need aortic valve replacement.

INTRODUCTION

Surgical alternatives for aortic valve replacement in young and middle aged adults (aged 18-65 years) are limited. Mechanical and bioprosthetic valves have benefits and drawbacks, but both are suboptimal in terms of survival and comorbidity. The pulmonary autograft procedure ('Ross procedure' hereafter) has been the only alternative restoring life expectancy to that of a gender and age matched general population, for at least 15 years postoperative[1-4]. Several single-center studies with extensive follow-up indicated that patients under 50 who have active lifestyles, a long life expectancy and a potential childbearing desire are better served with the Ross procedure [1, 2, 5-10]. Despite excellent results the Ross procedure remains an underused treatment, representing a mere 0.09% of all aortic valve replacements in 2010[11]. It's limited use is often attributed to the complexity of the procedure and concerns about increased risks of early mortality and late reintervention [12-14]. The most recent guidelines on valvular management do not recommend the Ross procedure in middle-aged patients and advise consideration only in selected young patients with contraindications or unwillingness to anticoagulation (Class IIb, evidence level C) [15]. The STS 2013 guideline does not recommend the Ross procedure (Class III, evidence level C) for middle-aged or older adults [16]. However, recent evidence indicating clear benefits of the Ross procedure in comparison to common alternatives in selected young and middle aged patients is accumulating [17] [18].

We present one of the largest multi-center studies on consecutive young and middle aged adults who underwent the Ross procedure by combining data from 6 centers that specialize in the Ross procedure in five countries worldwide.

METHODS

Study data

Patients operated in one of 6 high volume centers in Australia, Belgium, Brazil, Canada and Germany were pooled (for a list of the participating centers, please consult the Data Supplement A). All consecutive young and middle aged patients who were 18 through 65 years old at time of surgery and electively underwent the Ross procedure between January 1991 and December 2018 were included. Indications for the Ross procedure have been descripted by multiple reports by each center, including exact surgical techniques [10, 19-23]. Bicuspid aortic valves, isolated severe aortic regurgitation, concomitant coronary artery bypass surgery or replacement of the ascending aorta were not considered exclusion criteria. Patients who underwent emergency (<24 hour) operation, concomitant mitral valve replacement, or had an aortic dissection were excluded. Each

center prospectively and independently registered procedural and clinical outcomes as well as echocardiographic measurements according to center specific protocol [10, 19-23]. Anonymized individual patient data was merged into a single dataset and analyzed by an independent biostatistician (GP) from the Erasmus University Medical Center. The institutional review board of all participating centers reviewed and approved this study. All participants provided written informed consent.

Endpoints

Valve related events and outcomes were reported according to recommended guidelines [24]. Late all-cause mortality was thus defined as any death occurring beyond 30 days after surgery. Survival of our patient population was compared with the life-expectancy of a gender-, age- and birth country- matched general population. Mortality data was retrieved from 'The Human Life-Table Database' (www.lifetable.de) at the 3th of August 2019. Observed mortality of patients after operation was compared to expected mortality using life-expectancy from the operation date of matched individuals from the general population using the standardized mortality ratio (Data Supplement B) [25-27]. Ross related reintervention includes any type of reintervention on either the autograft or allograft or bioprosthesis (in case of RVOT reconstruction with a bioprosthesis) after the initial procedure, regardless of concomitant procedures involving other (cardiac) structures. The peak transvalvular gradient, and regurgitation grades were determined from a multi-window perspective using m-mode Doppler echocardiography on a yearly basis. Aortic regurgitation (AR) was scored on a scale from 0 (none) to 4 (severe) according to the guidelines for the assessment of valvular stenosis and regurgitation[28].

Statistical analysis

Continuous data are presented as means ± standard deviation (SD) or medians with range, after testing for normality using the Kolmogorov-Smirnov test. Categorical data is presented as absolute count with percentages. Descriptive analyses were performed with SPSS version 23.0 (IBM SPSS Inc., Chicago, IL, USA). Actuarial estimates of freedom from death and reintervention were performed using Kaplan-Meier techniques. Mixed effects models were used to analyze repeated measurements as gradient and dimensions. Multivariable proportional hazards models were used to investigate predictors for the clinical endpoints. Due to the low event rate and the high number of candidate predictors, a penalized likelihood approach was used for the multivariable Cox regression models. To account for missing covariate data we used a multiple imputation approach.. Associations between baseline characteristics and outcomes of interest were tested using the Wald test. The reported p-values are not adjusted for multiple testing. The regression analysis and mixed effect models were performed using R software version 3.6.1 (www.r-project.org). A more detailed description of the statistical analysis is

provided in the Appendix 3. All authors had direct access to any aspect of the data and take responsibility for its integrity.

RESULTS

Survival and Morbidity

The total study population consisted of 1431 patients (Australia [n=201], Belgium [n=174], Brazil [n=316], Canada [n=112], Germany [n=628]). Median age at operation was 48.5 years (inter quartile range 42.7-54.0). In total, 1048 (73.2%) had a bicuspid aortic valve and 1063 (74.3%) were males. All baseline characteristics and intraoperative and early outcome are presented in Table 1.

Table 1 Baseline and surgical characteristics

	Average ± sd or n (%)
Patients (n)	1431
Age (years)	47.7 ± 9.5
<20	20
20 – 40	192
40 – 60	1114
>60	105
Males (n)	1063 (74.3)
NYHA classification (n = 1426)	
I	372 (26.1)
II	724 (50.8)
III	316 (22.1)
IV	14 (1.0)
Hypertension (n) (n=1167)	371 (31.8)
Diabetes (n) (n=1055)	43 (4.1)
Aortic valve morphology (n=1022)	
Bicuspid	778 (76.1)
Tricuspid	191 (18.7)
Other/prosthetic	53 (5.2)
Concomitant procedures (n = 805)	
CABG	33 (4.1)
Other	
Previous cardiac surgery	85
Echocardiographic	
LVEDD (mm) (n=1198)	53±9.5
LVESD (mm) (n=1127)	34±8.5
LVEF (%) (n=967)	66±11.5

Table 1 Baseline and surgical characteristics (*continued*)

	Average ± sd or n (%)
Echo valve stenosis (	
Aorta valve Peak Gradient (mmHg)	70±33
Aorta valve Mean Gradient (mmHg)	44±21
Aortic valve regurgitation (n = 1117)	
Aortic regurgitation – no	141 (12.6)
Aortic regurgitation – trace	363 (32.5)
Aortic regurgitation – light	237 (21.2)
Aortic regurgitation – moderate	278 (24.9)
Aortic regurgitation – severe	98 (8.8)
Technique	
Root inclusion	355 (24.9)
Root replacement	485 (34.0)
Subcoronary	587 (41.1)
CPB time (min) (n=1313)	198 ± 41
Cross-clamp time (min) (n=1313)	173 ± 36
RVOT Conduit (n = 1206)	
Allograft	1189 (98.6)
Pulmonary	1185 (99.7)
Aortic	4 (0.3)
Bioprosthesis	17 (1.4)
In hospital mortality	10 (0.7%)

In-hospital mortality concerned 10 patients (0.7%). Median follow up was 9.2 years (13.015 total patient years) during which autograft endocarditis occurred in 14 patients (Linearized Occurrence Rate [LOR] 0.11%/patient-year), homograft endocarditis in 11 patients (LOR 0.08%/patient-year) and stroke in 37 patients (LOR 0.3%/patient-year). Overall survival after 10 and 15 years was 95.1% (95% CI 93.8–96.5%) and 88.5% (95% CI 85.9-91.1%), respectively (Figure 1).

Observed mortality (n=100) in our patient population was comparable to the expected mortality (n=114) of a sex, age, birth year and country matched general population ($\chi 2=1.82$, p=0.18). Freedom from cardiac mortality (n=30) at 10 and 15 years was 98.6% (95% CI 97.9-99.4%) and 96.5% (95% CI 95.0-98.0%), respectively (Figure 2).

Higher age at operation (HR 1.067, 95 CI 1.051-1.084), female sex (HR 1.423, 95 CI 1.010-2.010) and the preoperative comorbidities peripheral vascular disease (HR 9.422, 95 CI 3.923-22.627), chronic obstructive pulmonary disease (HR 5.063, 95 CI 2.595-9.876) and congestive cardiac disease (HR 1.067, 95 CI 1.051-1.084) were associated with an increased hazard of late death (Supplementary materials, Table 1).

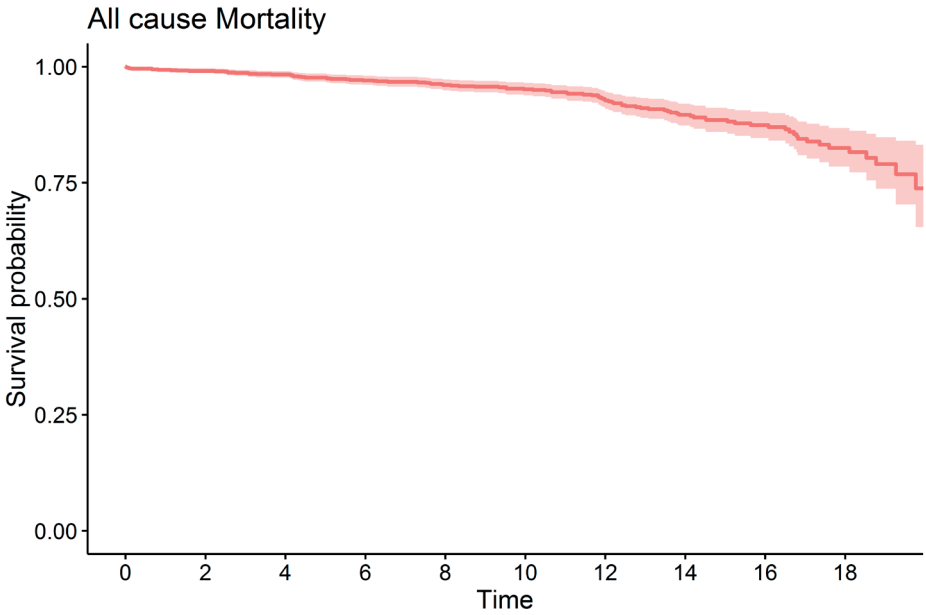


Figure 1 Kaplan Meier Plot Freedom from all-cause mortality

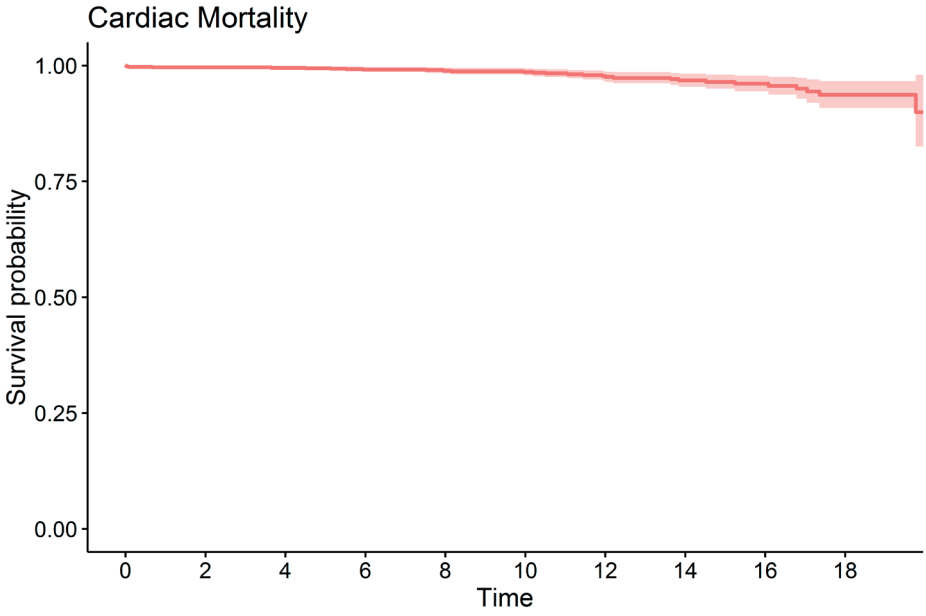


Figure 2 Kaplan Meier Plot Freedom from cardiac mortality

Reintervention

Freedom from any Ross related reintervention after 10 and 15 years was 93.9 % (95% CI 92.4-95.5%) and 90.8% (95% CI 88.6-93.1%), respectively (Figure 3, Supplementary materials, Table 3). Freedom from autograft reintervention at 10 and 15 years were 95.0% (95% CI 93.6-96.4%) and 92.0% (95% CI 89.8-94.2%) (Figure 4). Severe preoperative regurgitation was associated with an increased hazard of autograft reintervention (HR 3.065, 95% CI 1.019-9.22) (Supplementary materials, Table 4). All reinterventions on the RVOT involved allografts, which were used in 98.5% of all patients. Freedom from allograft reintervention at 10 and 15 years was 98.4% (95% CI 97.6-99.2) and 97.2% (95% 95.9-98.5%), respectively (Figure 5). Higher age of the allograft donor (HR 0.969, 95% CI 0.944-0.994) and larger allograft diameter (HR 0.773, 95% CI 0.662-0.903) were associated with a lower hazard of reintervention on the allograft (Supplementary materials, Table 6).

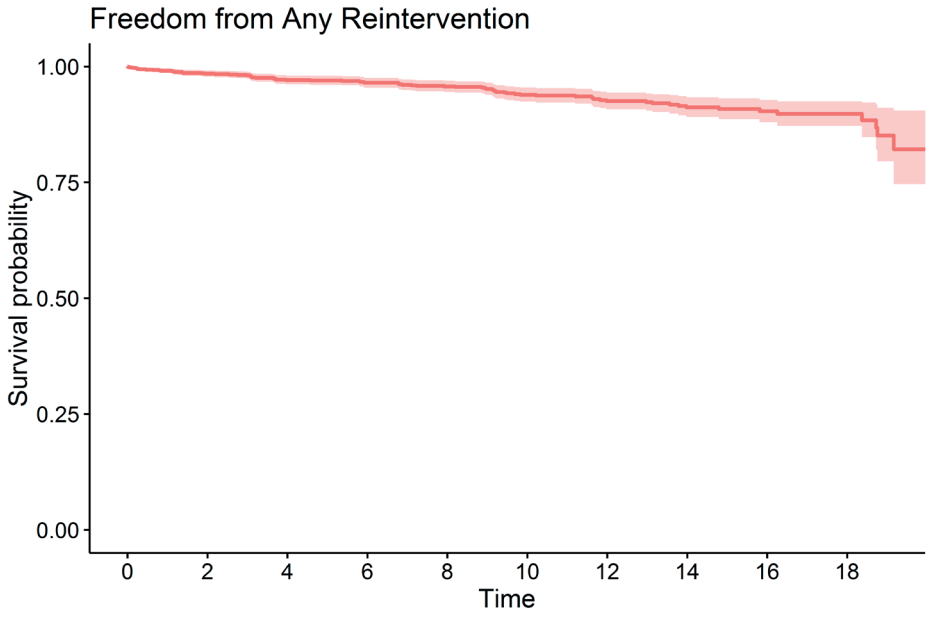


Figure 3 Kaplan Meier Plot Freedom from Any Reintervention

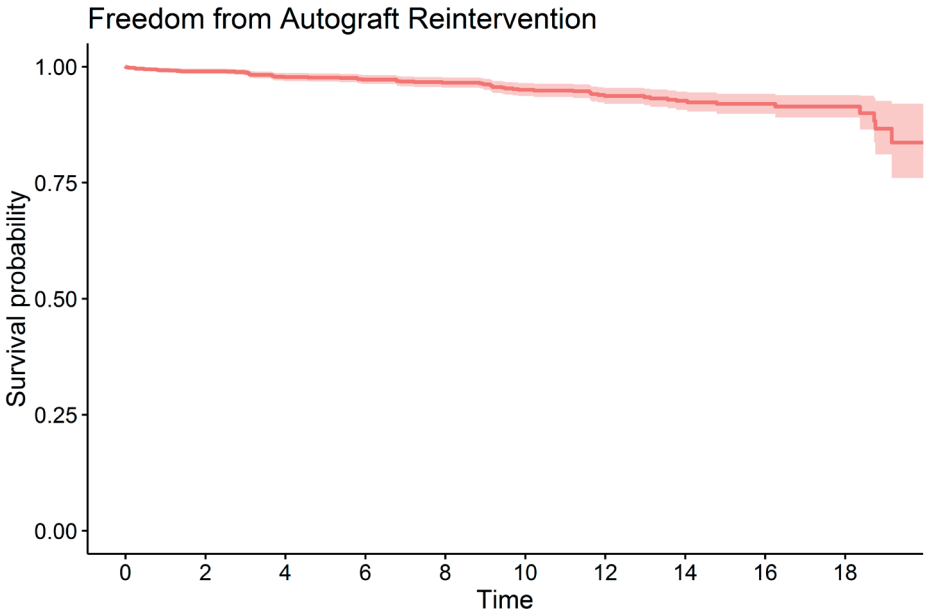


Figure 4 Kaplan Meier plot Freedom from Autograft reintervention

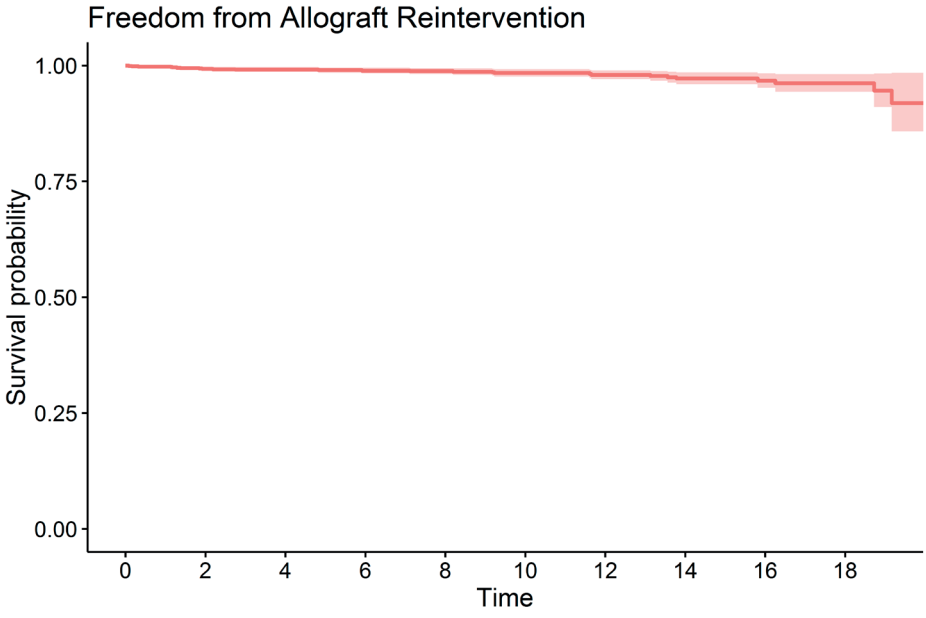


Figure 5 Kaplan Meier plot Freedom from Allograft reintervention

Echocardiographic

In total, 8655 postoperative echocardiographic measurements were available for 1150 (82.8%) (mean echo's available: 7.5, range 1-20) for a median period of 9.2 years (range 0.01-25.4 years). Figures 6 and 7 depict the predicted evolution of the autograft gradient and regurgitation grade for a patient with median characteristics, respectively. Female sex (p=0.034), a tricuspid native aortic valve (p=0.010) and higher preoperative gradient (p=0.002) were significantly associated with a higher autograft gradient (Supplementary materials, Table 6).

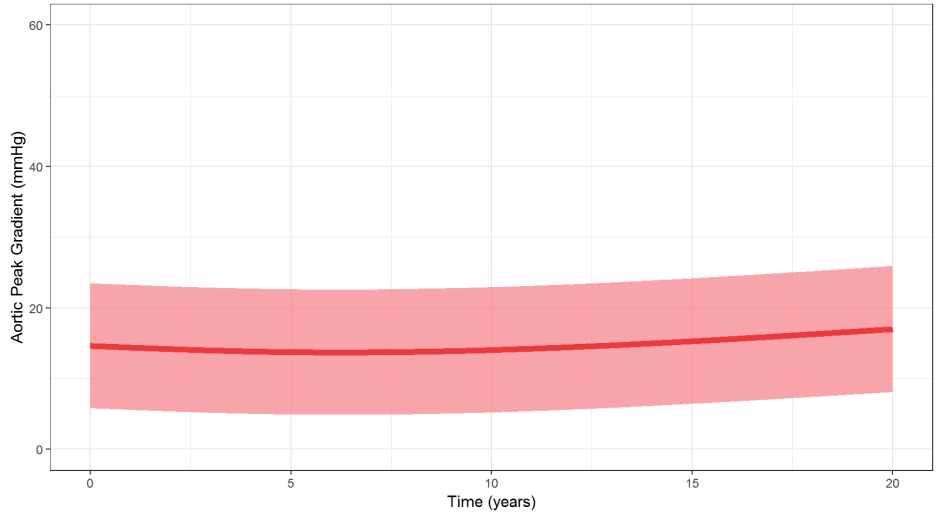


Figure 6 Effectplot of Autograft Gradient

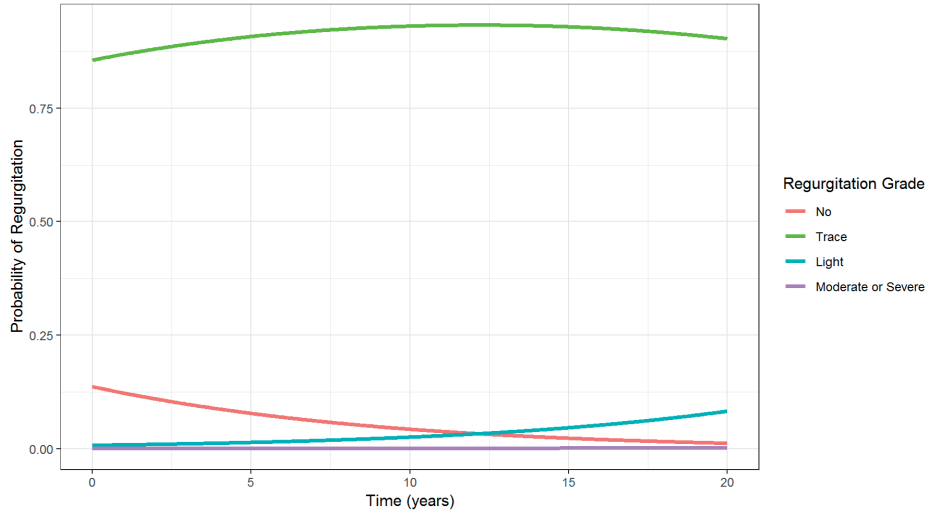


Figure 7 Effectplot of Autograft Regurgitation

Moderate (OR 2.72, 95% CI 0.968-7.641) or severe (OR 2.12, 95% CI 0.56-8.03) preoperative aortic valve regurgitation were not significantly associated with an increased likelihood to developed significant postoperative regurgitation (Supplementary materials, Table 8). Furthermore, the likelihood of developing significant regurgitation was independent from surgical technique (i.e. root inclusion vs. root replacement vs. subcoronary). The predicted prevalence of moderate or severe regurgitation after 20 years was less than 1%.

Figures 8 and 9 depict the predicted evolution of the gradient and regurgitation grade for the RVOT conduit, respectively. The gradient initially increases during the first postoperative decade after which it slopes down and plateaus during the second postoperative decade. Female sex was significantly associated with a lower gradient (p=0.025) (Supplementary materials, Table 7). Female sex (OR 2.63, 95% CI 1.60-4.32) and degenerative valve disease (OR 2.08, 95% CI 1.21-3.56) were associated with an increased likelihood of developing significant regurgitation. In contrast, use of a homograft instead of a bioprosthesis (OR 0.051, 95% 0.01-0.29) and older donor age (OR 0.97, 95% CI 0.95-0.99) were associated with a lower likelihood to develop significant regurgitation (Supplementary materials, Table 9).

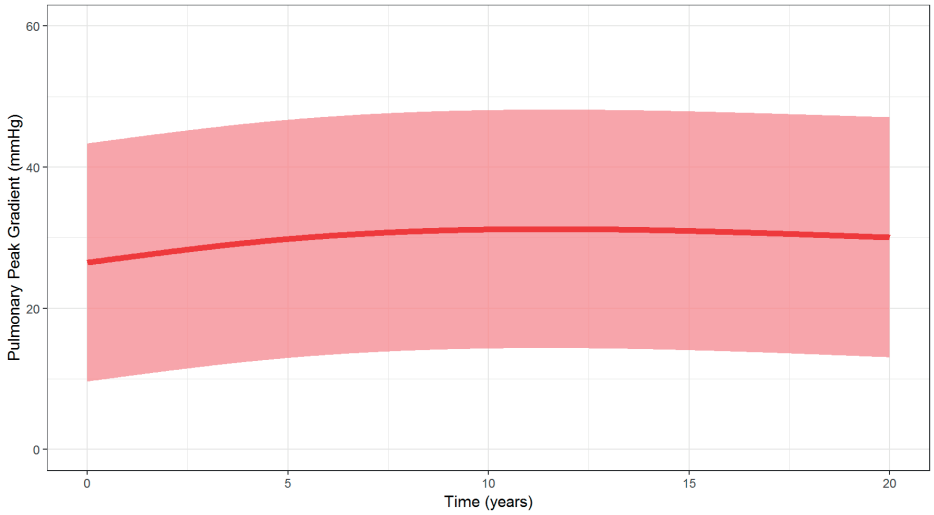


Figure 8 Effectplot of Peak Allograft gradient

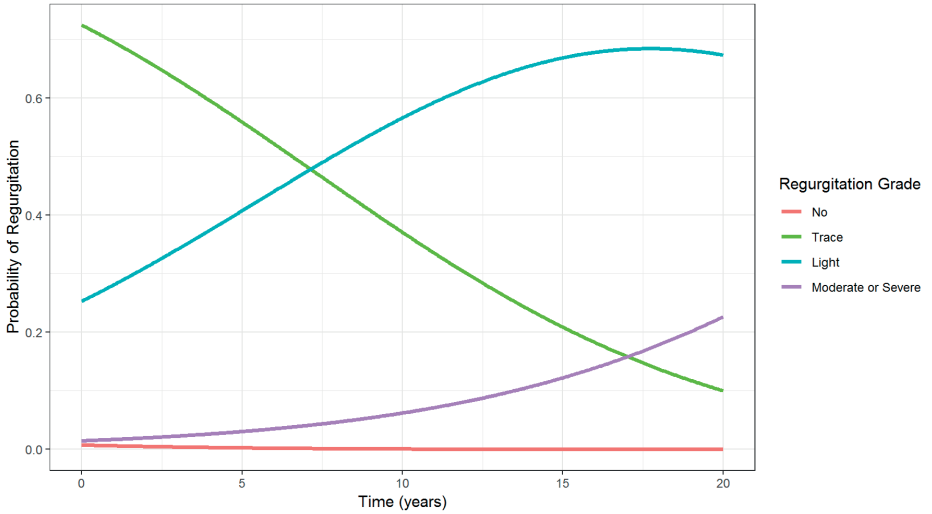


Figure 9 Effectplot of Allograft regurgitation

DISCUSSION

In one of the largest multicenter cohorts to date of consecutive young and middle aged adults undergoing the Ross procedure, long term hemodynamic performance and freedom from reintervention of both the autograft and allograft are excellent. Survival was comparable to what can be expected in an age, sex, birth year and country matched general population. Both the autograft and allograft show a stable and predictable evolution of transvalvular gradient during the first 20 years postoperatively, with low rates of reintervention on both the autograft and homograft.

Current challenges

Aortic valve replacement is a common procedure in adults with approximately 25% of all patients undergoing AVR currently younger than 60 years [29]. With life expectancy expected to rise during the next decennia, the aortic valve alternative that optimizes quality of life during this prolonged period is important. Despite several available alternatives, the optimal one is still elusive. The current study has again shown that the Ross procedure is an undervalued technique with potentially a significant opportunity loss in terms of survival and quality of life in young and middle aged adults up to a follow up of 15 years. The Ross procedure continues to be the only valve alternative in middle aged patients with survival at least comparable with a matched general population. Despite several recent studies unanimously indicating superior long term results of the Ross

procedure compared to conventional AVR [1, 2, 5-10], it represents a microscopic share of all AVR performed [11] and lacks recommendations by the guidelines [15, 16].

Early mortality

One of the main reasons for lagging interest in the procedure has been the complexity of both the initial procedure and reoperation suggesting limited generalizability of the results published by specialized centers [12-14]. An analysis of the Society of Thoracic Surgeons Adult Cardiac Surgery database suggested a threefold increased operative mortality (2.7% vs. 0.9%) compared to conventional mechanical AVR [11]. However, operative risks have a well-known inverse relationship with center volume, and a significant proportion of mortality was accountable to centers performing the procedure only sporadically [30]. Bouhout et al. showed by propensity matched comparison that the Ross procedure yields comparable perioperative outcomes and risks as mechanical AVR [31]. Early mortality in the current study was only 0.7% and ranges between 0.4% and 2.3% in experienced centers which is comparable to many routine surgical procedures [1, 2, 4, 5, 10, 31-35]. Technical complexities can be thus be overcome without increased early mortality given sufficient operative volumes.

Late survival

The Ross procedure is the only aortic valve alternative enabling life-expectancy and quality of life comparable to an age and gender matched population till at least 15 years of follow up [1-3, 36-38]. In our study, survival after 15 years was 88.5% with older age, female sex and significant preoperative comorbidity as risk factors for reduced survival. Still survival was comparable to that of a matched general population. Survival at 15 years in large contemporary series ranges between 88 and 97% [1, 2, 9, 19, 22, 39, 40], with survival being reported up to 97% at 20 years in experienced centers [2, 19]. In contrast, young and middle aged patients who undergo either mechanical AVR or bioprosthetic AVR both show excess mortality compared to an age matched general population [41-43].

Multiple propensity score matched comparisons have unanimously indicated freedom from both death and reintervention in favor of the Ross procedure compared to mechanical AVR [3, 4, 23, 31, 33, 44, 45]. Recently, the group of Skillington presented superior survival after 20 years (94% vs 84%) among 275 Ross patients who were matched with mechanical AVR patients. Again, mechanical AVR was an independent risk factor for mortality [23]. Saharabiani et al. showed that in a matched population of young adults who underwent either a Ross procedure, mechanical AVR or bioprosthetic AVR, the former two had comparable hazards for both death and reintervention which were superior to the bioprosthetic group [3]. Andreas et al. showed that Ross patients enjoyed survival comparable to an age and sex matched Austrian population. In contrast, ob-

served survival of patients who underwent mechanical AVR was significantly less than predicted, with mechanical AVR again being an independent risk factor for late mortality [44]. Mazine et al. showed that cardiac- and valve related mortality was less frequent in Ross patients than in a matched group of patients undergoing mechanical AVR [33]. Survival during the first postoperative decade of patients undergoing mechanical AVR has been equated to Ross patients in a setting of optimal anticoagulation therapy in terms of intensive monitoring and self-management [4]. Therefore, in multiple matched comparisons with both conventional AVR as well as survival of the general population, the Ross procedure has persistently been the best valvular alternative.

Reintervention

Potential failure of both valves in a patient who originally only suffered from single valve disease has been regarded as another major drawback [34]. Freedom from reintervention in our study after 15 years was only 97.2% for the homograft and 92.0% for the autograft. Freedom from reintervention in large contemporary series on the either the pulmonary autograft or homograft after 20 years ranges between 81.8 and 85.0%, and 82.6 and 95.0%, respectively [2, 9, 33, 35]. Transcatheter pulmonary valve implantation may be able to reduce the frequency of surgical reintervention even further [46]. Compared to AVR with bioprostheses or homografts, combined freedom from reintervention on both valves is superior in matched Ross patients [1, 47, 48]. Moreover, reintervention after mechanical AVR is not negligible with freedom from reoperation ranging between 82% and 96% after 10 years due to valve thrombosis, pannus, endocarditis or paravalvular leakage [49-51].

Common mechanisms of failure in Ross patients are nowadays better understood and often relate to dilatation at either the annulus, sinus or sino-tubular junction. Significant preoperative aortic regurgitation was confirmed to be a risk factor for autograft dysfunction. Mortality during reoperation is often associated with the complexity and site of valve dysfunction, with early mortality ranging between 0% and 5.6% at reintervention in large contemporary series [9, 12-14, 45, 52, 53]. Nowadays, it has become more clear which patients are especially at risk to develop aortic root dilatation which may lead to either a priori rejection or additional preventive surgical modifications of which many exists with good preliminary results [19, 54]. However, solid evidence is difficult to construct. Furthermore, if reoperation on the pulmonary autograft is required, restoration and preservation may sometimes be possible, preserving the benefits of the living valve. Therefore, the risks of reintervention after the Ross procedure are acceptable, are certainly manageable and should not be a reason to avoid the procedure all together.

Valve related events

One of the major advantages of the Ross procedure is the avoidance of permanent anticoagulation. Nodurable AVR alternative independent from anticoagulation is available. Especially for young and middle aged patients, there is an unambiguous need for a durable valve alternative without the lifestyle restraints and risks inherent to permanent anticoagulation. A recent meta-analysis in Ross patients showed linearized occurrence rates in adults of thrombo-embolism of 0.17% per patient-year, bleeding of 0.10% per patient-year, RVOT endocarditis of 0.14% per patient-year and autograft endocarditis of 0.18% per patient-year. The authors concluded that the risks of bleeding and thrombo-embolism in Ross patients are comparable to those the general population [17]. Note that the cumulative risks of severe stroke due to the permanent use of anticoagulation (e.g. in mechanical AVR patients) are extensive [42, 43, 49, 50, 55], causing young adults who undergo mechanical AVR to experience excess mortality compared to a gender and age matched general population [3, 23, 44, 50]. Younger age in patients undergoing mechanical AVR is an independent risk factor for mortality [42]. Furthermore, self-monitoring and lowering the therapeutic range of INR have had a limited effect on reducing thromboembolic or bleeding events and the subsequent hazard of death [56, 57]. Full appreciation of the long term prospect of different valve alternatives in young and middle-aged adults must include the undisputedly superiority of the Ross procedure in terms of valve related events.

Guidelines

All major guidelines currently recommend mechanical AVR in younger patient as they are relatively easy to implant, available in a diverse size range and have extensive durability [15, 16]. Although the current AHA/ACC guideline emphasizes the importance of individualized decision making, only mechanical and biological prostheses are recommended to be considered (class IIa, evidence B) [15]. Currently, the Ross procedure is not recommended in middle-aged patients and may only be considered in young patients given contraindications or unwillingness to anticoagulation (Class IIb, evidence level C) [15]. The current STS 2013 guideline does not recommend the Ross procedure (Class III, evidence level C) for middle-aged or older adults with suitable alternatives for AVR [16]. The current and other recent studies support the inclusion of the Ross procedure in new valvular guidelines with the recommendation to consider for middle-aged patients (Class IIa) based on level B evidence if valve repair is unfeasible. Persisting to omit the Ross procedure based on perceived high early mortality and late reintervention risks might lead to an opportunity loss at the direct expense of patient survival and quality of life [58]. Essential for satisfactory outcome are regular practice and careful selection of patients. Both patients and cardiologists should be aware that for patients with long

(>15 years) life-expectancy, feasible anatomy, a pregnancy wish, contra-indications to anti-coagulation or physically active lifestyles, the Ross procedure can a good choice.

STUDY STRENGTHS AND LIMITATIONS

The present study is one of the largest study on prospectively included young and middle aged patients undergoing the Ross procedure in experienced centers. We used advanced mixed effects models of serial echocardiographic measurements to identify risk factors for late graft deterioration and mortality. A limitation to the current results is that different surgeons and techniques were involved making it perhaps difficult for less-experienced surgeons to instantly mimic the results. Differences in surgeons and surgical techniques could not completely be accounted for. Another limitation is the absence of a comparison group. The positive results after the Ross procedure might be partially explained by the careful selection of patients, besides avoidance of anticoagulation and superior valve hemodynamics alone. Future studies should include even longer follow up ideally into the third decade, including matched comparisons with patients undergoing mechanical AVR and the general population. Furthermore, new studies addressing the quality of life given permanent oral anticoagulation are needed to more closely determine its impact on long term quality of life.

CONCLUSION

Given the excellent short and long term outcome in young and middle aged adults, the Ross procedure should be considered in young and middle aged adults who need aortic valve replacement.

REFERENCES

1. El-Hamamsy, I., et al., Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet, 2010. 376(9740): p. 524-31.
2. David, T.E., et al., The Ross procedure: outcomes at 20 years. J Thorac Cardiovasc Surg, 2014. 147(1): p. 85-93.
3. Sharabiani, M.T., et al., Aortic Valve Replacement and the Ross Operation in Children and Young Adults. J Am Coll Cardiol, 2016. 67(24): p. 2858-70.
4. Mokhles, M.M., et al., Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation, 2011. 123(1): p. 31-8.
5. Sievers, H.H., et al., Fourteen years' experience with 501 subcoronary Ross procedures: surgical details and results. J Thorac Cardiovasc Surg, 2010. 140(4): p. 816-22, 822 e1-5.
6. Klieverik, L.M., et al., The Ross operation: a Trojan horse? Eur Heart J, 2007. 28(16): p. 1993-2000.
7. Charitos, E.I., et al., Long-term results of 203 young and middle-aged patients with more than 10 years of follow-up after the original subcoronary Ross operation. Ann Thorac Surg, 2012. 93(2): p. 495-502.
8. Yacoub, M.H., et al., An evaluation of the Ross operation in adults. J Heart Valve Dis, 2006. 15(4): p. 531-9.
9. Martin, E., et al., Clinical Outcomes Following the Ross Procedure in Adults: A 25-Year Longitudinal Study. J Am Coll Cardiol, 2017. 70(15): p. 1890-1899.
10. Mastrobuoni, S., et al., The Ross procedure in young adults: over 20 years of experience in our Institutiondagger. Eur J Cardiothorac Surg, 2016. 49(2): p. 507-13.
11. Reece, T.B., et al., Rethinking the ross procedure in adults. Ann Thorac Surg, 2014. 97(1): p. 175-81.
12. Stulak, J.M., et al., Spectrum and outcome of reoperations after the Ross procedure. Circulation, 2010. 122(12): p. 1153-8.
13. Pettersson, G.B., et al., Reoperations after the ross procedure in adults: towards autograft-sparing/Ross reversal. J Heart Valve Dis, 2011. 20(4): p. 425-32.
14. Luciani, G.B., et al., Reoperations for aortic aneurysm after the Ross procedure. J Heart Valve Dis, 2005. 14(6): p. 766-72; discussion 772-3.
15. Nishimura, R.A., et al., 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2017.
16. Svensson, L.G., et al., Aortic valve and ascending aorta guidelines for management and quality measures. Ann Thorac Surg, 2013. 95(6 Suppl): p. S1-66.
17. Etnel, J.R.G., et al., The Ross Procedure: A Systematic Review, Meta-Analysis, and Microsimulation. Circ Cardiovasc Qual Outcomes, 2018. 11(12): p. e004748.
18. Mazine, A., et al., Ross Procedure in Adults for Cardiologists and Cardiac Surgeons: JACC State-of-the-Art Review. J Am Coll Cardiol, 2018. 72(22): p. 2761-2777.

19. Skillington, P.D., et al., The Ross procedure using autologous support of the pulmonary autograft: techniques and late results. J Thorac Cardiovasc Surg, 2015. 149(2 Suppl): p. S46-52.
20. Sievers, H.H., et al., Valve performance classification in 630 subcoronary Ross patients over 22 years. J Thorac Cardiovasc Surg, 2018. 156(1): p. 79-86 e2.
21. de Kerchove, L., et al., Ross operation in the adult: long-term outcomes after root replacement and inclusion techniques. Ann Thorac Surg, 2009. 87(1): p. 95-102.
22. da Costa, F.D., et al., Long-term results of the Ross operation: an 18-year single institutional experience. Eur J Cardiothorac Surg, 2014. 46(3): p. 415-22; discussion 422.
23. Buratto, E., et al., Improved Survival After the Ross Procedure Compared With Mechanical Aortic Valve Replacement. J Am Coll Cardiol, 2018. 71(12): p. 1337-1344.
24. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg, 2008. 85(4): p. 1490-5.
25. Liddell, F.D., Simple exact analysis of the standardised mortality ratio. J Epidemiol Community Health, 1984. 38(1): p. 85-8.
26. Woolson, R.F., Rank Tests and a One-Sample Logrank Test for Comparing Observed Survival Data to a Standard Population. Biometrics, 1981. 37(4): p. 687-696.
27. Finkelstein, D.M., A. Muzikansky, and D.A. Schoenfeld, Comparing Survival of a Sample to That of a Standard Population. JNCI: Journal of the National Cancer Institute, 2003. 95(19): p. 1434-1439.
28. Perry, G.J., et al., Evaluation of aortic insufficiency by Doppler colour flow mapping. J Am Coll Cardiol, 1987. 9.
29. Brown, J.M., et al., Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg, 2009. 137(1): p. 82-90.
30. Hughes, G.C., et al., Effects of institutional volumes on operative outcomes for aortic root replacement in North America. J Thorac Cardiovasc Surg, 2013. 145(1): p. 166-70.
31. Bouhout, I., et al., Is the Ross procedure a riskier operation? Perioperative outcome comparison with mechanical aortic valve replacement in a propensity-matched cohort. Interact Cardiovasc Thorac Surg, 2017. 24(1): p. 41-47.
32. Takkenberg, J.J., et al., The Ross procedure: a systematic review and meta-analysis. Circulation, 2009. 119(2): p. 222-8.
33. Mazine, A., et al., Long-Term Outcomes of the Ross Procedure Versus Mechanical Aortic Valve Replacement: Propensity-Matched Cohort Study. Circulation, 2016. 134(8): p. 576-85.
34. Mokhles, M.M., et al., Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. Eur Heart J, 2012. 33(17): p. 2213-24.
35. Poh, C.L., et al., The Ross procedure in adults presenting with bicuspid aortic valve and pure aortic regurgitation: 85% freedom from reoperation at 20 years†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy073-ezy073.
36. Zacek, P., et al., Quality of life after aortic valve repair is similar to Ross patients and superior to mechanical valve replacement: a cross-sectional study. BMC Cardiovascular Disorders, 2016. 16: p. 63.

37. Nötzold, A., et al., Quality of life in aortic valve replacement: pulmonary autografts versus mechanical prostheses. Journal of the American College of Cardiology, 2001. 37(7): p. 1963-1966.

38. Aicher, D., et al., Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg, 2011. 142(2): p. e19-24.

39. Mastrobuoni, S., et al., The Ross procedure in young adults: over 20 years of experience in our Institution. Eur J Cardiothorac Surg, 2016. 49(2): p. 507-12; discussion 512-3.

40. Sievers, H.H., et al., A multicentre evaluation of the autograft procedure for young patients undergoing aortic valve replacement: update on the German Ross Registrydagger. Eur J Cardiothorac Surg, 2016. 49(1): p. 212-8.

41. Goldstone, A.B., et al., Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. New England Journal of Medicine, 2017. 377(19): p. 1847-1857.

42. Kvidal, P., et al., Observed and relative survival after aortic valve replacement. J Am Coll Cardiol, 2000. 35(3): p. 747-56.

43. Mihaljevic, T., et al., Survival after valve replacement for aortic stenosis: implications for decision making. J Thorac Cardiovasc Surg, 2008. 135(6): p. 1270-8; discussion 1278-9.

44. Andreas, M., et al., The Ross procedure offers excellent survival compared with mechanical aortic valve replacement in a real-world setting. Eur J Cardiothorac Surg, 2014. 46(3): p. 409-13; discussion 413-4.

45. Karaskov, A., et al., Results of the Ross procedure in adults: a single-centre experience of 741 operations. Eur J Cardiothorac Surg, 2016. 49(5): p. e97-e104.

46. Gillespie, M.J., et al., Transcatheter Pulmonary Valve Replacement for Right Ventricular Outflow Tract Conduit Dysfunction After the Ross Procedure. Ann Thorac Surg, 2015. 100(3): p. 996-1002; discussion 1002-3.

47. David, T.E., S. Armstrong, and M. Maganti, Hancock II Bioprosthesis for Aortic Valve Replacement: The Gold Standard of Bioprosthetic Valves Durability? The Annals of Thoracic Surgery. 90(3): p. 775-781.

48. Smedira, N.G., et al., Are allografts the biologic valve of choice for aortic valve replacement in nonelderly patients? Comparison of explantation for structural valve deterioration of allograft and pericardial prostheses. J Thorac Cardiovasc Surg, 2006. 131(3): p. 558-564 e4.

49. Ikonomidis, J.S., et al., Twenty-year experience with the St Jude Medical mechanical valve prosthesis. The Journal of Thoracic and Cardiovascular Surgery, 2003. 126(6): p. 2022-2031.

50. Bouhout, I., et al., Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. J Thorac Cardiovasc Surg, 2014. 148(4): p. 1341-1346 e1.

51. Kulik, A., et al., Mechanical versus bioprosthetic valve replacement in middle-aged patients. Eur J Cardiothorac Surg, 2006. 30(3): p. 485-91.

52. Kumar, S.R., et al., Outcomes of Reintervention on the Autograft After Ross Procedure. Ann Thorac Surg, 2016. 102(5): p. 1517-1521.

53. Charitos, E.I., et al., Reoperations on the pulmonary autograft and pulmonary homograft after the Ross procedure: An update on the German Dutch Ross Registry. J Thorac Cardiovasc Surg, 2012. 144(4): p. 813-21; discussion 821-3.

54. David, T.E., et al., Dilation of the pulmonary autograft after the ross procedure. The Journal of Thoracic and Cardiovascular Surgery, 2000. 119(2): p. 210-220.

55. Van Nooten, G.J., et al., Twenty years' single-center experience with mechanical heart valves: A critical review of anticoagulation policy. Journal of Heart Valve Disease, 2012. 21(1): p. 88-98.
56. Heneghan, C., et al., Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. The Lancet, 2012. 379(9813): p. 322-334.
57. Matchar, D.B., et al., Effect of Home Testing of International Normalized Ratio on Clinical Events. New England Journal of Medicine, 2010. 363(17): p. 1608-1620.
58. Treasure, T., A. Hasan, and M. Yacoub, Is there a risk in avoiding risk for younger patients with aortic valve disease? Bmj, 2011. 342: p. d2466.

SUPPLEMENTAL MATERIALS

List of participating centers

Department of Cardiac Surgery, Santa Casa de Curitiba, Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

Department of Cardiac and Thoracic Vascular Surgery, University of Lübeck, Lübeck, Germany

Department of Cardiovascular Surgery, CHU Sainte Justine, Montreal, Canada, Montreal, QC, Canada

Department of Cardiothoracic Surgery, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Department of Cardiovascular and Thoracic Surgery, Saint Luc University Clinic, Brussels, Belgium

Department of Cardiovascular and Thoracic Surgery, St Luc's Hospital, Catholic University of Louvain, Brussels, Belgium

List of steps when comparison with the general population

1. Retrieving the lifetables per country from lifetables.de. For a complete list of the sources of the datatables per country, per year, see lifetables.de.
2. Matching based on year of operation, country of operation, sex and age at time of operation.
    a. Correcting for unavailable data: no life table data available for 2013 and 2014 of Germany. Lifetables from 2015 were used for operations performed in those years.
    b. Correcting for unavailable data: no life table data available for 1993, 1995, 1996, 1997 of Brazil. Life tables from 1998 were used for operations performed in those years.
    c. Based on the life-tables, for each of our patients, a match from the general population based on country of birth, operation year and age in that year, and sex was sought. The cumulative rate of mortality for this 'match-individual' for an equal period as the follow up period of the reference patient was calculated.
    d. The overall expected number of mortality was calculated from the cumulative mortality rate of all match-individuals combined as described by Finkelstein (2003). The cumulative mortality rate(i.e. the expected mortality rate) is therefore the sum of all mortality at each year of an equal follow up period as the reference patient, of all match-individuals.
    e. Observed mortality of our patient population was compared to expected mortality of the matched general population using the standardized mortality ratio

which follows a χ^2 distribution as described by Liddell 1984, also known as the one-sample log-rank test.

In depth description of the statistical analysis

Mixed-effects models for the Aortic Peak Gradient and the Pulmonary Peak Gradient

To analyze the repeated measurements of the Aortic Peak Gradient and the Pulmonary Peak Gradient, we used mixed-effects models. This type of models is appropriate for the analysis of repeated measurements over time as the within and between subject correlations are appropriately accounted for. To allow for non-linear subject-specific trajectories over time we used natural cubic splines with 1 knot placed at the median follow-up time, both for the fixed-effects and the random-effects structure of the models. Model assumptions were assessed using visual tools for the inspection of the residuals.

Mixed-effects models for the Aortic and Pulmonary Regurgitation Grades

To analyze the repeated measurements of the Aortic and Pulmonary Regurgitation Grades, we used continuation-ratio mixed-effects models. This type of models is appropriate for the analysis of ordinal outcomes over time. We assumed a linear evolution for the log-odds of regurgitation grade increase/decrease and we used a random-intercepts only model.

Penalized Likelihood Multivariable Cox Regression

For the analysis of the clinical endpoints we used multivariable Cox regression models. A penalized likelihood approach was used to account for the fact that the number of observed events was low relative to the numbers of candidate predictors considered. The ridge penalty was used for the penalization of the likelihood. The penalty parameter was selected using 10-fold cross-validation. The lambda with the lowest cross-validation error was then used. Multiple imputation (100 imputations) was used to account for missing covariate data and the results were subsequently pooled.

Table 1 Risk factor analysis by penalized Cox regression: All-cause mortality

Factor	HR	95% CI	P-value
Age at operation (years)	1.0672	(1.0506; 1.084)	0.000
Sex (female)	1.4233	(1.0081; 2.0096)	0.045
Weight at operation (kg)	1.0141	(0.9866; 1.0423)	0.319
Previous cardiac surgery	1.8626	(0.7385; 4.6979)	0.187
NYHA classification 1	1.3868	(1.0195; 1.8865)	0.038
Tricuspid aortic valve	0.8781	(0.3523; 2.1888)	0.781
Congenital heart disease	0.5097	(0.211; 1.2312)	0.134
Rheumatic heart disease	0.9222	(0.248; 3.4288)	0.904
Prosthetic valve in place	0.1537	(0.019; 1.2415)	0.079
Degenerative valve disease	1.0757	(0.753; 1.5368)	0.689
Active aortic valve endocarditis	0.8212	(0.1675; 4.0251)	0.808
Resolved aortic valve endocarditis	0.2800	(0.0475; 1.65)	0.160
Hypertension	0.9112	(0.7049; 1.1779)	0.477
Coronary artery disease	1.5068	(0.8048; 2.8213)	0.199
Peripheral artery disease	9.4216	(3.9231; 22.6265)	0.000
Congestive vessel disease	0.5678	(0.3166; 1.0182)	0.057
Dyslipidemia	0.9724	(0.5785; 1.6346)	0.917
Chronic obstructive pulmonary disease	5.0632	(2.5951; 9.8785)	0.000
Congenital heart defect	1.9232	(1.1553; 3.2014)	0.012
Peak aortic valve gradient (mmHg)	1.0000	(0.9672; 1.0339)	0.997
Mean aortic valve gradient (mmHg)	0.9802	(0.9297; 1.0335)	0.455
Aortic valve regurgitation - trace	0.6269	(0.1176; 3.3429)	0.585
Aortic valve regurgitation - light	0.7125	(0.2886; 1.7587)	0.463
Aortic valve regurgitation – mild	0.7695	(0.2644; 2.2394)	0.631
Aortic valve regurgitation – severe	0.6949	(0.1512; 3.1927)	0.640
Root implantation technique	0.5605	(0.2067; 0.5605)	0.255
Subcoronary implantation technique	1.1572	(0.7475; 1.7915)	0.512
Allograft (instead of biosprosthesis)	1.3047	(0.5004; 3.4023)	0.586
Age of allograft donor (years)	1.0010	(0.9777; 1.0248)	0.914
Sex of allograft donor (female)	0.8437	(0.5323; 1.3372)	0.468
Allograft diameter (mm)	0.9734	(0.8773; 1.0799)	0.607
Allograft cryopreservation	0.6427	(0.2553; 1.618)	0.347

NYHA = New York Health Association

Table 2 Risk factor analysis by penalized Cox regression: Cardiac mortality

Factor	HR	95% CI	P-value
Age at operation (years)	1.0544	(1.0219; 1.088)	0.001
Sex (female)	2.0037	(1.3355; 3.0063)	0.001
Weight at operation (kg)	1.0202	(0.9926; 1.0486)	0.163
Previous cardiac surgery	2.4968	(1.3127; 4.7487)	0.005
NYHA classification 1	1.3730	(0.6941; 2.7158)	0.362
Tricuspid aortic valve	1.5327	(0.4756; 4.9388)	0.475
Congenital heart disease	0.2985	(0.1105; 0.8063)	0.017
Rheumatic heart disease	0.0222	(0.0052; 0.0947)	0.000
Prosthetic valve in place	0.0110	(0.0011; 0.1113)	0.000
Degenerative valve disease	0.9589	(0.3508; 2.6208)	0.935
Active aortic valve endocarditis	2.3584	(0.5063; 10.9858)	0.274
Resolved aortic valve endocarditis	0.7430	(0.1006; 5.486)	0.771
Hypertension	0.5667	(0.3912; 0.8207)	0.003
Coronary artery disease	2.1990	(1.3551; 3.5684)	0.001
Peripheral artery disease	0.1304	(0.0255; 0.6674)	0.014
Congestive vessel disease	0.3296	(0.1816; 0.598)	0.000
Dyslipidemia	1.2611	(0.624; 2.5488)	0.518
Chronic obstructive pulmonary disease	8.1499	(1.6145; 41.1391)	0.011
Congenital heart defect	10.0644	(5.1383; 19.713)	0.000
Peak aortic valve gradient (mmHg)	1.0171	(0.9553; 1.083)	0.604
Mean aortic valve gradient (mmHg)	0.9512	(0.8557; 1.0574)	0.360
Aortic valve regurgitation - trace	1.7559	(0.2416; 12.7626)	0.578
Aortic valve regurgitation - light	0.7874	(0.1181; 5.2503)	0.805
Aortic valve regurgitation – mild	0.6949	(0.08; 6.0368)	0.741
Aortic valve regurgitation – severe	1.6603	(0.1269; 21.7262)	0.699
Root implantation technique	0.4877	(0.2205; 1.0787)	0.076
Subcoronary implantation technique	0.9763	(0.4253; 2.2413)	0.955
Allograft (instead of biosprosthesis)	11.2571	(2.2966; 55.1778)	0.003
Age of allograft donor (years)	1.0346	(0.9717; 1.1016)	0.286
Sex of allograft donor (female)	0.9484	(0.4539; 1.9817)	0.888
Allograft diameter (mm)	0.9012	(0.7496; 1.0835)	0.268
Allograft cryopreservation	5.3441	(0.5545; 51.5092)	0.147

NYHA = New York Health Association

Table 3 Risk factor analysis by penalized Cox regression: Freedom from any reintervention

Factor	HR	95% CI	P-value
Age at operation (years)	1.0111	(0.9895; 1.0331)	0.332
Sex (female)	0.6194	(0.4839; 0.7929)	0.000
Weight at operation (kg)	0.996	(0.9863; 1.0058)	0.370
Previous cardiac surgery	1.0865	(0.4752; 2.4846)	0.845
NYHA classification 1	1.0243	(0.777; 1.3503)	0.864
Tricuspid aortic valve	0.9277	(0.5143; 1.6736)	0.804
Congenital heart disease	0.6206	(0.3041; 1.2667)	0.189
Rheumatic heart disease	0.0618	(0.0021; 1.7884)	0.105
Prosthetic valve in place	0.0213	(0.0012; 0.3762)	0.009
Degenerative valve disease	1.006	(0.3484; 2.9048)	0.991
Active aortic valve endocarditis	0.4907	(0.0531; 4.5296)	0.530
Resolved aortic valve endocarditis	0.2085	(0.0229; 1.8945)	0.164
Hypertension	1.0953	(0.5647; 2.1244)	0.787
Coronary artery disease	1.2068	(0.8514; 1.7107)	0.293
Peripheral artery disease	0.0274	(0.0045; 0.1662)	0.000
Congestive vessel disease	1.2879	(0.8173; 2.0294)	0.276
Dyslipidemia	0.7276	(0.3811; 1.3893)	0.335
Chronic obstructive pulmonary disease	0.0325	(0.0059; 0.1807)	0.000
Congenital heart defect	3.6074	(2.3669; 5.4981)	0.000
Peak aortic valve gradient (mmHg)	1.0030	(0.9607; 1.0472)	0.876
Mean aortic valve gradient (mmHg)	0.9851	(0.9162; 1.0592)	0.678
Aortic valve regurgitation - trace	1.1354	(0.6623; 1.9464)	0.645
Aortic valve regurgitation - light	1.1924	(0.5797; 2.4529)	0.631
Aortic valve regurgitation – mild	1.7647	(0.9188; 3.3895)	0.088
Aortic valve regurgitation – severe	3.0771	(1.2589; 7.5215)	0.014
Root implantation technique	0.9666	(0.5142; 1.8169)	0.915
Subcoronary implantation technique	0.8114	(0.4632; 1.4213)	0.464
Allograft (instead of biosprosthesis)	1.3951	(0.7841; 2.4824)	0.258
Age of allograft donor (years)	0.994	(0.9709; 1.0177)	0.596
Sex of allograft donor (female)	0.7196	(0.392; 1.3213)	0.289
Allograft diameter (mm)	0.903	(0.7423; 1.0986)	0.306
Allograft cryopreservation	1.4248	(0.648; 3.1328)	0.379

NYHA = New York Health Association

Table 4 Risk factor analysis by penalized Cox regression: Freedom from autograft reintervention

Factor	HR	95% CI	P-value
Age at operation (years)	1.0131	(0.9895; 1.0372)	0.250
Sex (female)	0.6623	(0.4458; 0.984)	0.042
Weight at operation (kg)	0.9980	(0.9844; 1.0118)	0.811
Previous cardiac surgery	1.2129	(0.507; 2.9014)	0.665
NYHA classification 1	0.6690	(0.5124; 0.8733)	0.003
Tricuspid aortic valve	1.2461	(0.6214; 2.4988)	0.536
Congenital heart disease	0.4868	(0.2201; 1.0766)	0.075
Rheumatic heart disease	0.0579	(0.0022; 1.5046)	0.086
Prosthetic valve in place	0.0201	(9e-04; 0.44)	0.013
Degenerative valve disease	1.0953	(0.2981; 4.0247)	0.891
Active aortic valve endocarditis	0.6730	(0.0906; 4.9982)	0.699
Resolved aortic valve endocarditis	0.1588	(0.0222; 1.1341)	0.067
Hypertension	1.0920	(0.5185; 2.2997)	0.817
Coronary artery disease	1.2738	(0.743; 2.1837)	0.379
Peripheral artery disease	0.0288	(0.003; 0.2739)	0.002
Congestive vessel disease	1.1152	(0.6621; 1.8783)	0.684
Dyslipidemia	0.4356	(0.2892; 0.6562)	0.000
Chronic obstructive pulmonary disease	0.0466	(0.0062; 0.3489)	0.003
Congenital heart defect	5.1914	(2.9348; 9.1831)	0.000
Peak aortic valve gradient (mmHg)	1.0070	(0.9608; 1.0555)	0.780
Mean aortic valve gradient (mmHg)	0.9685	(0.8972; 1.0454)	0.407
Aortic valve regurgitation - trace	1.1196	(0.575; 2.1802)	0.739
Aortic valve regurgitation - light	1.3418	(0.5996; 3.0028)	0.475
Aortic valve regurgitation – mild	1.4434	(0.5859; 3.5559)	0.425
Aortic valve regurgitation – severe	3.0649	(1.0187; 9.2213)	0.046
Root implantation technique	0.659	(0.3618; 1.2005)	0.174
Subcoronary implantation technique	0.4352	(0.246; 0.7698)	0.004
Allograft (instead of biosprosthesis)	1.2573	(0.6508; 2.4292)	0.495
Age of allograft donor (years)	1.0020	(0.973; 1.0319)	0.906
Sex of allograft donor (female)	0.7906	(0.3769; 1.6584)	0.534
Allograft diameter (mm)	0.8985	(0.7727; 1.0449)	0.169
Allograft cryopreservation	1.3951	(0.6573; 2.9613)	0.387

NYHA = New York Health Association

Table 5 Risk factor analysis by penalized Cox regression: Freedom from allograft reintervention

Factor	HR	95% CI	P-value
Age at operation (years)	0.9851	(0.9698; 1.0007)	0.052
Sex (female)	0.4300	(0.1936; 0.9548)	0.038
Weight at operation (kg)	0.9940	(0.9671; 1.0217)	0.677
Previous cardiac surgery	1.0618	(0.5337; 2.1127)	0.865
NYHA classification 1	2.0751	(1.6563; 2.5997)	0.000
Tricuspid aortic valve	0.5706	(0.1362; 2.3911)	0.443
Congenital heart disease	0.8702	(0.2502; 3.027)	0.828
Rheumatic heart disease	0.0398	(0.011; 0.144)	0.000
Prosthetic valve in place	0.1175	(0.0296; 0.4671)	0.002
Degenerative valve disease	0.6791	(0.4857; 0.9495)	0.023
Active aortic valve endocarditis	0.6460	(0.3085; 1.3525)	0.246
Resolved aortic valve endocarditis	0.8228	(0.3992; 1.6959)	0.597
Hypertension	1.4348	(0.9563; 2.1527)	0.082
Coronary artery disease	0.9048	(0.6019; 1.3603)	0.632
Peripheral artery disease	0.0831	(0.0112; 0.6182)	0.015
Congestive vessel disease	1.2105	(0.3808; 3.8474)	0.746
Dyslipidemia	1.4859	(0.9411; 2.3459)	0.089
Chronic obstructive pulmonary disease	0.0737	(0.0103; 0.5293)	0.010
Congenital heart defect	1.3485	(0.3787; 4.8022)	0.645
Peak aortic valve gradient (mmHg)	0.9960	(0.969; 1.0237)	0.772
Mean aortic valve gradient (mmHg)	1.0070	(0.9626; 1.0535)	0.767
Aortic valve regurgitation - trace	1.4219	(0.807; 2.5054)	0.223
Aortic valve regurgitation - light	0.6942	(0.3614; 1.3333)	0.274
Aortic valve regurgitation – mild	1.1457	(0.5815; 2.2573)	0.694
Aortic valve regurgitation – severe	1.3034	(0.2776; 6.1193)	0.737
Root implantation technique	1.4492	(0.3339; 6.2905)	0.620
Subcoronary implantation technique	4.1704	(1.7297; 10.0547)	0.001
Allograft (instead of biosprosthesis)	18.1378	(4.0734; 80.7631)	0.000
Age of allograft donor (years)	0.9685	(0.9441; 0.9935)	0.011
Sex of allograft donor (female)	0.5036	(0.2237; 1.1336)	0.097
Allograft diameter (mm)	0.7734	(0.6624; 0.9029)	0.001
Allograft cryopreservation	1.5465	(0.1877; 12.7427)	0.685

NYHA = New York Health Association

Table 6 Model Coefficients for peak autograft gradient

	Peak aortic gradient		
Factor	**Coefficient**	**95% CI**	**P-value**
Age at operation (years)	-0.032	(-0.065; 0)	0.0489
Sex (female)	0.767	(0.056; 1.477)	0.0344
Weight at operation (kg)	0.021	(0; 0.042)	0.0525
Previous cardiac surgery	0.432	(-0.934; 1.798)	0.5347
NYHA classification 1	-0.348	(-1.08; 0.383)	0.3498
Tricuspid aortic valve	2.217	(0.524; 3.91)	0.0103
Congenital heart disease	0.441	(-1.093; 1.975)	0.5726
Rheumatic heart disease	-0.491	(-3.646; 2.663)	0.7599
Prosthetic valve in place	-0.829	(-4.189; 2.53)	0.628
Degenerative valve disease	-0.060	(-0.84; 0.719)	0.8793
Active aortic valve endocarditis	1.627	(-6.746; 10)	0.7028
Resolved aortic valve endocarditis	2.478	(-5.566; 10.522)	0.5454
Hypertension	0.707	(0.056; 1.359)	0.0334
Coronary artery disease	-1.11	(-2.432; 0.212)	0.0997
Peripheral artery disease	1.893	(-2.957; 6.743)	0.4437
Congestive vessel disease	0.413	(-1.004; 1.829)	0.5674
Dyslipidemia	0.148	(-0.568; 0.865)	0.6842
Chronic obstructive pulmonary disease	-0.067	(-1.965; 1.831)	0.9445
Congestive Heart disease	3.023	(-0.574; 6.619)	0.0993
Peak aortic valve gradient (mmHg)	0.077	(0.029; 0.124)	0.0017
Mean aortic valve gradient (mmHg)	-0.107	(-0.183; -0.03)	0.0063
Aortic valve regurgitation - trace	-0.134	(-1.277; 1.008)	0.8173
Aortic valve regurgitation - light	-0.439	(-1.637; 0.759)	0.472
Aortic valve regurgitation – mild	-0.64	(-1.896; 0.617)	0.3178
Aortic valve regurgitation – severe	0.054	(-1.803; 1.91)	0.9546
Timing (elective)	-1.226	(-4.162; 1.71)	0.4123
Root replacement technique	1.272	(-2.226; 4.77)	0.4754
Subcoronary technique	1.610	(-0.88; 4.1)	0.2045
Allograft (instead of biosprosthesis)	-3.585	(-6.051; -1.118)	0.0045

NYHA = New York Health Association

Table 7 Model Coefficients for peak allograft gradient

	Peak pulmonary gradient		
Factor	**Coefficient**	**95% CI**	**P-value**
Age at operation (years)	-1.949	(-3.647; -0.251)	0.0245
Sex (female)	0.074	(0.024; 0.125)	0.0039
Weight at operation (kg)	-0.125	(-3.184; 2.934)	0.9361
Previous cardiac surgery	-1.14	(-2.773; 0.493)	0.1708
NYHA classification 1	-1.991	(-5.608; 1.627)	0.2802
Tricuspid aortic valve	-4.266	(-7.882; -0.65)	0.0208
Congenital heart disease	4.604	(0.228; 8.98)	0.0392
Rheumatic heart disease	1.944	(-5.784; 9.671)	0.6215
Prosthetic valve in place	-0.609	(-2.352; 1.135)	0.493
Degenerative valve disease	-1.195	(-17.905; 15.516)	0.8884
Active aortic valve endocarditis	2.892	(-13.962; 19.746)	0.7362
Resolved aortic valve endocarditis	21.64	(10.351; 32.93)	<.0001
Hypertension	-0.529	(-3.407; 2.349)	0.7182
Coronary artery disease	-1.147	(-10.314; 8.02)	0.8059
Peripheral artery disease	3.883	(0.792; 6.975)	0.0139
Congestive vessel disease	1.051	(-0.656; 2.758)	0.2271
Dyslipidemia	-1.875	(-5.916; 2.166)	0.3625
Chronic obstructive pulmonary disease	10.95	(6.603; 15.304)	<.0001
Congestive Heart disease	-0.012	(-0.106; 0.082)	0.8012
Peak aortic valve gradient (mmHg)	0.065	(-0.084; 0.215)	0.3908
Mean aortic valve gradient (mmHg)	-1.022	(-3.361; 1.317)	0.391
Aortic valve regurgitation - trace	-0.123	(-2.614; 2.367)	0.9227
Aortic valve regurgitation - light	-0.659	(-3.335; 2.018)	0.6289
Aortic valve regurgitation – mild	1.795	(-1.735; 5.325)	0.3183
Aortic valve regurgitation – severe	-1.141	(-6.208; 3.927)	0.6586
Timing (elective)	-1.448	(-5.07; 2.174)	0.4326
Root replacement technique	1.604	(-3.84; 7.048)	0.5629
Subcoronary technique	-5.114	(-12.914; 2.685)	0.1983
Allograft (instead of biosprosthesis)	-2.047	(-19.374; 15.28)	0.8166

NYHA = New York Health Association

Table 8 Odds Ratios, 95% CI's and Univariate Wald tests of covariates with autograft regurgitation

	Autograft Regurgitation		
Factor	**Odds ratio**	**95% CI**	**P-value**
Time (years)	1.132	(1.106; 1.159)	<.0001
Age at operation (years)	1.026	(0.998; 1.054)	0.0641
Sex (female)	0.808	(0.452; 1.444)	0.4719
Weight at operation (kg)	0.983	(0.966; 1.001)	0.0654
Previous cardiac surgery	0.620	(0.217; 1.777)	0.3740
NYHA classification 1	0.465	(0.259; 0.834)	0.0102
Tricuspid aortic valve	0.634	(0.179; 2.246)	0.4797
No bicuspid or tricuspid aortic valve	0.748	(0.201; 2.785)	0.6656
Congenital heart disease	0.582	(0.185; 1.834)	0.3556
Degenerative valve disease	1.957	(1.043; 3.67)	0.0364
Endocarditis	0.374	(0.162; 0.863)	0.0212
Hypertension	0.878	(0.516; 1.494)	0.6310
Mean aortic valve gradient (mmHg)	0.998	(0.984; 1.013)	0.7855
Aortic valve regurgitation - trace	1.503	(0.604; 3.739)	0.3804
Aortic valve regurgitation - light	2.262	(0.873; 5.857)	0.0928
Aortic valve regurgitation – mild	2.720	(0.968; 7.641)	0.0577
Aortic valve regurgitation – severe	2.121	(0.56; 8.031)	0.2684
Dyslipidemia	0.687	(0.377; 1.252)	0.2200
Timing (elective)	1.352	(0.22; 8.298)	0.7448
Root replacement technique	1.118	(0.275; 4.554)	0.8760
Subcoronary technique	0.207	(0.029; 1.462)	0.1143
Allograft (instead of bioprosthesis)	0.120	(0.016; 0.896)	0.0387
Age of allograft donor (years)	1.002	(0.981; 1.024)	0.8507

NYHA = New York Health Association

Table 9 Odds Ratios, 95% CI's and Univariate Wald tests of covariates with allograft regurgitation

	Allograft Regurgitation		
Factor	**Odds ratio**	**95% CI**	**P-value**
Time (years)	1.160	(1.134; 1.187)	<.0001
Age at operation (years)	0.992	(0.97; 1.015)	0.5113
Sex (female)	2.633	(1.604; 4.323)	0.0001
Weight (kg)	1.008	(0.993; 1.024)	0.2837
Previous cardiac surgery	1.521	(0.616; 3.759)	0.3634
NYHA classification 1	0.783	(0.477; 1.283)	0.3317
Tricuspid aortic valve	0.915	(0.31; 2.696)	0.8715
No bicuspid or tricuspid aortic valve	1.114	(0.367; 3.381)	0.8482
Congenital heart disease	1.038	(0.388; 2.774)	0.9409
Degenerative valve disease	2.079	(1.213; 3.563)	0.0078
Endocarditis	0.962	(0.479; 1.935)	0.9143
Hypertension	0.763	(0.486; 1.198)	0.2395
Mean aortic valve gradient (mmHg)	0.991	(0.979; 1.003)	0.1338
Aortic valve regurgitation - trace	0.923	(0.421; 2.027)	0.8424
Aortic valve regurgitation - light	1.229	(0.541; 2.794)	0.6219
Aortic valve regurgitation – mild	0.827	(0.34; 2.014)	0.6759
Aortic valve regurgitation – severe	1.123	(0.358; 3.517)	0.8425
Dyslipidemia	1.846	(1.11; 3.069)	0.0182
Timing (elective)	0.653	(0.132; 3.224)	0.6007
Root replacement technique	1.725	(0.46; 6.47)	0.4190
Subcoronary technique	1.284	(0.233; 7.072)	0.7737
Allograft (instead of bioprosthesis)	0.051	(0.009; 0.289)	0.0008
Age of allograft donor (years)	0.967	(0.949; 0.985)	0.0003

NYHA = New York Health Association

12

Dutch Experience with Percutaneous Pulmonary Valve Implantation: Long-Term Outcome and Serial Echocardiographic Assessment

Jamie LR Romeo, Annemien van den Bosch, Kendis Euson, Anthonie L Duijnhouwer, Roland van Kimmenade, Tim ten Cate, Arie PJ van Dijk, Ad JJC Bogers, M Mostafa Mokhles, Maarten Witsenburg

Open Heart

ABSTRACT

Background

Percutaneous pulmonary valve implantation (PPVI) is a promising therapy for patients with dysfunctional conduits in their right ventricular outflow tract. Long term outcomes are still unknown however. This study aims to investigate the long -term clinical and hemodynamic outcomes.

Methods

A multicenter retrospective observational study was performed including all consecutive patients between May 2004 and April 2018. Serial electrocardiographic and echocardiographic measurements were analyzed using mixed effects models.

Results

Eighty consecutive patients underwent catheterization with the intent of PPVI at a mean age of 28±10 years (range 12-54 years). Hemodynamic indications were severe stenosis in 51 (63.8%), severe regurgitation in 9 (11.3%) and mixed stenosis and regurgitation in 20 (25.0%). The most common diagnosis was Tetralogy of Fallot (n=24; 32%). In 76 (95%), PPVI was successful. Four procedures were discontinued due to conduit rupture resulting in conversion (n=1), hemathorax (n=1), right coronary compression (n=1) and a too wide RVOT after pre-stenting (n=1). The mean peak transvalvular gradient assessed by catheter decreased from 44±24 to 12±9 mmHg (p<.001) after PPVI and all patients were discharged without moderate or severe regurgitation. During a median follow up of 4.1 years (total patient-years reporting 336 years), 2 patients died due to end stage heart failure. Fourteen cases of endocarditis occurred in 13 (17.1%) patients (linearized occurrence rate (LOR) 4.2%/year), from which 3 patients died. Four patients needed pacemaker/ICD implants (LOR 1.2%/year), not related to PPVI. Eleven patients underwent 12 reinterventions (7 surgical-PVR, 4 redo PPVI, 1 balloon dilatation) after 4.9±4.2 years of which 6 were indicated by severe obstruction and 6 by endocarditis. Freedom from valve replacement at 5 years was 88±5%. At 5 years, the mean peak gradient assessed by echocardiography increased to 39±7 mmHg. Fractional area change, TAPSE and QRS duration remained stable during the first 5 years post implantation.

Conclusion

PPVI provides an excellent relieve of obstruction and regurgitation of conduits in RVOT position. However, the durability is limited by the occurrence of infective endocarditis and restenosis.

INTRODUCTION

The prevalence of adults with congenital heart disease (CHD) is expected to grow extensively, due to increasing birthrate, life expectancy and survival of pediatric patients [1, 2]. Approximately 20% of all CHD involves the pulmonary valve [3]. Reconstruction of the right ventricular outflow tract (RVOT) is therefore often necessary [4]. Valve conduit alternatives are, however, limited and structural valve deterioration necessitating repeat intervention is common among all alternatives [4-7]. This has led to pulmonary valve replacement (PVR) becoming the most frequently performed surgery in adult patients with CHD [8].

Percutaneous pulmonary valve implantation has been widely accepted since its introduction in 2000 [9]. It is estimated that over 13.000 patients since then have been successfully treated, with an overall procedural success rate of 96.2% and acceptable mid-term results by extending conduit function and delaying surgical reintervention [10]. Favorable mid-term valve performance and durability have been associated with improved exercise tolerance, quality of life and cardiac remodeling [10-12]. Currently, the increased risk of endocarditis is still a major concern, estimated to have an annualized occurrence rate of 1.4% per year [10].

We present the long-term Dutch multi-center experience with PPVI, including extensive serial analyses of echocardiographic valve and ventricular function.

MATERIAL AND METHODS

Patients

All consecutive patients from the Erasmus University Medical Center and the Radboud University Medical Center who underwent heart catheterization and angiography with the intention to implant a percutaneous valve between May 2004 and April 2018 were retrospectively studied. All procedures were performed at tertiary referral university medical centers in the Netherlands and discussed in weekly multidisciplinary meetings between congenital cardiologists, interventional cardiologists, congenital cardiac surgeons and radiologists. Patients with severe pulmonary stenosis (PS) (peakgradient > 64 mmhg) and/or severe pulmonary regurgitation (PR) were considered for PPVI. Patients without contraindications underwent prior transthoracic echocardiography, cardiopulmonary exercise stress-testing, cardiac MRI and CT angiography to assess cardiac function and dimensions and determine the spatial relationship with coronary arteries. Two patients were identified who were rejected for PPVI based on coronary anatomy assessed by CT. The institutional review board approved this study prior to onset and waived individual informed consent (MEC 2017-1076).

Intervention

All procedures were performed under general anesthesia with antibiotic prophylaxis by experienced interventional cardiologists in congenital cardiology. Right heart access was generally accomplished through the femoral or jugular veins. Arterial entry for angiography was preferably femoral. In case of severe stenosis predilatation with a high pressure Mullins-X balloon (BV Medical, Leicestershire, United Kingdom) or Z-med (B. Braun Interventional Systems Inc., Pennsylvania, USA) was performed. Inflation of the Mullins or Z-med balloon while simultaneously performing coronary angiography was performed to dismiss any doubt about coronary compression. Valve implantation usually directly followed pre-stenting which was performed in all but three early cases with covered Cheatham Platinum stents (Numed, New York, United States) on a balloon in balloon. In subsequent cases of severely stenotic homografts which had a limited diameter (n=1) pre-stenting was not performed. Additional covered or bare metal stents were placed occasionally in case of recoil. Melody Valves® (Medtronic, Minneapolis, United States) (N=73; 91.3%) were deployed using the Ensemble Delivery system (Medtronic, Minneapolis, United States) using direct fluoroscopic guidance. In case of large diameter landingzones, a SAPIEN XT Pulmonic® (Edwards Lifesciences, California, United States) (N=7; 8.7%) was deployed using a similar procedure. If significant residual gradients across the RVOT persisted, post-dilatation was performed using a high-pressure Mullins Balloon. Pre- and post-pressure measurements by catheterization were obtained to assess the hemodynamic effect of valve implantation and confirm competency.

Follow up

Successful valve implantation was defined as PPVI with a gradient <30 mmHg by Doppler echocardiography, without significant (moderate-severe) regurgitation and need for surgical intervention before discharge. Valve function was assessed during the procedure by catheterization and by TTE before discharge. Regular visits to the outpatient's clinic were scheduled after 1, 6 and 12 months, and annually thereafter.

Two-dimensional transthoracic continuous and color wave Doppler echocardiography was performed during outpatient's visits. Transvalvular peak gradient and regurgitation grade were assessed from a multi-window perspective and calculated with the modified Bernoulli equation. Right ventricular (RV) systolic pressure was based on the systolic tricuspid regurgitation jet velocity. QRS duration was retrieved from computerized measurements of standardized 12-lead (25 mm/s, 10 mm/mV) surface ECG's. Late events were classified according to the guidelines for reporting valve related morbidity and mortality, and included death, stroke/TIA, endocarditis, myocardial infarction and reintervention [13]. Endocarditis was defined according to the modified Dukes criteria [14].

Figure 1 Flowchart of patients

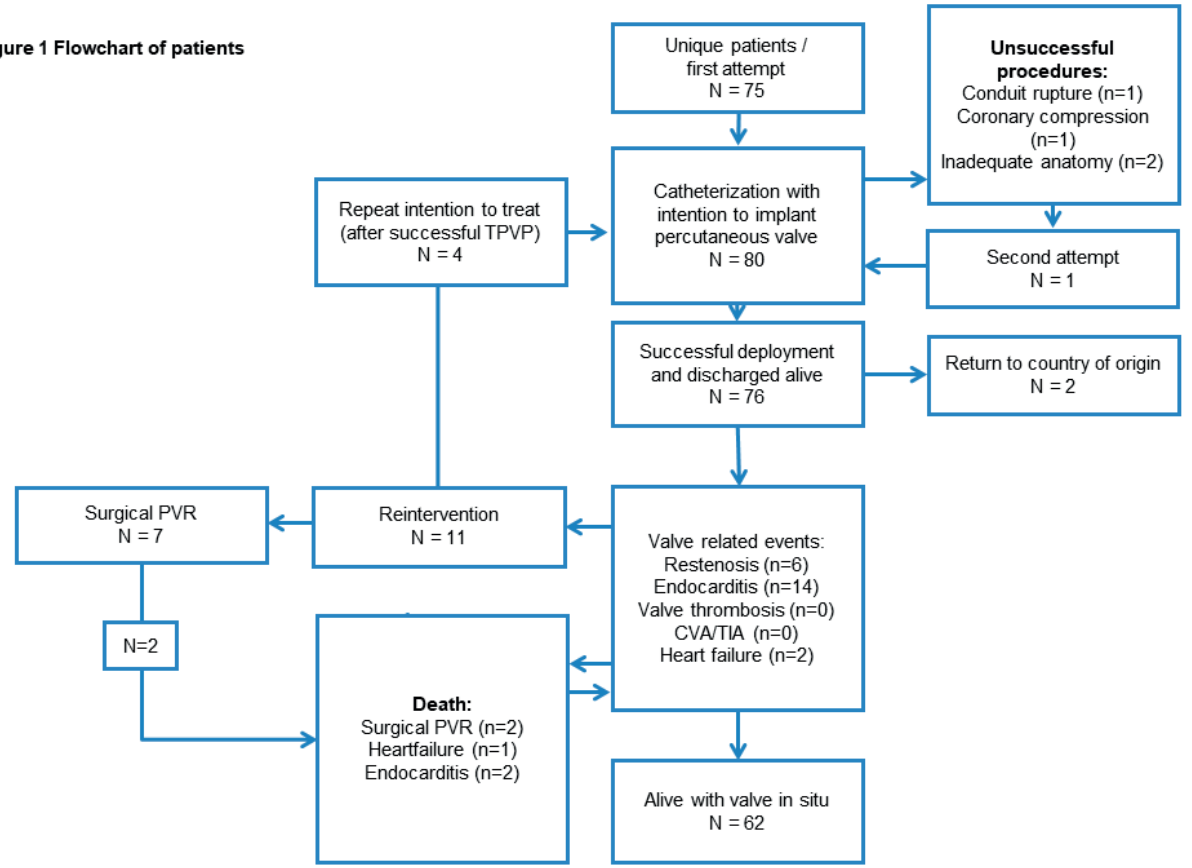


Figure 1 Patient flowchart

Statistical Analysis

Continuous variables are presented as means with standard deviations (SD) or medians with absolute range, as appropriate. Normality was assessed using the Kolmogorov-Smirnov test, after which comparisons were made with paired t-tests. The Kaplan-Meier method was used to depict freedom from valve related events after TPV. Serial echocardiographic measurements and QRS duration were assessed with mixed effects models, as recommended by the guidelines on reporting morbidity and mortality after valvular interventions [15]. Mixed effects models facilitate the optimal use of measurements by including random effects to account for any imbalance in timing and number of the observations within patients. Missing echocardiographic and electrocardiographic values were assumed to be missing at random. A p-value of 0.05 was considered significant throughout the analyses. Statistical analyses were performed with SPSS 24.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) and R (R Core Team, 2013).

RESULTS

Baseline characteristics

Between May 2004 and January 2018, 80 consecutive catheterizations were performed with the intention to implant a percutaneous valve. Patient characteristics are shown in Table 1. Fifty-four (67.5%) patients were male and mean age was 28±10 years (range 12-54). The most common hemodynamic indication was isolated stenosis (n=51; 63.8%) with Tetralogy of Fallot being the most common original diagnosis (n=26; 32.5%). Most patients (n=71; 89%) were in NYHA classification I or II prior to procedure with good systolic right (n=29; 36.3%) and left ventricular function (n=44; 55.0%). After a mean duration of 4.6±2.9 years (range 0.2-12.2 years) follow-up was 97.4% complete. Two patients were lost to follow up due to direct return to their country of origin after the procedure.

Procedural characteristics and outcomes

Seventy-three (91.3%) Melody valves and 7 (8.7%) Edwards Sapien valve were implanted. The preferred route for valve delivery was femoral. In four cases a jugular approach was used due to inaccessibility of the femoral vein (5%).

Table 1. Baseline patient characteristics

RVOT hemodynamics	Overall N (%) or Mean±SD	Isolated Stenosis N (%) or Mean±SD	Isolated Regurgitation N (%) or Mean±SD	Mixed hemodynamics N (%) or Mean±SD
Procedures (n)	80	51 (63.8)	9 (11.3)	20 (25.0)
Sex (male)	54 (67.5)	37 (72.5)	5 (55.6)	12 (60.0)
Age initial correction (years)	6.7±8.5	8.2±9.6	1.2±1.0	5.2±6.1
Prior open heart surgeries (yes)	2 (1-5)	2 (1-5)	2 (2-5)	2 (1-4)
Diagnosis				
Tetralogy of Fallot	26 (32.5)	13 (25.5)	4 (44.4)	9 (45.0)
Pulmonary Atresia + VSD	14 (17.5)	7 (13.7)	4 (44.4)	3 (15.0)
TGA after Rastelli	8 (10.0)	5 (9.8)	0 (0)	3 (15.0)
Aortic Valve Disease (Ross)	24 (30.0)	18 (35.3)	1 (11.1)	5 (25.0)
Truncus Arteriosus Communis	3 (3.8)	3 (5.9)	0 (0)	0 (0)
DORV after Rastelli	5 (6.3)	5 (9.8)	0 (0)	0 (0)
Time since initial correction (years)	21.4±8.4	21.0±8.6	24.0±8.7	21.4±8.0
Age at catheterization (years)	28.0±10.4	28.9±10.6	26.2±8.6	26.7±9.8
Range	(11.6-53.7)	(13.0-53.7)	(12.1-42.2)	(11.6-46.4)
RVOT Landingzone				
Homograft	71 (88.8)	44 (86.3)	8 (88.9)	18 (95.0)
Native valve	1 (1.3)	1 (2.0)	0 (0)	0 (0)
Previous Melody	4 (8.0)	4 (7.8)	0 (0)	0 (0)
Bioprosthesis	3 (3.8)	2 (3.9)	0 (0)	1 (5)
Transannular patch	1 (1.3)	0 (0)	1 (11.1)	0 (0)
RVOT gradient (mmHg)	62.7±26.5	69.7±21.7	18.9±8.2	64.5±24.8
QRS duration (ms)	137±36	132±35	166±25	140±37
Rhythm				
Right Bundle Branch Block (n)	47 (58.8)	25 (49.0)	7 (77.8)	15 (75.0)
Left Bundle Branch Block (n)	1 (1.3)	0 (0)	0 (0)	1 (5)
AV block (n)	5 (6.3)	2 (3.9)	1 (11.1)	2 (10.0)
Paced rhythm (n)	4 (5.0)	4 (7.8)	0 (0)	0 (0)
NYHA class				
I	28 (35.0)	20 (39.2)	2 (22.2)	6 (30.0)
II	43 (53.8)	24 (47.1)	7 (77.8)	12 (60.0)
III	7 (8.8)	5 (9.8)	0 (0)	2 (10.0)
IV	2 (2.5)	2 (3.9)	0 (0)	0 (0)
Echocardiographic RV systolic function				
Normal (EF>55%)	29 (36.3)	21 (41.2)	1 (11.1)	7 (35.0)
Mild (EF 45-54%)	25 (31.3)	13 (25.5)	4 (44.4)	8 (40.0)
Moderate (EF 30-44%)	22 (27.5)	15 (29.4)	3 (33.3)	4 (20.0)
Severe (EF<30%)	4 (5.0)	2 (3.9)	1 (11.1)	1 (5.0)
Echocardiographic LV systolic function				
Normal (EF>55%)	44 (55.0)	30 (58.8)	4 (44.4)	10 (50.0)
Mild (EF 45-54%)	29 (36.3)	17 (33.3)	4 (44.4)	8 (40.0)
Moderate (EF 30-44%)	7 (8.8)	4 (7.8)	1 (11.1)	2 (10.0)
Severe (EF<30%)	0 (0)	0 (0)	0 (0)	0 (0)

DORV = Double Outlet Right Ventricle, EF = Ejection Fraction; LV = Left ventricular; NYHA = New York Health Association; RV = Right ventricular; RVOT = Right ventricular outflow tract; TGA = Transposition of the Great Arteries; VSD = Ventricular Septal Defect

Table 2. Procedural characteristics

	Data available	N (%) or mean±sd / median (range)
Successful PPVI	80	76 (95.0)
Approach	80	
Femoral		76 (95.0)
Jugular		4 (5.0)
Conduit diameter (mm)		
At surgical placement	52	23 (13-26)
At angiography pre PPVI	30	18 (5-23)
Predilatation	64	34 (53.1)
Prestenting	67	
0		2 (3.0)
1		48 (71.6)
>1		17 (25.4)
Brand		
Melody	73	73 (91.2)
Edwards Sapien	7	7 (8.8)
Valve size (mm)	60	
18		13 (21.7)
20		8 (13.3)
22		33 (55.0)
23		2 (3.3)
26		4 (6.7)
Post-dilated	65	43 (53.8)

PPVI = Percutaneous Pulmonary Valve Implantation

The one patient in which prestenting was not performed was a 16 year old female, corrected for pulmonary atresia with a homograft which had become severely stenotic (peakgradient 108 mmHg), and had a diameter of only 11 mm on CT. Of 80 attempts, 76 (95%) resulted in successful deployment of a functional valve at discharge. Reasons for abortion were conduit rupture resulting in conversion (n=1), hemathorax (n=1), right coronary artery compression (n=1) and a too wide RVOT after pre-stenting (n=1). The surgical conversion was necessary in a 23 year old female who had received a homograft for her pulmonary atresia at the age 8 months. Acute rupture of her conduit was irresolvable despite immediate surgical conversion after which the patient died. Other complications were controllable ventricular fibrillation (n=2), hemathorax (n=2) and a small proximal aortic dissection which was treated conservatively (n=1). The hemathorax was confirmed by CT-angiography and originated from a small leakage at the proximal border of the stent.

In all patients, the transpulmonary gradients and RV systolic pressures normalized and aortic systolic pressures increased (Table 3). Overall, the peak gradient decreased from 44.0 to 12.0 mmHg ($p<.001$). In patients with predominant stenosis, the peak gradient decreased from 53.9 to 13.8 mmHg ($p<.001$). Peak gradient in patients with predomi-

nant regurgitation decreased from 16.9 to 9.6 mmHg (p<.001). None of the patients had significant PR at discharge.

Late events

The median follow up time was 4.2 years (range 0.2-12.2 years). Five late deaths occurred 5.4±3.7 years (range 0.2-9.5) after implantation that were all cardiac related. These patients already presented with mild or moderately impaired biventricular function before PPVI. Two patients died after infective endocarditis resulting in multi-organ failure without surgical options.

Table 3. Hemodynamic outcome of successful PPVI

	Data available	Prior to PPVI	n	Post PPVI	P-value
Cardiac MRI					
RV end diastolic volume (mL)	37	225±98		…	
RV end systolic volume (mL)	22	108±47		…	
RV ejection fraction (%)	37	48±16		…	
LV end diastolic volume (mL)	38	154±45		…	
LV end systolic volume (mL)	22	66±25		…	
LV ejection fraction (%)	40	55±8.5		…	
Catheterization					
RA Pressure (mmHg)	46	10±4	38	10±5	.406
RV Systolic pressure (mmHg)	56	74±24	53	47±12	<.001
RV Diastolic pressure (mmHg)	49	7±6	47	7±5	.379
RV Mean pressure (mmHg)	31	13±11	34	12±7	.150
AP Systolic pressure (mmHg)	44	30±14	48	35±10	.006
AP Diastolic pressure (mmHg)	42	10±5	46	16±10	.002
AP Mean pressure (mmHg)	42	17±6	42	23±12	.003
Aortic Systolic pressure (mmHg)	36	101±24	24	119±20	<.001
Aortic Diastolic pressure (mmHg)	34	59±13	21	61±10	<.001
RV-PA gradient (mmHg)	47	44±24	48	12±9	<.001
RVOT Regurgitation (echo)	76				
None		17 (22.4)		46 (60.5)	NA
Trace		7 (9.2)		22 (28.9)	
Light		25 (32.9)		8 (10.5)	
Moderate		11 (14.5)		0 (0)	
Severe		16 (21.1)		0 (0)	

AP = Arteria Pulmonalis, MRI = Magnetic Resonance Imaging, RA = Right Atrial, RV = Right ventricular, RVOT = Right Ventricular Outflow Tract, PPVI = Percutaneous Pulmonary Valve Implantation

Table 4. Late events

Successfully deployed valves	76	
Lost to follow up	2 (2.6)	
	Mean ± SD	**Median (range)**
Follow up time (years)	4.6 ± 3.0 (0.1-12.2)	4.1 (0.1-12.2)
Echoparameter at last follow up		
Pulmonary peak gradient (mmHg)	30.1±17.9	25 (5-100)
Pulmonary mean gradient (mmHg)	19.9±12.1	16 (7-58)
Right ventricular systolic pressure (mmHg)	41.6±18.5	37 (18-88)
TAPSE (mm)	16.4±4.0	16 (8-26)
Fractional area change (%)	45.6±8.9	44 (24-66)
	N	**LOR**
Device related reintervention	12	3.5%
Catheter	5	1.5%
Balloon dilatation	1	0.3%
Second TPVI	4	1.2%
Surgical	7	2.1%
Valved conduit	7	2.1%
Endocarditis	14	4.2%
Successfully resolved with iv antibiotics	6	1.8%
Died	2	0.6%
Eventually requiring surgery[8]	6	1.8%
Died in hospital after surgery	1	0.3%
Stent Fracture		
Late thrombo-embolic events	0	0%
Late bleeding events	0	0%
Stroke/TIA	0	0%
All-cause mortality	5	1.5%
Non-cardiac death	0	0%
Cardiac death	5	1.5%
Valve related mortality	4	1.2%
Non-valve related mortality	1	0.3%

LOR = Linearized Occurrence Rate, RVOT = Right Ventricular Outflow Tract, TAPSE = Tricuspid Annular Plain Systolic Excursion, TIA = Transient Ischemic Attack

* = endocarditis could not be resolved despite adequate i.v. antibiotics alone, indicating surgery.

One other patient died directly after surgical valve explantation indicated by endocarditis. Two patients died due to end-stage heart failure of which one underwent re-PPVI due to restenosis after successful implantation 2 years earlier.

Eleven patients underwent 12 reinterventions (7 surgical-PVR, 4 redo PPVIs, 1 balloon dilatation) after 4.9±4.2 years of which 6 indicated by severe restenosis and 6 by endocarditis irresolvable by antibiotics (Table 4). In total, 4 patients underwent a second PPVI due to severe restenosis based on stent fractures (n=3) and sternal compression (n=1) after a mean follow-up period of 8.4±3.5 years. Actuarial mean time till cardiac death, valve related reintervention and valve replacement were 10.9±1.1 years, 9.9±1.2 years and 10.1±1.2 years, respectively (Figure 2).

Table 5. Endocarditis

Original diagnosis	TPV	History of endocarditis	Time (years)	LZ	Micro-organism	Suspected entry point	Treatment	Survival
TOF	Melody	No	8.9	allograft	Streptococcus Sanguinis	Unknown	IVAB	yes
TGA	Melody	No	9.5	allograft	Hemophylus-para-influenza	Dental care	IVAB + SPVR	no
PA-VSD	Melody	No	1.6	allograft	Rothia Dentocariosa	Unknown	IVAB + SPVR	yes
TOF	Melody	Str. Viris	0.2	allograft	Staphylococcus epidermus	Unknown	IVAB	no
TAC	Melody	No	4.2	allograft	Staphylococcus aureus	Pneumonia	IVAB	no
DORV	Melody	No	4.3	allograft	Streptococcus Oralis.	Dental care	IVAB + SPVR	yes
ROSS	Melody	No	6.2	allograft	Streptococcen Dysglactiae.	Unknown	IVAB	yes
TOF	Melody	No	3.9	hancock	Streptococcus gordonii	Dental care	IVAB	yes
TGA	Melody	No	3.2	native	Streptococcus sanguis	Unknown	IVAB	yes
PA-VSD	Melody	No	2.8	allograft	Staphylococcus aureus	Unknown	IVAB	yes
TOF	Melody	No	0.6	allograft	Corine bacterium species	Unknown	IVAB + SPVR	yes
ROSS	Melody	No	0.7	allograft	Staphylococcus aureus	Dental care	IVAB + SPVR	yes
ROSS	Melody	No	1.5	allograft	Streptococcus mitis	Dental care	IVAB + SPVR	yes

DORV = Double Outlet Right Ventricle, IVAB = Intravenous antibiotics, PA = Pulmonary Atresia, ROSS = Pulmonary Autograft procedure, SPVR = Surgical Pulmonary Valve Replacement, TAC = Truncus Arteriosus Communis, TGA = Transposition of the Great Arteries, TOF = Tetralogy of Fallot, VSD = Ventricular Septal Defect

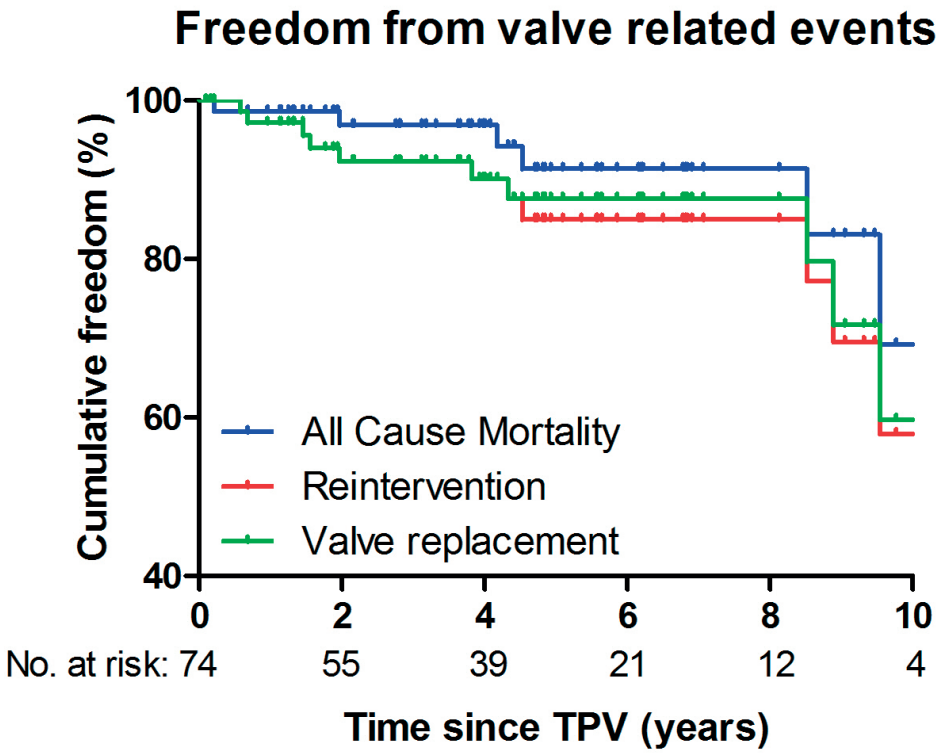


Figure 2 Freedom from mortality, reintervention and valve replacement

Endocarditis

During follow-up, 14 episodes of Dukes positive endocarditis were observed (linearized occurrence rate: 4.2%/year) in 13 patients (Table 5). The most often suspected entry point was oral mucosa with recent dental care and lack of adequate prophylaxis. Six patients were successfully treated with antibiotics, 2 patients died without surgical reintervention (previously described) and in 6 cases surgical PVR was eventually required. One of these 6 patients died due to end-stage heartfailure during the postoperative course. Of the six patients who were successfully treated with antibiotics, one patient underwent surgical PVR 8.3 years later due to repeat endocarditis and one patient received a second Melody valve due to severe restenosis 1 year later. The other four patients currently still have their valves in place and are in good clinical condition (all NYHA I) after a mean follow-up period of 2.5 years (range 0.4-4.1 years) after the diagnosis of endocarditis. No thrombo-embolic or hemorrhagic events occurred during the study period.

Serial measurements

In total, 362 post implantation echocardiograms could be retrieved for 69 (91%) procedures. Figures 3A-E show the individual temporal trends of serial echocardiographic

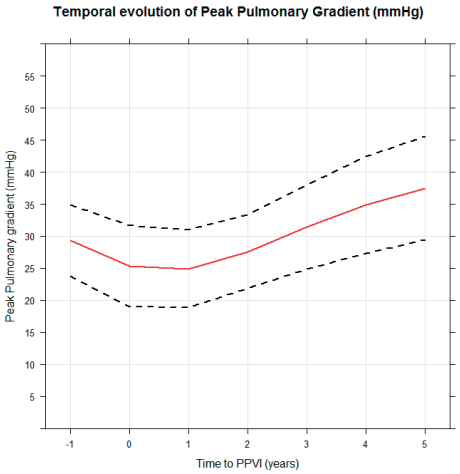


Figure 3a Temporal evolution of peak pulmonary gradient (mmHg)

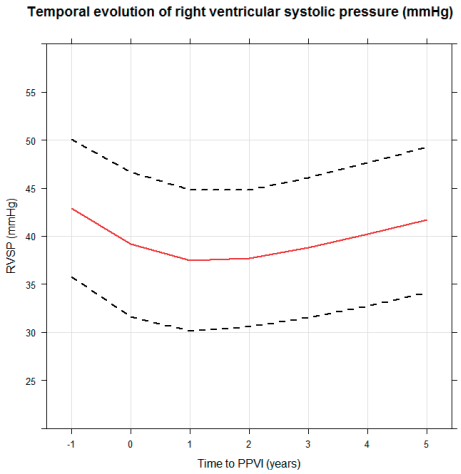


Figure 3b Temporal evolution of right ventricular systolic pressure (mmHg)

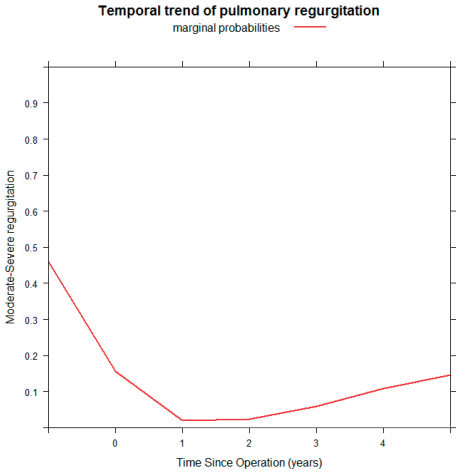


Figure 3c Temporal trend of pulmonary regurgitation

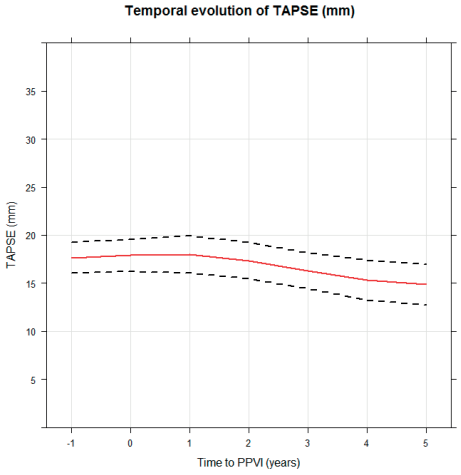


Figure 3d Temporal evolution of TAPSE (mm)

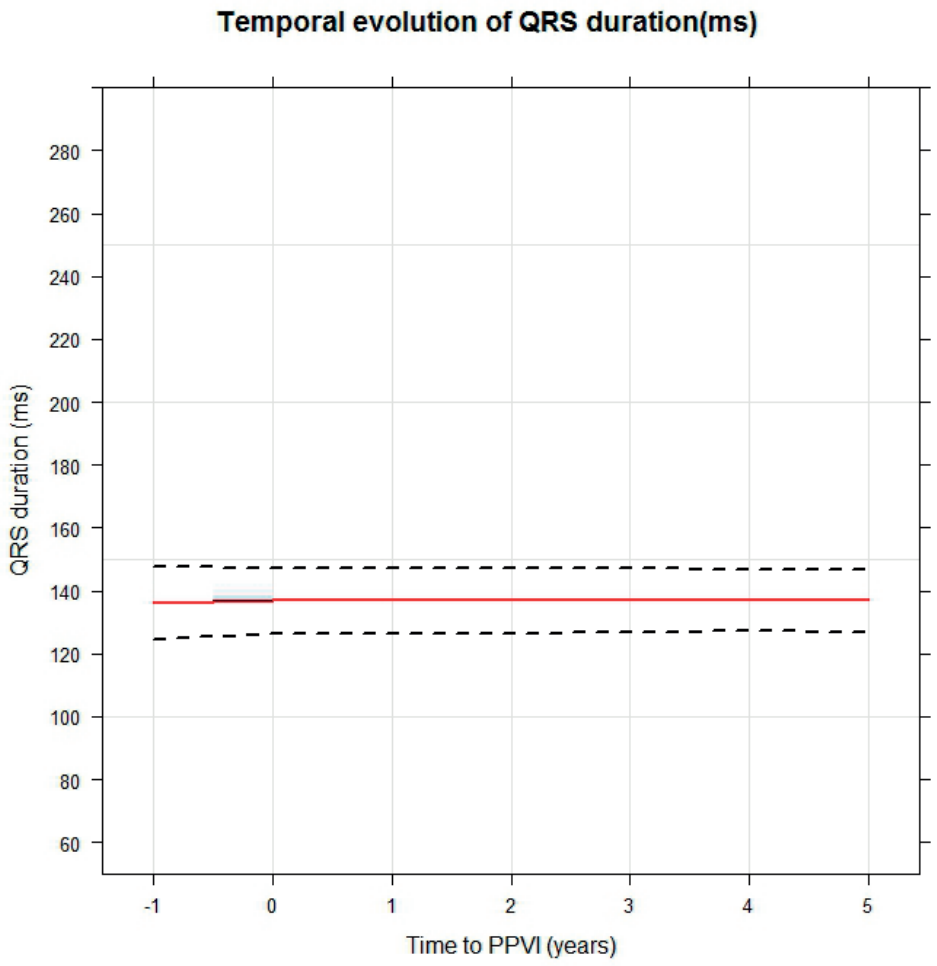


Figure 3e Temporal evolution of QRS duration (ms)

and QRS measurements over time starting at one year prior to PPVI. The average peak pulmonary gradient increases steadily to 39±4 mmHg after 5 years (Figure 3A), with a parallel incline in RV systolic pressure (Figure 3B). The prevalence of significant pulmonary regurgitation increases to 14% after 5 years (Figure 3C). The tricuspid annular plane systolic excursion (TAPSE) remains stable during the first 5 years (Figure 3D), as well as the QRS duration (Figure 3E).

DISCUSSION

PPVI after surgical RVOT reconstruction with a conduit can be performed with low procedural risks and good long-term clinical outcome. Post implantation serial echocardiographic and electrocardiographic measurements indicate stable valvular and ventricular function, and QRS width during the first 5 years. A relatively high annual occurrence rate of endocarditis of 4.2% was observed, however, underscoring close follow up and strict endocarditis prophylaxis adherence in high-risk procedures.

The current report confirms that PPVI can be performed safely and is able to restore valve function of severely dysfunctional conduits. There was an overall significant reduction in peak RVOT gradient and regurgitation grades, and improvement in RV systolic pressures and systemic arterial pressure. The observed success rate of 95% in this study is comparable to the results published in a recent meta-analysis [10]. Significant compression of a right coronary artery during test inflation presented in only one case and led to an uneventful termination of the procedure. Rupture of a homograft conduit occurred once in our series and has been predominantly described in homografts [16, 17], with calcified homografts being more prone to rupture [18, 19].

Early in our experience, 2 patients successfully underwent PPVI without prestenting due to small homografts. Prestenting has become standard care, aimed at straitening and preparing the landingzone for adequate valve deployment and mitigating some of the radial forces [20, 21] hereby reducing reintervention based on stent fractures [22, 23]. Hemodynamically relevant stent fractures have been reported mostly in early series, and generally occur within a year after implantation [21]. Observed stent fractures in our cohort were rare with 3 hemodynamically relevant cases leading to reintervention. Furthermore, we have not observed any valve collapse, migration of fragments or acute hemodynamically unstable patients based on stent fractures.

Although several studies with clinical outcomes after PPVI have been published, the exact temporal evolution of both valvular and ventricular function is unclear. Studies using Kaplan Meier techniques, which only consider first and last measurements, generally indicate stable evolutions [11, 17, 24]. By application of advanced statistical methods this study shows that RV function remains stable after PPVI as indicated by a stable fractional area change and TAPSE. Thereby, improvement of RV function after PPV was not observed. Furthermore, the prevalence of significant PR increased only modestly. QRS width also remained stable, which has been mentioned as a surrogate marker for right ventricular remodeling [25]. This is consistent with the finding that cardiac function is stable and further remodeling is not apparent beyond the immediate post implantation period [26]. The RVOT gradient and RV systolic pressures gradually increased, however, stressing close attention to symptoms of chronic pressure overload during follow-up. Late cardiac death occurred predominantly among patients who underwent PPVI as a

palliative strategy and who had already presented with severe biventricular dysfunction prior to PPVI. At most recent follow up, the majority of patients were in good cardiac health, with a low prevalence of significant regurgitation.

An alarmingly high prevalence of endocarditis after PPVI was found. Half of the cases in which surgical re-PVR was performed was indicated by IE. The relatively high incidence of IE in our cohort is in accordance with the range of 1.3-9.1% per year as reported by others [27], but exceeds the pooled annualized occurrence rate of 1.4% as estimated by a recent meta-analysis [10]. None of the endocarditis cases occurred within the first year of implantation making procedural contamination unlikely. Concurrently, the annualized occurrence rate of IE in 701 consecutive homografts in our center is only 0.38% [4]. Furthermore, a recent meta-analysis reported an incidence of IE of 5.4% in bovine jugular veins, regardless of surgical or percutaneous placement, which is higher than the incidence generally found in homografts [28-30]. Patel et al. have proposed that the inherent material and structural properties of the Melody valve might be more prone to attract and facilitate infectious microorganisms [31]. This was consistent with in-vitro experiments indicating a higher adhesion propensity of S. aureus to the wall of bovine jugular veins, compared to homografts [32, 33]. In our study, endocarditis could not be related to stenting, conduit type or patient characteristics. Prestenting [34] and male gender [30] have occasionally been associated with an increased risk but have yet to be confirmed by other reports. Reactivation of previous infectious microbes did not occur in our cohort, as only one of the cases with IE had a positive history of endocarditis prior to PPVI with a different microorganism. The most frequently assumed entry point was oral mucosa within the context of poor dental hygiene or inadequate prophylaxis during a recent dental procedure.

As a temporary alternative to surgical PVR, PPVI appears to compare well, offering at least a delay from surgical reintervention, shorter hospital stay and occasionally costs reductions [35, 36]. Steinberg et al. found surgical PVR to be associated with longer hospitalization compared to PPVI but no difference in hospital costs or a composite outcome of in-hospital morbidity and 30-day mortality [36]. After 5 years, surgical PVR seems to have a costs advantage due to a higher reintervention rate after PPVI [37]. Although biventricular functional and volumetric improvements have been demonstrated after both surgical PVR and PPVI, valid comparisons are difficult given the different and constantly evolving referral criteria and therefore indication bias [38].

Study Strengths and Limitations

We presented the results of our multicenter experience with PPVI in the Netherlands. We used serial echocardiographic data and showed a stable long-term valve and ventricular function. Limitations are inherently due to the retrospective nature leading to missing data and limited follow up time. Cardiac MRI and catheterization data were only

retrievable in a limited number of patients. Due to the limited event rate, extensive risk factor modeling was not possible. Due to constantly evolving intervention criteria, it is unknown which patients who underwent surgical intervention were considered for TPVI. In the corresponding study period, 276 patients underwent surgical PVR in our center, of which 65 underwent re-PVR in which a deteriorated homograft was replaced by a new one [4].

Conclusion

Percutaneous pulmonary valve implantation can be performed safely, with good long-term results indicated by stable valvular and ventricular performance. Endocarditis remains a serious problem leading to substantial morbidity, reintervention and mortality.

REFERENCES

1. van der Bom, T., et al., The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. Am Heart J, 2012. 164(4): p. 568-75.
2. Gilboa, S.M., et al., Congenital Heart Defects in the United States: Estimating the Magnitude of the Affected Population in 2010. Circulation, 2016. 134(2): p. 101-9.
3. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
4. Romeo, J.L.R., et al., Long-term clinical outcome and echocardiographic function of homografts in the right ventricular outflow tract†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy265-ezy265.
5. Mercer, C.W., et al., Polytetrafluoroethylene conduits versus homografts for right ventricular outflow tract reconstruction in infants and young children: An institutional experience. J Thorac Cardiovasc Surg, 2018.
6. Sandica, E., et al., Bovine Jugular Veins versus Homografts in the Pulmonary Position: An Analysis across Two Centers and 711 Patients-Conventional Comparisons and Time Status Graphs as a New Approach. Thorac Cardiovasc Surg, 2016. 64(1): p. 25-35.
7. Christenson, J.T., et al., Homografts and xenografts for right ventricular outflow tract reconstruction: long-term results. Ann Thorac Surg, 2010. 90(4): p. 1287-93.
8. Mascio, C.E., et al., Outcomes in adult congenital heart surgery: Analysis of the Society of Thoracic Surgeons Database. The Journal of Thoracic and Cardiovascular Surgery, 2011. 142(5): p. 1090-1097.
9. Bonhoeffer, P., et al., Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet, 2000. 356(9239): p. 1403-5.
10. Chatterjee, A., et al., Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies. J Am Heart Assoc, 2017. 6(8).
11. Morray, B.H., et al., Multicenter Experience Evaluating Transcatheter Pulmonary Valve Replacement in Bovine Jugular Vein (Contegra) Right Ventricle to Pulmonary Artery Conduits. Circulation: Cardiovascular Interventions, 2017. 10(6).
12. Hager, A., et al., Five-year results from a prospective multicentre study of percutaneous pulmonary valve implantation demonstrate sustained removal of significant pulmonary regurgitation, improved right ventricular outflow tract obstruction and improved quality of life. EuroIntervention, 2017. 12(14): p. 1715-1723.
13. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
14. Li, J.S., et al., Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis, 2000. 30(4): p. 633-8.
15. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg, 2008. 85(4): p. 1490-5.
16. Cabalka, A.K., et al., Relationships Among Conduit Type, Pre-Stenting, and Outcomes in Patients Undergoing Transcatheter Pulmonary Valve Replacement in the Prospective North American and European Melody Valve Trials. JACC Cardiovasc Interv, 2017. 10(17): p. 1746-1759.

17. Markham, R., et al., Outcomes Following Melody Transcatheter Pulmonary Valve Implantation for Right Ventricular Outflow Tract Dysfunction in Repaired Congenital Heart Disease: First Reported Australian Single Centre Experience. Heart Lung Circ, 2017. 26(10): p. 1085-1093.
18. Berman, D.P., et al., Feasibility and short-term outcomes of percutaneous transcatheter pulmonary valve replacement in small (<30 kg) children with dysfunctional right ventricular outflow tract conduits. Circ Cardiovasc Interv, 2014. 7(2): p. 142-8.
19. Boudjemline, Y., et al., Predictors and outcomes of right ventricular outflow tract conduit rupture during percutaneous pulmonary valve implantation: a multicentre study. EuroIntervention, 2016. 11(9): p. 1053-62.
20. Nordmeyer, J., et al., Risk Stratification, Systematic Classification, and Anticipatory Management Strategies for Stent Fracture After Percutaneous Pulmonary Valve Implantation. Circulation, 2007. 115(11): p. 1392-1397.
21. Nordmeyer, J., et al., Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. Heart, 2011. 97(2): p. 118-23.
22. Cheatham, J.P., et al., Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. Circulation, 2015. 131(22): p. 1960-70.
23. McElhinney, D.B., et al., Stent Fracture, Valve Dysfunction, and Right Ventricular Outflow Tract Reintervention After Transcatheter Pulmonary Valve Implantation. Patient-Related and Procedural Risk Factors in the US Melody Valve Trial, 2011. 4(6): p. 602-614.
24. Borik, S., et al., Percutaneous pulmonary valve implantation: 5 years of follow-up: does age influence outcomes? Circ Cardiovasc Interv, 2015. 8(2): p. e001745.
25. Paech, C., et al., QRS Width as a Predictor of Right Ventricular Remodeling After Percutaneous Pulmonary Valve Implantation. Pediatr Cardiol, 2017. 38(6): p. 1277-1281.
26. Lurz, P., et al., Early versus late functional outcome after successful percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? J Am Coll Cardiol, 2011. 57(6): p. 724-31.
27. Abdelghani, M., et al., Infective Endocarditis After Melody Valve Implantation in the Pulmonary Position: A Systematic Review. J Am Heart Assoc, 2018. 7(13).
28. Sharma, A., et al., A Systematic Review of Infective Endocarditis in Patients With Bovine Jugular Vein Valves Compared With Other Valve Types. JACC Cardiovasc Interv, 2017. 10(14): p. 1449-1458.
29. Ugaki, S., et al., An increased incidence of conduit endocarditis in patients receiving bovine jugular vein grafts compared to cryopreserved homograft for right ventricular outflow reconstruction. Ann Thorac Surg, 2015. 99(1): p. 140-6.
30. Van Dijck, I., et al., Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. Heart, 2015. 101(10): p. 788-793.
31. Patel, M., et al., Percutaneous pulmonary valve endocarditis: incidence, prevention and management. Arch Cardiovasc Dis, 2014. 107(11): p. 615-24.
32. Veloso, T.R., et al., Bacterial adherence to graft tissues in static and flow conditions. The Journal of Thoracic and Cardiovascular Surgery, 2018. 155(1): p. 325-332.e4.
33. Jalal, Z., et al., Selective propensity of bovine jugular vein material to bacterial adhesions: An in-vitro study. International Journal of Cardiology, 2015. 198: p. 201-205.

34. Buber, J., et al., Bloodstream Infections Occurring in Patients With Percutaneously Implanted Bioprosthetic Pulmonary Valve. A Single-center Experience, 2013. 6(3): p. 301-310.
35. Vergales, J.E., et al., Cost-analysis of percutaneous pulmonary valve implantation compared to surgical pulmonary valve replacement. Catheterization and Cardiovascular Interventions, 2013. 82(7): p. 1147-1153.
36. Steinberg, Z.L., et al., Early outcomes in patients undergoing transcatheter versus surgical pulmonary valve replacement. Heart, 2017. 103(18): p. 1455-1460.
37. Gatlin, S.W., D.W. Kim, and W.T. Mahle, Cost analysis of percutaneous pulmonary valve replacement. Am J Cardiol, 2011. 108(4): p. 572-4.
38. Zablah, J.E., et al., Comparison of Patients Undergoing Surgical Versus Transcatheter Pulmonary Valve Replacement: Criteria for Referral and Mid-Term Outcome. Pediatr Cardiol, 2017. 38(3): p. 603-607.

13

Discussion

The aim of this thesis was to obtain an improved insight into determinants of outcomes after right ventricular outflow tract (RVOT) reconstruction with a homograft and optimization of the timing of intervention. This chapter puts the findings in a broader context and discusses the potential implications for current and future research. Clinical outcomes in terms of survival, durability and quality of life will be addressed first. Next, focus will be on specific patient populations undergoing RVOT reconstruction. Finally, echocardiographic homograft function and our statistical approach will be discussed.

CLINICAL OUTCOMES AFTER RVOT RECONSTRUCTION

Right ventricular outflow tract (RVOT) reconstruction is a common cardiac surgery procedure in neonates, children and adults with congenital heart disease [1]. Diagnoses requiring RVOT reconstruction at some point during patients' life include Tetralogy of Fallot, Pulmonary Atresia, Transposition of the Great Arteries, Double Outlet Right Ventricle, Truncus Arteriosus. In addition RVOT reconstruction is done during the Ross procedure, when a diseased aortic valve is replaced by the patients pulmonary valve.

The birth rate of children with congenital heart disease (CHD) is expected to increase due to absolute population growth. Assuming continually improving healthcare resulting in improved patient survival, this will lead to increasing prevalence of adults with CHD and a growing demand for RVOT reconstruction [2, 3]. RVOT reconstruction has become the most common surgical intervention in adults with CHD [1]. This thesis indicates that clinical outcome after RVOT reconstruction with homografts is generally good, predictable but dependent on the diagnosis, associated cardiac and non-cardiac malformation and type and timing of operation (Chapters 3, 4, 7, 9, 10 and 12).

Homografts and bioprostheses are common alternatives for RVOT reconstruction as they are easily implantable, do not require permanent anticoagulation and have acceptable risks of endocarditis. Limited durability is still the major disadvantage of both homografts and bioprostheses and is attributed to a combination of fibrosis, calcification, immunological factors and degeneration [4-7]. Comparison studies have consistently indicated superior performance of homografts over bioprostheses in terms of structural valve deterioration and endocarditis risks [6, 8-10]. The experience of the Cardio-Thoracic Surgery department of the Erasmus University Medical Center concerns a consecutive cohort of 701 patients exclusively receiving homografts [11]. Clinical outcome has been consistently good in terms of survival and reoperation rate, and other major cardiovascular events (Chapters 3, 4, 7). Survival of 89% at 10 years and 84% at 20 years in our cohort is comparable to other reports on survival after cryopreserved homograft implantation[12, 13]. Long term hemodynamic function as assessed by trans thoracic echocardiography was favorable as well (Chapter 3). Despite probably being

the most durable and low-risk valvular alternative suitable for RVOT reconstruction, structural valve deterioration ultimately leading to reintervention remains a concern in most patients [11]. Patient factors associated with limited homograft durability are non-Ross procedures, younger age at implantation, smaller sized grafts and aortic grafts which also were confirmed by multivariable analysis in our study [13-16]. Later in this discussion we will detail these associations with homograft durability more elaborately.

Other alternatives for RVOT reconstruction are mechanical prostheses, tissue engineered heart valves and adaptations to standard homografts like decellularization. Mechanical prostheses are rarely used because they require lifelong use of oral anticoagulants which carries significant lifestyle restrictions. Furthermore, permanent anticoagulant use in a relatively young population induces an unacceptable lifetime risk of severe bleeding and stroke and increases the risk of complications during pregnancy for both mother and fetus [17-20]. In addition, their inherent thrombogenicity is exacerbated in the low flow right sided position leading to substantial rates of valve thrombosis and dysfunction despite proper anticoagulation and monitoring [17].

Decellularization of homografts is an attempt to reduce immunogenicity and hereby graft degeneration, especially in young patients. Some studies present promising short term results of decellularized homografts with persistent low gradients and rates of endocarditis and explantation when compared with standard homografts or bovine jugular veins [21, 26, 27]. Other studies report higher gradients in specific patient populations like the Ross procedure [28] or indicate no differences in regurgitation grade, stenosis and reoperation rates when compared with standard homografts [29, 30]. The value of decellularized homografts remains elusive however, given that there are no reports with large patient volumes and extensive follow up duration.

Recent innovations like tissue engineered heart valves have not yet reached the phase of broad scale clinical implementation [21-23]. Tissue engineered heart valves may occupy a role in valve reconstruction one day potentially offering a solution to the two major disadvantages of homografts: durability and availability. Tissue engineered heart valves usually entail a scaffold, which after implantation will be coated with, and replaced by the patients stem cells and other progenitor cells. This premise of restoring heart valve tissue equivalent to native healthy tissue with growing and remodeling capacity is unique and eventually expected to be a revolution in terms of durability and long term functionality [24, 25]. However, major hurdles in terms of scaffold optimization, seeding methods and scaling of the production process need to be overcome first.

Surgical reintervention after homograft implantation can be postponed by transcatheter implantation of a bioprosthesis. This practice of transcatheter pulmonary valve implantation (TPVI) is currently being performed with low procedural mortality and good mid-term results of valvular hemodynamics [31]. Outcome of TPVI in the Erasmus University Medical Center was favorable as well in terms of in-hospital mortality,

gradient reduction and right ventricular systolic pressure reduction (Chapter 5). Peak transvalvular gradient and right ventricular pressure decreased significantly and only gradually increased in the subsequent years. However, late morbidity, stent fractures, endocarditis and valve related reintervention remain relatively frequent, often leading to restenosis and surgical reintervention [31]. Another current limitation is that relatively large or native annuli are rarely suitable for transcatheter valve implantation. Based on these findings and our experience we conclude that the indication of treating a patient with TPVI should only follow a well-considered tradeoff between the inherent risks and the potential benefits of surgical postponement and temporary gradient reduction.

Therefore, among the alternatives available for RVOT reconstruction, only homografts and bioprostheses have proven long term durability and functionality. Outcome of homografts is often superior to bioprostheses in terms of durability and complication risks. Moreover, echocardiographic functionality of homografts can be predicted to a certain extent for individual patients using patient characteristics and relatively easily measurable biomarkers. Biomarkers associated with patient outcome and homograft durability will be discussed next.

Risk factors

Patient outcome after RVOT reconstruction with homografts is good but not perfect. Morbidity and reintervention are relatively common, but strongly differ from patient to patient. Predicting clinically relevant events and echocardiographic functionality, ideally on a patient-specific level, can be helpful before, during and after RVOT reconstruction. In this thesis, several risk factors for homograft deterioration were identified.

Homograft size and patient age

A smaller homograft size, which is often needed in young patients, is an independent risk factor for earlier valve deterioration [11, 32]. Calcification and therefore radial reduction leads to a relatively larger reduction of the lumen of homografts that are smaller. Younger age at RVOT reconstruction is also an independent risk factor for shorter durability. Part of the shorter durability can also be attributed to immunological factors more prominent in young patients [33-35]. Unfortunately, these are not the only difficulties young patients undergoing RVOT reconstruction face. As homografts have a limited growth capacity, young patients experiencing their growth spurt tend to outgrow their valve. Furthermore, availability of right sized homografts is limited due to the relatively low number of donors of smaller sized valves required for infants and young children (Chapter 3 and 4) [4, 36, 37]. Currently, there are no readily solutions as small bioprostheses in infants deteriorate relatively quick as well [38-41]. Although bicuspidalization has partly countered the shortage of right sized homografts without compromising valve integrity (Chapter 4), accelerated deterioration still remains a problem [32, 42-45].

Tissue engineered heart valves, potentially able to evolve along with the patient, would be an ideal solution both in terms of growth ability and immunological resistance as mentioned in the previous section [24].

Sex and pregnancy

The prevalence of grown-ups with congenital heart disease (GUCH) is expected to increase due to constantly improving surgical and clinical treatment options [2, 46, 47]. RVOT reconstruction has already become the most frequently performed procedure in GUCH comprising approximately 10% of all adult procedures [1]. This has led to a relatively new and growing population of women who are contemplating or experiencing pregnancy after RVOT reconstruction. There is paucity however in sex specific research, especially relating to pregnancy after RVOT reconstruction. This thesis shows that female sex is associated with longer homograft durability independent from age, homograft diameter, diagnosis and homograft type (i.e. aortic or pulmonary) (Chapters 3, 4, 9). Also in patients undergoing the Ross procedure, women experience a longer freedom from homograft reintervention (Chapter 3). An exact pathophysiological explanation was outside the scope of this thesis but may in part relate to immunological and hormonal differences between men and women [48]. Literature dedicated to male and female differences in cardio-vascular research has been limited. A recent study showed that in general, women with CHD are more susceptible to pregnancy related complications before, during and even after labor compared to women in the general population [49]. The association between pregnancy and homograft durability in RVOT position had not been studied as extensively as for aortic valve replacement [50, 51]. This paucity in literature committed to right sided valvular disease is also reflected by the most recent guidelines for the management of cardiovascular disease during pregnancy, in which women who are in need of PVR are not explicitly mentioned [52]. In this thesis, to the best of our knowledge, the results of pregnancy in women who underwent RVOT reconstruction with a homograft have been reported for the first time (Chapter 11) [53]. No maternal mortality or prelabor child loss was observed. Spontaneous premature labor was more frequent compared to the general Dutch population and significant (i.e. moderate-severe) regurgitation was a risk factor for preterm labor. Although these results need confirmation in comparable cohorts, the results may have important clinical implications as significant regurgitation is frequently seen after correction of tetralogy of Fallot, and develops in a significant proportion of right sided homografts [11]. The timing of reintervention to restore right sided valve competence could, therefore, take into account a potential pregnancy wish. Pregnancy was, according to the study in Chapter 12, not associated with homograft durability, indicating that women in good cardiac health can undergo pregnancy safely without influencing homograft durability. These results stress the importance of regular monitoring before, during and after

pregnancy by both a cardiologist and gynecologist, preferably in the formal setting of a Pregnancy Heart Team.

Ross patients

Homografts are often used in the Ross procedure to reconstruct the RVOT and have a better durability in this patient population compared to bioprostheses (Chapter 3) [6, 8-10]. In our international multicenter analysis of Ross patients who underwent surgery between ages 18 and 65, a homograft was used in 98.8% of the procedures and freedom from RVOT reintervention after 15 years was 97.1% (Chapter 9). Patients undergoing the Ross procedure represent a special population undergoing RVOT reconstruction due to the absence of right sided structural heart defects. In fact, these patients are often selected based in part on the excellent properties of their right ventricle and pulmonary valve. This thesis has shown that homograft durability in our Ross patients is excellent and significantly longer than in patients with right sided diagnoses (Chapters 3 and 9). These observations were supported by both the time-to-event analyses and longitudinal models of echocardiographic function.

Although several centers have repeatedly published favorable patient outcome after the Ross procedure [54-58], its' use has been steadily declining after initial enthusiasm peaking in the late 90s [59]. In recent years, however, there is a revival in dedicated centers across the world, making an explicit plea for its comeback [60-63]. Their plea is backed by multiple observational reports, propensity score matched comparisons, and meta-analyses, unanimously indicating good results in terms of survival, both left and right sided graft durability and stroke [54-58]. Our multicenter analysis in patients between ages 18 and 65 also indicated good hemodynamic performance. Combined freedom from homograft and autograft reintervention was comparable to mechanical aortic valve replacement [64-68] and survival comparable to the sex and age matched general population (Chapter 9). The Ross procedure remains the only alternative for AVR that offers both excellent valve durability and a life expectancy comparable to an age and sex matched general population [56, 57, 69-73]. It is, therefore, remarkable that the Ross procedure is underused and still not recommended by clinical practice guidelines [74-76]. One of the reasons relates to the complexity of the Ross procedure ideally mandating centralized practice preferably by a few dedicated centers that apply standardized approaches. The learning curve can be overcome, however, and the Montreal Heart Institute even offers a special training program dedicated to the procedure [77, 78]. Its value in children for whom very few aortic valve alternatives are available, has been acknowledged already. Its potential role in active young and middle aged patients with or without a pregnancy wish should be underlined much more as the drawbacks of the permanent use of anticoagulation may be undervalued. The preference for mechanical prostheses is reflected by all major guidelines recommending mechanical AVR in young

and middle aged patients as they are relatively easy to implant, available in a diverse size range and have extensive durability [74-76]. Although the current AHA/ACC guideline emphasizes the importance of individualized and shared decision making, only mechanical and biological prostheses are recommended to be considered (class IIa, evidence B) [75]. Currently, the Ross procedure is not recommended in middle-aged patients and may only be considered in young patients given contraindications or unwillingness to use anticoagulation (Class IIb, evidence level C) [75]. The results presented in this thesis and other recent studies support the inclusion of the Ross procedure in new clinical practice guidelines for valvular and aortic disease with the recommendation to consider it for patients between ages 18 and 65 (Class IIa) based on level B evidence.

Tetralogy of Fallot patients

Another group of patients in whom homografts are often used to reconstruct the RVOT concerns Tetralogy of Fallot, the most prevalent congenital heart disease. Since surgical correction of Tetralogy of Fallot was proven possible in 1954 [79], life expectancy has drastically improved with currently over 95% of patients reaching adult life [80-82], less than 2% surgical mortality [83] and 2.9% 30-day mortality (Chapter 6). The prevalence of adult survivors with corrected TOF has, concomitantly, vastly increased. During the late 1990s and early 2000s, it became clear that along with the additional life years, a significant proportion of patients experience comorbidities and increased mortality predominantly in the second and third post-surgical decade [84, 85]. Nevertheless, patients with corrected TOF are in general coping well with a self-reported quality of life comparable or even better than reported by a matched Dutch population (Chapter 3) [86]. The increased mortality and morbidity rates have been attributed to residual anatomic lesions resulting in significant chronic right ventricular (RV) pressure and/or volume loads, initially considered harmless [85, 87-90]. The current paradigm states that chronic pulmonary regurgitation leads to progressive RV dilatation and dysfunction predisposing to adverse cardiovascular events like arrhythmia, heart failure and sudden cardiac death. In the mid-2000s, PVR became a widely accepted surgical intervention in patients with corrected TOF and other right sided congenital heart defects to treat pulmonary valve dysfunction, making it the most common operation in adults with CHD [91]. The current guidelines by the ESC, AHA and ACC state that PVR is indicated in case of symptomatic severe PR with or without RV dilatation but also in asymptomatic severe PR with progressive RV dilatation and dysfunction [92, 93].

The effects and optimal timing of PVR are disputed however [94-98]. Although pre-PVR RV volumetric parameters are often predictive of their own change after PVR, no clear thresholds have been set [99]. Often used thresholds range between 160 and 190 ml indexed by body surface area [94-98]. The broad thresholds can be partially explained by the fact that there is still little evidence about the long term effects of PVR.

There is currently only evidence on the short term outcome indicating that PVR does result in less symptoms, shortening of QRS duration, reduction in RVEDV and RVESV and improvement in both left and right ventricle function [99, 100]. However, improvements in exercise and performance capabilities and reduced incidence of adverse late events such as sustained ventricular tachyarrhythmia, and heart failure have never been convincingly shown [101-104].

Quality of life

While most reports on long term outcome after RVOT reconstruction with homografts focus on clinical outcome, quality of life (QoL) is less often considered. We assessed QoL in patients who underwent RVOT reconstruction with a homograft and found two important things (Chapter 3). The first was that QoL was comparable to a sex and age matched general Dutch population on the items physical functioning, social functioning, role physical and mental health. Patients scored lower however on general health perception and vitality. The second important observation was that QoL remained stable over a 5 year interval, despite an average increase in peak homograft gradient. Quality of life should become a standard outcome measure in addition to hard clinical endpoints. In the Erasmus University Medical Center it has become more standardized to administer Quality of Life assessments before and after cardiac surgery.

ECHOCARDIOGRAPHIC OUTCOME

Longitudinal echocardiographic outcome

Echocardiography is an important diagnostic imaging modality in cardiology. It is easy, cheap, fast, non-invasive and very informative. It evolved into the cornerstone of cardiologic examination since its first description in 1953, Homograft functionality is predominantly evaluated using m-mode and Doppler echocardiography, described by the peak and mean transvalvular gradient, and regurgitation grade.

Throughout this thesis we have repeatedly analyzed longitudinal echo data of different patient populations after RVOT reconstruction, using mixed effects models. In addition, we have critically evaluated the current statistical approach by authors attempting to define the optimal timing of PVR in patients with repaired Tetralogy of Fallot and made suggestions about the use of mixed effects models (Chapters 2 and 8). We proposed that mixed effects models can be very useful to adequately analyze repeatedly assessed right ventricular dimensions in an observational study setting. We have also used mixed effects models to analyze QRS duration in a cohort of corrected patients with Tetralogy of Fallot who subsequently underwent PVR (Chapter 7). The results indicate that there

is a predictable interval during which PVR should be performed to prevent progressive QRS prolongation.

Mixed effects models

Durability of homografts can be evaluated as a gradual change over time in echocardiographic parameters like peak gradient and regurgitation grade. Predicting the change and the slopes requires statistical methods that are able to deal with repeatedly acquired measurements or longitudinal data in multiple patients. This can be challenging because especially in retrospective and clinical settings, patients usually differ in both the number and timing of measurements, are lost to follow up and outcomes can be censored. Furthermore, missing data is common. All these factors result in a complex and unbalanced dataset.

Commonly used statistical methods are t-tests, and time to event analysis using Kaplan-Meier plots and Cox-regression. Unbalanced longitudinal data from multiple patients is oftentimes unsuitable for standard statistical methods. Comparisons using standard t-tests creates summary statistics, and would hereby lead to loss of information about patients with missing data. Comparisons using repeated measurements ANOVA relies on strong assumptions and balanced data which is uncommon in clinical practice, and impossible in case of missing data. We are often interested in the probability of a particular patient developing significant homograft stenosis or regurgitation. In this case, Kaplan-Meier plots or Cox Regression do take into account the timing of measurements but are only capable of using single observations per patient. We would hereby wrongfully assume these measurements to be events instead of processes. Linear regression is also not suitable because repeated measurements within patients are positively correlated, violating the assumption of independent observations that underlies classic regression analysis.

The statistical methods employed throughout this thesis analyze longitudinal data in a correct statistical manner. Mixed effects models use all repeated measurements per patient and include random effects which account for the correlation of measurements within but also between patients. Mixed effects models are hereby ideal to compare the evolution between groups, identify risk factors, estimate treatment effects and make individual predictions. Using these advanced statistical methods, we were able to show that in adults, homograft peak gradient increases during the first 5 to 10 postoperative years after which it plateaus for the next ten years (Chapter 3). Clinically significant moderate or severe homograft regurgitation is rare in adult patients after RVOT reconstruction with prevalence being 12% after 20 years of follow-up. In Ross patients, the peak gradient of the autograft increases very slowly and the peak gradient of the allograft, again, plateaus after ten years (Chapter 9). Moderate-severe regurgitation of both the autograft and allograft is prevalent in about 1 and 21% respectively after 20

years, warranting close follow up and attention to symptoms associated with chronic volume overload of the right ventricle. This pattern of initial increase in gradient and subsequently sloping down and stabilization is common among young and middle aged adults who underwent RVOT reconstruction with homografts. This is different for young patients however, in which the gradient increases continuously with time and significant regurgitation is more common at 36% after 14 years (Chapters 3 and 4).

The results from our analyses have been published online as interactive applications on a freely available website (https://cts-erasmusmc.shinyapps.io/homograft-durability). Clinicians are hereby able to predict the expected durability of homografts for individual patients using the homograft type and diameter, and the patient's sex, age and diagnosis. To the best of our knowledge, this has been the first time an online application about valve function after cardiac surgery was published. We hope that these statistical methods and this new way of interactively presenting results will become more standardized and common as it can improve the direct translation of research findings into clinical use.

Outcome prediction using joint models

Commonly used prediction models like the Cox proportional hazards model are only able to include static baseline characteristics. However, the hazards of certain outcomes are oftentimes also dependent on constantly evolving biomarkers which are repeatedly measured throughout the clinical course. For instance, the hazard of sudden cardiac death is probably dependent on the right ventricular volume which increases constantly over time in patients with repaired Tetralogy of Fallot. In this thesis the focus has been on the development of gradients and regurgitation grades over time in homografts. To understand the association between an increase in homograft stenosis of regurgitation on the probability of e.g. death, Joint models are appropriate. Joint models are different from the standard Cox proportional hazards model. The classical Cox proportional hazards model for time dependent events does not acknowledge the relationship between longitudinal biomarkers and the hazard of the event of interest. Joint models do, and hereby reduce bias when estimating treatment effects on both the time to event as well as the longitudinal biomarker. Hereby we can explore the association between changes in valve hemodynamics on the probability of reintervention, heart failure and even death. In Chapter 12 we used joint models to examine the effect of pregnancy on homograft replacement in women who underwent RVOT reconstruction prior to pregnancy. No association was found. This is one of the many potential applications of joint models.

Despite reporting guidelines recommending the use of mixed and joint models for repeated measurement analyses since 2008, their reported use in clinical research is still limited [105]. The Journal of Thoracic and Cardiovascular Surgery is one of the first to explicitly adopt submission guidelines pertaining to quality preservation in case of

complex statistics and use of techniques for time varying outcomes [106]. Guidelines and journals should continue to urge authors to use correct statistics when handling complex longitudinal data. Simultaneous integration into standard university methodology courses and common statistical software are also necessary. SPSS (IBM) has recently included mixed effects models into their latest version, potentially lowering the threshold for introduction into clinical practice.

Translation of complex models to clinical practice and treatment decision making

Patients with heart valve disease are regularly confronted with difficult health care decisions. For example, an adult considered for replacement of a severely calcified homograft without symptoms can opt for either replacement or watchful waiting for the development of symptoms. Both scenarios have drawbacks and advantages which are valued differently from patient to patient and clinician to clinician. The choice of elective surgery given absence of symptoms is highly dependent on patient preferences, values and lifestyle. Therefore, decisions regarding different therapies or the timing of (re)intervention are inherently difficult and can only be answered after consensus between clinician and patient while considering the unique set of preferences of the patient. These difficult decisions may lead to feelings of uncertainty known as decisional conflict [107].

The practice of enabling and allowing patients to actively participate in their care is called shared decision making. Patient portals can facilitate consensus by providing the patient with the time and access to process a lot of information in a comprehensible manner and context which can reduce decisional conflict and improve patient satisfaction. Patient portals, patient decision aids and prediction applications can increase patient comprehension and therefore enable more active participation. Patient portals are currently being used in the Erasmus University Medical Center as well, providing patients with real time insight into their own healthcare records. Digital decision aids like www.hartklepkeuze.nl and www.mijnaha.nl enhance patient engagement by simplifying and contextualizing complex medical matters into daily life and recognizable dilemmas. The models predicting long term homograft durability as presented throughout this thesis have been published online as freely available applications providing both patients and clinicians with realistic expectations. They can be incorporated in future decision support tools providing patient with specific and personalized reintervention probabilities and predicted evolutions of instance laboratory results, and echocardiographic measurements.

The models and techniques used and proposed throughout this thesis can be seen as building blocks towards more advanced algorithms. The value of vast amounts of data, also known as big data to improve our understanding and treatment of disease

is dependent on our ability to aggregate and analyze it efficiently. Machine learning techniques and artificial intelligence will play a significant and indispensable role in designing and refining models. In this thesis, the paradigm of our current understanding of pathophysiological relations shaped our models. In the future, machine learning and artificial intelligence may reveal relations not thought of before, hereby models shaping our understanding instead.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this thesis determinants of durability and clinical outcome after RVOT reconstruction with homografts have been investigated. We have presented longitudinal echocardiographic follow up using innovative yet underused statistical methods and presented our results in online interactive applications. These results extend the current knowledge about homografts by showing durability for individual patients, indicating vast differences based on age, sex, homograft tissue type and diagnosis. We furthermore presented outcome on the Ross procedure in middle aged patients and outcome of women, with special attention to pregnancy, given that male-female differences are often underappreciated.

The determinants of both homograft durability and patient survival after cardiac surgery as presented in this thesis can be included in new models predicting outcomes with different biomarkers. For instance, it would be extremely interesting to use mixed effects models on repeated volumetric measurements by MRI in patients with repaired Tetralogy of Fallot. Furthermore, our results stress the need for attention to male-female differences which are currently still poorly acknowledged. More sex specific research, like our focus on outcome after RVOT reconstruction in women with and without pregnancy, should be conducted potentially leading to sex specific recommendations and guidelines. The future will hopefully entail patient centered medicine with shared decision making, supported by patient information portals and decision aids that embed predictive models based on the statistical methods used throughout this thesis. Perceived and real barriers towards implementation and use of new and more complex statistics need to be overcome by education, introduction in general statistic courses and software, and improved interdisciplinary collaboration between clinicians and biostatisticians.

REFERENCES

1. (STS), T.S.o.T.S., Adults - Spring 2017 Harvest. 2017.
2. Gilboa, S.M., et al., Congenital Heart Defects in the United States: Estimating the Magnitude of the Affected Population in 2010. Circulation, 2016. 134(2): p. 101-9.
3. O'Leary, J.M., et al., The Changing Demographics of Congenital Heart Disease Hospitalizations in the United States, 1998 Through 2010. Jama, 2013. 309(10): p. 984-986.
4. Poinot, N., et al., Pulmonary valve replacement after right ventricular outflow tract reconstruction with homograft vs Contegra(R): a case control comparison of mortality and morbidity. J Cardiothorac Surg, 2018. 13(1): p. 8.
5. Mery, C.M., et al., Risk factors for development of endocarditis and reintervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. J Thorac Cardiovasc Surg, 2016. 151(2): p. 432-9, 441 e1-2.
6. Vitanova, K., et al., Which type of conduit to choose for right ventricular outflow tract reconstruction in patients below 1 year of age?dagger. Eur J Cardiothorac Surg, 2014. 46(6): p. 961-6; discussion 966.
7. Urso, S., et al., The Contegra conduit in the right ventricular outflow tract is an independent risk factor for graft replacement. Eur J Cardiothorac Surg, 2011. 40(3): p. 603-9.
8. Meyns, B., et al., Factors influencing the survival of cryopreserved homografts. The second homograft performs as well as the first. Eur J Cardiothorac Surg, 2005. 28(2): p. 211-6; discussion 216.
9. Forbess, J.M., et al., Cryopreserved homografts in the pulmonary position: determinants of durability. Ann Thorac Surg, 2001. 71(1): p. 54-9; discussion 59-60.
10. Tweddell, J.S., et al., Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation, 2000. 102(19 Suppl 3): p. III130-5.
11. Romeo, J.L.R., et al., Long-term clinical outcome and echocardiographic function of homografts in the right ventricular outflow tract†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy265-ezy265.
12. Kalfa, D.M., et al., Pulmonary position cryopreserved homograft in non-Ross patients: how to improve the results?†. European Journal of Cardio-Thoracic Surgery, 2012. 42(6): p. 981-987.
13. Troost, E., et al., Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration. Eur Heart J, 2007. 28(20): p. 2503-9.
14. Daenen, W. and M. Gewillig, Factors influencing medium-term performance of right-sided cryopreserved homografts. J Heart Valve Dis, 1997. 6(4): p. 347-53; discussion 353-4.
15. Bando, K., et al., Outcome of pulmonary and aortic homografts for right ventricular outflow tract reconstruction. J Thorac Cardiovasc Surg, 1995. 109(3): p. 509-17; discussion 517-8.
16. Kalfa, D., et al., How to choose the best available homograft to reconstruct the right ventricular outflow tract. The Journal of Thoracic and Cardiovascular Surgery, 2011. 142(4): p. 950-953.
17. Dehaki, M.G., et al., Long-Term Outcome of Mechanical Pulmonary Valve Replacement in 121 Patients with Congenital Heart Disease. Thorac Cardiovasc Surg, 2015. 63(5): p. 367-72.
18. Steinberg, Z.L., et al., Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves. Journal of the American College of Cardiology, 2017. 69(22): p. 2681.

19. Ayad, S.W., et al., Maternal and Fetal Outcomes in Pregnant Women with a Prosthetic Mechanical Heart Valve. Clin Med Insights Cardiol, 2016. 10: p. 11-7.
20. van Hagen, I.M., et al., Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation, 2015. 132(2): p. 132-42.
21. da Costa, F.D.A., et al., Decellularized Versus Standard Pulmonary Allografts in the Ross Procedure: Propensity-Matched Analysis. The Annals of Thoracic Surgery, 2018.
22. Mayer, J.E., Decellularized vs. Standard Pulmonary Allografts in the Ross Procedure: Propensity Matched Analysis (Commentary). The Annals of Thoracic Surgery, 2017.
23. da Costa, F.D.A., et al., Decellularized Allografts for Right Ventricular Outflow Tract Reconstruction in Children. World J Pediatr Congenit Heart Surg, 2017. 8(5): p. 605-612.
24. Huygens, S.A., et al., What is the potential of tissue-engineered pulmonary valves in children? Ann Thorac Surg, 2018.
25. Rippel, R.A., H. Ghanbari, and A.M. Seifalian, Tissue-engineered heart valve: future of cardiac surgery. World J Surg, 2012. 36(7): p. 1581-91.
26. Sarikouch, S., et al., Decellularized fresh homografts for pulmonary valve replacement: a decade of clinical experience. Eur J Cardiothorac Surg, 2016. 50(2): p. 281-90.
27. Serghei, C., et al., Use of Fresh Decellularized Allografts for Pulmonary Valve Replacement May Reduce the Reoperation Rate in Children and Young Adults. Circulation, 2011. 124(11_suppl_1): p. S115-S123.
28. Bechtel, J.F., U. Stierle, and H.H. Sievers, Fifty-two months' mean follow up of decellularized SynerGraft-treated pulmonary valve allografts. J Heart Valve Dis, 2008. 17(1): p. 98-104; discussion 104.
29. Burch, P.T., et al., Clinical performance of decellularized cryopreserved valved allografts compared with standard allografts in the right ventricular outflow tract. Ann Thorac Surg, 2010. 90(4): p. 1301-5; discussion 1306.
30. Konuma, T., et al., Performance of CryoValve SG decellularized pulmonary allografts compared with standard cryopreserved allografts. Ann Thorac Surg, 2009. 88(3): p. 849-54; discussion 554-5.
31. Chatterjee, A., et al., Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies. J Am Heart Assoc, 2017. 6(8).
32. Romeo, J.L.R., et al., Downsized cryopreserved and standard-sized allografts for right ventricular outflow tract reconstruction in children: long-term single-institutional experience. Interactive CardioVascular and Thoracic Surgery, 2018: p. ivy057-ivy057.
33. Hawkins, J.A., et al., Class I and class II anti-HLA antibodies after implantation of cryopreserved allograft material in pediatric patients. J Thorac Cardiovasc Surg, 2000. 119(2): p. 324-30.
34. Hawkins, J.A., et al., Immunogenicity of decellularized cryopreserved allografts in pediatric cardiac surgery: comparison with standard cryopreserved allografts. J Thorac Cardiovasc Surg, 2003. 126(1): p. 247-52; discussion 252-3.
35. Shaddy, R.E., et al., Prospective analysis of HLA immunogenicity of cryopreserved valved allografts used in pediatric heart surgery. Circulation, 1996. 94(5): p. 1063-7.

36. Mercer, C.W., et al., Polytetrafluoroethylene conduits versus homografts for right ventricular outflow tract reconstruction in infants and young children: An institutional experience. J Thorac Cardiovasc Surg, 2018.
37. Yong, M.S., et al., Medium-term outcomes of bovine jugular vein graft and homograft conduits in children. ANZ J Surg, 2015. 85(5): p. 381-5.
38. Holmes, A.A., et al., The Contegra conduit: Late outcomes in right ventricular outflow tract reconstruction. Ann Pediatr Cardiol, 2012. 5(1): p. 27-33.
39. Breymann, T., et al., European Contegra multicentre study: 7-year results after 165 valved bovine jugular vein graft implantations. Thorac Cardiovasc Surg, 2009. 57(5): p. 257-69.
40. Carrel, T., Bovine valved jugular vein (Contegra) to reconstruct the right ventricular outflow tract. Expert Rev Med Devices, 2004. 1(1): p. 11-9.
41. Breymann, T., et al., The Contegra bovine valved jugular vein conduit for pediatric RVOT reconstruction: 4 years experience with 108 patients. J Card Surg, 2004. 19(5): p. 426-31.
42. Francois, K., et al., Small-sized conduits in the right ventricular outflow tract in young children: bicuspidalized homografts are a good alternative to standard conduits. Eur J Cardiothorac Surg, 2017.
43. Perri, G., et al., Outcome of Standard and Bicuspidalized Cryopreserved Homografts for Primary Right Ventricular Outflow Tract Reconstruction. J Heart Valve Dis, 2015. 24(1): p. 83-8.
44. Cleuziou, J., et al., Durability of down-sized homografts for the reconstruction of the right ventricular outflow tractdagger. Eur J Cardiothorac Surg, 2015.
45. Yang, J.H., et al., Midterm results of size-reduced cryopreserved homografts for right ventricular outflow tract reconstruction. Ann Thorac Surg, 2010. 89(6): p. 1821-6.
46. van der Bom, T., et al., The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. Am Heart J, 2012. 164(4): p. 568-75.
47. van der Linde, D., et al., Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol, 2011. 58(21): p. 2241-7.
48. Rajani, B., R.B. Mee, and N.B. Ratliff, Evidence for rejection of homograft cardiac valves in infants. J Thorac Cardiovasc Surg, 1998. 115(1): p. 111-7.
49. Greutmann, M. and P.G. Pieper, Pregnancy in women with congenital heart disease. European Heart Journal, 2015. 36(37): p. 2491-2499.
50. Arabkhani, B., et al., Does Pregnancy Influence the Durability of Human Aortic Valve Substitutes? Journal of the American College of Cardiology, 2012. 60(19): p. 1991-1992.
51. Cleuziou, J., et al., Pregnancy does not accelerate biological valve degeneration. Int J Cardiol, 2010. 145(3): p. 418-21.
52. Regitz-Zagrosek, V., et al., 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. European Heart Journal, 2018. 39(34): p. 3165-3241.
53. Romeo, J.L.R., et al., Outcomes of Pregnancy After Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit. Journal of the American College of Cardiology, 2018. 71(23): p. 2656-2665.

54. Poh, C.L., et al., The Ross procedure in adults presenting with bicuspid aortic valve and pure aortic regurgitation: 85% freedom from reoperation at 20 years†. European Journal of Cardio-Thoracic Surgery, 2018: p. ezy073-ezy073.

55. Martin, E., et al., Clinical Outcomes Following the Ross Procedure in Adults: A 25-Year Longitudinal Study. J Am Coll Cardiol, 2017. 70(15): p. 1890-1899.

56. Sievers, H.H., et al., A multicentre evaluation of the autograft procedure for young patients undergoing aortic valve replacement: update on the German Ross Registrydagger. Eur J Cardiothorac Surg, 2016. 49(1): p. 212-8.

57. Mastrobuoni, S., et al., The Ross procedure in young adults: over 20 years of experience in our Institutiondagger. Eur J Cardiothorac Surg, 2016. 49(2): p. 507-13.

58. Skillington, P.D., et al., The Ross procedure using autologous support of the pulmonary autograft: techniques and late results. J Thorac Cardiovasc Surg, 2015. 149(2 Suppl): p. S46-52.

59. Reece, T.B., et al., Rethinking the ross procedure in adults. Ann Thorac Surg, 2014. 97(1): p. 175-81.

60. El-Hamamsy, I. and N.C. Poirier, What is the role of the Ross procedure in today's armamentarium? Can J Cardiol, 2013. 29(12): p. 1569-76.

61. Ghoneim, A., et al., Expanding Eligibility for the Ross Procedure: A Reasonable Proposition? Can J Cardiol, 2018. 34(6): p. 759-765.

62. Pettersson, G.B. and E.H. Blackstone, Is it Time to Reconsider Use of the Ross Procedure for Adults? J Am Coll Cardiol, 2018. 71(12): p. 1345-1346.

63. Yacoub, M.H., et al., Under-use of the Ross operation--a lost opportunity. Lancet, 2014. 384(9943): p. 559-60.

64. Um, K.J., et al., Hemodynamic outcomes of the Ross procedure versus other aortic valve replacement: a systematic review and meta-analysis. J Cardiovasc Surg (Torino), 2018.

65. Buratto, E., et al., Improved Survival After the Ross Procedure Compared With Mechanical Aortic Valve Replacement. J Am Coll Cardiol, 2018. 71(12): p. 1337-1344.

66. Bouhout, I., et al., Is the Ross procedure a riskier operation? Perioperative outcome comparison with mechanical aortic valve replacement in a propensity-matched cohort. Interact Cardiovasc Thorac Surg, 2017. 24(1): p. 41-47.

67. Sharabiani, M.T., et al., Aortic Valve Replacement and the Ross Operation in Children and Young Adults. J Am Coll Cardiol, 2016. 67(24): p. 2858-70.

68. Mazine, A., et al., Long-Term Outcomes of the Ross Procedure Versus Mechanical Aortic Valve Replacement: Propensity-Matched Cohort Study. Circulation, 2016. 134(8): p. 576-85.

69. David, T.E., et al., The Ross procedure: outcomes at 20 years. J Thorac Cardiovasc Surg, 2014. 147(1): p. 85-93.

70. Karaskov, A., et al., Results of the Ross procedure in adults: a single-centre experience of 741 operations. Eur J Cardiothorac Surg, 2016. 49(5): p. e97-e104.

71. Miskovic, A., et al., A 17-year, single-centre experience with the Ross procedure: fulfilling the promise of a durable option without anticoagulation?dagger. Eur J Cardiothorac Surg, 2016. 49(2): p. 514-9.

72. Mokhles, M.M., et al., Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation, 2011. 123(1): p. 31-8.
73. Sievers, H.H., et al., Valve performance classification in 630 subcoronary Ross patients over 22 years. J Thorac Cardiovasc Surg, 2018. 156(1): p. 79-86 e2.
74. Svensson, L.G., et al., Aortic valve and ascending aorta guidelines for management and quality measures. Ann Thorac Surg, 2013. 95(6 Suppl): p. S1-66.
75. Nishimura, R.A., et al., 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2017.
76. Baumgartner, H., et al., 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal, 2017. 38(36): p. 2739-2791.
77. Bouhout, I., et al., Impact of the Learning Curve on Early Outcomes Following the Ross Procedure. Can J Cardiol, 2017. 33(4): p. 493-500.
78. Mazine, A., A. Ghoneim, and I. El-Hamamsy, The Ross Procedure: How I Teach It. Ann Thorac Surg, 2018.
79. Lillehei, C.W., et al., Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. Ann Surg, 1955. 142(3): p. 418-42.
80. d'Udekem, Y., et al., Intersurgeon variability in long-term outcomes after transatrial repair of tetralogy of Fallot: 25 years' experience with 675 patients. J Thorac Cardiovasc Surg, 2014. 147(3): p. 880-6.
81. Murphy, J.G., et al., Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med, 1993. 329(9): p. 593-9.
82. Nollert, G., et al., Long-term results of total repair of tetralogy of Fallot in adulthood: 35 years follow-up in 104 patients corrected at the age of 18 or older. Thorac Cardiovasc Surg, 1997. 45(4): p. 178-81.
83. Ooi, A., et al., Medium term outcome for infant repair in tetralogy of Fallot: Indicators for timing of surgery. Eur J Cardiothorac Surg, 2006. 30(6): p. 917-22.
84. Gatzoulis, M.A., et al., Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. The Lancet, 2000. 356(9234): p. 975-981.
85. Therrien, J., et al., Pulmonary valve replacement in adults late after repair of tetralogy of fallot: are we operating too late? J Am Coll Cardiol, 2000. 36(5): p. 1670-5.
86. Cuypers, J.A., et al., Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. Circulation, 2014. 130(22): p. 1944-53.
87. Frigiola, A., et al., Pulmonary regurgitation is an important determinant of right ventricular contractile dysfunction in patients with surgically repaired tetralogy of fallot. Circulation, 2004. 110(11): p. II153-II157.
88. Geva, T., et al., Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol, 2004. 43(6): p. 1068-1074.

89. Knauth, A.L., et al., Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart, 2008. 94(2): p. 211-6.

90. Gatzoulis, M.A., et al., Right and left ventricular systolic function late after repair of tetralogy of Fallot. Am J Cardiol, 2000. 86(12): p. 1352-7.

91. Mascio, C.E., et al., Outcomes in adult congenital heart surgery: Analysis of the Society of Thoracic Surgeons Database. The Journal of Thoracic and Cardiovascular Surgery, 2011. 142(5): p. 1090-1097.

92. Baumgartner, H., et al., ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J, 2010. 31(23): p. 2915-57.

93. Warnes, C.A., et al., ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). Circulation, 2008. 118(23): p. 2395-451.

94. Lee, C., et al., Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement. J Am Coll Cardiol, 2012. 60(11): p. 1005-14.

95. Chalard, A., et al., Effect of Pulmonary Valve Replacement on Left Ventricular Function in Patients With Tetralogy of Fallot. The American Journal of Cardiology, 2012. 110(12): p. 1828-1835.

96. Harrild, D.M., et al., Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. Circulation, 2009. 119(3): p. 445-51.

97. Oosterhof, T., et al., Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation, 2007. 116(5): p. 545-51.

98. Buechel, E.R., et al., Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J, 2005. 26(24): p. 2721-7.

99. Hallbergson, A., et al., Right ventricular remodeling after pulmonary valve replacement: early gains, late losses. Ann Thorac Surg, 2015. 99(2): p. 660-6.

100. Ferraz Cavalcanti, P.E., et al., Pulmonary Valve Replacement After Operative Repair of Tetralogy of Fallot: Meta-Analysis and Meta-Regression of 3,118 Patients From 48 Studies. Journal of the American College of Cardiology, 2013. 62(23): p. 2227-2243.

101. Geva, T., et al., Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients with Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort. Circulation, 2018.

102. Bokma, J.P., et al., A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart, 2018. 104(9): p. 738-744.

103. Heng, E.L., et al., Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Circulation, 2017. 136(18): p. 1703.

104. Bokma, J.P., et al., A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart, 2017.

105. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg, 2008. 85(4): p. 1490-5.

106. Blackstone, E.H. and R.D. Weisel, The conclusion of papers published in the Journal should be supported by an appropriate statistical analysis. The Journal of Thoracic and Cardiovascular Surgery, 2014. 148(6): p. 2479.

107. Stacey, D., et al., Shared Decision Making Interventions: Theoretical and Empirical Evidence with Implications for Health Literacy. Stud Health Technol Inform, 2017. 240: p. 263-283.

Summary

Right ventricular outflow tract interventions are relatively frequently necessary. Pulmonary valve replacement with congenital heart disease has already become the most often performed cardiac surgical intervention in adults. Human donor valves, also known as homografts, are one of the most used valvular alternatives due to their durability, independence from permanent anticoagulation and low endocarditis risk. Still, long term outcome and hemodynamic performance may differ strongly between patients and reintervention is common. Furthermore, the current population of adults with congenital heart disease is new and offers a lot of challenges. Careful deliberation between the drawbacks and benefits of intervention at any moment requires reliable information about all treatment options.

This thesis aimed to describe the long term outcome after pulmonary valve replacement with the use of novel statistical techniques with serial echocardiographic measurements. This information could be useful when determining both indication and timing of repeated intervention and reducing unnecessary risks.

In clinical chronological order the life course of patients who underwent surgical intervention involving their RVOT is addressed. A broad range of heart diseases will be addressed, including both congenital and acquired cardiac defects.

Chapter 1 Introduction

Chapter 1 offers an introduction on the use of homografts in patients with congenital heart disease. The current and future challenges for this constantly developing patient population are addressed which will form the basis of the main research questions of this thesis.

Chapter 2 Tetralogy of Fallot

The largest group of patients undergoing RVOT reconstruction consist out of patients with corrected Tetralogy of Fallot. Surgical correction at early age entails closure of the ventricular septal defect and relief of the pulmonary stenosis. Most surgeons aim to preserve at much of the pulmonary valve as possible hereby reducing the amount of pulmonary regurgitation. Especially when relief can only be accomplished by using a transannular patch which invariably leads to regurgitation, the long term morbidity caused by progressive right ventricular dilatation can be substantial. In an attempt to prevent heart failure and arrhythmia, many patients undergo pulmonary valve replacement at a later stage.

In Chapter 2, results of a systematic review and meta-analysis including 143 published articles about clinical outcome after surgical correction of Tetralogy of Fallot are presented. Correction can be performed at an early age and is associated with a low 30-day mortality of about 2%. Also asymptomatic patients are increasingly being operated. Down syndrome is the most commonly associated genetic syndrome. The use of

a transannular patch has been reduced since the raised awareness about the long term adverse effects of severe chronic regurgitation. The surgical intentions and possibilities of reducing the size of the transannular patch and preserve the native pulmonary valve are often stated. However, there is limited evidence that monocusp reconstruction reduces the probability of reintervention or reduces late mortality. Correction in older patients is generally associated with a more frequent use of transannular patches and a high mortality rate. Correction in adults patients is possible but associated with a substantial 30-day mortality of 7.55%.

Severe arrhythmia, heart failure and diminished exercise tolerance determine both quantity and quality of life after correction. We now know that this is directly related to the degree of pulmonary regurgitation and right ventricular dilatation. We can treat this be replacing the pulmonary valve, often 15 to 20 years after correction. Determining the optimal timing of this procedure has been, and still is the center of fierce debate. A randomized controlled trial could provide answers, however practical and ethical concerns prohibit its conception. A good alternative might be analyzing and relating longitudinal volumetric measurements gathered by MRI with clinical outcome using mixed and joint modeling.

Chapter 3 Pulmonary Atresia with and without systemic collateral arteries

Chapter 3 describes outcome and performance of pulmonary homografts implanted in patients with pulmonary atresia (PA) with and without systemic collateral arteries (SYPCAs). Patients with PA lack a direct continuation between the right ventricle and pulmonary artery. Therefore, patients with PA need pulmonary valve replacement already at a young age in contrast to patients with TOF to restore this continuation. Lungflow before correction is dependent on a persistent ductus arteriosus or SYPCAs. Pulmonary vasculature can be variably developed. In the Erasmus Medical Center, we adopted a staged approach performing one or multiple unifocalizations before definite correction, when SYPCAs are present. If no SYPCAs are present, patients are corrected in a single stage procedure. In Chapter 3, we sought whether there is a difference in hemodynamic performance and durability between homografts implanted in patients with and without SYPCAs. Differences in development of pulmonary vasculature could be of influence to the homograft, inducing predominantly regurgitation in case of severe pulmonary hypertension. After a median follow-up period of 20 years, we found that severe pulmonary regurgitation was more often an indication for valve replacement in patients who had SYPCAs. Reintervention in general was common in both groups, mainly consisting from repeated pulmonary valve replacements and percutaneous dilatations of localized narrowing of the pulmonary vasculature. Data about the long term outcome, ideally

patients who reached 50 to 60 years of age, are needed because clinical course at that age is still largely unknown.

Chapter 4 Bicuspidalization and patients younger than 2 years

Chapter 4 describes the clinical course of homografts in patients operated before the age of 2 years. We demonstrated that operative correction with pulmonary valve replacement is save and provides long term survival. Nevertheless, most if not all of these patients will face repeated valvular intervention within 20 years due to the limited growth capacity of the homograft and resistance to progressive calcifications. To accommodate the shortage of right sized homografts, bicuspidalization was proposed in 1994. We demonstrated using mixed effects modeling that this procedure does not affect durability and hemodynamics of the valve. Both regurgitation and stenosis develop equally fast.

Chapter 5 Letter to the Editor of the European Journal of Cardio Thoracic Surgery

The use of novel statistical methods which can account for the number and timing of different measurements between patients has been a central aspect of this thesis. The analysis of processes that develop with time, without accounting for the variance between measurements is wrong. Chapter 5 is a letter we addressed to the editors of the European Journal of Cardio Thoracic Surgery (EJCTS), in which we try to address the importance of this fact. The reduction of continuous processes to events inevitably leads to loss of important information. We furthermore reflect on the use of Propensity Score Matching (PSM) as an increasingly employed method to compare groups. PSM is a method to correct for differences in patient characteristics between two non-randomized groups who undergo different interventions. The aim is to ascribe differences in outcome to the different intervention methods. In order for the matching to be qualitatively good, a high percentage of matches in necessary and as little as possible differences in preoperatively known variables. Both aspects were lacking in the study published by our colleagues in the EJCTS.

Chapter 6 All homografts

Chapter 6 provides a very detailed overview of outcome after pulmonary valve replacement of all patients who were operated in the Erasmus University Medical Center. We demonstrated that durability is the greatest in patients who received a pulmonary homograft at adult age. Durability was also greatest in women and patients who underwent the Ross procedure. Furthermore, we presented the very first report of repeated assessed quality of life in this specific population. We found self-reported quality of life of patients being lower than that of a comparable Dutch reference population. Remark-

ably, patients who received a new homograft during the 5 year interval, did no display a reduction in one of the subscales of the Short-Form 36, as compared to patients who did not undergo repeated pulmonary valve replacement. Serial echocardiographic measurements were analyzed using mixed effects models and presented as an interactive freely available online application. This online application allows any combination of diagnosis, age, valve type and valve size to be entered to predict the average echocardiographic evolution.

Chapter 7 PVR in Tetralogy of Fallot and QRS duration

In Chapter 7 serial measurements of QRS duration in patients with corrected Tetralogy of Fallot were analyzed before and after pulmonary valve replacement. All patients who underwent correction of Tetralogy of Fallot with a transannular patch in the Erasmus University Medical Center were included. Of 158 consecutive patients, 155 survived till discharge. We found a relationship between the time between correction and pulmonary valve replacement and the development of QRS duration after PVR. We know from the literature that QRS duration has a clear clinical correlation with heart failure, both left and right ventricular dimensions and the probability of arrhythmia and sudden death. Our analysis suggested that progressive prolongation of QRS duration can be prevented by performing pulmonary valve replacement within 17 years in patients corrected at the age of 6 months.

Chapter 8 Letter to the Editor of Circulation

Chapter 8 addressed our concerns with a recent study published in Circulation about the optimal timing of pulmonary valve replacement in corrected patients with Fallot. No solution was however offered in the article. The patient population was limited and in our opinion to homogenous to provide a real answer with conventional statistical techniques. We proposed a fundamentally different statistical approach considering mixed effect modeling. We feel that mixed effects modelling is still being used to little within the medical science especially interested in the longitudinal analysis of biomarkers.

Chapters 9 and 10 Pregnancy

Most patients who undergo pulmonary valve replacement at a young age survive well into their fertile period. In chapter 9, we addressed pregnancy in patients who underwent pulmonary valve replacement. Outcome was good for both mother and child. Clinical deterioration was rare and almost always treatable. Most outcomes were comparable to those of the general Dutch Population. Prematurity and a low birth weight were relative more frequent however, compared to the general Dutch population.

In chapter 10 we used mixed and joint effects models to demonstrate that pregnancy does not affect the long term outcome of pulmonary homografts. Women who ex-

perienced pregnancy did not have a higher rate of mortality nor did they have more valve related events or interventions, compared with women who never experienced pregnancy. This is important during the counseling of women contemplating or already experiencing pregnancy.

Chapter 11 The Ross Procedure

In chapter 11 the results were presented of five large centers that regularly perform the Ross procedure in middle aged patients. Both clinical and echocardiographic outcomes were pooled and collectively analyzed using mixed effects models. We found that valve related mortality, morbidity and reintervention are very rare the first 15 years after surgery. This may be partially ascribed to the avoidance of lifelong anticoagulance. This is a great advantage especially in young patients considering pregnancy or have an active lifestyle. Given these positive results, it is remarkable that none of the three major guidelines about aortic valve replacement, recommends the Ross procedure to be even considered in adults.

Chapter 12 Percutaneous pulmonary valve intervention

Repeated surgical intervention becomes increasingly complex and hazardous. Therefore less invasive, percutaneous intervention methods have been conceived. Percutaneous right sided valve implantation is possible. Most often the Melody Valve is used. We analyzed Melody valve implantations by pooling data from the Erasmus University Medical Center, Radboud University, and Maastricht University Medical Center. Implantation is relatively save. However, late endocarditis risk is relatively high. Furthermore, the valve displays a relatively high rate of stenosis making surgical intervention ultimately inevitable. Still, in selected patients percutaneous valve implantation can be a good alternative to delay surgical reintervention in failing homografts.

Chapter 13 Discussion

In chapter 13 we summarize our findings and place them within a more general context. We also provide our thoughts and recommendations for future investigations.

Samenvatting

Operaties en interventies aan de rechter ventrikel uitstroombaan zijn relatief frequent nodig. In volwassenen met aangeboren hartafwijkingen is pulmonalisklepvervanging reeds de meest verrichte hartoperatie. Menselijke pulmonale donorkleppen oftewel homografts zijn vanwege hun duurzaamheid, onafhankelijkheid van permanent antistolling en lage vatbaarheid voor endocarditis een van de meest gangbare alternatieven wanneer klepvervanging geïndiceerd is. Desondanks kunnen klinische uitkomsten sterk verschillen van patiënt tot patiënt, en is reïnterventie op enig moment vaak nodig. De groep volwassenen die bestaat uit patiënten met gecorrigeerde aangeboren hartafwijkingen is nieuw en biedt een hoop uitdagingen. Een zorgvuldige afweging tussen de voordelen en nadelen van wel of geen (re)interventie op enig moment vraagt om betrouwbare informatie over alle alternatieve behandelstrategieën.

De doelstellingen van dit proefschrift waren om de lange termijn uitkomsten van pulmonalisklep-vervangende therapieën te beschrijven alsmede nieuwe statistische concepten toe te passen op echografische metingen over tijd. Dit alles ten behoeve van het verbeteren van de indicatiestelling en timing van herhaalde interventie, en risico's zo veel mogelijk te beperken.

Min of meer in klinisch chronologische volgorde is het beloop van patiënten na chirurgische correctie en klepimplantatie met een verscheidenheid aan zowel aangeboren als verworven aandoeningen ter sprake gekomen.

Hoofdstuk 1 Inleiding

In hoofdstuk 1 wordt een introductie gegeven over het gebruik van menselijke donorkleppen voor patiënten met aangeboren hartafwijkingen. De huidige en toekomstige uitdagingen van een continue ontwikkelende patiëntenpopulatie worden voorgelegd die aanleiding geven voor de onderzoeksvragen die centraal staan in dit proefschrift.

Hoofdstuk 2 Tetralogie van Fallot

Niet alle patiënten krijgen tijdens hun eerste correctie direct een nieuwe pulmonaalklep. De grootste groep patiënten die een reconstructie van de rechter ventrikel uitstroombaan met een klep ondergaat, bestaat uit patiënten met gecorrigeerde tetralogie van Fallot (TOF). Chirurgische correctie op de jonge leeftijd bestaat uit het sluiten van het ventrikel septum defect en opheffen van de vernauwing ten hoogte van de pulmonalisklep. Hierbij wordt geprobeerd de vernauwing op te heffen zonder (veel) lekkage te veroorzaken. Met name wanneer de vernauwing alleen kan worden opgeheven door de klep te verwijden met een weefselpatch (een zogenaamde transannulaire patch), zullen lekkage van de klep oftewel pulmonaalinsufficiëntie en progressieve verwijding van de rechter ventrikel onvermijdelijk zijn met hartfalen en ritmestoornissen tot gevolg. Hierdoor zal de patiënt doorgaans een pulmonaalklepvervanging op latere leeftijd ondergaan ter behandeling van de ernstige lekkage en de gevolgen daarvan.

In **Hoofdstuk 2** zijn resultaten gepresenteerd van een systematic review en meta-analyse van 143 gepubliceerde artikelen over de resultaten van chirurgische correctie van TOF. Correctie kan plaatsvinden op een jonge leeftijd en gaat doorgaans gepaard met een lage 30 dagen mortaliteit van ongeveer 2%. Steeds vaker ondergaan ook patiënten die geen symptomen ervaren een correctie. Van een grote verscheidenheid aan mogelijke geassocieerde anatomische en genetische afwijkingen, is het syndroom van Down het meest voorkomend. Chirurgische correctie kan op steeds jongere leeftijd met uitstekende resultaten. Correctie ging voorheen vaker gepaard met een transannulaire patch (TAP), echter werd dit gebruik verminderd zodra meer bekend werd over de nadelige gevolgen van chronische insufficiëntie. De intentie en mogelijkheden om klepsparend te opereren worden inmiddels expliciet uitgesproken. Er zijn echter weinig aanwijzingen dat aanbrengen van een nieuw klepblad binnen de transannulaire patch, zogeheten 'monocusp reconstructie' , de kans op reïnterventie of later mortaliteit gunstig beïnvloed. Daarnaast werd gevonden dat een benadering door het rechter ventrikel steeds minder frequent wordt toegepast, mede te verklaren door het toegenomen bewustzijn van de maligne aard van de hieruit volgende schade. Studies die een latere leeftijd van correctie, een hoger gebruik van een TAP of voorgaande palliatie beschreven, rapporteren gemiddeld een hogere mortaliteit. Correctie in volwassenen is mogelijk maar gaat gepaard met een 30-dagen mortaliteit van ongeveer 7.55%.

Na correctie beperken ritmestoornissen, hartfalen en een verminderde inspanningstolerantie kwaliteit en duur van leven. Bovendien is dit gerelateerd aan de ernst van de insufficiëntie en rechter ventrikeldilatatie. Derhalve bestaat er ondanks de sterk verbeterde levensverwachting sinds de mogelijkheid van correctie, nog steeds een verhoogde mortaliteit en morbiditeit ten opzichte van de doorsnee populatie. De insufficiëntie wordt doorgaans behandeld door een klepvervanging; vaak 15 – 20 jaar later. Juiste criteria die het moment van deze electieve ingreep moeten bepalen zijn nog altijd onderwerp van een langdurige intense discussie. Idealiter zou een definitief antwoord gevonden kunnen worden door middel van een randomized controlled trial. Echter zullen ethische en praktische bezwaren de mogelijkheden hiertoe beperken waardoor deze hoogstwaarschijnlijk nooit opgezet zal worden. Een goed alternatief is wellicht het analyseren van longitudinale volumetrische metingen op basis van MRI die middels mixed en joint modeling met klinische uitkomsten geassocieerd kunnen worden.

Hoofdstuk 3 PA VSD met en zonder systeem collateralen

In **Hoofdstuk 3** beschrijven we het beloop van rechtszijdige pulmonaalkleppen die zijn geïmplanteerd in patiënten met pulmonalisatresie (PA) met en zonder systeemcollateralen. Patiënten met een pulmonalisatresie hebben geen direct verbinding tussen het rechter ventrikel en de arteria pulmonalis. Hierdoor ondergaan patiënten met pulmonalisatresie in tegenstelling tot patiënten met TOF vaak wel op jongere leeftijd

een klepvervanging om de doorgankelijkheid te herstellen. Continuïteit van de rechter ventrikel naar de longcirculatie is dus onderbroken waardoor het bloed door het ventrikelseptumdefect (VSD) moet en de longcirculatie afhankelijk is van een persisterende ductus arteriosus of systeem-pulmonale collateralen. Die collateralen ontspringen vaak vanaf de aorta en voorzien verschillende longsegmenten van bloed. Het centrale longvaatbed laat bij deze patiënten vaak een wisselende mate van ontwikkeling zien. In het Erasmus Medisch Centrum wordt gekozen voor een gefaseerde correctie waarbij unifocalisatie uiteindelijk gevolgd wordt door definitieve correctie in patiënten met systeem-pulmonale collateralen. Unifocalisatie is de naam voor de procedure waarbij de collateralen die longsegmenten van bloed voorzien, losgemaakt worden van de aorta en verbonden worden met het centrale arteriële longvaatsysteem. Patiënten zonder collateralen ondergaan uiteraard geen unifocalisatie maar direct herstel van de continuïteit door middel van pulmonalisklepvervanging. In beiden wordt de pulmonalisklep vervangen door een homograft. In dit hoofdstuk is onderzocht of er verschil bestaat in de prestaties van de homograft tussen patiënten met PA-VSD met en zonder collateralen. De hypothese is namelijk dat verschillen in ontwikkeling van pulmonaalvasculatuur (meestal verminderd in de aanwezigheid van systeemcollateralen zich uitend als pulmonale hypertensie) en ingrepen aan het longvaatbed, via een verhoogde longvaatweerstand, insufficiëntie kan induceren. Na een mediane periode van ruim 20 jaar werd dit inderdaad gezien. Ernstige insufficiëntie van de homograft was vaker een indicatie voor vervanging in patiënten met de collateralen. Reïnterventie kwam veelvuldig voor, gekenmerkt door nieuwe pulmonalisklepvervangingen en percutane interventies van gelokaliseerde vernauwingen in het pulmonale vaatbed. Lange termijnstudies met volwassen patiënten die idealiter de 50 en 60 jaar bereiken zijn nodig om meer informatie te verschaffen over het late klinische beloop. Het is vooralsnog evident dat herhaalde interventie, en levenslange en regelmatige follow up noodzakelijk zijn in het overgrote merendeel van de patiënten.

Hoofdstuk 4 Bicuspidalisatie en patiëntjes jonger dan 2 jaar

In **Hoofdstuk 4** wordt het beloop beschreven van homografts in patiëntjes jonger dan 2 jaar. We hebben aangetoond dat voor de jongste patiënten operatieve correctie met een klepvervangende interventie een veilige methode is die langdurige overleving geeft. Desondanks zullen vrijwel al deze patiënten na 15 à 20 jaar opnieuw een klep interventie ondergaan ten gevolge van het beperkte vermogen van de klep zich mee te ontwikkelen met de groeispurt, en weerstand te bieden tegen de progressieve calcificaties en daarmee vernauwing van de klep. Om tegemoet te komen aan het tekort aan passende homografts werd reeds in 1994 voorgesteld drieslippige (*tricuspide*) pulmonaliskleppen te verkleinen tot tweeslippige (*bicuspide)* kleppen. Wij toonden aan dat het verkleinen van de klep van een tricuspide naar een bicuspide klep om tegemoet

te komen aan het tekort aan geschikte kleppen, geen invloed heeft op de duurzaamheid en hemodynamiek van de klep. Zowel vernauwing als lekkage ontwikkeling zich even snel. Wel is het zo dat deze jonge groep patiënten vaak binnen 20 jaar een nieuwe pulmonaalklepvervanging moet ondergaan.

Hoofdstuk 5 Brief aan de Editor van de European Journal of Cardio Thoracic Surgery

Centraal binnen dit proefschrift staan de toepassing en het gebruik van statistische methoden die met disbalans in zowel meetmomenten als –aantal efficiënt kan omgaan. Het analyseren van processen die per definitie met tijd veranderen, zonder de variatie aan meetmoment te overwegen in de analyse is een ernstige kunstfout. **Hoofdstuk 5** bestaat uit een brief aan de editor van de European Journal of Cardio Thoracic Surgery (EJCTS) waarin we proberen auteurs en lezers van het blad hiervan bewust te maken. Met name het reduceren van continue processen tot dichotome gebeurtenissen leidt tot verlies aan waardevolle informatie. Dit komt doordat een echografische meting zoals pulmonalisinsufficiëntie reeds langer bestaan heeft voordat het geconstateerd werd. Daarnaast reflecteren we in deze brief op het gebruik van Propensity Score Matching (PSM) om twee groepen patiënten te vergelijken. PSM is een methode om te corrigeren voor verschillen in preoperatieve kenmerken van patiënten die verschillende interventies ondergaan. De wens is namelijk vergelijkbare groepen zodat eventueel verschil in uitkomsten in zijn geheel kan worden toegekend aan de verschillende interventies. Helaas zijn voor een goede matching procedure een hoog percentage aan matches gewenst en zo vergelijkbaar mogelijke preoperatieve kenmerken. Beide waren helaas niet het geval bij de studie van de collega's die werd gepubliceerd in het EJCTS.

Hoofdstuk 6 Alle homografts

In **Hoofdstuk 6** wordt een update gegeven over de klinische uitkomsten van alle patiënten die in het Erasmus Medisch Centrum Rotterdam een pulmonaalklepvervanging zijn ondergaan. Het onderzoek toonde aan dat duurzaamheid het grootst is voor patiënten die op volwassen leeftijd een pulmonaal klep hebben ontvangen. Duurzaamheid van homografts is ook groter in Ross patiënten en vrouwen. Daarnaast was het de eerste studie ooit die herhaald kwaliteit van leven in deze populatie heeft onderzocht. Hoewel zelf gerapporteerde kwaliteit van leven geleidelijk daalt met leeftijd, is die van patiënten lager dan dat van een vergelijkbare Nederlandse referentie populatie. Patiënten die in de tussentijd een nieuwe homograft hadden gekregen lieten echter geen regressie zien in één van de subschalen van de Short Form-36, in tegenstelling tot de patiënten die geen nieuwe homograft hadden gekregen. Tenslotte werden de resultaten besproken van de seriële echoanalyse middels een gratis toegankelijke website. Op deze website is het

mogelijk om voor elke combinatie van diagnose, leeftijd, klepsoort en klepgrootte, het gemiddelde echografische beloop wat betreft vernauwing en lekkage te voorspellen.

Hoofdstuk 7 Fallot PVR QRS

In **Hoofdstuk 7** zijn seriële metingen van QRS duur van gecorrigeerde patiënten met TOF geanalyseerd, voor en na pulmonaalklepvervanging. Alle patiënten die in het Erasmus Medisch Centrum Rotterdam een pulmonaalklepvervanging ondergingen na correctie met een transannulaire patch zijn hierbij geïncludeerd. Van de 158 overleefden 155 de operatie tot ontslag. Er werd een verband gevonden tussen de tijd die verstrijkt tussen correctie en pulmonaalklepvervanging, en de ontwikkeling van QRS duur na de klepvervanging. QRS duur heeft een duidelijke klinische correlatie met zowel hartfalen, rechter en linker ventrikel dimensies als de kans op ritmestoornissen en plotse hartdood. Onze analyse suggereerde dat progressieve verlenging van QRS duur voorkomen kan worden door patiënten die op de leeftijd van 6 maanden een correctie ondergingen, binnen 17 jaar een nieuwe pulmonalisklep te geven.

Hoofdstuk 8 Brief aan de Editor van Circulation

In **Hoofdstuk 8** wordt een recente studie over het bepalen van het moment van pulmonaalklepvervanging in patiënten met TOF besproken die werd gepubliceerd in Circulation. Hoewel de auteurs de intentie hadden om een zeer relevant vraagstuk te beantwoorden, droegen ze geen oplossing aan. De patiëntenpopulatie was beperkt en ons inziens te homogeen om met gangbare statistische technieken een antwoord te vinden. Een fundamenteel andere benadering en denkwijze werd voorgesteld middels een brief, namelijk mixed effect modeling. Vooralsnog wordt mixed effect modeling weinig gebruikt binnen medisch wetenschappelijk onderzoek waarbij de aandacht ligt bij het longitudinaal opvolgen van biomarkers.

Hoofdstuk 9 en 10 Zwangerschappen

Nadat de tienerjaren na pulmonaalklepvervanging succesvol overbrugt zijn, bereiken de meeste patiënten gezond de vruchtbare leeftijd. In **Hoofdstuk 9** beschrijven we dat vrouwelijke patiënten die in het verleden een rechtszijdige klepvervanging zijn ondergaan veilig en succesvol een zwangerschap kunnen doorstaan met goede uitkomsten voor zowel moeder als kind. Verergering van bestaande klachten, alsmede het ontstaan van nieuwe klachten zijn zowel zeldzaam, als zelden onbehandelbaar. De meeste uitkomsten waren dan ook gelijk aan die van de doorsnee Nederlandse populatie. Wel waren prematuriteit en een relatief laag geboortegewicht meer frequent dan in de Nederlandse populatie.

Daarnaast hebben we met speciale statistische technieken in **Hoofdstuk 10** aangetoond dat zwangerschap geen invloed heeft op de lange termijn uitkomsten van

homografts in rechtszijdige positie. Vrouwen die een zwangerschap hadden doorgemaakt hadden geen hogere mortaliteit en geen verhoogde kans op klepgerelateerde problemen en reïnterventie, vergeleken met vrouwen die tot dan toe nog nooit een zwangerschap hadden doorgemaakt. Dit gegeven is belangrijk in de counseling en informatievoorziening voor de cardioloog die betrokken is bij de levenslange opvolging en begeleiding van de groeiende groep vrouwelijke patiënten.

Hoofdstuk 11 De Ross procedure

In **Hoofdstuk 11** worden de resultaten beschreven van een internationale samenwerking tussen centra die nog veelvuldig Ross procedures uitvoeren in patiënten van middelbare leeftijd. Bij de Ross procedure wordt bij patiënten met ernstig aortakleplijden een nieuwe aortaklep gemaakt van de eigen pulmonaalklep (autograft) en de pulmonalisklep vervangen door vaak een menselijke donorklep (homograft) of eventueel een biologische klep. De 5 centra hebben jarenlange ervaring en vervolgen hun patiënten nauwlettend. Zowel de klinische als seriële echografische uitkomsten werden gebundeld en geanalyseerd met geavanceerde statistische methoden. Het resultaat was dat klepgerelateerde mortaliteit, morbiditeit en reïnterventie de eerste 15 jaar zeldzaam zijn. Deels kan dit succes waarschijnlijk toegeschreven worden aan het feit dat levenslange bloedverdunners niet geïndiceerd zijn door de Ross procedure. Het vermijden van levenslange bloedverdunners is een groot voordeel in jonge patiënten, met name bij vrouwen met een zwangerschapswens. Het is daarom bijzonder opmerkelijk dat geen van de drie grote richtlijnen over aortaklepvervanging de Ross procedure adviseert ook maar te overwegen in volwassen patiënten met aortakleplijden.

Hoofdstuk 12 Percutane klepimplantaties

Het progressief toenemende risico van herhaalde chirurgische ingrepen, drijft de zoektocht naar veiligere interventiemogelijkheden. Dit heeft de ontwikkeling van percutane, transcatheter klepimplantaties versneld. Hierbij worden hartkleppen via de bloedvaten opgevoerd naar het hart. Zoals ook mogelijk is voor de aortaklep, is op soortgelijke manier een transcatheter pulmonaalklepimplantatie mogelijk. Dit gebeurt veelal met de zogeheten Melody klep. Door gegevens van het Erasmus MC, Radboud (Nijmegen) en UMC Maastricht te bundelen, hebben we de uitkomsten van Melody klepimplantaties kunnen analyseren en beschrijven in **Hoofdstuk 12**. We vonden dat implantatie relatief veilig kan gebeuren maar gepaard gaat met een niet-verwaarloosbaar verhoogd risico op endocarditis. De kleppen vernauwen daarnaast geleidelijk waarna herhaald chirurgisch ingrijpen doorgaans onvermijdelijk blijft. Desondanks is de Melody klep voor geselecteerde patiënten een goed alternatief om (herhaald) chirurgisch ingrijpen uit te stellen en de klepfunctie van een falende homograft al dan niet tijdelijk te herstellen.

Hoofdstuk 13 Discussie

In hoofdstuk 13 worden de bevindingen van dit proefschrift ter beantwoording van de onderzoeksvragen samengevat en in bredere context geplaatst en bediscussieerd. Daarnaast delen we onze aanbevelingen en gedachten voor toekomstig onderzoek.

Dankwoord/ Acknowledgements

Aan mijn promotoren en copromotor

Aan alle drie dank voor het creëren, behouden en beschermen van een omgeving waarin veel jonge onderzoekers de kans, tijd en ruimte krijgen zich te ontwikkelen. Bedankt voor het geduld, het vertrouwen en de vrijheid om mijn eigen weg te vinden.

Professor Takkenberg

Beste **professor Takkenberg**, bedankt voor alle steun en vertrouwen die u me over de jaren hebt gegeven. U heeft me enorme vrijheid en mogelijkheden gegeven om mijn richting te bepalen. Ik bewonder uw mensenkennis en vaardigheden. Uw inzet voor gelijke kansen en rechten is geweldig. De omgeving die u creëert voor jonge onderzoekers is uniek en zou een voorbeeld moeten zijn voor anderen.

Professor Bogers

Beste **professor Bogers**, bedankt voor alle tijd en energie die u in mij heeft gestoken. Bedankt voor het onvoorwaardelijke vertrouwen. Bedankt dat ik altijd ongevraagd en onaangekondigd door uw open deur mocht stappen en beginnen te praten. U had altijd tijd, en uw feedback en commentaren zijn steevast de eerstvolgende zondagochtend in de inbox te verwachten. Een 'tandje erbij, Jamie' was een tandje erbij en ik hoop dat het is gelukt.

Dr. Mr. Mokhles

Beste **Mostafa**, ik heb nooit aan jou gevraagd waarom jij mij aannam tijdens mijn coschappen in 2015. Met de verdiensten die jij zelf bij elkaar hebt gevochten heb je twee jonge 'vreemden' aangenomen. Jij hebt mij kansen en mogelijkheden gegund die ik je voor altijd dankbaar zal zijn. Bedankt voor het ongelofelijke en onvoorwaardelijke vertrouwen in mij, het geduld, de begeleiding en het mentorschap. Bedankt voor alles.

Grigorios Papageorgiou

Greg, what would I be without my Greek numerical wizard. Thank you for always having my back and being there, offering your guidance and advice. You never said 'no' to one of your colleagues, students, or clients. Your genuine friendliness and willingness to help others is very much visible and appreciated. Your higher dimension thinking was often far beyond my grasp but I think we have made a nice team. Your directions and advise are reflected in much of my work and the translation from cold hard data to clinical practical medicine would not have been the same without you. I am sure that a great career lies ahead of you. Σας εύχομαι καλή τύχη

De Commissie

Beste **professor Roos-Hesselink**, bedankt voor uw betrokkenheid en steun bij mijn onderzoeken gericht op vrouwen en zwangerschappen. Ik bewonder uw inzet en talent voor een zeer, zeer complexe en relatieve nieuwe populatie patiënten. Daarnaast bewonder ik uw inzet voor jonge onderzoekers en artsen en de manier waarop u voor iedereen om u heen mogelijkheden en kansen creëert. **Beste professoren Helbing en Hazekamp**. Bedankt dat jullie in mijn commissie wilden plaatsnemen. Bedankt voor jullie inzet in zowel de kliniek als het onderzoek binnen ons vakgebied. Zowel direct als indirect heeft uw inzet bijgedragen aan mijn proefschrift en opleiding. Daar ben ik u zeer dankbaar voor.

Beste **professor Eijkemans**, ook u bedankt voor deelname in de commissie. Dank voor uw inzet binnen de statistiek, de ontwikkeling daarvan en het slaan van de brug van getal naar kliniek.

Aan mijn collega's

Staf Thoraxchirurgie Erasmus MC

Bedankt Professor Bogers, dr. Jos Bekkers, dr. Margreet Bekker, dr. Ozcan Birim, dr. Peter de Jong, dr. Charles Kik, dr. Wouter van Leeuwen, dr. Alexander Maat, dr. Edris Mahtab dr. Frans Oei, dr. Frank van Schaagen, dr. Yannick Taverne, en dr. Pieter van de Woestijne. Bedankt dat ik werkzaam mag zijn op onze afdeling en veel van jullie heb mogen leren. Beste dr. Bekkers, bedankt voor uw deelname in mijn commissie. Wouter, bedankt voor de strenge telefoontjes zo nu en dan om me scherp te houden. Beste Pieter, bedankt voor jouw betrokkenheid bij een significant deel van de artikelen. Je hebt, samen met de andere congenitaal chirurgen, een groot deel van de homografts geïmplanteerd die de basis vormen van dit proefschrift. Jullie hebben je toegewijd aan wellicht de meest complexe populatie binnen een al extreem complex vak. Allen, bedankt voor alles.

Aan mijn collega onderzoekers

Beste **Pepijn**, **Rhahat**, **Stan**, **Andras**, **Daan**, **Milan**, **Kelly**, **Arjen**, **Gerdien**, **Isabel**, **Djamila**, **Kevin**, **Simone**, **Christine**, **Jonathan**, **Saya**, **Sahar, Milad**, **Lauren** en **Kendis**, Dank aan jullie die mijn promotietijd tot een leuke en gezellige periode hebben gemaakt. Bedankt voor de congressen, kerstdiners, borrels, lunches en gezelligheid in het oude BD gebouw. Bedankt voor de hulp, overleggen, discussies en feedback. **Pepijn**, het is altijd gezellig om met jou om te gaan. Je was al mijn maat en nu zijn we ook nog eens buren. Bedankt dat je mijn paranimf wilde zijn. **Rhahat**, briljante gozer, bedankt voor de gesprekken en de vriendschap. Je bent een geweldige gozer en ik weet zeker dat je een goede cardioloog zal worden.

Secretariaat
Lieve **Maureen**, **Usha**, **Wilma**, **Titia**, **Liesbeth**, **Caroline**, **Sylvia**, **Solita** en **Jos**. Jullie hebben allemaal op jullie eigen manier direct en indirect bijgedragen aan mijn proefschrift. Ik waardeer jullie voor jullie betrokkenheid, inzet en oprechte interesse. Jullie zijn werkelijk onmisbaar voor de afdeling.

Aan mijn vrienden
Beste **Rishal, Jerald, Lotte, Denise, Naomi, Miriam, Daisy, Esma, Cherry, Ting & Rosaline, Jamie, Ghislain** en **Abbas,** ik wil jullie bedanken voor de leuke tijden, jullie onvoorwaardelijke steun en ongecensureerde commentaar. Bedankt voor de gesprekken, de motivatie, de ruzies en de ervaringen. Ik dank jullie voor jullie geduld, jullie inzichten en adviezen, jullie vriendschap en liefde en jullie trouw. Beste **Wim** en **Annegien**, bedankt dat ik altijd bij jullie welkom ben geweest om mee te eten.

Lieve oud collega's van het Niios. Bedankt voor de vijf jaren die ik bij jullie heb mogen werken. In het bijzonder mijn dank aan **Jacqueline van der Wees**, **Kristin Mangundap**, **Anita Sajet**, **Esther Groeneveld**, **Lamis Badun** en **Gerrit Mellis**, die mij ook in de laatste periode bij het Niios altijd hebben gesteund. Ik ben jullie nooit vergeten.

Beste **Roy Westerkamp**, bedankt dat u vroeger mijn mentor was. Ondanks dat ik al lang weg ben van het Calvijn ben ik u en uw mentorschap nooit vergeten. U bent en blijft een voorbeeld en inspiratiebron voor velen en ik bewonder uw grenzeloze inzet.

Mijn dank aan alle patiënten die hun gegevens, hun tijd en hun energie ter beschikking hebben gesteld in het verzamelen van de benodigde data. Hoewel zelden op onwil gestuit mag het niet vanzelfsprekend worden geacht dat patiënten zonder meer meewerken aan wetenschappelijk onderzoek en de voortgang van onze medische praktijk. Mijn dank en respect voor een ieder die mij heeft toegelaten in zijn en haar leven en mij het vertrouwen heeft gegeven in het voltooien van dit werk.

Ma en Pa, bedankt dat jullie mij en mijn zus altijd alles hebben kunnen geven wat we nodig hadden. Bedankt voor de goede zorgen. Lieve **Valerie**, ik ben blij dat we zulke goede maatjes zijn. Bedankt dat je me altijd ophaalt en mee uit eten gaat. Ik ben heel trots dat jij mijn zus bent.

Lieve **Oma en Opa**, mijn laatste alinea is uiteraard aan jullie. Bedankt voor jullie onvoorwaardelijke liefde en warmte. Bedankt dat ik altijd een thuis bij jullie had. Lieve opa, uw schilderij prijkt op de omslag van mijn proefschrift. In mijn gedachten bent u er altijd bij.

Portfolio

PHD PORTFOLIO

Name PhD student:	Jamie Leslie Robin Romeo
Erasmus MC Department:	Cardio-Thoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD Period:	February 2017 – December 2019
Title thesis:	Prediction of Clinical Outcome after Right Ventricular Outflow Tract Intervention
Promotors:	Prof. Dr. J.J.M. Takkenberg
	Prof. Dr. A.J.J.C. Bogers
Co – promotor:	Dr. Mr. M.M. Mokhles

ACADEMIC EDUCATION

2014 – 2018:	Master degree Medicine - Erasmus University Medical Center
2012 – 2013:	Master degree Finance and Investments - Erasmus University
2011 – 2014:	Bachelor degree Medicine - Erasmus University Medical Center
2010 – 2011:	Second degree teaching license - Erasmus University
2009 – 2012:	Bachelor degree Psychology - Erasmus University
2008 – 2012:	Bachelor degree Business Administration - Erasmus University

COEUR COURSES

24-02-2017	Congenital Heart Disease part 1 course	0.5
25-05-2018	Congenital Cardiology in children and adults	0.5
15-03-2017	Intensive Care Part I	0.5
07-06-2017	Intensive Care Part II	0.5
21-04-2017	Cardiovascular Imaging and Diagnostics part 2	0.5
24-03-2017	Endovascular thrombectomy in acute ischemic stroke	0.5
16-03-2018	Pathophysiology of ischemic heart disease part 1	0.5
23-03-2018	Pathophysiology of ischemic heart disease part 2	0.5
29-03-2018	ACE Congenital Heart Disease	0.5
13-04-2018	Aneurysmal Disease	0.5

NIHES COURSES

27/31-03-2017	Repeated Measurements	1.4
03/05-05-2017	Quality of Life Measurement	0.9
09/11-05-2017	Maternal and Child Health	0.9
07/11-08-2017	Logistic Regression	1.4
14/18-08-2017	Joint Models for Longitudinal and Survival Data	0.7
14/18-08-2017	Cohort Studies	0.7

21/25-08-2017	Markers and Prediction Research	0.7
14/17-08-2017	Master class: Advances in Genomics Research	0.4

ADDITIONAL COURSES

2017	Scientific Integrity	0.3
2018	Brok Course	1.5
2018	Biomedical English Writing & Communication	3.0
2015	Advanced Research Methods	5.0
2015	Health Technology Assessment	5.0
2015	Economics and Financing of Health Care Systems	5.0

CONGRESS AND SYMPOSIA ATTENDANCE

2018	Scientific Research Meetings CTS	2.0
2017	Heart Valve Society Monaco	1.2
2018	Heart Valve Society New York	1.2
2019	Heart Valve Society Barcelona	1.2
2017	NVT najaarsvergadering Antwerpen	1.2
2018	NVT voorjaarsvergadering Utrecht	1.2
2018	NVCC Utrecht	1.2
2018	EACTS Vienna	1.2
2018	ESC Munich	1.2
2018	World Congress of Cardiology Dubai	1.2
2017	Omics in Cardiovascular Medicine	0.4
2017	Coeur Day	0.3
2018	Coeur Day	0.3

PRESENTATIONS

2017	Heart Valve Society Monaco (poster presentation)	0.6
2018	Heart Valve Society New York (poster presentation)	0.6
2018	NVCC 2018 (poster presentation)	0.6
2018	EACTS 2018 (oral presentation)	1.2
2018	ESC Munich (poster presentation)	0.6
2018	World Congress of Cardiology Dubai (oral presentation)	1.2
2019	Heart Valve Society Barcelona (oral presentation)	1.2

EDUCATIONAL TASKS

2017	Supervision of third year medical students	0.6
2017	Supervision of fourth year medical students	0.6
2018	Supervision of sixth year medical students	0.6

List of publications

Publications in this thesis

Outcome after Surgical Repair of Tetralogy of Fallot: a Systematic Review and Meta-Analysis. **Jamie LR Romeo**, Jonathan RG Etnel, Johanna JM Takkenberg, Jolien W Roos-Hesselink, Wim A Helbing, Pieter van de Woestijne, Ad JJC Bogers, M Mostafa Mokhles. *Journal of Thoracic and Cardio-Vascular Surgery DOI: https://doi.org/10.1016/j.jtcvs.2019.08.127*

Homograft Durability After Complete Correction of Pulmonary Atresia With and Without Systemic Pulmonary Collateral Arteries. Pieter van de Woestijne, **Jamie LR Romeo**, Ingrid van Beynum, Maarten Witsenburg, M Mostafa Mokhles, Ad JJC Bogers *In preparation*

Downsized cryopreserved and standard-sized allografts for right ventricular outflow tract reconstruction in children: long-term single-institutional experience. **Jamie L.R. Romeo**, Grigorios Papageorgiou, Pieter C. van de Woestijne, Johanna J.M. Takkenberg, Lauren E.H. Westenberg, Ingrid van Beynum, Ad J.J.C. Bogers and Mostafa M. Mokhles *Interactive CardioVascular and Thoracic Surgery 27 (2018) 257–263*

Long term clinical and echocardiographic outcome in 1431 young and middle aged adults undergoing the Ross procedure. **Jamie Romeo**, Grigorios Papageorgiou, Francisco da Costa, Hans Sievers, Ad Bogers, Ismail el-Hamamsy, Peter Skillington, Rochelle Wynne, Stefano Mastrobuoni, Gebrine El Khoury, Johanna Takkenberg, Mostafa Mokhles *Jama Cardiology*

The right time-dependent statistics: this is the moment. **Jamie L.R. Romeo**, Grigorios Papageorgiou, Johanna J.M. Takkenberg and M. Mostafa Mokhles. *European Journal of Cardio-Thoracic Surgery, Volume 54, Issue 6, December 2018, Page 1145*

Long-term clinical outcome and echocardiographic function of homografts in the right ventricular outflow tract. **Jamie L.R. Romeo**, M. Mostafa Mokhles, Pieter van de Woestijne, Peter de Jong, Annemien van den Bosch, Ingrid M. van Beynum, Johanna J.M. Takkenberg and Ad J.J.C. Bogers *European Journal of Cardio-Thoracic Surgery, Volume 55, Issue 3, March 2019, Pages 518–526, https://doi.org/10.1093/ejcts/ezy265*

Optimal Timing of Pulmonary Valve Replacement in Patients with Corrected Tetralogy of Fallot. **Jamie LR Romeo**, Johanna JM Takkenberg, Judith AAE Cuypers, Natasha MS de Groot, Pieter van de Woestijne, Nico Bruining, Ad JJC Bogers, M Mostafa Mokhles *European Journal of Cardio-Thoracic Surgery*

Letter by Romeo et al Regarding Article, "Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot: A Prospective Cardiovascular Magnetic Resonance and Clinical Study". **Jamie L.R. Romeo**, Ad J.J.C. Bogers, , Mostafa M. Mokhles. *Circulation. 2018 May 15;137(20):2184-2185*

Outcomes of Pregnancy After Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit. **Jamie L.R. Romeo**, Johanna J.M. Takkenberg, Jolien W. Roos-Hesselink, Milad Hanif, Jerome M.J. Cornette PHD, Wouter J. van Leeuwen, Arie van Dijk, Ad J.J.C. Bogers, M. Mostafa Mokhles *J Am Coll Cardiol. 2018 Jun 12;71(23):2656-2665. doi: 10.1016/j.jacc.2018.03.522.*

Influence of pregnancy on long-term durability of allografts in right ventricular outflow tract. **Jamie LR Romeo**, Grigorios Papageorgiou, Johanna JM Takkenberg, Jolien W Roos-Hesselink, Wouter J van Leeuwen, Jerome MJ Cornette, Dimitris Rizopoulos, Ad JJC Bogers, M Mostafa Mokhles *J Thorac Cardiovasc Surg. 2019 Oct 4. pii: S0022-5223(19)31866-5. doi: 10.1016/j.jtcvs.2019.08.083. [Epub ahead of print]*

Multi-Centre Dutch Experience with Percutaneous Pulmonary Valve Implantation: Mid-Term Outcome and Serial Echocardiographic and Electrocardiographic Assessment. **Jamie LR Romeo**, Annemien van den Bosch, Kendis Euson, Toon Duijnhouwer, Roland van Kimmenade, Tim ten Cate, Arie van Dijk, Ad JJC Bogers, M. Mostafa Mokhles, Maarten Witsenburg. *Open Heart*

Other work

Skeletonized internal mammary artery harvest with diathermy and cold dissection. Durko A, Mahtab E, **Romeo J**, Bogers A. *Multimed Man Cardiothorac Surg. 2017 Dec 12;2017. doi: 10.1510/mmcts.2017.023.*

Survival benefit of physician-staffed Helicopter Emergency Medical Services (HEMS) assistance for severely injured patients. Den Hartog, D. **Romeo, J**. Ringburg, A. N. Verhofstad, M. H. Van Lieshout, E. M. *Injury 2015.*

About the author

Jamie Romeo, son of Leslie Romeo and Renette Sastrowidjojo, was born in the Havenziekenhuis in Rotterdam on the 16th of September 1990. After graduating high school in 2008, he started business administration at the Rotterdam School of Management of the Erasmus University. A year later he also enrolled into psychology. In 2011 he started Medical School at the Erasmus University Medical school and finished his bachelors in business administration and psychology during the same year. During his bachelor medicine he also earned a teaching license for Economics and a Master degree in Finance and Investments. During the start of his clinical rotations in 2015, he was accepted as a PhD candidate at the Cardio-Thoracic Surgery department of professor Bogers with a personal grant of doctor Mokhles. In 2018 he started working as a resident not in training at the Cardio-Thoracic Surgery department.

Financial support for the publication of this thesis was generously provided by: Axiflex b.v., Axiflex Academy, House of Afangaro, Dutch Heart Foundation, ABN AMRO, Chipsoft b.v., Cardialysis b.v., Thoraxchirurgie Erasmus MC, and studiehulpveiling.nl