Reconstruction of the RVOT with a conduit

Lifetime follow up

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2016

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ISBN 978-91-628-9700-0 (hard copy)
ISBN 978-91-628-9701-7 (e-pub)
http://hdl.handle.net/2077/40889

Cover illustration: “Time with inspiration from Salvador Dali” by Jakob Skoglund

Printed by Kompendiet, Gothenburg, Sweden 2016

”Kroppen behöver hjärtat för att pumpa blod, men man behöver också kärlek. Då pumpar hjärtat bättre.”

Matilda, 7 år

ABSTRACT

Background: The use of a conduit is an established surgical method for reconstruction of the right ventricular outflow tract in congenital heart disease. The most commonly used conduit is a homograft. Its limited durability makes reinterventions almost inevitable but the actual durability of a conduit in the adult population is poorly described. The introduction of transcatheter pulmonary valve replacement (TPVR) has expanded the possibilities for conduit reintervention but the impact of this new technique on clinical practice is unknown. Furthermore, little is known on the influence of reinterventions on quality of life. Conduit surgery and reintervention is among the most common surgical procedures in adult congenital heart disease but relative lack of knowledge complicates decision making.

Method: Paper 1: The PubMed database was searched in May 2015 with the terms "homograft AND pulmonary valve," generating 665 hits. Studies involving more than 50 patients with a mean or median age >18 years were included. Papers 2–4: The Swedish registry of congenital heart disease (SWEDCON) was used to collect data. Patients were identified by codes for classification of surgical procedures and a group variable specific for patients with a conduit.

Results: Paper 1: Six studies with a cumulative total of 560 patients were found and included. Perioperative mortality was 0%–2.9%, and long-term mortality was 2%–8.8% at 8.1–10 years. Reinterventions of homografts were common during patients' lifespans, with a 10-year event-free survival of 78%–80%. Early postoperative echocardiographic or magnetic resonance imaging defects appear to predict rapid homograft degeneration. *Paper 2*: Data on quality of life (EQ-5D) from the first and latest visit were collected from 103 patients with a mean age of 31 years. Mean time from first to latest visit was 3 years. Health perception (mean EQ-VAS) declined from 84.4 (SD=14.6) at the first visit to 78.6 (SD=18.3) at the latest visit (P=0.001). This decline was not observed in patients with reinterventions between visits (n=18). Low EQ-VAS was associated with symptoms and NYHA class II–IV. Problems in the EQ-5D dimension "usual activities" were more common in patients with reinterventions (25%) than in those without reinterventions (7%) (P=0.04). *Paper 3*: From 2000 to 2014, there was an increase in the number of adult patients with conduits from 122 to 536, including 60 surgical conduit replacements, 40 TPVRs, and 176 new conduit implantations. There was a significant increase in new implantations (P=0.007) and surgical conduit replacements (P=0.024) across all three time periods. Patients with new implantations were older (median age, 32 years) compared with those in the reoperation and TPVR groups (median age, 26 years), with the majority of patients having tetralogy of Fallot (57%). The majority of conduit reinterventions were surgical also after the introduction of TPVR in 2007, with no significant difference regarding diagnosis, gender, age, or previous number or longevity of conduits between surgical replacement and TPVR. *Paper 4*: A total of 574 patients with a conduit (mean age 36.1 years) were identified. Tetralogy of Fallot represented the largest group (45%). There were 769 operations and 50 TPVRs. Long-term survival after the first conduit operation (mean age 20.2 years) including perioperative mortality (<1%) was 93% at 20 years. The most common cause of death was cardiac-related. Higher age at first conduit operation was associated with an increased mortality risk. Event-free survival was 77% and 54% at 10 and 20 years, respectively. Ten-year event-free survival after the first conduit reintervention (n=176) was 70%, significantly lower than after the first conduit operation (P=0.04). Higher age at the first conduit operation had a protective association, whereas male gender and complex malformations were associated with an increased risk of further reintervention.

Conclusion: Patients perceive a decline in their health over time after right ventricular outflow tract surgery. This decline was not observed in patients with further reinterventions. The number of patients with a conduit is increasing, and reinterventions for conduits are common. Since the introduction of TPVR, less than half of all patients with conduit failure are treated by this technique. Long-term mortality after conduit surgery and reinterventions is low, but the need for conduit reinterventions is substantial. Perioperative mortality is low in relation to cardiac-related death.

Keywords: congenital heart disease • RVOT surgery • conduit • quality of life • outcome • TPVR.

ISBN 978-91-628-9700-0 (hard copy) http://hdl.handle.net/2077/40889
ISBN 978-91-628-9701-7 (e-pub)

LIST OF PAPERS

This thesis is based on the following papers.

I Kristofer Skoglund, Peter Eriksson, Gunnar Svensson, Mikael Dellborg. Homograft reconstruction of the right ventricular outflow tract in adults with congenital heart disease: a systematic review.
Interact CardioVasc Thorac Surg 2015; doi:10.1093/icvts/ivv264.

II Kristofer Skoglund, Malin Berghammer, Peter Eriksson, Gunnar Svensson, Ulf Thilén, Mikael Dellborg. Decline in Self-reported Health (EQ-5D) over Time after Surgical Reconstruction of the Right Ventricular Outflow Tract: A Longitudinal Cohort Study of 103 Patients.
Congenit Heart Dis. 2015;10:E54-E59.

III Kristofer Skoglund, Gunnar Svensson, Ulf Thilén, Mikael Dellborg, Peter Eriksson. National registry study of RV to PA conduits: Impact of transcatheter pulmonary valve replacement in adults.
Submitted

IV Kristofer Skoglund, Gunnar Svensson, Ulf Thilén, Mikael Dellborg, Peter Eriksson. Predictors of Long-term Outcome after RV to PA Conduit Surgery and Reintervention.
Submitted

SAMMANFATTNING PÅ SVENSKA

En grupp patienter med medfött hjärtfel saknar eller har en underutvecklad lungartär, dvs koppling mellan höger kammare och lungcirkulationen. Den största gruppen omnämns ibland som ”blue babies” och innefattar patienter med Fallots tetrad som utgör ca 10% av alla medfödda hjärtfel. Många av dessa patienter har opererats som barn med palliativ kirurgi i form av en shunt som säkerställer lungblodflödet men även tidigt korrektivt syftande kirurgi utförs. Hos många patienter måste en kirurgisk koppling mellan höger kammare och lungartären skapas, en sk conduit. Denna metod har använts sedan 60-talet men i allt större omfattning. Utvecklingen av barnhjärtkirurgin har varit enastående med ökande överlevnad till följd och nu finns fler vuxna än barn med komplexa medfödda hjärtfel. Då hållbarheten av conduiten är begränsad behövs nya operationer och kateteringrepp under patientens livstid för att säkerställa en god hjärtfunktion. Att patienten har ett livslångt behov av uppföljning och ofta genomgår flera kirurgiska ingrepp gör att även att tillståndet kan tänkas påverka livskvaliteten.

Denna avhandling syftar till att studera vuxna patienter i Sverige med conduit med avseende på livskvalitet, trender avseende behandling samt överlevnad och behov av nya operationer eller kateteringrepp.

Studien har gjorts med hjälp av det svenska kvalitetsregistret för medfödda hjärtfel, SWEDCON. Ungefär 1000 vuxna patienter har genomgått någon form av kirurgi av kopplingen mellan höger kammare och lungartären. Av dessa har 574 stycken en sk conduit varav ca 70% är av typen homograft dvs består av vävnad från avlidna donatorer. Antalet vuxna patienter med conduit har fyrfaldigats under 2000-talet både genom överföring av patienter från barnsjukvården men även genom operation av vuxna patienter. Antalet conduitoperationer har också ökat kraftigt i denna tidsperiod, såväl nya implantationer som reoperationer. Kateterburen klaffimplantation introducerades i Sverige 2007 och utgör sedan dess knappt hälften av reoperationerna. I valet mellan öppen operation eller kateterburen klaffimplantation hade diagnos, kön, ålder samt antal eller hållbarhet av tidigare conduits hade ingen betydelse. Patienternas generella hälsorelaterade livskvalitet mättes med det validerade hälsoskattningsformuläret EQ-5D. Vi kunde här konstatera att patienternas självskattade hälsa försämrades över tid. De som genomgick någon form av ingrepp mellan mätningarna försämrades dock inte. Det fanns också en koppling mellan sämre hälsoskattning och förekomst av symtom eller försämrad funktionsklass (NYHA). Långtidsöverlevnaden efter första conduitoperationen är tämligen god, över 90% efter 20 år. Dödligheten inom 30 dagar från operation är mindre än 1% även inkluderande reoperationer. De patienter som avlidit under studiens gång hade i majoriteten av fallen orsakats av hjärtsjukdom. Högre ålder vid första korrigerande operation med conduit var förenat med ökad dödlighet. Överlevnad utan reoperation eller kateterburen hjärtklaffimplantation var 54% efter 20 år vilket indikerar att det är var mycket vanligt med förnyade ingrepp. Manligt kön, låg ålder eller att ha mer komplex anatomi var associerat med kortare tid till nytt ingrepp eller död. Analys av överlevnad utan reoperation eller perkutan klaffimplantation i befintlig conduit visade att denna verkar vara signifikant sämre jämfört med den första operationen.

Vi drar slutsatsen att långtidsöverlevnaden efter conduitoperation är tämligen god men begränsas i första hand av hjärtorsakad död. Behovet av nya ingrepp för att säkerställa en god hjärtfunktion är stor. Hållbarheten vid reoperation är kortare än vid första operationen vilket är oroande i ljuset av att fler och fler patienter behöver upprepade ingrepp. Då patienten har ett livslångt behov av uppföljning och nya ingrepp är livskvalitetsaspekten viktig och bör beaktas.

CONTENTS

ABBREVIATIONS

GUCH	grown-up congenital heart disease
CHD	congenital heart disease
PVR	pulmonary valve replacement
TPVR	transcatheter pulmonary valve replacement
TOF	tetralogy of Fallot
RVOT	right ventricular outflow tract
RV	right ventricular
PA	pulmonary artery
RV-to-PA	right ventricle to pulmonary artery (conduit)
PR	pulmonary valve regurgitation
PS	pulmonary stenosis
VSD	ventricular septal defect
SWEDCON	Swedish registry of congenital heart disease
MRI	magnetic resonance imaging
VT	ventricular tachycardia

INTRODUCTION

I had the opportunity to start a clinical fellowship at the Grown-Up Congenital Heart Disease (GUCH) Center at Sahlgrenska University hospital/Östra in 2011. During my first months of practice, I remember meeting patients with conduits, many of them with conduit replacements because of conduit failures before they reached adulthood. Despite this, many patients seemed to live a good life. This raised several questions for me and, in some cases, for the patients. Today, on reading my notes from the course "Introduction to research" for PhD students, I found the following questions:

> *How is health-related quality of life affected in these patients, given that conduit reinterventions are common? Is this a growing group of patients, since more patients with congenital heart disease are reaching adulthood? What is the impact of transcatheter pulmonary valve replacement, and is surgery needed less frequently now? What is the long-term survival and what is the lifetime mortality after reinterventions? What is the expected event-free survival after conduit surgery and after conduit reinterventions? Can we expect improved conduit longevity after conduit reinterventions, since somatic growth is no longer a factor?*

The subject of this thesis was chosen following my own observations of adults with conduits and their almost inevitable need for repeated surgery or reinterventions during their lifetime. This thesis highlights adult patients with a conduit as viewed from a congenital cardiologist's perspective. Many cardiologists will meet such patients, all of whom are in need of lifetime follow up.

BACKGROUND

Malformations of the right ventricular outflow tract (RVOT)

There are several cardiac malformations for which a conduit is used for reconstruction of the right ventricular outflow tract (RVOT). Such malformations can present in different phenotypes ranging from mild to severe. This is a brief presentation of relevant malformations in conduit surgery and a few relevant clinical aspects.

Tetralogy of Fallot (TOF) is named after Étienne-Louis Arthur Fallot who described the condition in 1888. It is the most common cyanotic congenital heart defect, consisting of ventricular septal defect (VSD), overriding aorta, pulmonary stenosis, and right ventricular hypertrophy (1). The patients are sometimes referred to as "blue babies" and represent around 10% of all congenital heart malformations, with a male predominance. Adults with TOF who are considered for conduit surgery mainly fall into the following categories: (a) patients operated on as children for TOF using a transannular patch, leaving the patient with severe pulmonary valve regurgitation (PR); (b) patients with TOF who undergo subvalvular resection and/or valvular commissurotomy while remaining at risk for PR and late RV failure; (c) patients who undergo conduit surgery in early life in cases where the RVOT is not amenable to surgical repair (Figure 1).

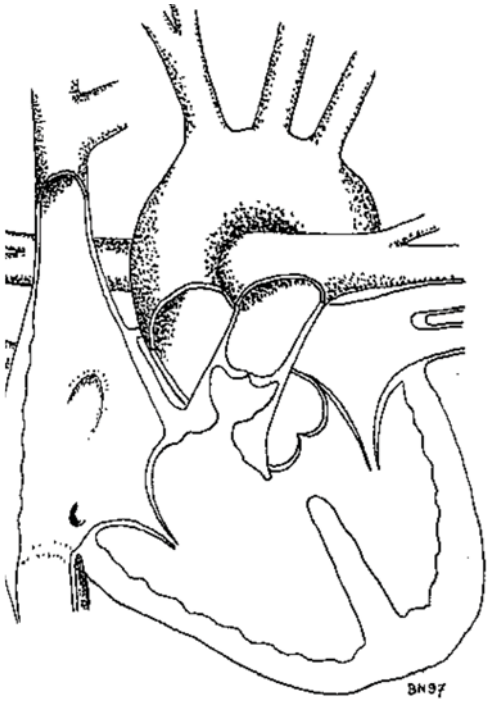

Figure 1. Anatomy of Tetralogy of Fallot composed of its four features: pulmonary stenosis, VSD, right ventricular hypertrophy and overriding aorta. (Courtesy of Boris Nilsson)

Pulmonary valve abnormalities can present both as isolated forms and in association with other lesions. The most common forms are valvular and subvalvular stenosis, followed by supravalvular stenosis (Williams or Noonan syndrome). Subvalvular stenosis can also arise from RV hypertrophy. Patients presenting at the GUCH unit as adults often have undergone intervention with balloon valvuloplasty or surgical commissurotomy as children and now present with severe PR and a large right ventricle. Subinfundibular stenosis and double-chambered right ventricle can also be present and in association with VSD.

Pulmonary atresia with VSD has similarities to TOF and is sometimes referred to as an "extreme Fallot." It varies from simple to complex forms, which can have atresia of both the main pulmonary artery (PA) and PA branches. Major aortopulmonary collateral arteries (MAPCA) from the aorta to the pulmonary circulation are common. Surgical management has similarities to that applied to TOF. Pulmonary valve atresia with intact ventricular septum is a different entity to PA with VSD, and is characterized by a hypoplastic right ventricle and ductus or coronary fistulas supplying blood to the lungs. If the RV size is adequate, biventricular repair is possible, and an RV-to-PA conduit can be used to establish RV-to-PA continuity.

Double-outlet right ventricle presents with great variation from Fallot-like to single-ventricle physiology. Surgical management using an RV-to-PA conduit is often possible.

Truncus arteriosus basically consists of a single artery arising from the heart supplying both systemic and pulmonary circulation. It also presents with great variation, with a commonly applied classification. Surgical repair in early life includes establishing RV-to-PA continuity through a conduit arising from the right ventricle via a ventriculotomy (2).

Transposition of the great arteries is described as a malformation whereby the aorta arises from the right ventricle and the PA from the left ventricle. VSD and pulmonary outflow obstructions are commonly associated lesions. In the presence of a large and subaortic VSD a Rastelli operation can be performed, using the VSD to direct blood from the left ventricle to the aorta. A conduit is then used to connect the right ventricle to the PA via a ventriculotomy, thus surgically creating an RVOT (3) (Figure 2).

Aortic valve stenosis in early life is often treated with commisurotomy. Further management in young patients for avoiding small sized valve prosthesis includes the Ross procedure where the aortic valve is reconstructed using the native PA, which is translocated to the aortic position (4). The PA is then reconstructed with a conduit. Thus it is not a malformation of the RVOT. The method is also used in selected adult patients with aortic valve disease for example after endocarditis (Figure 3).

Initial surgical repair

Surgical management of RVOT problems is sometimes staged, but initial repair is also possible. Management in early life often includes palliative procedures such as

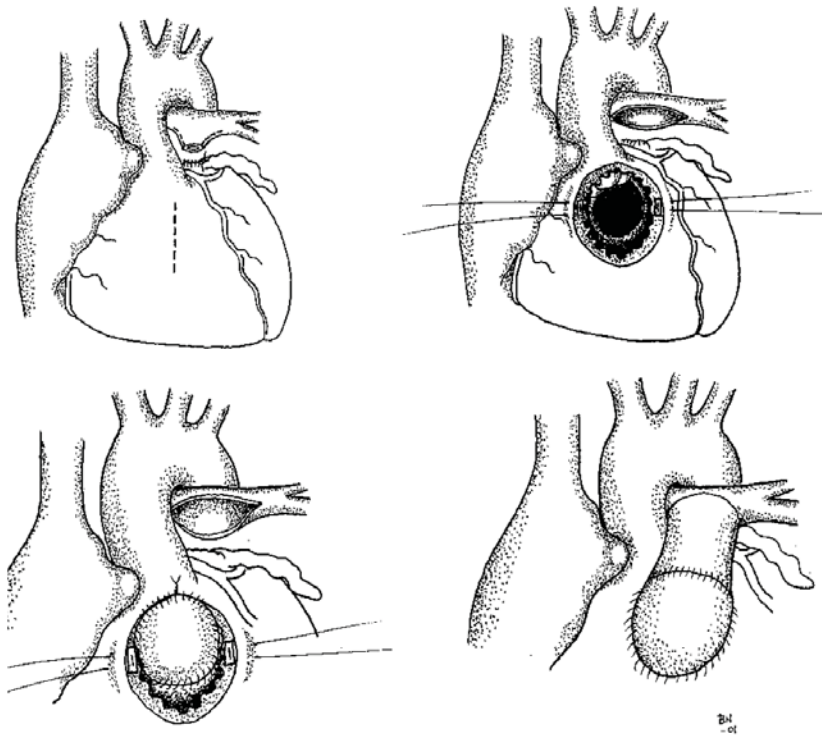

Figure 2. Illustration of the Rastelli operation for transposition, VSD and pulmonary stenosis. The VSD is closed directing the blood from the left ventricle to the aorta via a ventriculotomy of the anterior wall of the right ventricle. A conduit is then used to connect the right ventricle to the pulmonary artery. (Courtesy of Boris Nilsson)

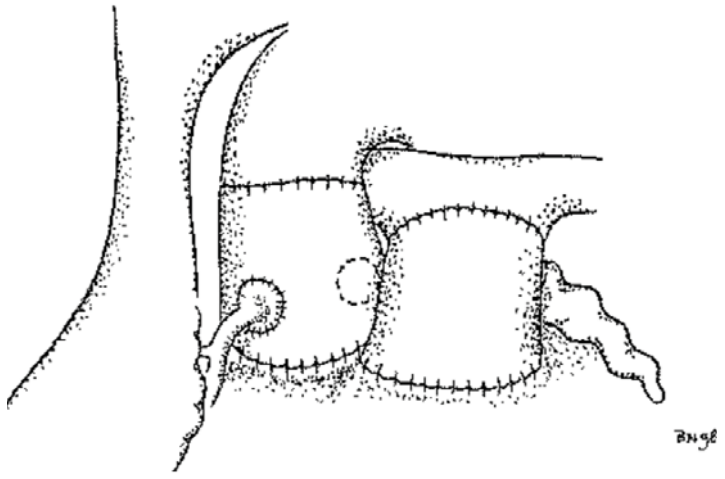

Figure 3. Illustration of the Ross procedure. The aortic valve is reconstructed using the native pulmonary artery as an autograft with reimplantation of the coronary arteries. The pulmonary artery is then reconstructed with a conduit. (Courtesy of Boris Nilsson)

a Blalock–Taussig shunt connecting the subclavian artery to the PA. Initial surgical repair is possible, for example, in patients with TOF, whereby the VSD is closed and RVOT obstruction relieved. Late management is most commonly for PR but can also be used for RVOT obstruction. There has been a trend over time toward avoidance of transannular procedures, thus attempting to preserve pulmonary valve annulus integrity when possible (5). When the RVOT is not amenable to repair, a valved conduit can be used for reconstruction. Surgical reconstruction of the RVOT with a conduit (homograft) has been performed since the 1960s (6). This advance has led to excellent palliation for affected patients. In many countries the use of biological valves in the RVOT is common for TOF. However, in Sweden a conduit, preferably a homograft, is considered the treatment of choice. The placement of biological valves in pulmonary locations is rarely implemented.

Rastelli repair for transpositions with VSD and repair of the truncus arteriosus are somewhat different in this setting in that they lack native RVOT. This leaves the surgeon with the task of reconstructing not only the PA and valve but also the entire RVOT. These malformations, as well as double-outlet right ventricle and pulmonary atresia, are rarely reconstructed after childhood, although cases of late reconstructions in adults have been reported.

The evolution of surgery has reduced mortality in children to the extent that the number of adults with complex congenital heart disease (CHD) now outnumbers childhood counterparts (7-9).

Management of native or postoperative RVOT dysfunction

Despite successful initial repair, reoperation with pulmonary valve replacement (PVR) is common later in life. However, clinical outcome data after PVR are inadequate and sometimes conflicting, and robust data for the optimal timing of PVR are not available. Studies on the effects of PVR are most often conducted on surrogate variables or matched comparisons, primarily from patients with TOF for whom clinical practice is analogous to that for Fallot-like (pulmonary atresia with VSD) and other malformations (10). In asymptomatic patients there is even less evidence for the timing of PVR, reflected in the wide variations in referral patterns in asymptomatic patients (11). There are also variations in age at PVR, indicating insufficient scientific support (12). Suggestions for managing these patients, taking into account several aspects besides symptoms such as tricuspid valve regurgitation, biventricular function and size, exercise capacity, arrhythmias, and symptom progression over time, are available (13).

One of the great challenges in patients with RVOT dysfunction is the tradeoff between the potential benefits and risks of RVOT intervention. All valves or conduits essentially become dysfunctional over time. Moreover, since life expectancy of the patient is longer than the expected longevity of the implanted valve, this tradeoff will take place repeatedly throughout the patient's life. Management is even more complex, as this is a heterogeneous population with various malformations and previous surgery. Data reporting an increasing number of adults with complex CHD indicate that this

clinical problem will only continue to grow in the future (7). PVR and conduit surgery are among the fastest growing segments of CHD and the most common surgical procedures in adults with CHD in the United Kingdom (14). Furthermore, the number of PVRs increased annually from 2004 to 2012 in both children and adults in a survey of 35 centers in the United States (12). Given the necessity for reoperations, multiple reoperations or reinterventions are often needed before the patients reach adulthood (15). In a retrospective study of repeated sternotomy for RVOT reconstruction, researchers found no evidence of increased risk for repeated sternotomies in a study of 220 patients with RVOT reconstruction (16).

Indications for pulmonary valve replacement (PVR)

At this point some brief comments on clinical aspects of native or postoperative RVOT obstructions are pertinent. Patients with PS often have more symptoms than those with PR. Doppler gradients can be misleading (overestimation) in long stenosis or stenosis in series, which is often the case in patients with conduits. Furthermore, lesions are often combined. There is consensus, reflected in European Society of Cardiology (ESC) guidelines, to relieve RVOT obstructions (in native or postsurgical TOF or conduit) when RV pressure is more than 60 mmHg in symptomatic patients. For asymptomatic patients 80 mmHg is recommended or when arrhythmias, progressive RV size or function impairment, or progressive tricuspid valve regurgitation occurs. In the American College of Cardiology/American Heart Association guidelines from 2008, the recommendation regarding RV pressure is even lower, at 50 mmHg. For those with severe PR there is consensus to recommend PVR in symptomatic patients. For asymptomatic patients PVR should be considered when arrhythmias, progressive RV size or function impairment, or progressive tricuspid valve regurgitation occurs (10, 17) (Table 1).

Reconstruction of the RVOT and reintervention

Various methods have been used for reconstruction of the pulmonary valve and RVOT, all of which unfortunately become dysfunctional over time and need replacement or reintervention (18). Choice of valve or conduit is dependent on factors such as anatomy, age, and local routine. By far the most commonly used method in Sweden is a homograft conduit, although there are also biological and mechanical alternatives. Increasing recognition for transcatheter pulmonary valve replacement (TPVR) has expanded the possibilities for reintervention in conduits where earlier only stenting was performed. TPVR has also been reported to be feasible for reintervention in native RVOT. Clinical practice in Sweden, however, is limited to reintervention in conduits.

Conduits

Homograft

The first experience of RVOT reconstruction with a homograft was by Ross and Somerville in 1966 (6). Homograft (or allograft) is tissue from human diseased donors that is explanted under sterile conditions shortly after death. Both pulmonary and aortic origins are exploited. There are several different techniques for preservation such as irradiation, cryopreservation (below −150°C), and refrigeration (+4°C). Prior

Table 1. Summary of ESC guidelines from 2010, including indications for PVR after repair of TOF and reintervention of RV-PA conduits. Class, class of recommendations; Level, level of evidence; RVOTO, right ventricular outflow obstruction; TR, tricuspid valve regurgitation

Indications for intervention after repair of tetralogy of Fallot	**Class**	**Level**
PVR should be performed in symptomatic patients with severe PR and/or stenosis (RV systolic pressure >60 mmHg, TR velocity >3.5 m/s)	1	C
PVR should be considered in asymptomatic patients with severe PR and/or PS when at least one of the following criteria is present: • Decrease in objective exercise capacity • Progressive RV dilatation • Progressive RV systolic dysfunction • Progressive TR (at least moderate) • RVOTO with RV systolic pressure >80 mmHg (TR velocity >4.3 m/s) • Sustained atrial/ventricular arrhythmias	2a	C
Indications for intervention in patients with right ventricular to pulmonary artery conduits		
Symptomatic patients with RV systolic pressure >60 mmHg (TR velocity >3.5 m/s; may be lower in case of reduced flow) and/or moderate/severe PR should undergo surgery	1	C
Asymptomatic patients with severe RVOTO and/or severe PR should be considered for surgery when at least one of the following criteria is present: • Decrease in exercise capacity (CPET) • Progressive RV dilatation • Progressive RV systolic dysfunction • Progressive TR (at least moderate) • RV systolic pressure >80 mmHg (TR velocity >4.3 m/s) • Sustained atrial/ventricular arrhythmias	2a	C

to storage in the homograft bank, the graft is sterilized with a solution of antibiotics. At implantation, homografts have technical advantages such as good hemostatic properties (19, 20). Homografts also have good hemodynamic characteristics and low rates of thromboembolism, which makes anticoagulation unnecessary. There are also reports on lower incidence of endocarditis with homografts in comparison with biological alternatives (21). Obvious disadvantages are the limited number of donors and limited access to valve banks.

Early results of irradiated homografts have been discouraging, with calcification and degeneration often within the first year (2, 22). Instead there has been an increasing use of fresh and cryopreserved grafts because of better results and increased availability from valve banks (23, 24).

Biological conduit valves

Biological valves are manufactured from porcine or bovine pericardium, porcine aortic valve, or bovine jugular veins. The vascular tube is often constructed from synthetic material. Various valves are available from several manufacturers. The Hancock® bioprosthetic valved conduit (Medtronic) is a commonly used conduit consisting of a

porcine aortic valve with a woven fabric conduit. The Contegra® pulmonary valved conduit (Medtronic) is derived from bovine jugular vein with three leaflets. It is preserved in glutaraldehyde and rinsed in isotonic saline before surgical implant, and comes in sizes up to a maximum of 22 mm. There are also conduits mounted on a woven polyester conduit (Dacron) such as the Carpentier-Edwards bioprosthetic valved conduit (Edwards Lifesciences), in sizes from 12 to 30 mm. Contemporary analysis from 1992 to 2008 showed no difference in reintervention rates between porcine and pericardial valves (25).

In a recent report from Sweden the conduit RVOT Elan™ (Vascutek, Renfrewshire, UK) porcine stentless valve and a vascular graft demonstrated excellent short-term performance (26).

Mechanical valves

Mechanical valve prosthesis is another alternative for PVR in CHD. The success of this method, however, is limited because of the risk of valve thrombosis, especially in patients with severe RV failure. Anticoagulation with warfarin plus antiplatelet therapy is often needed (27, 28). This method can be used in selected patients with concomitant indications for anticoagulation.

Comparison of homograft and other conduits

In a review of outcomes after PVR in patients with TOF, the authors concluded that there is conflicting evidence as to whether homografts or xenografts have the best results (18). Studies are often matched comparisons, and historical controls and randomized trials are lacking. There are studies of mainly children indicating that xenografts are superior to homografts (29-32), but also reports stating that homografts have better long-term durability than xenografts in children (33, 34). In one study the Contegra xenograft was superior to homograft and porcine xenograft in children but was implanted in the most recent era, which may have had some impact on the results (29).

In a large cohort of 293 homografts and 54 Contegras mainly in children and adolescents, the authors found three independent risk factors for graft replacement: graft size ≤20 mm, nonanatomical position, and Contegra conduit. The main reason for dysfunction of the Contegra conduit was stenosis of the distal conduit anastomosis. Ten-year freedom from graft replacement was 81.4% in the homograft group and 63.5% in the Contegra group (35). Another study comparing xenografts and homografts also found more supravalvular stenosis in the xenograft group (36).

Nonhomograft conduits have been associated with an increased risk of hemodynamic conduit dysfunction in adults (37). There are no studies of adults that show superiority of xenografts over homografts.

Factors influencing conduit durability

Studies have identified a number of risk factors for reduced conduit durability and reoperation. Data are predominantly from studies of pediatric patients or mixed cohorts

of infants, children, adolescents, and adults. Both congenital right heart malformations and Ross-operated aortic valve disease are often included in the studies.

Young age is a dominant risk factor for conduit failure, especially in younger age groups (30, 32, 33, 38-44). Furthermore, diagnosis and anatomy are important. Several studies show that conduit implantation in a nonanatomical position (such as truncus arteriosus) performs worse, than for example TOF, whereas Ross-operated aortic valve disease seems to experience the best outcome (29, 30, 33, 35, 42, 45-47). A smaller size of conduit is associated with reduced longevity but is related to young age and diagnosis (33, 43, 46). Oversizing of valves, however, is not associated with increased longevity (48). Among patients with a conduit, conduit size appears to be correlated with age. Adult sizes are implanted after approximately 8 years of age (15, 46). For homografts, some reports indicate that aortic grafts perform worse than pulmonary grafts in the RV-PA position in children (24, 40, 43, 44, 49). Similar conclusions have been reached in several studies of mainly adolescents and adults (41, 45, 50, 51). However, reports that do not confirm these findings also exist (52).

Pediatric studies indicate that implantation of a homograft is associated with systemic inflammation (53), and this has led to studies on blood group and HLA compatibility. There are reports that HLA or ABO mismatch in young children could lead to earlier graft failure and calcification (38, 50, 54), although others do not confirm this finding (34, 55). Neither has treatment with azathioprine after implantation of cryopreserved homografts showed reduction of immune response to HLA alloantigens or improved graft function in a prospective randomized trial of 13 children (56). However, postoperative prophylaxis with ibuprofen has been associated with improved longevity of homografts in children (Travelli et al., Abstract at ACC 2015).

Explanted homografts demonstrate changes in cellularity and inflammation (57), and implantation of homografts has been associated with postoperative systemic inflammatory response (53). Furthermore, HLA or ABO incompatibility has been associated with graft calcification and worse early outcome in some reports (38). This has led to the development of a decellularized homograft to reduce cellularity, called SynerGraft® (Cryolife Inc.) (58). Short-term results of the cryopreserved decellularized homograft indicate a decreased immunologic response, but limited hemodynamic advantage and no reduced rate of reintervention in comparison with conventional homografts (59, 60). However, decellularized fresh homografts seem to have better durability than cryopreserved homografts and xenografts in a matched comparison, although the cohort size was limited to 38 patients per group (61). There was also a tendency for adaptive growth of the decellularized grafts.

Early hemodynamic defects on echo or magnetic resonance imaging (MRI) have been associated with reduced longevity (32, 62, 63). Patients with TOF without early postoperative PS or PR are unlikely to have homograft dysfunction or replacement within 10 years (64).

Recent reports of adults and adolescents indicate that a high body mass index and smoking are associated with conduit dysfunction (37, 39). One possible explanation

for this finding is mediation via systemic inflammation, which previously has been associated with atherosclerosis.

Regarding outcomes after conduit replacement (surgical conduit reinterventions), reports have not conclusively stated an association with reduced or improved longevity compared with the first conduit. Studies imply that conduit longevity is equal (or better) at reoperation (15, 46, 62). However, Buber et al. concluded that placement of conduits before index surgery represented a risk factor for conduit dysfunction in their cohort of adults undergoing conduit surgery (37).

Transcatheter pulmonary valve replacement

In Sweden, TPVR has been available for the treatment of conduit failure since 2007. Sahlgrenska University Hospital/Östra started using this method in adults in January 2008. In 2009, the Health Technology Assessment Center in Gothenburg made an assessment of this method and concluded that TPVR seems less inconvenient for the patient in comparison with surgery but that long-term data and comparisons with conventional surgery are lacking. The most widely used valve for TPVR in Sweden is the Melody® valve (Medtronic), although in other cases the Edwards SAPIEN valve (Edwards Lifesciences) has been used.

The Melody valve is a stent-mounted bovine jugular vein expandable to 18–22 mm. Indications for use are in postsurgical RVOTs with a conduit (>16 mm) or bioprosthesis. Contraindications for implantation are no central venous access, conduit dimension >22 mm, or proximity to coronaries with risk of compression. In 2000, Bonhoeffer et al. described the first successful implantation of a transcatheter pulmonary valve (65). This introduced a new way of managing patients with dysfunctioning RV-PA conduits that were previously treated with percutaneous stents or reoperation for replacement of the conduit. There are now data from up to 7 years of follow up with the Melody valve after TPVR in obstructed or regurgitant conduits (66). Technical success is approximately 90% in several studies. Sustained hemodynamic improvement has been reported, with low gradients and reduction in PR with subsequent reduction in RV volume (66, 67). Five-year freedom from reintervention and explant were 76% and 92%, respectively (66). Stent fractures requiring reintervention were common in the early experience, but have become infrequent since the advent of pre-stenting. Valve in valve is reported to be feasible in selected patients. Coronary compression was the main reported cause of perioperative mortality, with an occurrence rate of 1% (67). Conduit rupture is also a known complication (68, 69). In a cross-sectional registry study in the United States, the most common complications were vascular related, in 14% of the patients. The risk of death was 1.7%, and 3.5% needed open heart surgery (70, 71) (Figure 4).

There are also reports on short-term follow up of the Edwards SAPIEN valve in dysfunctional conduits (72). The technical success for this valve was 97% in this small study of 36 patients. The advantage of this valve is that it is available in larger sizes of 23, 26, and 29 mm (SAPIEN XT), making it potentially feasible for dilated conduits. A positive hemodynamic and clinical outcome at 6 months was reported on conduits 16–24 mm in size.

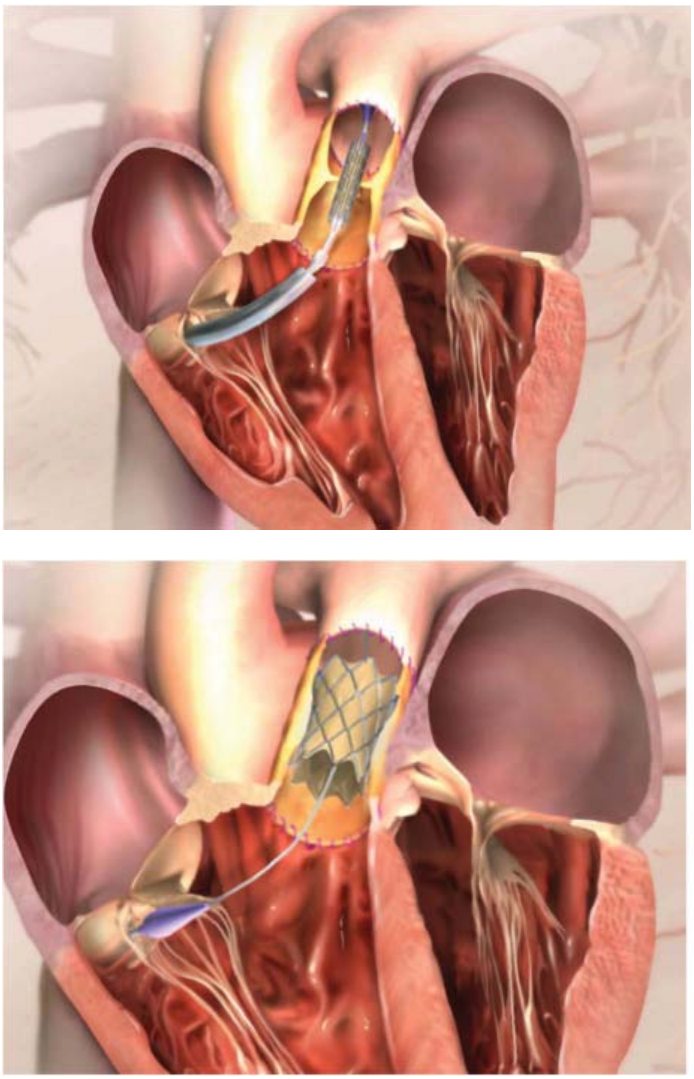

Figure 4. Implantation of the Melody valve in a RV to PA conduit . Valve delivery, preexpansion (on top). Valve implanted (below). Courtesy of Medtronic.

There are reports on the use of both Melody and Edwards in small conduits (<16 mm) and nonconduit or postsurgical native RVOTs (73, 74). Implantation in postsurgical conduit-free RVOT has been shown to be feasible in a two-step procedure whereby valve implantation is preceded by a bare-metal stent 2 months earlier, creating a landing zone of <24 mm for the valve (74).

Several reports on the increased risk of endocarditis after TPVR have raised concerns for the long-term outcome of the Melody valve. The incidence of endocarditis was 5% over 2.5 years of follow up (75). A retrospective study concluded that both the Melody

valve and the Contegra conduit have an increased incidence of infectious endocarditis (7.5% at 2 years) compared with homografts (2.4% at 6 years) (21).

Development of new and improved devices for large or native RVOTs is ongoing. The self-expanding Venus P valve has recently been presented as an alternative in patients with TOF and previous transannular plasty or dilated conduit (76).

Long-term results

Short- and long-term mortality

Perioperative mortality is approximately 1% in adults after conduit surgery (37). In a meta-analysis of children and adults subject to PVR (including conduits), the pooled 30-day mortality was less than 1% while the 5-year mortality and redo PVR were 2.2% and 4.9%, respectively (77). TPVR is reported to have a perioperative mortality of 1% (67).

The long-term mortality after conduit surgery in adults is not negligible, with survival rates of 87% and 81% at 10 and 15 years' follow up, respectively (37). In a study of mainly children from the early surgical era, 10- and 20-year survival rates were 77% and 59%, respectively (30), excluding perioperative mortality. Long-term survival after TPVR was 98% at 5 years (66).

Event-free survival and need for reintervention

Large cohort studies of patients with conduits are predominantly of children with various malformations, and show an event-free survival of 82%–84% and 55%–58% at 5 and 10 years, respectively (30, 33). In adults (median age 19 years) with a conduit larger than 18 mm at implantation, Buber et al. found an event-free survival of 95% and 81%, respectively, at 5 and 10 years. The probability of survival without hemodynamic conduit dysfunction was even lower, with a 5- and 10-year probability of 87% and 63%, respectively, indicating that hemodynamic dysfunction is common and precedes the need for conduit reintervention (37). Adult patients with aortic valve disease operated with Ross procedure seems to have the best outcome, with more than 90% freedom from conduit reintervention or replacement after 15 years (78). For TPVR, 5-year freedom from reintervention and explant was 76% and 92%, respectively (66).

Effect of PVR on right ventricle size and function

It has been known for a long time that PVR after PR reduces RV volume (79). There are also well-recognized reports that wide QRS duration is related to RV size and predicts malignant ventricular arrhythmias, and electrophysiological data showing that RV volume and pressure overload are associated with inducible sustained ventricular tachycardia (VT) (80, 81). Moreover, there is evidence of a clinical relationship between PR and ventricular arrhythmia and sudden death (82). Further reports conclude that a volume-overloaded right ventricle and ventricular functional impairment predict an adverse outcome (83). There are also mechanistic reports concluding that RV overload with a dyskinetic RVOT leads to conduction delay, bundle block, and further RV dysfunction (84).

MRI for the measurement of ventricular volume, function, and techniques for measuring flow has since its introduction become increasingly available, and is now routinely used in the clinical follow up of these patients. The main surrogate outcome variables after PVR are reduction in RV volume and improvement in systolic function. Measurement of pulmonary flow (regurgitation fraction) can also be of value. Data indicate that operating before systolic function deteriorates is positive for postoperative RV function (85). Moreover, several studies indicate a preoperative threshold above which RV volume as measured by MRI will not recover to normal after PVR. This threshold is between 150 and 170 ml/m^2 RV end-diastolic volume (RVEDV) (86-89) and 80 ml/m^2 RV end-systolic volume (88, 90, 91). Above this threshold there is a risk that the point of no return is reached. These data seem to have started a trend toward a more proactive approach to PVR, and this is reflected in ESC guidelines (10). However, conflicting reports exist. In a matched comparison, Quail et al. concluded that there is no volumetric cutoff and that progression of disease is slow (92).

The impact on PVR can also extend beyond the right ventricle, since there are reports of improved left ventricular function after PVR in patients with TOF. Moreover, such improvement was related to pre-PVR RVEDV (93).

It has been speculated that changes preceding impaired RV function and increased size are of importance, since patients developing PVR at a younger age have better outcomes despite recovery of RV function after PVR (87). For example, there is evidence of ventricular fibrosis in patients with CHD and TOF (94, 95).

Given the available data, therefore, one may well ask whether we are studying the appropriate surrogates. There are studies of various other variables such as RV output power measured by MRI (96) and deformation imaging that predicts postoperative ventricular function and functional class (97).

Frigola et al. studied adult survivors after initial correction but not subjected to further PVRs. They concluded that this group has normal RV ejection fraction and only mild dilation of the right ventricle, with a mean RVEDV of around 100 ml/m^2. Mild RV outflow obstruction was common, and exercise capacity was near the normal reference (98). The authors concluded that many patients with simple TOF (mild phenotype) who have had early initial repair may not be in need of PVR even over the longer term. This study highlights the variations in outcomes in this group of patients.

Effect of PVR on quality of life and exercise capacity

Patients with CHD are known to have reduced exercise capacity. Multiple factors besides the actual CHD influence exercise capacity, for example lung function. Among patients with CHD, reduced peak oxygen consumption (peak VO_2) identifies patients at higher risk of hospitalization or death (99). However, patients with TOF and severe PR can preserve exercise capacity for a long time despite RV dilatation (100). It is also reported that restrictive RV physiology predicts superior exercise performance (101). High preoperative peak VO_2 at cardiopulmonary exercise testing has been shown to predict early surgical outcome in adults with TOF after PVR (102).

Studies of surgical PVR in patients with TOF and PR indicate limited effect on peak VO_2 after PVR. There was, however, an improvement in the ventilator response to carbon dioxide (VE/VCO_2) at anaerobic threshold, with the best results in the youngest patients (87, 103). In studies of TPVR there are reports of improved peak VO_2 after TPVR (104). Reduction of the RVOT gradient is a predictor of improved peak VO_2 (105) indicating the effect of TPVR primarily in patients with PS. In other studies improved VE/VCO_2 has been reported after Melody PVR, but with no improvement in peak VO_2 (66, 106).

Several studies have shown an improvement in New York Heart Association (NYHA) functional class and symptoms after surgical PVR or TPVR (66, 69, 87, 103, 107, 108). There are also reports on improved quality of life (QoL) (Short-Form 36-Item Health Survey; SF-36) after TPVR (104). Furthermore, postoperative QoL (SF-36) has been found to be comparable with that of the general population after surgical PVR (41).

There are discussions regarding why there seems to be an improvement in symptoms, NYHA class, and VE/VCO_2 slope, but not peak VO_2, after PVR and TPVR. One suggestion is that patients breathe more easily after PR is relieved, which could improve ventilator efficacy. There are, however, many factors besides PR and PS that affect exercise capacity, such as pulmonary dysfunction at spirometry (66).

Effect of PVR on arrhythmia and survival

Studies on the effect of PVR on arrhythmia and survival are mainly from observational studies of patients with TOF. Gatzoulis et al. reported a 2% risk of sudden cardiac death over 8 years of follow up in a landmark study of patients with TOF. Wide QRS and PR as a dominating hemodynamic lesion was considered to be associated with an increased risk for VT or sudden death (80, 82). There are also reports of increased mortality risk from pulmonary stenosis (109). Furthermore, increasing RV size is found to be related to death or VT (83). Longitudinal left ventricular function also seems to be associated with sudden cardiac death and life-threatening arrhythmias in patients with TOF (110). Moreover, RV hypertrophy and reduced right or left ventricular function, as well as supraventricular tachycardia, have been associated with death and VT. Valente et al. conclude that prolonged PR or PS may be risky (109). Since PVR has been associated to some extent with reduction of QRS width (111), there are hopes that PVR can improve survival and reduce the risk of sudden death.

However, the impact of PVR on arrhythmia and survival in the advanced stages is disappointing. Despite normalization of RV volume and a positive effect on symptoms and functional class, there are observations suggesting no survival benefit or no reduced risk of malignant arrhythmia in a matched comparison, albeit the analysis is limited by low incidence (103). Another study concluded that PVR had no impact on survival and VT in a comparison with matched controls; neither was there narrowing QRS after PVR. However, there were differences between the PVR and control groups regarding RV size and function at baseline, where the PVR group had a significantly larger right ventricle (112).

VT ablation has no significant impact on arrhythmia-free survival after PVR (113). However, there are reports of a positive effect on post-PVR atrial and ventricular arrhythmias when combining PVR with cryoablation in patients with pre-existing arrhythmias (114). Furthermore, the benefit of surgical RVOT remodeling has been studied in a randomized trial of resection of the noncontractile aneurysm in RVOT, with no significant effect on early outcomes (115).

Summary of timing and effects of PVR

The current assumption for the management of PVR may be summarized as: "PR leads to RV dilatation and RV dilatation is associated with adverse outcomes. Thus, PVR to eliminate PR, reduce RV volume, and improve RV function should prevent bad outcomes." However, to date there is no evidence that earlier PVR leads to reduced risk of malignant arrhythmias or death. Therefore, the optimal timing for PVR is yet to be determined.

In conclusion, no study to date has shown reduced mortality after earlier PVR. However, there are multiple reports on reduction of RV size and improved RV function after PVR. The risks of repeated operations should therefore be set against the risks of irreversible RV failure, arrhythmia, and death. There is evidence to indicate that surgical PVR or TPVR leads to improved NYHA functional class, QoL, and, to some extent, improved exercise capacity.

Quality of life and health outcome

More children born with CHD are living through adolescence and adulthood (9). With increasing survival there is an increasing interest not only in studying surgery and care but also the patients´ QoL. There is, however, no universal definition of QoL, which makes measurement problematic and limits the validity of studies (116). Tools for measuring QoL have changed over time. In early studies NYHA functional class, employment, and symptoms were commonly used as surrogates for QoL. Over the years validated instruments such as the SF-36 or EQ-5D have increasingly been employed (117), although there is no consensus concerning the optimal instrument for measuring QoL. When studying QoL in individuals with a disease, the term health-related QoL (HRQoL) is used to highlight that QoL is affected by the impact of the disease or treatment on the patient's physical, psychological, or social functioning according to Bowling et al. Since CHD is a chronic condition sometimes accompanied by lifelong impairment, QoL and HRQoL are key outcome measures (118). Furthermore, there is a need for longitudinal and interventional studies, since these are very rarely conducted (119). QoL in patients with CHD has been reported to be equivalent to (or better than) that of the general population (120, 121), although there are conflicting reports on this matter (122). A study from Sweden shows a correlation between symptoms, age, NYHA class, and female gender, and poorer health outcome (EQ-5D). Furthermore, 20% of the patients who considered themselves asymptomatic still reported problems with pain/discomfort and anxiety-related depression. These findings should encourage health care providers to actively ask the patients about their symptoms and well-being (123).

Little is known about QoL in patients with previous RVOT surgery or conduits. There are reports on improved QoL after TPVR in accordance with increasing SF-36 scores (104). QoL late after surgical PVR has been studied (41). Patients scored lower on physical functioning and general health in comparison with the general population, although no longitudinal analysis was carried out.

AIMS

Overall aim

To study QoL, trends of treatment and survival, event-free survival, and the need for reintervention in adults with a conduit, using the SWEDCON/GUCH registry.

Specific aims

Paper I to report outcomes after surgical RVOT reconstruction with a homograft as described in the scientific literature.

Paper II to examine longitudinal self-reported health measured by the EQ-5D questionnaire in patients with previous RVOT surgery.

Paper III to investigate trends of implantation of conduits (new and reoperation) and TPVR over a 15-year period; whether the introduction of TPVR has led to a reduced need for conduit surgery; and the impact of age, diagnosis, and the longevity or number of previous conduits on deciding between surgical replacement and TPVR.

Paper IV to examine survival, event-free survival, and predictors of survival in patients with a conduit after a first conduit operation and after conduit reintervention.

PATIENTS AND METHODS

Ethics

This study was approved by the regional board of ethics and the board of directors of the SWEDCON registry. The study complies with the World Medical Association declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

SWEDish registry of CONgenital heart disease (SWEDCON)

Both adult and pediatric cardiology and cardiac surgery have had several local registries dating back as far as the 1980s. A nationwide Swedish registry of adult patients with CHD called "GUCH-registret" was created in 1998. These data were later incorporated into the SWEDCON registry in 2009 when adult and pediatric CHD was merged into one nationwide database. A Web-based platform was created in 2005 in collaboration with Uppsala Clinical Research Center (UCR). SWEDCON has four parts: fetal cardiology, pediatric cardiology, SWEDCON/GUCH (adult CHD), and congenital heart surgery. Inclusion criteria in SWEDCON/GUCH are: care at a clinic participating in SWEDCON, CHD, and ≥16 years of age. All parts of the registry share the same baseline characteristics regarding birth date, diagnosis (ICD), surgery, pacemaker implantations, and percutaneous interventions for surgical procedures. Group variables help to identify relevant groups of patients, for example, patients with a RV-to-PA conduit. Each part of the registry also has a specific dataset created to meet its specific needs. There are data regarding gender, marital status, employment, education, and smoking. Physiological data such as ECG, echocardiography findings, blood tests, and medication are also included as well as physical functional status according to the NYHA classification scored by the cardiologist or nurse. Furthermore, symptoms reported by the patients and physical activity are documented in the registry. Patient-reported outcome measurements (PROM) are included. Since 2005, health outcome has been reported using the self-administered questionnaire EQ-5D.

Since 2008 congenital heart surgery of both children and adults has been performed in two centers, Lund and Gothenburg, covering the entire Swedish population. TPVR is currently performed in three centers, namely Gothenburg, Lund, and Stockholm. All seven university hospitals have been covered by the registry since 1998: Akademiska sjukhuset Uppsala, Karolinska universitetssjukhuset Solna, Norrlands universitetssjukhus Umeå, Skånes universitetssjukhus Lund/Malmö, universitetssjukhuset Linköping, universitetssjukhuset Örebro, and Sahlgrenska universitetssjukhuset/Östra Göteborg. There are also GUCH units at several other hospitals covered by the registry: Falun, Gävle, Halmstad, Jönköping, Kalmar, Karlskrona, Karlstad, Kristianstad, Skövde, Sunderbyn, Sundsvall, Södersjukhuset, Växjö, and Östersund. Coverage for pediatric cardiology is even broader.

Input of data was in the beginning only implemented by the seven university hospitals. Over the last years input has also been done by GUCH units at an increasing number of local hospitals. Data input is done in several ways. Patients transferred from pediatric to adult care have their data transferred at the first visit as adults. Patients included

in the registry as adults are included in the registry after informed consent, and have their historical data entered retrospectively. The two national centers for congenital heart surgery carry put their data input at the date of surgery. Older or missing data are entered at follow up visits at the GUCH center or GUCH unit. Efforts have been made to catch up with input of older data. SWEDCON is different from many other registries in that data input is longitudinal with no defined end. Other quality registries often include patients after a specific event and then follow the patients for a prespecified time period.

In the yearly report from 2014, 11 313 patients were included in the registry. According to demographic data (124, 125) there are likely around 30 000 adult patients with CHD in Sweden, leaving the coverage rate at 30% compared with around 20% 5 years ago. According to the SWEDCON 2014 annual report, there has been an increase in the number of patients in the registry from 4152 patients in 2004 to 11 313 patients in 2014. There has been a yearly increase of approximately 1000 patients per year in recent years. Data quality assessment is being performed in 2015, but results are not available at the time of writing.

SWEDCON is funded by the Swedish association of local authorities and regions (SKL, Sveriges kommuner och landsting) and the national board of health and welfare (SoS, Socialstyrelsen). The purpose of the registry is to assess the quality of care, surgery, or percutaneous intervention, and to distribute data for scientific research and Swedish national guidelines. The website is www.ucr.uu.se/SWEDCON.

EQ-5D questionnaire

EQ-5D is a generic instrument used to evaluate health perception and status, comprising two parts: the EQ-VAS and EQ-5D-3L. The EQ-VAS consists of a 20-cm-long vertical visual analog scale ranging from 0 to 100. The patient is asked to grade his or her general health state, where 100 (on the top) is the best imaginable health state and 0 is the worst imaginable health state. EQ-5D-3L is a scoring system for five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. The score obtained from each dimension can then be combined to a five-digit number that can be converted into a single summary index using an index tariff. An index value of 1 represents full health, and 0 corresponds to death. The validated self-administered questionnaire EQ-5D was developed by the EuroQoL group in 1990 and is applicable to a number of health conditions (126, 127).

In 2014, EQ-5D was used in more than 40 Swedish quality registries that use patient reported outcome measures (www.promcenter.se). It has been used in SWEDCON since 2005 to measure health outcomes. According to the PROM center, EQ-5D is considered to measure HRQoL and is often used together with other instruments, but recently on its own, preferably in health economy to calculate quality-adjusted life years. EQ-5D is not disease-specific. A standard set of sociodemographic questions is provided with the questionnaire. Other disease-specific PROM are available, however, including for example CAMPHOR, used in pulmonary hypertension registries.

Methodological considerations and validity

As SWEDCON has not been subject to a formal study of internal validation, a validation study of diagnosis, date of surgery, and surgical code is included in Papers 3 and 4. Internal validity regarding mortality is via the cause of death registry, and should therefore be close to 100%. Patients who moved abroad are the only patients not covered by death registry. Regarding external validity, there was a concern that the expansion of the registry is still ongoing and coincides with the present studies. Estimated patient coverage is approximately 30% according to SWEDCON, which raises some concern about the external validity of the registry. Coverage of university hospitals (n=7) and tertiary centers (n=3), however, is 100% since 1998. Since complex patients or patients in need of surgery or percutaneous reinterventions are given care at these hospitals, coverage is estimated to be substantially better than 30% in this group. External validity and, thus, generalizability of the results should therefore be adequate. All patients in need of RVOT surgery or TPVR are discussed in multidisciplinary conferences in one of the tertiary centers, which should limit selection bias for choosing surgery or TPVR.

Evaluation of literature

Paper 1 is a systematic review of outcomes after surgical RVOT reconstruction with a homograft in adult patients with CHD. With the assistance of a qualified librarian, a search was performed in PubMed and the Cochrane database from their inception to May 2012. The search term in the PubMed NLM catalog Medical Subject Heading (MeSH) database was "homograft OR homografts AND pulmonary valve." The search was repeated in May 2015 also including the term "allograft." This process identified 665 articles, of which 133 were retrieved after screening of abstracts and cross-check of reference lists to full paper review by two authors. For reporting we used the proposed guidelines from the "Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group" (128).

Study population

In *Papers 2–4*, data were collected from the SWEDCON/GUCH registry. Data in Paper 2 were collected in December 2012. After completion of Paper 2 a new, more specified data collection was performed in April 2015. These data were used for Papers 3 and 4.

Paper 2 is a retrospective longitudinal cohort study of patients with previous RVOT surgery identified by codes for classification of surgical procedures.

Paper 3 is a retrospective longitudinal study of patients with a conduit identified by a group variable specific to RV-to-PA conduits.

Paper 4 is a retrospective cohort study of patients with a conduit identified by a group variable specific to RV-to-PA conduits.

In *Papers 2–4*, all patients were extracted from SWEDCON/GUCH; i.e., they were at least 16 years of age and had at least one visit to a GUCH unit. ICD coding was used

for classification of diagnosis in all three papers. In Paper 2, the NOMESCO classification of surgical procedures (http://www.nordclass.se/NCSP_1_16.pdf) of surgical codes associated with RVOT surgery was used to identify patients. In Papers 3 and 4, classification of surgical procedure codes was used as well as a registry-specific group variable to identify patients with an RV-to-PA conduit.

Statistics

Paper 2. Descriptive statistics were used for demographics and baseline data, and to display frequencies in the EQ-5D data. The Wilcoxon signed-rank test was used for repeated-measures analysis of EQ-VAS, and a Poisson regression model was used for analysis of EQ-5D and EQ-VAS between-groups data. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SAS 9.3 software (SAS Institute Inc., Cary, NC). All statistical analysis was performed in close cooperation with and under supervision of a biostatistician.

Paper 3. Descriptive data are expressed as mean, median, and range, as well as frequencies and percentages where applicable. Data are presented for the entire study period 2000–2014, and also for the three equal time periods 2000–2004, 2005–2009, and 2010–2014, to study the trends regarding interventions. The yearly number of surgical procedures and TPVRs were compared across time periods using analysis of variance (ANOVA). Post hoc testing was performed with Tukey's honestly significant difference test in conjunction with ANOVA. Changes in characteristics between time periods were evaluated using the Kruskal–Wallis test and Chi-square test for continuous and categorical variables, respectively. To evaluate continuous variables regarding the treatment groups (new implantation, surgical conduit replacement, and TPVR), the Kruskal–Wallis test was used to compare all three groups, and the Mann–Whitney U test was used for pairwise comparisons. The Chi-square test was used for categorical variables except when predicted cases per cell were fewer than 5, when Fisher's exact test was used. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed after counsel with a biostatistician.

Paper 4. Continuous and categorical data are presented as counts, percentage, mean, and median when appropriate. Cumulative survival and cumulative event-free survival were determined by the Kaplan–Meier method. Event-free survival was defined as time from conduit operation to reoperation, TPVR, death, or censor. Point estimates are presented as percentage and standard error (SE). Comparison of survival and event-free survival for different groups of diagnosis was performed using the log-rank test. Multivariable Cox regression was used to identify predictors of survival and event-free survival, and is presented with hazard ratio (HR) and 95% confidence interval (CI). Age was set as an independent variable, and diagnosis group and gender were factors. All statistical tests were two-sided, and a P value of less than 0.05 was considered statistically significant. All statistical analyses were performed in close cooperation with and under supervision of a biostatistician.

Statistical analysis for Papers 3 and 4 was done using SPSS (version 20; SPSS Inc., Chicago, IL).

SUMMARY OF RESULTS

Paper 1

The PubMed database and Cochrane library was searched in May 2012 and once again in May 2015, with the terms "homograft AND pulmonary valve" and "allograft" generating 665 hits. Only studies of patients with right heart malformations involving more than 50 patients with a mean or median age >18 years were included. Six studies with a cumulative total of 560 patients were ultimately included in the study. Perioperative mortality was 0%–2.9%. Long-term mortality was 2%–8.8% at 8.1–10 years. Reintervention of homografts were common during patients' lifespans, with a 10-year event-free survival of 78%–80%. Early postoperative echocardiographic or MRI defects appear to predict rapid homograft degeneration (Figure 5, Table 2).

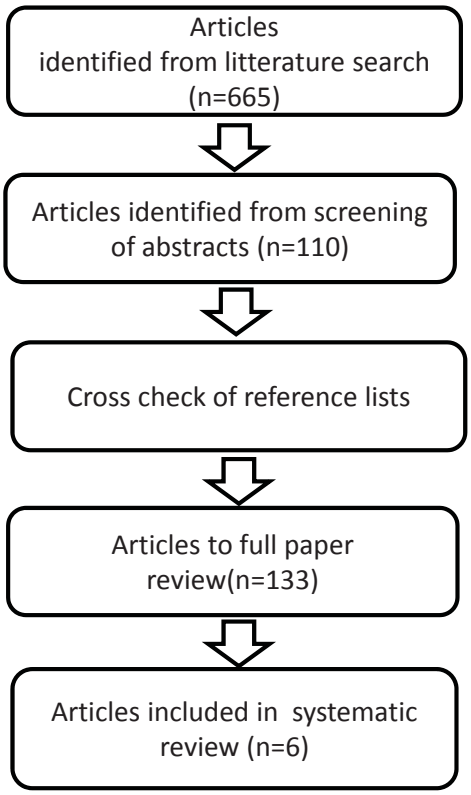

Figure 5. Illustration of the article selection process in Paper 1.

Table 2. Outcome data in included studies, Paper 1

Publication author year, (n)	Early mortality	Late mortality	Event-free survival
Hazekamp 2001, (51)	2%	4% at 1.7 yrs	
Oosterhof 2006, (158)		2% at 5.1 yrs	78% at 10 yrs
Troost 2007, (68)	2.9%	9% at 8.4 yrs	79% at 10 yrs
Nordmeyer 2009, (60)	0%	0% at 3.3 yrs	95% at 3.3 yrs
Scherptong 2010, (90)	0%	2% at 5.5 yrs	78% at 10 yrs
v d Woestijne 2011, (133)	1.5%	8% at 8.1 yrs	80% at 10 yrs

Paper 2

All patients with previous RVOT surgery and EQ-5D data from their first and latest visit were included. Among 103 patients (65 male, 38 female), mean age 31 (range 19–78) years, the diagnoses were: TOF (n=66); truncus arteriosus, transpositions, and double-outlet right ventricle (n=23); and Ross-operated congenital aortic valve disease (n=14). The mean time from first to latest visit was 3 years (range 1–7 years). Eighteen patients underwent 26 reinterventions in the observational period from the first to latest visit, including 18 operations and percutaneous interventions and eight pacemaker implantations and ablations.

Health perception measured by the mean EQ-VAS declined from 84.4 (SD=14.6) at the first visit to 78.6 (SD=18.3) at the latest visit, P=0.001. The decline was not observed in patients with reinterventions between the first and latest visit. Low EQ-VAS was associated with patient-reported symptoms and NYHA class II–IV. Patient-reported problems in the EQ-5D dimension "usual activities" were more common in the patients having reinterventions (25%) than those without reintervention (7%), P=0.04 (Figure 6).

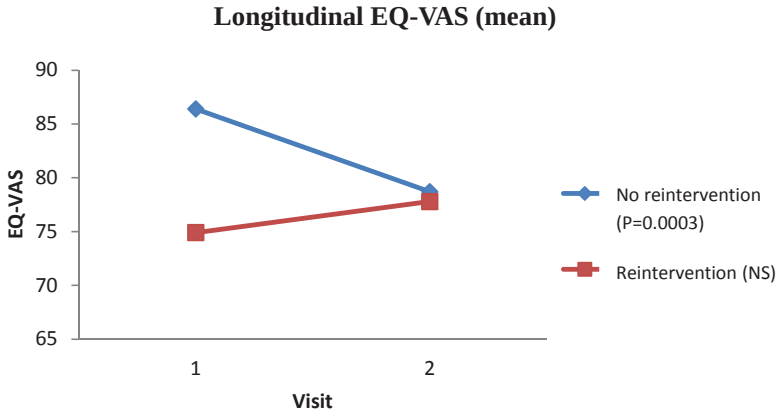

Figure 6. Longitudinal EQ-VAS for patients with no reinterventions (n=85) and with reinterventions (n=18) between the first and latest visit.

Internal validation of Papers 3 and 4

Internal validity was assessed by randomly selecting 50 patients with conduit in SWEDCON, and data regarding main diagnosis, surgical codes, and date of the last surgical procedure were compared across patient charts. Seven missing or false data were found in five patients, one (2%) regarding the main diagnosis and three (6%) for surgical code and date of surgery, respectively. Thus the overall validity was 95%.

Paper 3

From 2000 to 2014 there was an increase in adult patients with conduits included in SWEDCON/GUCH, from 122 to 536. There were 60 surgical conduit replacements, 40 TPVRs, and 176 new conduit implantations in the study period. Perioperative mortality was <1%. The yearly number of new implantations and reoperations both doubled over the study period. There was a significant increase in new implantations (P=0.007), surgical conduit replacements (P=0.024), and a combination of surgical replacement and TPVR (P=0.011) across all three time periods. Patients with new implantations were older (median age, 32 years) compared with the reoperation and TPVR groups (median age, 26 years), with the majority of patients having TOF (57%). The majority of conduit reinterventions were surgical, also after the introduction of TPVR in 2007, with no significant difference regarding diagnosis, gender, age, or previous number or longevity of conduits between surgical replacement and TPVR (Figure 7, Table 3).

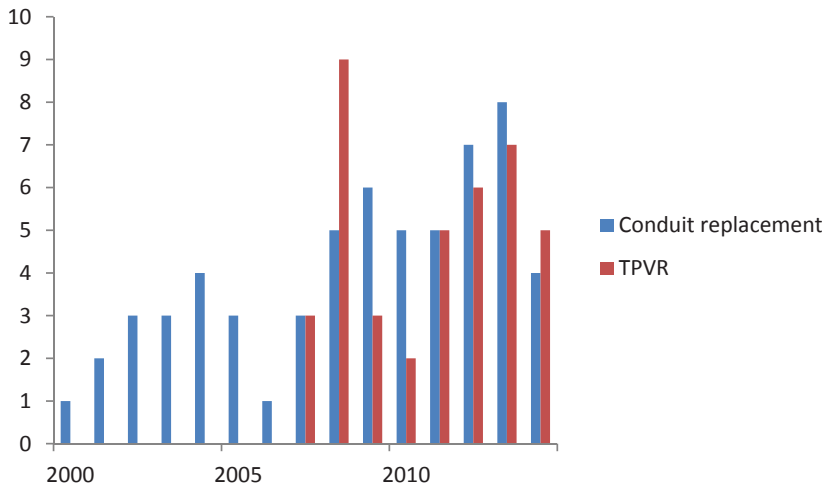

Figure 7. Number of surgical conduit replacements and TPVR per year in the time period 2000 to 2014.

Table 3. Patients' characteristics by procedure for 2000–2014. P-value refers to analysis across all procedures.

	New implantation	Conduit replacement	TPVR	P-value
Procedures, n	176	60	40	
mean age yr (median)	35,9 (32)	31,4 (26)	29,1 (26)	P=0.001
male, n (%)	107 (61)	43 (72)	23(58)	NS
Previous conduits, n mean (median)		1,5 (1)	1,4 (1)	NS
Conduit mean age at replacement, yr		13,7 (11)	13,6 (14)	NS
TOF, n (%)	101 (57)	21(35)	15(38)	P=0.002
Ross, n (%)	21 (12)	4(7)	6(15)	P=0.002
Mixed, n (%)	54 (31)	35(58)	19(47)	P=0.002

Paper 4

A total of 574 adult patients with a conduit (mean age 36.1 years) were identified in SWEDCON/GUCH. The TOF group was the largest (45%). In total, from 1967 there were 769 operations and 50 transcatheter PVRs. Mean age at first conduit operation was 20.2 years. Long-term survival after the first conduit operation, including accumulated perioperative mortality (<0.5%), was 93% at 20 years. The most common cause of death was cardiac-related. Higher age at first conduit operation was associated with increased mortality risk. Event-free survival was 77% and 54% at 10 and 20 years, respectively. Higher age at first conduit operation had a protective association, whereas male gender and complex malformations were associated with increased risk of further reintervention. Conduit reinterventions were common (n=245), the majority being in patients within the group including complex CHD (57%). Mean number of conduit operations and conduit reinterventions was 1.4 per patient. Ten-year event-free survival after the first conduit reintervention (n=176) was 70%, significantly lower than after the first conduit operation (P=0.04) (Table 4, Figure 8 and 9).

Table 4. Characteristics of patients with conduit reinterventions

	Reintervention 1	Reintervention 2	Reintervention 3	Reintervention 4
Patients, *n*	176	54	12	3
Mean age at reintervention (median)	19.1 (16.7)	21.7 (17.9)	27 (26)	35 (40)
TOF, *n* (%)	65 (37)	17 (31)	6 (50)	1
Mixed CHD, *n* (%)	101 (57)	37 (69)	6 (50)	2
Ross, *n* (%)	10 (6)	0	0	0

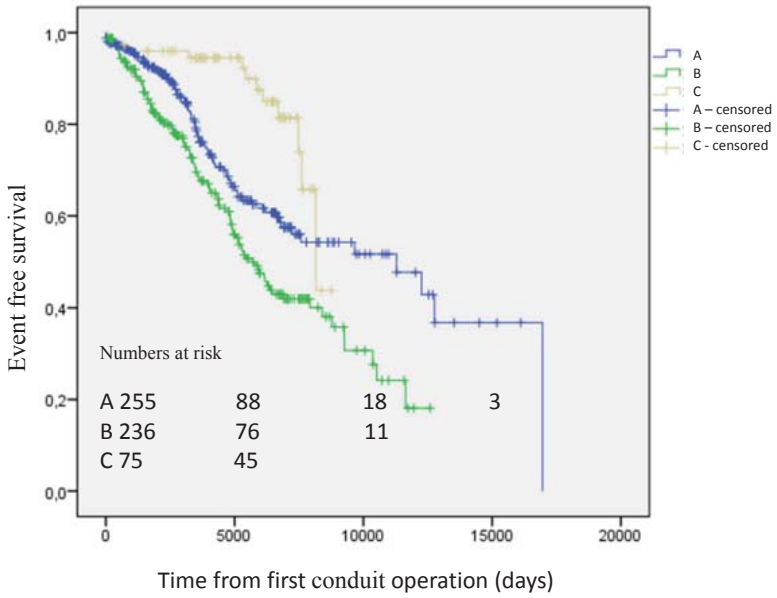

Figure 8. Kaplan-Meier estimated event free survival after first conduit implantation separated by diagnosis. (A: TOF, B: Mixed CHD, C: Aortic valve disease.) Log-rank P<0.001.

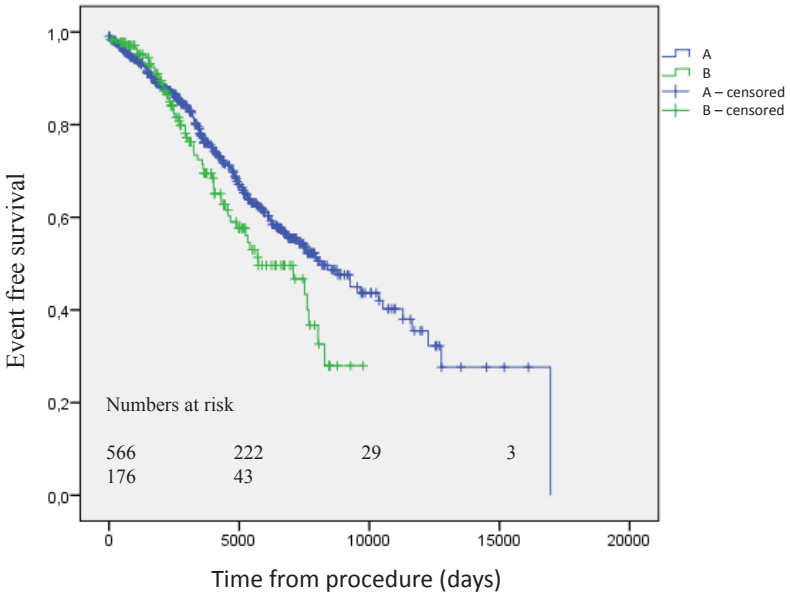

Figure 9. Kaplan-Meier estimated event free survival after first conduit operation (A) and first conduit reintervention (B), Log rank P=0.04.

DISCUSSION

One of the main findings of this thesis relate to declining health perception in patients after RVOT surgery. This decline is almost exclusively seen in patients with no further reinterventions in the study period. Other main findings relates to studies of outcome. Long-term survival is 93% at 20 years. Event-free survival after conduit or homograft surgery is 77% at 10 years, indicating that reinterventions are common. Less than half of the reinterventions in adults were TPVRs after its introduction in 2007. Outcomes after conduit reinterventions are worse than after the first conduit implantation.

Discussion of the specific content of papers is available in each respective paper. This is a general discussion of the overall findings of this thesis translated to the patients who inspired my interest for this area of research. From the results of this thesis, am I now able to answer my own questions from the beginning of my PhD studies, and, it is hoped, eventually use this knowledge in my clinical practice?

"Is this a growing group of patients since more patients with CHD are reaching adulthood?"
The number of adult patients with an RV-to-PA conduit is increasing. This affects health care providers, since there is an increasing need for conduit surgery or conduit reinterventions as well as the number of outpatient visits and imaging scans. Optimal timing for PVR is not addressed in this study, but ongoing data in this field will likely have a further impact on the future number of conduit operations or reinterventions. Besides the increase in the number of adults with complex CHD, improvements in cardiac surgery and care in addition to an increased focus on the timing of PVR may already have influenced clinicians in moving from a reactive to a more proactive approach (7, 102). Thus, the increased use of conduits late after initial repair for TOF can theoretically be linked to less toleration for PR late after TOF repair, leading to a more proactive approach. These are possible explanations for the increasing number of adults subject to the implantation of conduits. Development of new methods for TPVR in both native and large RVOT will likely also have a sizable impact in the future.

"What is the impact of TPVR in adults, and is surgery needed less frequently now?"
The number of surgical conduit replacements has increased despite the introduction of TPVR. This tells us that the increase in all conduit reinterventions cannot be explained by the introduction of TPVR alone. TPVR could otherwise have been considered less invasive, causing a shift in indications for PVR. Neither is the increase in surgical conduit reinterventions a result of failing TPVRs, since this rarely occurred. Even in the most recent era (2010–2014), more than half of the conduit reinterventions were surgical despite increasing recognition for TPVR in failing conduits. Age, diagnosis, gender, and the number and durability of previous conduits appeared to have no impact on deciding between surgical conduit replacement or TPVR. This suggests that the need for concomitant surgery, or anatomical factors such as proximity of the conduit to coronary arteries or conduit size, has a greater influence on this decision. Future expansion of TPVR to nonconduit RVOTs and new devices for various ana-

tomical settings will have a large impact on the need for surgery. Surgical conduit replacements and TPVR in a national perspective has not been studied before. There are however reports on increasing numbers of PVR in patients with TOF from registries in the United States (12).

"How is HRQoL affected in these patients, given that conduit reinterventions are common?"

I have met many patients who describe worse HRQoL in periods of worsening symptoms and functional impairment. From Paper 2 and study of the literature, I consider this likely to be a common problem, since symptoms and NYHA class higher than I was associated with worse perceived health according to a lower EQ-VAS score. The decline in health perception seen over time could be linked to this fact. Moreover, this decline is almost exclusively seen in patients with no further reinterventions. One possible explanation for this is that symptoms (associated with low EQ-VAS) trigger decisions for reinterventions with the aim of relieving symptoms. There is likely a lower threshold for reinterventions in symptomatic than in asymptomatic patients. However, what about the impact of reinterventions on HRQoL? The study was not primarily designed to answer this question. The small numbers in the study limit the analysis, although no improvement after reinterventions was seen. On the other hand, neither does reintervention seem to have a negative impact on health perception. Problems in the dimension "usual activities," however, were more common in reintervention patients. There was a concern that the findings in Paper 2 might indicate a gender bias, since reinterventions were more common in men. Further testing, however, did not reveal any gender difference in EQ-VAS score (data not included in this study). Further longitudinal studies on how reinterventions and reoccurring symptoms affect long-term HRQoL may be of importance. Longitudinal studies on HRQoL in patients with CHD are lacking (119).

"What is the long-term survival in this group and what are the mortality risks of conduit reinterventions?"

The estimated survival 20 years after conduit surgery is more than 90% from a mean age of 20 years old. This indicates low, but certainly not negligible, long-term mortality. Perioperative mortality, however, is low (<1%) even after conduit reinterventions which is in line with previous reports (37, 77). This tells us that the accumulated perioperative mortality risk of conduit reinterventions in the patient's lifespan is low in relation to total mortality, which is dominated by cardiac-related death. From an adult congenital heart cardiologist's point of view, it is evident that these patients need lifetime follow up of their well-being and hemodynamics. The fact that higher age at complete correction with a conduit is associated with an increased risk of mortality is interesting and worth bearing in mind when addressing these patients. Furthermore, it could contribute to the ongoing discussion about the timing of PVR.

"What is the expected event-free survival after conduit surgery?"

Conduit reinterventions are common, with nearly half of the patients with a conduit being subject to reoperation or reintervention at 20 years' follow up. Evaluation of the literature suggests similar findings. Anatomy and diagnosis has a great impact on outcome after conduit operations (30, 33, 42, 45, 46). When studying the event-free

survival curves and output from Cox regression, the Ross procedure has event-free survival superior to that of TOF. Moreover, the mixed group including complex malformations and nonanatomical position appears to achieve the worst outcome. The survival curve after the Ross procedure reflects the longevity of the conduit under optimal hemodynamic conditions, and is almost flat for 10 years with very few events, reflecting what seems to be the longevity of the actual conduit before it degenerates. When anatomy is increasingly complex the event-free survival decreases, reflecting the abnormal hemodynamic situation, for example in nonanatomical positions. There could also be kinking of the conduit and compression against the chest wall. Furthermore, TOF and complex lesions often have a malformed right ventricle that might already have been exposed to unfavorable hemodynamic conditions such as PS or PR. Young age is a dominant risk factor for reintervention especially in younger age groups, in both this study and previous reports. The fact that male gender is associated with worse outcomes is difficult to explain and warrants further analysis.

"Can we expect improved conduit durability in conduit reinterventions, since somatic growth may no longer be a limiting factor?"

Young age is a risk factor for conduit reinterventions in the literature as well as in this study (30, 32, 33). In light of the growing population of adults with conduits and the fact that conduit reinterventions are common, there is a growing need for data on repeated procedures. One of my patients asked me: "Somatic growth is no longer a problem. Can I expect increased durability this time?" Unfortunately, this study does not confirm this wish and hope. Previous studies report equal or longer durability at reoperations (15, 46, 62). However in Paper 4 the event-free survival is around 70% at 10 years after conduit reinterventions, which is significantly lower than that after the first conduit operation. Although there are limitations to this analysis, the findings do raise concern for the future. If longevity is shorter after conduit reinterventions, we will encounter even more often the problem of risk-benefit calculation for PVR. This will demand increasingly complex decisions, and thus calls for new ways of managing these patients. There are some possible mechanistic explanations for the decreasing durability of the second conduit; for example, immunologically the first conduit (homograft) could negatively affect the durability of the second. Another possible explanation might be reflected in the Cox regression analysis, which reveals higher age at first conduit operation to be associated with higher risk after first conduit reintervention. Is this a result of sustained negative effect of late initial correction with a conduit? This can be discussed from the model of a patient with TOF. Initial repair for TOF is most often to relieve the RV of a RVOT obstruction. As a result of the initial repair many patients are left with pulmonary regurgitation. If a patient with severe post initial repair PR is operated with a conduit at an older age he/she has longer time with volume loading of the RV than a patient operated at a younger age. Furthermore, at conduit reinterventions the hemodynamic conditions can be different with a degenerated and stenotic conduit. Thus, the previously volume loaded RV is now subject to pressure loading. What does these alterations in hemodynamics and time with pressure and volume loading mean in a lifetime perspective? Taking initial palliation with a shunt into account the situation gets even more complex. Perhaps the key to successful reinterventions later in life is a strategy with very little volume or pressure loading of the RV in children?

The main strength of this thesis is its national perspective. All Swedish tertiary centers for surgery and TPVR have been included in SWEDCON since 1998. Furthermore, a publicly financed health care system limits selection bias from sociodemographic causes. Follow up on mortality is close to 100%, since SWEDCON is linked to the cause of death registry. Decisions for conduit operations or reinterventions are taken at multidisciplinary conferences specifically for patients with CHD, limiting selection bias for surgery versus TPVR. However, the advantages of a large database are often associated with a loss of specific patient-related data, thus limiting the scope of analysis.

Multidisciplinary conference discussions about patients with conduits should be mandatory. Competencies in congenital cardiac surgery, structural interventions, imaging, and congenital cardiology are needed for a structured management plan. Treatment strategy should reach beyond initial correction or the current correction, and planning for the entire lifespan is warranted. In a multidisciplinary conference it is mandatory for those clinicians present to have knowledge of perioperative mortality, long-term mortality, and expected event-free survival to enable qualified and accurate decision making. Lifetime management of patients with a conduit is a constant balance between risks and benefits of operations or reinterventions while simultaneously taking into account the preferences and QoL of patients.

CLINICAL IMPLICATIONS

This study likely reflects the results of conduit surgery conducted in prime settings of dedicated tertiary centers, providing surgery and care with ready availability, from a publicly financed health care system. In this retrospective cohort, long-term mortality after conduit surgery is relatively low, and in fact numerically lower than that reported in other studies such as by Buber et al. (37). The low long-term mortality is potentially the consequence of an active treatment approach over the last decades. Despite a significant need for conduit reintervention, in this as well as other studies the accumulated perioperative mortality is low in relation to cardiac-related death. Although this is not a mechanistic study, I consider that this finding, together with increased mortality after RVOT reconstruction with a conduit at an older age, supports the benefits of a proactive approach to PVR rather than a more conservative one.

Since conduit reinterventions are very common, or almost inevitable, our focus should be on efforts to improve conduit longevity, thus reducing the need for reinterventions. Since anatomy is of importance and early hemodynamic defects seem to predict an adverse outcome (Paper 1), special attention should be paid to patients with early postoperative hemodynamic defects. Perhaps the focus should already be set in the operating room to optimize anatomy and evaluate hemodynamics at a very early stage. Many centers, including Gothenburg, manage patients with failing conduits according to the principle "surgery when necessary, percutaneous when possible." From this follows a strategy of limiting the number of open heart surgeries, creating less inconvenience for patients. In Paper 3, a percutaneous approach was chosen for less than half of the patients. Conduit anatomy likely is the key to the feasibility of TPVR, and new and improved methods will have a considerable impact on the feasibility of TPVR in more patients. Given that long-term event-free survival after conduit reintervention is shorter than after the first conduit operation, it is reasonable to surmise that the need for reinterventions will be a major issue throughout the patient's lifespan, with significant impact on recurring symptoms and HRQoL (Paper 2). TPVR seems less inconvenient than surgery for the patient, and there is no indication in the literature that outcome after TPVR is worse in comparison with surgery. Thus I agree that "surgery when necessary, percutaneous when possible" is the best current approach. In practice, this should mean optimizing the first conduit operation and then managing the patient with a percutaneous approach for as long as possible. Since the number of patients with a conduit is increasing (Paper 3), this will call for reallocation of health care resources to tertiary centers and expansive training of congenital heart interventionists.

Decreasing event-free survival after the first conduit reintervention is a concern. For patients undergoing repeated reinterventions with short event-free survival, this might call for an individualized approach. Possible approaches in such cases are optimizing anatomy if possible, changing conduit type, and in selected cases even treatment with ibuprofen.

TPVR in nonconduit RVOTs should be considered in selected patients with suitable anatomy and increased surgical risk. This strategy can postpone the first conduit operation, which in some cases can be an advantage to the patient under lifetime management.

This study is not designed to compare different conduits. However, the vast majority of conduits in Sweden are homografts. Given the outcome data in this study in relation to others, I see no reason to question the use of homografts per se. Furthermore, there are no other studies in adults giving robust support to other conduits in preference to homografts. Recent data from other groups on the higher incidence of infectious endocarditis in xenografts and TPVRs in comparison with homografts lends yet more support to the use of homografts.

CONCLUSIONS

Event-free survival after conduit surgery is close to 80% at 10 years, but the event-free survival time significantly shortens after conduit reinterventions. Long-term mortality after conduit surgery is low and dominated by cardiac-related death. The population of patients with a conduit is increasing, and conduit reinterventions are common. Since the introduction of TPVR, fewer than half of affected patients have received this treatment for conduit reintervention. Patients have declining perceived health over time after RVOT surgery, but such a decline was not observed in patients undergoing further reinterventions.

The data on outcome and QoL can be used in a structured multidisciplinary management plan using complementary surgical and percutaneous methods to treat the patient during lifetime management.

FUTURE PERSPECTIVES

Mechanistic studies of failing conduits are needed for the further understanding of the pathophysiological process of conduit failure and the possibility of improving conduits. One way forward is to study the relationship between conduit hemodynamic defects, inflammation, and subsequent degeneration.

Further studies on the decision for surgery versus TPVR can also be useful. There are other relevant factors (e.g., proximity to coronary arteries, conduit size) beyond the scope of this study. One possible study design would be assessment of the decisions taken during multidisciplinary conferences at tertiary sites.

It is essential that we have knowledge of the optimal timing for PVR. This is important both at initial repair and in reoperations. The fact that timing of procedures in childhood is reflected in outcome in adults indicates that there are very long cycles of follow up before the results of decisions taken in pediatric care can be transitioned to improved outcomes in adults. One example is the possible benefits of a very proactive surgical approach to PVR in children, aiming at a very limited gradient and no PR. This calls for increasing collaboration between adult and pediatric care. Furthermore, low mortality and a time interval of often a decade until reoperations make it challenging to study the effects of outcome changes in practice. Multicenter studies and international collaboration are needed in this area of research.

The SWEDCON registry offers a possibility to perform registry-based randomized controlled trials in this field.

Patients with a conduit have a lifelong need for follow up. Recurring symptoms and the need for reintervention likely has an impact on HRQoL. Further research on longitudinal HRQoL and patient-reported outcomes and experience could help, also in relation to outcomes after various procedures such as surgical PVR or TPVR.

There is also a need for improved materials. Conduits with better durability are an obvious example, but new and improved TPVRs for various anatomical settings including native RVOTs are also required. Since reintervention is common, there is also a need for surgical preparation of RVOT as a landing zone for TPVR.

Given the importance of anatomy for conduit durability, one option could be to modulate the preoperative setting to improve the eventual outcome. There are studies of resection of RVOT aneurysm with neutral results, perhaps opening avenues to other approaches.

Both the durability and longevity of conduits are of major importance. There is a difference between echocardiographic failure and dysfunction requiring reoperation. Many patients likely live with dysfunctional conduits for many years. Further study of differences in tolerability is warranted.

ACKNOWLEDGEMENTS

Först och främst vill jag tacka mina huvudhandledare och bi-handledare, *Peter Eriksson* och *Mikael Dellborg*. Ni har inte bara varit handledare utan också fantastiska mentorer och förebilder. Tack för att ni inspirerat och uppmuntrat mig under mitt doktorandarbete. Ni har betytt mycket både dagar då solen skiner och när taket på huset bokstavligt talat rasat in. En bättre miljö för en doktorand går inte att få!

Jag vill också tacka min bi-handledare *Gunnar Svensson* som med kirurgisk precision kritiskt granskat mina texter och levererat skalpellskarpa analyser.

Ulf Thilén, medförfattare och länk till Swedcon. Tack för all hjälp. Ditt engagemang har haft stor betydelse för mitt arbete.

Tack *Kjell Pettersson* och *Georgios Lappas* för statistisk konsultation och värdefulla diskussioner inom statistik.

Malin Berghammer, medförfattare och expert på hälsorelaterad livskvalitet. Tack för värdefull hjälp med mina studier.

Tack *Håkan Berggren* och *Mats Synnergren* för kloka synpunkter och för att ni tålmodigt svarat på mina frågor och funderingar om kongenital hjärtkirurgi.

Ett särskilt tack också till *Boris Nilsson* som låtit mig använda dina illustrationer i min ramberättelse.

Eva-Lotte Daxberg på sjukhusbiblioteket, stort tack för din hjälp med litteratursökningar.

Mina vänner i det glada, omtänksamma och proffsiga teamet på GUCH-centrum: *Eva Furenäs, Thomas Gilljam, Anders Ahnfelt, Gunilla Andulv, Ingvor Mårtensson, Marie Jinesjö, Karin Olander* och *Kerstin Lundblad*. Tack för allt stöd och för att ni tagit hand om mina patienter under tiden jag forskat.

Tack *Helen Sjöland* och *Putte Abrahamsson* för ert stöd under min doktorandtid och GUCH-ST.

Eva Thydén, Helena Dellborg och *Görel Hultsberg Olsson*. Tack för ert fantastiska engagemang i allt ifrån forskning till social gemenskap.

Per-Olof Hansson och *Henry Eriksson*, Tack för att ni anställde mig 2005 på Östra sjukhuset och introducerade mig till forskning.

Kurt Andersson och *Maria Schaufelberger*, tack för vänskap och handledning under min ST i kardiologi.

Per, Anders, Zacharias, Anders, Erik, Naqib, Jonas, Salim och alla vänner och kollegor som gör vardagen på kliniken och forskningen så trivsam!

Mina vänner från Örebro; *Johan, Per, Bror* och *Lotta*. Tack för att ni finns där i alla lägen.

Mina härliga kursare *Johan, Joakim, Fredrik* och *Öivind* som jag fortfarande har så roligt tillsammans med.

Mina föräldrar *Marie-Louise* och *Helge* som med kärlek gett mig möjlighet att välja väg och lärt mig att allt är möjligt.

Min underbara *Johanna* och mina barn *Jakob* och *Matilda*. Ni betyder allt för mig!

The studies in this thesis were supported by grants from the Swedish Heart and Lung Foundation, grants from the Swedish state under the LUA/ALF agreement, and grants from the Health and Technology Assessment Center of Sahlgrenska University Hospital.

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Appendix Paper 3 and 4

SWEDCON/GUCH is supposed to cover all conduit procedures in Sweden. Patients with conduit were identified using the group variable EPGID 1017 in SWEDCON/GUCH. This variable is unique to patients with RV to PA conduits.

Codes for classifying surgical procedures were used to identify relevant surgical procedures and TPVR (www.nordclass.se/NCSP_1_16.pdf).The procedures were defined as follows:

Conduit surgery: FDC 00, FDC 10, FDC 20, FDC 96, FHE 40, FHF 10, FHF 30, FHG 20, FJD 20, FJF 10, FJF 20, FMD 40, and FMW 96.

Transcatheter pulmonary valve replacement (TPVR): FJF 12 or FJF 96.