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Long-term results after implantation of cardiovascular homografts

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Long-term results after implantation of cardiovascular homografts

Long-term results after implantation of cardiovascular homografts

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Long-term results after implantation of cardiovascular homografts

Abstract:

Background: Homograft tissue is a vital material used in the operative reconstruction of children with congenital heart disease. Assessing its long-term performance in children and how it compares with other operative materials is important in guiding treatment paradigms.

Aims: To assess the durability of aortic arch repair with branch pulmonary artery homograft patches throughout different types of operative repairs in different groups of patients; to assess performance of valved homograft conduits used to reconstruct the right ventricular outflow tract (RVOT) in various diagnoses and to compare it with other alternatives; to assess pulmonary homograft tissue used to perform pulmonary arterioplasty and to compare it with other alternatives; and, to assess the endocarditis risk of surgical valved homograft conduits and to compare it with other surgical and percutaneous alternatives.

Methods: Registries maintained by the tissue bank and the division of cardiac surgery in Lund were reviewed and formed the basis of the material assessed in this thesis. Longitudinal outcomes of interest were drawn from the medical record and corroborated with other registries. Survival curve analyses were produced for evaluation and comparison. Cox regression analyses were performed for risk factor evaluation.

Results: Operative results from Lund compared similarly if not favorably with similar reported studies. Aortic arch reconstruction with branch pulmonary artery homograft patches yielded durable long-term results with low rates of restenosis. Evaluation of RVOT reconstruction with valved biologic conduits showed that the demonstrated superior performance of pulmonary homograft may not be as prominent once the effects of other variables are controlled for; and that, irrespective of conduit type, small conduits implanted in small patients are at risk for early replacement. Rates of reintervention for pulmonary arterioplasty were similar between pulmonary homograft and autologous pericardial patches. Homografts used in the RVOT had better freedom from endocarditis that bovine jugular vein (BJV) grafts – either surgical or percutaneous – placed in the same position.

Conclusions: Homograft tissue has been and continues to be a necessary material used in the surgical reconstruction of several pediatric congenital heart disease diagnoses. While other materials are and will be available, they should be evaluated in light of the long-term results achievable with homograft tissue.

Key words: Homograft, congenital heart disease, pediatric, pulmonary homograft, aortic homograft, bovine jugular vein graft, BJV, Contegra, Melody, aortic arch reconstruction, right ventricular outflow tract, RVOT, pulmonary arterioplasty, autologous pericardium, pulmonary valve, percutaneous, endocarditis

Signature	Date 2024-10-03

Long-term results after implantation of cardiovascular homografts

Michael J. Lewis

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Supervisors
Torsten Malm, Associate Professor
Petru Liuba, Professor

To Oskar, Elsa, and Anna, my three absolute faves

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List of Papers

Papers included in this thesis:

Lewis MJ, Johansson Ramgren J, Hallbergson A, Liuba P, Sjöberg G, Malm T. *Long-Term Results of Aortic Arch Reconstruction with Branch Pulmonary Homograft Patches.* J Card Surg. 2020 Apr;35(4):868-74.

Lewis MJ, Malm T, Hallbergson A, Nilsson F, Johansson Ramgren J, Tran K, Liuba P. *Long-Term Follow-Up of Right Ventricle to Pulmonary Artery Biologic Valved Conduits Used in Pediatric Congenital Heart Surgery.* Pediatric Cardiology. 2023;44(1),102–15.

Lewis MJ, Malm T, Hallbergson A, Johansson Ramgren J, Liuba P. *Evaluation and Comparison of Patch Materials Used for Pulmonary Arterioplasty in Pediatric Congenital Heart Surgery.* JTCVS Open. 2023; 15:424-32.

Lewis MJ, Malm T, Hallbergson A, Odermarsky M, Liuba P. *Prosthetic Pulmonary Valve Infective Endocarditis in Pediatric Congenital Heart Disease Patients.* Planned submission Fall, 2024.

Papers not included in this thesis:

Maker VK, **Lewis MJ**, Donnelly MB. *Ongoing Faculty Evaluations: Developmental Gain or Just More Pain?* Curr Surg. 2006 Jan-Feb;63(1):80-4.

Herrmann JL, **Lewis MJ**, Fuller S, Mascio CE. A*neurysm Formation After the Norwood Procedure: Case Report and Review of the Literature.* J Thorac Cardiovasc Surg. 2014 Apr;147(4):e55-6.

Spray TL, **Lewis M**. "Tetralogy of Fallot with Complete Atrioventricular Canal." In Lacour-Gayet, et al (ed.), *Surgery of Conotruncal Anomalies*. Chapter 9, First Edition. New York: Springer, 2016.

Ganta S, Ryan J, **Lewis MJ**, Nigro JJ. *3D Anatomical Modeling in DORV.* Planned submission Fall, 2024.

Abbreviations

ANOVA	analysis of variance
APC	antigen presenting cell
ASD	atrial septal defect
BJV	bovine jugular vein
BT shunt	Blalock-Taussig shunt
DMSO	dimethylsulfoxide
FCR	freedom from conduit replacement
FFR	freedom from reintervention
FPI	freedom from prosthetic pulmonary valve infectious endocarditis
FRO	freedom from reoperation
HLA	human leukocyte antigen
HLHS	hypoplastic left heart syndrome
IAA	interrupted aortic arch
IE	infectious endocarditis
LPA	left pulmonary artery
LVOT	left ventricular outflow tract
MHC	major histocompatibility complex
OHT	orthotopic heart transplant
OS	overall survival
PA	pulmonary artery
PA/VSD	pulmonary atresia with ventricular septal defect
PA/VSD/MAPCA	pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries
PDA	patent ductus arteriosus
PPVI	percutaneous pulmonary valve implantation
PPVIE	prosthetic pulmonary valve infectious endocarditis

PTFE	polytetrafluoroethylene
PV	pulmonary valve
PVI	pulmonary valve implantation
RPA	right pulmonary artery
RV	right ventricle
RVOT	right ventricular outflow tract
SPVI	surgical pulmonary valve implantation
SVR	single ventricle reconstruction
TA	truncus arteriosus
TGA	transposition of the great arteries
TGA/VSD/PS	transposition of the great arteries with ventricular septal defect and pulmonary stenosis
TOF	tetralogy of Fallot
VSD	ventricular septal defect

Populärvetenskaplig sammanfattning

Medfött hjärtfel är den vanligaste medfödda missbildningen och förekommer hos 1-2 procent av alla nyfödda. Cirka 500-600 barn med medfödda hjärtfel behöver opereras varje år. Det har tagit generationer av dedikerade klinikers och forskares insatser för att utveckla diagnostik och kirurgiska metoder för att behandla medfödda hjärtfel. Det har lett till att i Sverige är 30-dagars mortaliteten efter kirurgi idag omkring 1% och överlevnaden till vuxen ålder 97%.

Denna avhandling fokuserar på att analysera långtidsresultaten efter användning av homograft - vävnad som donerats av en avliden människa - jämfört med alternativa protesmaterial. För analyserna har data från den barnhjärtkirurgiska verksamheten i Lund, uppföljningsdata från bl.a. det svenska registret för medfödda hjärtfel Swedcon och Vävnadsbanken i Lunds databas använts.

Studie I är en retrospektiv studie av patienter som opererats med homograftpatchar från pulmonalisartärens grenar. Patcharna användes för att vidga en underutvecklad aortabåge inom tre komplexa diagnosgrupper: coarctationer med hypoplastisk aortabåge, avbruten aortabåge eller hypoplastiskt vänsterkammarsyndrom. Användningen av homograftpatchar i aortabågen var en ny metod och krävde en systematisk uppföljning av långtidsresultaten för att undersöka sena komplikationer och risken för utveckling av aneurysm (säckbildning i patchområdet). Resultaten redovisas i detta arbete och visar god långtidsöverlevnad och ingen risk för aneurysmutveckling. Om reintervention, på grund av nytillkommen förträngning var nödvändig, kunde denna oftast göras med kateterteknik.

Studie II redogör för långtidsresultaten efter rekonstruktion av höger kammares utflödestrakt i olika diagnosgrupper med avsaknad av eller förträngt utflöde till pulmonalisartären. Tre conduit med klaff har jämförts: pulmonalishomograft, aortahomograft och Contegragraft (bovin jugularven med klaff). Pulmonalishomograft har använts mest med lägst behov av conduitbyte jämfört med såväl aorta homograft som Contegra conduit. Multivariatanalys visade dock att fördelen med pulmonalishomograft inte var lika påtaglig. Pulmonalishomograft och Contegragraft har jämförbara långtidsresultat avseende reoperationsfrekvens och överlevnad medan endokarditfrekvensen är signifikant högre i Contegragraft. Aortahomograft har en tendens till tidigare försämring men fungerar tillräckligt väl för att användas på vissa indikationer. Några diagnoser var riskfaktorer för conduitbyte. Betydande riskfaktorer för tidig reintervention var låg patientålder vid operationen och små graftstorlekar.

I studie III analyserades långtidsresultaten efter vidgning av förträngningar i lungpulsåderns grenar. Patientgruppen är heterogen och inkluderar barn med en- och tvåkammarcirkulation. Förträngningarna är antingen medfödda eller uppkomna

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efter tidigare operationer för att studera om det finns någon skillnad i resultat. Pulmonalishomograft patchar jämfördes med patchar av patientens eget perikard (autologa) och en mindre grupp som fått syntetiska patchar. Risken för behovet av reintervention var likartad för pulmonalishomograftpatchar och autologt perikard. Förträngningarna grupperades efter olika egenskaper och typer och visade sig inte vara någon riskfaktor för reintervention.

Fokus i studie IV är risken för infektion (endokardit) i implanterade lungpulsåderklaffar i höger kammares utflödestrakt. Tre olika biologiska klaffar (pulmonalis- och aortahomograft samt Contegra) som är kirurgiskt implanterade och en (Melody) insatt med kateterburen teknik studerades. Homograft hade en lägre incidens av endokardit jämfört med BJV (Contegra och Melody). Vanligaste bakterier som orsakade endokardit var stafylokocker och streptokocker. Endokardit uppkom tidigare i BJV proteser jämfört med homograft. Många endokarditer kunde framgångsrikt behandlas med antibiotika och reintervention göras i lugnt skede.

Sammantaget visar denna avhandling lovande långtidsresultat upp till 30 år för barn opererade med homograft för komplexa medfödda hjärtfel och jämfört med annat biologiskt protesmaterial. Klaffbärande homograft fungerar väl under lång tid men degenererar och behöver bytas ut, tidigare ju yngre patienten är. Homograftpatchar är ett värdefullt protesmaterial för att vidga förträngningar i lungpulsådergrenarna och i stora kroppspulsådern hos små barn. Homograft är fortsatt ett viktigt och säkert protesmaterial i behandlingen av barn med komplexa hjärtfel.

Introduction and Background

Cardiac surgery today is built upon the incredible contributions of the clinicians and scientists that came before us. What is now regarded as routine practice is the result of their careful, thoughtful, innovative, daring, and often controversial steps forward. While that same spirit infuses the care of children with congenital heart defects today, present-day efforts tend to focus on collaboration, safety, and improvement of comorbidities.

Many attribute the first cardiac operation performed to Daniel Hale Williams in Chicago in 1893, who treated a patient with a stab wound to the left chest [1]. While Williams did indeed close a hole in the pericardium, the source of bleeding was a chest wall vessel. The first successful cardiac operation was performed by Ludwig Rehn in Frankfurt, Germany, in 1896 [2], who successfully closed a traumatic hole in the heart (also from a stab wound) with three sutures.

Several decades later in 1937, in an attempt to improve poor outcomes for patients undergoing pulmonary embolectomy, John Gibbon started his work on a pump oxygenator [3]. John Lewis used hypothermia during closure of an atrial septal defect (ASD) in 1952 [4], work which was later expanded on by Hikasa and colleagues in Kyoto, Japan [5] in 1967. Together with the discovery of the anticoagulant heparin by McLean and Howell in 1916 [6] and of cardioplegia -- initially by Melrose and colleagues in 1955 [7] and later revised throughout the early 1970's [8,9] – the tools used to perform modern cardiac surgery were now available.

Cardiac surgical technique advanced in parallel with technological progress. In 1938, Robert Gross performed the first successful ligation of a patent ductus arteriosus [10] at Boston Children's Hospital. Clarence Crafoord performed the first successful aortic coarctation repair in 1944 in Stockholm, Sweden [11]. And in 1944 at Johns Hopkins University, the collaboration of Helen Taussig, Alfred Blalock, and Vivien Thomas led to the first palliative shunt for a patient with Tetralogy of Fallot (TOF), which still bears their names today [12].

Despite successful operative closure of an ASD by Gibbon in 1953 [13], three operative mortalities cooled clinical interest in mechanical cardiopulmonary bypass. In 1954, Lillehei and colleagues at the University of Minnesota successfully repaired a series of patients with a diagnosis of ventricular septal defect (VSD) using *controlled cross-circulation* [14], in which the circulations of a patient and his relative were connected during operation. Further work in 1955 by Lillehei [15] and Kirklin and colleagues at the Mayo Clinic [16] led to the reincorporation of mechanical cardiopulmonary bypass. In the decades that followed, operative techniques were devised to treat the spectrum of congenital heart disease – diagnoses such as

transposition of the great arteries (TGA) [17] and hypoplastic left heart syndrome (HLHS) [18] -- which continue to be refined to this day.

Throughout the 1960's, mechanical valve prostheses and implantation techniques were developed [19,20]. Aortic valve replacement with aortic *homograft* (human tissue) was reported in 1962 by Heimbecker in Toronto [21] and Ross in London [22]. A few years later, Ross would report on his experience using homograft to reconstruct the right ventricular outflow tract (RVOT) [23]. *Xenograft* or *heterograft* – non-human -- tissue valves were developed in the early 1960's, with Carpentier and colleagues reporting on both fixing porcine valves in glutaraldehyde and using a mounting stent to produce a bioprosthesis [24-26].

While not surgical *per se*, cardiac catheterization is an invasive important, evolving modality for the care of children with heart disease. It, too, has a fascinating history. Werner Forssmann performed the first heart catheterization – a right heart catheterization performed on himself – in Germany in 1929 [27], ultimately going on to share the Nobel Prize in Physiology or Medicine in 1956. The first-in-human percutaneous pulmonary valve implantation (PPVI) was performed in 2000 on a pediatric patient with right ventricle (RV)-pulmonary artery (PA) conduit dysfunction by suturing a bovine jugular vein (BJV) valve into a vascular stent that was thereafter implanted in an 18-mm pulmonary homograft with complete elimination of pulmonary regurgitation and stenosis [28]. The valve design was later acquired and refined by Medtronic (Medtronic Inc., Minneapolis, MN, USA) under the name of Medtronic Melody valve. The first Melody valve implantation in Europe was performed in London in 2003. Four years later, Boston Children´s Hospital reported the first Melody valve implantation in the United States.

Homografts and conduits

Broadly stated, the goal of much of modern congenital heart surgery is to correct the patient as early as possible, to an as much as normal circulation as possible, and with as little foreign (or *prosthetic*) material as possible. When, why, and how this is achieved is what the daily work of the field is predicated upon. Young, small, fragile patients (e.g., low birthweight, prematurely born children) often are better first served with a period of growth and stabilization. Certain diagnoses, such as a small secundum ASD, can be closed with only a row of sutures, thereby replicating normal human physiology with an absolute minimum of newly introduced repair material. This is classically referred to as an *anatomic repair*. The correction of certain other diagnoses is not so straightforward, requiring both a significant amount of foreign material for correction and having the patient arrive after operative correction to a physiologic state different from a child's normal circulation. These are called *palliative repairs*. An illustrative example is HLHS in which a patient

typically undergoes three different procedures in the first years of life with significant prosthetic material, always landing in a state of deranged human physiology after operative repair.

As mentioned in the introduction, the Blalock-Taussig (BT) shunt was a milestone event in the history of congenital heart surgery. While used less often today, the modern version of the BT shunt still has its uses. Most commonly, a small (3 to 6 mm in diameter) polytetrafluorethylene (PTFE) tube is used to route blood from one place to another. This is an example of a *conduit*. Again, broadly stated, preventing backward flow in the human circulation is preferred. It has not yet been possible to create a durable valve in such small tubes without creating a significant pressure gradient across it, one which a fragile heart would have trouble pumping blood across. These small conduits remain, therefore, valveless.

Valved conduits also exist, of course. While the heart has four valves, two of them exist intimately associated with two major blood vessels (Figure 1). The aortic valve sits within the aorta and together they serve as the outflow from the left side of the heart to the body. Oxygen-rich blood which has returned from the lungs is pumped against the relatively high resistance of the entire body except for the lungs (termed *systemic vascular resistance*). The thick-walled aorta handles the pressure load placed upon it, while the aortic valve prevents blood from being inefficiently pumped back into the heart. Oxygen-poor blood returns to the right side of the heart after its course through the human body, waiting to be pumped to the lungs for oxygenation. This happens via the RVOT made up of the pulmonary artery and its associated pulmonary valve. The pressure against which this portion of the circulation flows (*pulmonary vascular resistance*) is normally significantly lower than its systemic counterpart, and the pulmonary artery's anatomy reflects that, being more thin-walled and pliable than the aorta.

Figure A

Atrial septum

Right atrium

Right ventricle

Left atrium

Left ventricle

Ventricular septum
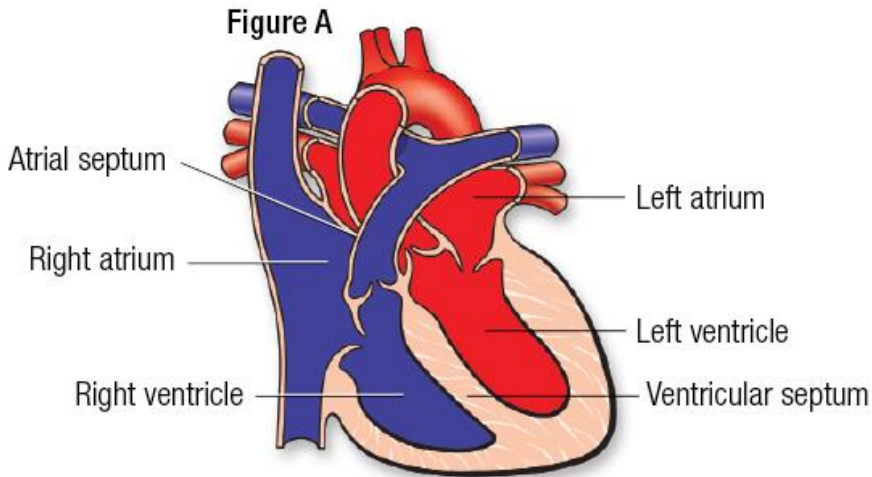
Figure 1 – Anatomy of the heart
Illustration used with permission from https://www.heart.org/en/health-topics/congenital-heart-defects

As mentioned in the introduction and to be expanded on in the following section, these two valved conduits (*cardiovascular homografts*) were used early in the practice of congenital heart surgery. Their use remains prominent and essential today. How long they last, how well they function in different capacities, and how they compare with other alternatives is the focus of this thesis.

There are other ways to create valved conduits. Mechanical valves can be placed in a tube of manufactured material such as PTFE creating a synthetic conduit. Valves made from non-human tissue (*hetero-* or *xeno-graft*) can also be used. Or entire valved conduits derived from non-human animal tissue can be used. These biologic conduits (together with cardiovascular homografts) make up the bulk of what has been used in Lund for reconstructive pediatric heart surgery.

No perfect conduit exists. Donald Ross – mentioned in the introduction – brought into popular use the operation that bears his name as an operative repair for valvular aortic stenosis. A pulmonary valve from that same patient (referred to as an *autograft*) is used as a substitute for the malfunctioning aortic valve; a prosthetic valve is then used in place of the harvested autograft. While not perfect either, the pulmonary autograft functions quite well. No such operation exists for patients with disease in the RVOT, so – assuming the pulmonary valve (PV) can not be repaired -- the choice is left to among those options discussed. Using biologic conduits in children has, among others, the following advantages: presence of a conduit in

addition to a valve, providing necessary length for a number of reconstructive operations; availability of smaller sizes (down to 12- and 14-mm diameters); and freedom from the need to take long-term anti-coagulation.

Why is reconstructive material needed?

TOF – discussed earlier with the advent of the BT shunt – remains a congenital heart disease diagnosis frequently in need of surgical repair, often with reconstructive materials investigated in this thesis. Arthur Fallot was a French physician in Marseille who described in 1888 the characteristic features of the heart defect that bears his name [29]. The *Tetra*-logy refers to the four features that are seen in the diagnosis: an anteriorly deviated conal septum (a component of the interventricular septum which separates the right and left ventricles), which gives rise to a prominent VSD; due to this malalignment, the aorta "overrides" (i.e., is on both sides of) the ventricular septum and is enlarged; RVOT obstruction secondary to stenosis alone or a combination thereof at the PV, below the PV, or above the PV; and, hypertrophy of the RV (Figure 2).
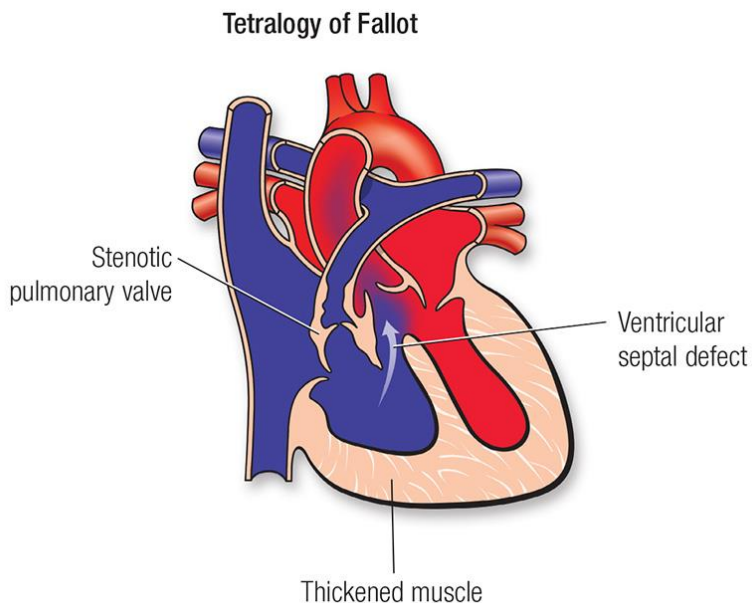
Figure 2 – Tetralogy of Fallot (TOF)
The defining anatomic characteristics of TOF. *Illustration used with permission from* https://www.heart.org/en/health-topics/congenital-heart-defects

Definitive surgical repair of TOF always involves closing the VSD [30]. How much prosthetic material is used is dependent on the degree of malformation, underdevelopment, or obstruction from the RVOT. Often some degree of muscle bundle resection is required in the RV. Patch enlargement can be performed below, at, or above the PV and even out into the branch pulmonary arteries (Figure 3). A prominent coronary artery (e.g., the left anterior descending artery) crossing over the RVOT can prohibit incising across it, in which case a valved conduit may need to be inserted, bypassing the stenotic area entirely and providing a route of blood flow to the lungs.
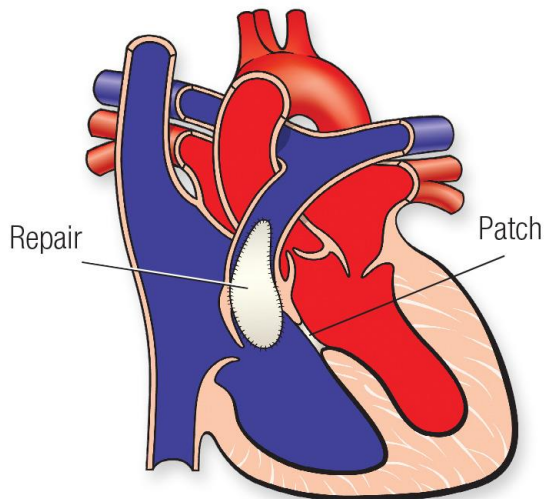
Figure 3 – Tetralogy of Fallot (TOF) repair
Trans-annular patching of the right ventricular outflow tract (RVOT) for treatment of TOF. *Illustration used with permission from https://www.heart.org/en/health-topics/congenital-heart-defects*

So here, contained within a single diagnosis, exists a multitude of reconstructive configurations and choices. In Lund the VSD is closed with a flat, round *patch* of PTFE, though this is but one of several choices of materials. This portion of the operation is usually performed first after cardioplegia is given and the heart is arrested. Reconstruction of the RVOT and pulmonary circulation are performed

next and can be performed with the heart beating. Patches of homograft and autologous pericardium (harvested from the patient at the time of reconstruction) are used to augment the pulmonary circulation. And valved, biologic conduits – homografts and BJV conduits – are used as the particulars of the reconstruction dictate. TOF patients are followed clinically throughout their lives for evaluation of their native anatomy (e.g, PA stenosis), of the components used in their operative correction (e.g., RV-PA conduits), and of consequent pathology seen later in life (e.g., RV dilation).

There are other congenital heart defects whose correction requires augmenting the outflow to the systemic circulation (as opposed to the pulmonary circulation in TOF). Perhaps the most dramatic of these is the first stage (of three) palliative repair of HLHS, the aforementioned Norwood operation. Simply stated, the left-sided heart structures – the mitral valve, left ventricle, aortic valve, and ascending aorta – fail to develop normally in HLHS (see Figure 4). Such patients survive by pumping blood to the body through persistent fetal pathways (a patent – open -- ductus arteriosus, or PDA) powered by the single, well-formed and well-functioning ventricle that they do have.
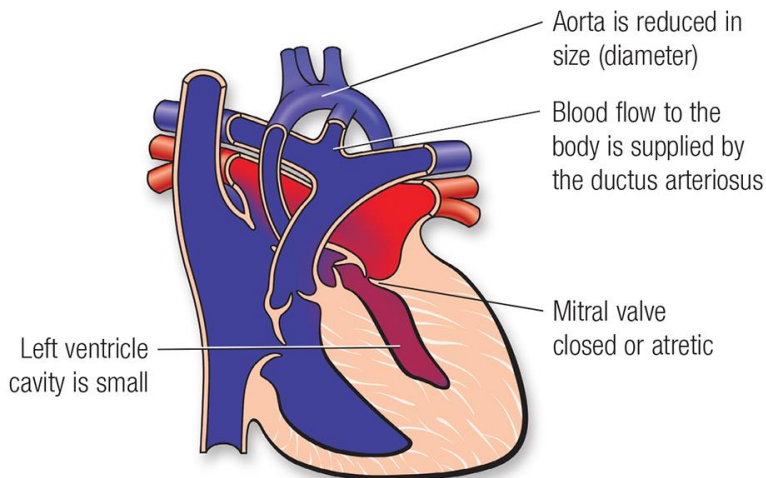
Figure 4 – Hypoplastic left heart syndrome (HLHS)
The defining anatomic characteristics of HLHS. *Illustration used with permission from* *https://www.heart.org/en/health-topics/congenital-heart-defects*

The Norwood operation has three primary goals: ensure that the blood returning from the body to the heart can reach the pumping ventricle, fashion a route for blood to reach the lungs for oxygenation and create a robust arterial outflow from the heart to the body. The first goal is easy to visualize. If there remains in place an atrial septum, it is removed. The second goal has been the subject of much debate and study [31]. A shunt similar to the BT shunt was used in Norwood's original description of his repair, modified to the extent that a PTFE tube (usually 3 to 3.5 mm in diameter) instead of the subclavian artery was used, thus referred to as a *modified BT shunt*. Another solution is to place a shunt (slightly larger, usually 5 – 6 mm in diameter) directly between the RV and the pulmonary circulation, referred to either as an *RV-PA shunt* or *Sano shunt*.

The third facet of the Norwood operation is extensive. The PDA is ligated, divided and all ductal tissue is removed. The connection of the RVOT to the pulmonary circulation is divided. The diminutive left ventricular outflow tract (LVOT) and RVOT are sewn together so that there is one common outflow from the heart. This common outflow is then augmented with a large patch of pulmonary homograft from the diminutive ascending aorta, through the transverse aortic arch down to the descending thoracic aorta where the ductus arteriosus had previously existed (see Figure 5), incorporating the common arterial outflow from the heart. Once completed, this leaves the patient with a circulation whereby the single ventricle pumps blood to both the pulmonary and systemic circulations, referred to as a *parallel circulation*.
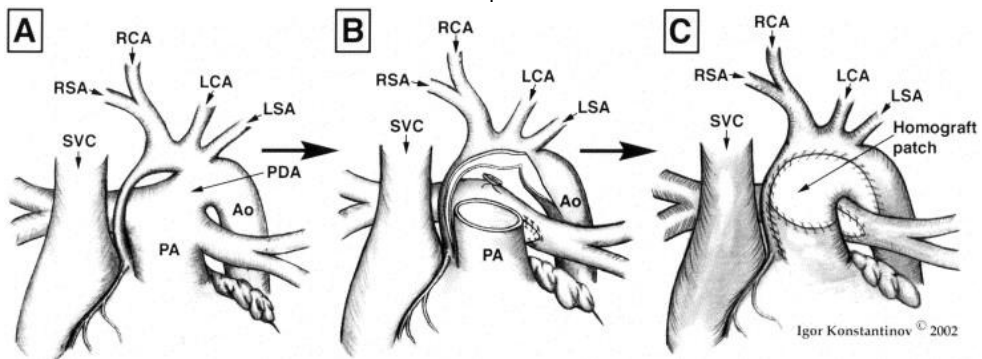

Figure 5 – Norwood operation
Major components of the first stage surgical palliation (Norwood repair) for hypoplastic left heart syndrome (HLHS). *Illustration used with permission from Burkhart et al., J Thorac Cardiovasc Surg. 2005, https://doi.org/10.1016/j.jtcvs.2005.02.060, https://creativecommons.org/licenses/by/4.0/*

The mental conceptualization of stabilizing a parallel circulation in a staged repair using a single ventricle takes significant effort. The actual operation is no different. It is a long operation requiring alternative cannulation strategies and periods of deep cooling and subsequent rewarming performed on small patients. Even after a technically well-performed operation, several of the patient's organ systems – neurologic, renal, and hematologic, to name a few – remain in a tenuous, vulnerable state.

So, an important common piece to the treatment of a number of congenital heart disease diagnoses of varying complexity is the material used in their reconstruction.

Homograft donation and storage

Tissues used to reconstruct children's heart defects often need to be small enough to match their own diminutive anatomy. That can only be achieved via tissue donation from a child who has died. The means by which one life is saved is made possible through the strength of parents experiencing a tragedy. Thoughtful care is used to ensure such a precious gift is put to its intended use.

Once the decision is made to donate tissues, contact is made with the tissue bank. According to European tissue bank guidelines, a standardized process is then followed to ensure the quality of the donated tissue. A tissue coordinator evaluates the donor to assess for contraindications for donation, including blood samples to rule out infectious disease. The donated heart is transported to the tissue bank where -- under sterile conditions -- the aortic and pulmonary valves are harvested with their respective vessels. Patches from the pulmonary artery branches are dissected and harvested if possible. The homografts are carefully examined for fenestrations in the valves, arteriosclerosis in the vessel wall and other pathologies. About 40 % (19-65% depending on the tissue bank) of all cardiovascular tissue is discarded due to structural impairment and microbiological contamination [32]. The homograft is carefully documented for diameter, length, and tissue quality; and, photographed to give the surgeon a thorough impression of the graft. The graft preparation is followed by decontamination in antibiotics. Microbial cultures are taken at each stage of the process. The grafts are rinsed and finally packed in sterile bags and prepared for cryopreservation. The cryopreservation follows a standardized freezing process. The homografts are stored in the gas phase of liquid nitrogen at -180 to -196 C for up to ten years. Most homografts are distributed for surgery within months.

At the request of the operating team, homograft tissue is then sent to the requesting center in a cooler and stored locally until operation. At the time of operation, homografts are gradually warmed in a series of baths, often taking around 30 minutes to thaw. The tissues are then used as described.

Tissue banks

The tissue bank in Lund is the largest in Scandinavia. It processes, stores, and provides tissues for operative repair not only for cardiac surgery, but also for cornea transplantation, orthopedic surgery, ear bone replacement, and skin donation for large burn injuries. It also provides tissue for education and research. Tissues are distributed mainly to centers in Scandinavia but occasionally to centers in other European countries.

The tissue bank's beginning in Lund coincided with a series of visits in the early 1980's from Magdi Yacoub, a prominent heart surgeon from Great Britain. The necessity and feasibility of using homografts was thus introduced, and ground was broken on the tissue bank in Lund in connection with the University Hospital in 1985. Initially fresh homografts were used; cryopreservation was introduced in 1989 and has been in use since that time. The tissue bank in Lund underwent a major renovation, completing a move to larger, updated premises in 2017. An operating room for tissue retrieval was built in direct communication with the tissue bank facility in 2021. Today the tissue bank supplies around 150 cardiovascular homografts per year, around half of which are used in Lund. Of those, about two-thirds are used in children.

Operative use

Pediatric heart surgery was centralized in 1992-1993 to Gothenburg and Lund. With a population of slightly more than 10 million citizens, Sweden sends its children with congenital heart defects for operative repair to either of these two centers with virtually no patients requiring interventional care at centers outside its borders. Additionally, patients from Iceland have been sent to Lund for their cardiac surgery needs since 2011.

Cardiovascular homografts have been used as a component of operative repair since the time of Yacoub's visit. The organizational structure within both the cardiac surgery department and the tissue bank in Lund has allowed for thorough, long-term follow-up of these patients. Furthermore, data are corroborated with national registries which can be less developed in other countries due to, for example, their organizational structure or larger size.

Clinical consequences

Implanting anything in the body elicits a defense response from the recipient. Shortly summarized, homografts implanted in children are treated as more than simply an indwelling suture line but less than a solid organ transplant. How that paradigm was arrived it deserves some discussion. The following distillation of that knowledge is condensed in an effort to enlighten but not to distract from the focus on those points germane to this thesis. However, several points in and of themselves are worthy of – and have been – theses of their own.

Again, trauma surgery provided the stimulus for innovation, and it was the German military who utilized arterial and venous homografts for battlefield limb revascularization during World War I [33]. While Gross helped usher homograft use into American medicine and heart surgery in the late 1940's [34, 35], it has been the field of vascular surgery that has performed the largest body of research on vascular homografts [36].

Central to the reaction between the donor homograft and the human recipient are homograft cell surface antigens genetically encoded by the major histocompatibility location (MHC) complex. The most prominent of these are the human leukocyte antigens (HLAs), which are divided into class I and class II antigens. Class I surface antigens (HLA-A, -B, and -C) are targets of "direct" recognition by recipient T-lymphocytes. Class II antigens (HLA-DR, -DP, and -DQ) require presentation by antigen presenting cells (APCs) to T-lymphocytes and thus compose the "indirect" pathway. Minor histocompatibility antigens are also important and are assessed in a patient's workup for organ transplantation, for instance. These are encoded outside of the genetic locus of the MHC complex. Blood group antigens (ABO) are encoded in a different location than the MHC complex and are of particular importance in highly vascularized transplanted organs [36].

Research on homografts decades before the time of Gross showed that such implants became nonviable after implantation, evolving into a fibrotic replacement of the homograft's cellular constituents while still retaining its original gross morphology via its connective tissue architectural scaffolding [37]. Later, canine models elucidated failure mechanisms in biologic conduits, with progressive loss and replacement of vascular wall layers with dense connective tissue [38]. With this basic understanding, attempts were made to preserve homograft elements thought beneficial to its structure and function while decreasing those elements that increased the host defense response against it.

Successive studies – though often non-systematic – guided the modern usage of homografts. Despite the difficulties of procurement and storage, homografts were preferred over synthetic alternatives. This was particularly true in vascular surgery studies where small-caliber synthetic tubes were prone to thrombosis, often in areas

of low blood flow, high vascular resistance, and infection. Experimental models showed that canine xenografts performed worse than homografts [39]. While frozen homografts increased availability they were also found to be less antigenic than fresh homografts [40,41]. Cryopreservation with liquid nitrogen was found to cause less cellular damage than conventional freezing techniques potentially allowing for viability of cellular elements upon thawing [42,43]. Smooth muscle components were found to be more antigenic than elastic cellular components [44]. Sterilization with antibiotics and irradiation was important in both inhibiting infection and decreasing antigenicity [45]. Preservative solutions with both formaldehyde and dimethylsulfoxide (DMSO) were evaluated to enhance homograft storage [38].

Treating donor homografts with immunosuppressive medical therapy prior to implantation did not show better results than those tissues not undergoing treatment. While studies of immunosuppressed patients who also received homografts showed longer homograft survival [46], this did not translate into routine immunosuppressive therapy for patients [47,48]. The cost of immunosuppression both in monetary terms and in incidence of complications – particularly in young patients – was prohibitive. Blood group matching between homograft and recipient showed mixed results and decreased the pool of available homograft / recipient pairs [49].

What is reported in this study is typical for modern usage at most centers. Non-irradiated, cryopreserved grafts prepared in DMSO are used based on their morphologic properties and thawed at the time of operation and implanted. Routine anticoagulation is not needed. Patients often experience the sequelae of a mounted inflammatory response post-operatively, due both to the enormity of heart surgery and the implanted homograft. This can often be appreciated as fever and increased hematologic markers of inflammation, such as an increased C-reactive protein level. This is often treated simply with anti-inflammatory medication once other potential etiologies (e.g., infection) have been ruled out.

Aims

The overall aim of this thesis was to analyze the long-term results of homograft implantation in children surgically treated for congenital heart defects in terms of survival, complications, and need for reintervention.

The specific aims of the individual studies were as follows:

Paper 1

To evaluate the long-term performance of pulmonary homograft patches used to augment the aortic arch;

Paper 2

To evaluate the performance of valved homografts used to reconstruct the RVOT and to compare them with other biologic valved conduits;

Paper 3

To evaluate branch pulmonary homograft patches used to augment the pulmonary arterial circulation and to compare them with other commonly used materials; and

Paper 4

To evaluate the occurrence of endocarditis in valved homografts used to reconstruct the RVOT and to compare them with both other biologic valved conduits and percutaneously implanted pulmonary valve prostheses.

Patients and Methods

Registries, databases, and ethical approval

Children – under the age of 18 years at the time of operation -- who underwent cardiac surgery in Lund are the focus of all four studies in this thesis. A careful accounting of them was both of utmost importance and an early step in laying out each study. Beginning in the early 1990's, the use of an electronic registry was instituted within the department of cardiac surgery and continues to this day. The tissue bank likewise maintains a similar registry. While we as clinicians (and humans!) care first and foremost for the patients undergoing operative repair of their heart defects, the clinical question posed in this thesis was centered around the performance of the material (namely, homografts) used in such repairs. These two registries served primary roles in this thesis in both elaboration of initial study parameters and ensuring data validity.

The ethics application and its subsequent approval marked, perhaps, the official beginning of this thesis. In Lund, the ethics application is collaboratively created by the research team and sent to the regional ethical review board. From 2004 to 2018, the ethical review was conducted at six regional review boards located in Gothenburg, Linköping, Lund, Stockholm, Umeå and Uppsala. In 2019 the Swedish Ethical Review Authority was established with its headquarters in Uppsala. The application is reviewed and sent back to the research team for possible revision. Once approved, it sets forth the conditions under which clinical research may be performed on our specific patient population. The backbone of all four of the studies was a retrospective query of the aforementioned surgical and tissue bank registries. While congenital heart disease in general and specifically those who require surgery for it is by no means common (with respect to hypertension, for example), the length of the studies allowed an accrual of a significant number of patients. As such, the likelihood that a specific patient could be identified during the course of data presentation was essentially zero. The ethics board, thus, did not require individual patient consent for inclusion into each study.

Study proposal review and approval is important for a few reasons. First and foremost (and perhaps most obvious) are the *ethics* involved in human subject research. Among others, issues of patient privacy and respect and study utility are addressed. Also, perhaps more practically, all journals publishing such clinical research require – either implicitly in the publishing process or, more often, explicitly stated in the body of the published articles themselves – a statement of the terms under which patient consent for entry into the study in question was obtained. And finally, there are purely pragmatic issues. Research teams – like the one conducting this thesis – are often limited in personnel and resources. Obtaining

consent from the families of thousands of patients would be impractical and resource consuming. Arriving at a tenable solution with regards to consent facilitates the research process.

Two additional layers of accounting exist and contributed to the validation of patient data in this thesis. The first is the national population registry which was used to confirm patients' vital status. While perhaps taken for granted this is often a difficult step in performing modern clinical research in significantly larger countries. The second is Swedcon, the Swedish national database of patients with congenital heart defects [50]. It contains the complete clinical histories of all patients in Sweden with a congenital heart disease diagnosis, surgical or not.

Most patient data were available via the electronic medical record. In rare cases, retrieval of archived paper charts was needed. After having received their operation in Lund, a small number of patients were living outside of Sweden at the time of each study. In all cases, the number of patients was small (less than 5% of the total study population) and the patients were excluded from their respective study in order to ensure data validity. The homografts used were processed, procured, and tracked exclusively from the Tissue Bank in Lund.

Statistics

The bulk of the statistical analysis was performed using the SPSS statistical software package, from version 24 in the first article to version 28 in the last. SPSS was originally an acronym for Statistical Package for Social Sciences and stood for both the statistical software itself and the company that developed it. It was purchased and maintained by IBM in 2009 and the acronym was rebranded as Statistical Product and Service Solutions. It is the statistical program licensed and continually updated by Skåne University Hospital and the one with which the research team had the most experience.

Even as individual statistical packages evolve, other packages offer different approaches to processing and representing data. R is statistical software package with a quirky name, an unwieldy interface, and nimble adaptabilities. Its genesis was at the University of Auckland, its name is based on a combination of preceding computer languages and developers' names, and it is free and open source. Because of its availability and utility, its use is becoming more and more prevalent in clinical research. It was used as a supplement to SPSS in this thesis.

This was a retrospective study of patients from 2001 to 2016 who underwent aortic arch reconstruction using pulmonary homograft. Patients were grouped according to the method of operative intervention used and whether the enlarging patch was used at the patient's first operation or after having had a prior intervention. The operative groups were Norwood reconstruction (discussed in Background), aortic arch reconstruction (see Figure 6, for a diagnosis of aortic arch hypoplasia), and interrupted aortic arch (IAA) reconstruction (see Figure 7).
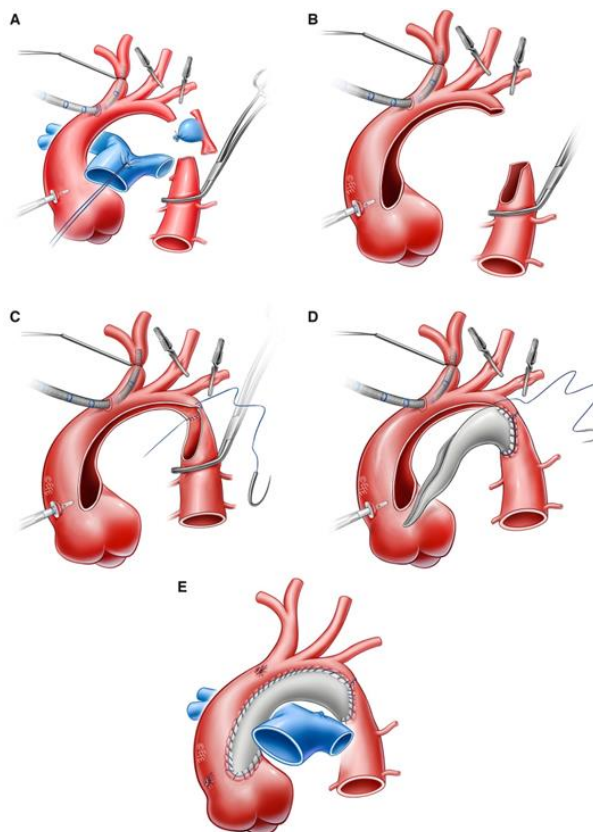
Figure 6 – Repair of aortic arch hypoplasia
The surgical steps used to patch augment a hypoplastic aortic arch. *Illustration used with permission from Patukale et al., Interact CardioVasc Thorac Surg. 2022, https://doi.org/10.1093/icvts/ivac135, https://creativecommons.org/licenses/by/4.0/*
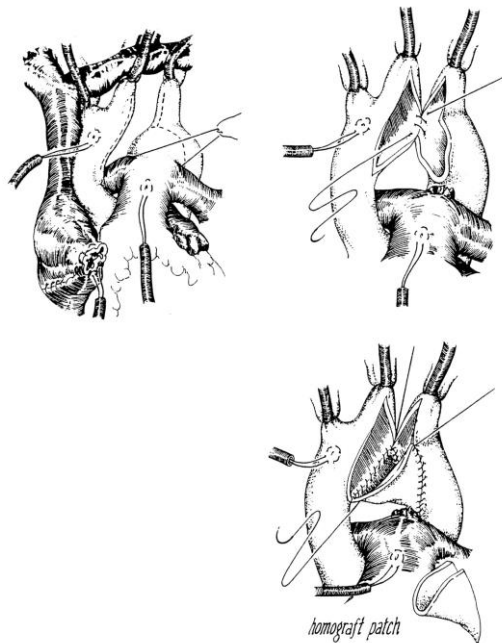
Figure 7 – Repair of interrupted aortic arch (IAA)
The surgical steps used to patch repair IAA. *Illustration used with permission from Jacobs et al., Circulation. 1995, https://doi.org/10.1161/01.cir.92.9.128, https://creativecommons.org/licenses/by/4.0/*

As discussed earlier, William Norwood and his team first performed his eponymous operation at Boston Children's Hospital in 1979 [18]. His revolutionary technique took some years to be adopted throughout the world. In Lund, the first Norwood operation was performed – successfully -- in April 1993. Initial experience in the first five years entailed 22% operative mortality, compared with 1% in the last ten years (unpublished data). The commencement for enrollment in this study was January 1, 2001, as operative technique had stabilized by then, allowing for a closer focus on the performance of the reconstructive homograft patches. December 31, 2016 was chosen as the end date for study enrollment.

All patients requiring homograft patch enlargement of the aortic arch were selected from the registry from the department of cardiac surgery, which was further validated by the Tissue Bank registry. Patient survival was ascertained via the national population registry. Coordination with the cardiac catheterization lab was necessary – both in Lund and at the Karolinska Institute in Stockholm – to assess for all interventions performed on the patients that occurred after operation.

Outcomes assessed were patient death, orthotopic heart transplant (OHT), and reoperation or catheter-based reintervention in the area of patch placement. Overall survival (OS) was chosen as a primary outcome as opposed to transplant-free survival as the enlarging patches remained in place after OHT. Reintervention was defined as either a surgical or catheter-based intervention in the area of patch reconstruction. Freedom from reintervention (FFR) was selected as an additional primary outcome of interest.

Statistics

Patient characteristic values were represented as counts, percents, medians, and ranges, as appropriate. Primary outcomes (OS and FFR) were represented as Kaplan-Meier survival estimates and between-group comparisons were performed using the log rank sums test. P-values less than 0.05 were used to ascribe statistical significance. All analyses were performed using SPSS version 24.

Paper 2

This was a retrospective study of patients from 1990 to 2019 who underwent placement of a biologic valved conduit between the RV and PA. The three conduits assessed were aortic homograft, pulmonary homograft, and BJV graft (Contegra, Medtronic, Minneapolis, USA). The normal human RVOT *in situ* is the perfect valved conduit: it has a low gradient to blood flow, has good valve function, is resistant to infection and thrombosis, and grows with the patient. None of the conduits used in this study – and throughout the world – possess all these properties and are thus necessarily prone to eventual dysfunction and replacement. Thus, several patients had not only an initial conduit placed but several subsequent conduits. The conduits were grouped by type, number, and patient diagnosis.

The most relevant clinical question central to these patients is: how long will the conduit last? The primary outcomes selected to study were thus freedom from conduit replacement (FCR) and FFR. Conduit replacement was defined as a surgical replacement of the previously placed conduit with another conduit. Reintervention was defined as either a conduit replacement or a catheter-based intervention of the previously placed conduit.

While Contegra grafts did not come into use in Lund until 2002, the operative techniques for conduit placement have been stable for some time. Thus, the commencement date for entry into this study was considerably earlier (January 1,

1990) than that of Paper 1. A 30-year follow-up period allowed for substantial patient enrollment.

There has been mounting evidence that – all things considered – pulmonary homograft is the optimal conduit of choice in children with congenital heart defects. Aortic homograft has a thicker muscular wall. Its use has been advocated for in cases in which the patient's pulmonary vascular resistance is high, for example. However, the extra tissue tends to be prone to earlier, more severe calcification, ultimately requiring earlier conduit exchange. There also has been reported evidence that Contegra grafts perform similarly compared to pulmonary homograft. We hoped to learn how these conduits performed in our patient population.

Earlier adoption of any technique naturally can lead to a preference for it. In our case, for example, homograft use began earlier than Contegra use. This is an example of *bias*. There are also particular parameters in which certain conduits are better suited than others. For instance, Contegra conduits do not come in diameters smaller than 12 mm (homografts do). Additionally, cost, availability, and cultural norms can dramatically alter the conduits available for use. Analytic discrimination of these and other factors was necessary to truly evaluate conduit performance. Perhaps the expression *comparing apples to apples* is the most succinct expression of the process.

Statistics

Treatment biases, conduit availability, and many other variables make answering the very simple question 'What conduit is better?' a tricky one. Adjusting the baseline variables so that similar patients were treated with similarly sized conduits was a first step in this process. We manually selected operative cases that were similar in baseline variables (patient age, weight, gender, and conduit diameter) across the three conduit types to better compare them.

While this technique allowed for the comparison of all conduit types, conclusively showing differences among them was difficult as it was we the researchers who selected the cases for comparison. However, from this first step in the process we took which two conduit types should be compared further in the propensity score matched subgroup analysis. At the cost of losing a comparison group, this step in the analysis lent itself to a more statistically robust comparison.

This propensity score is the *probability* that the clinical variables selected for use in our study predicted one of two conduit types. Appropriate variables must be selected for creation of a reliable score. It was important that any one variable was not correlated with another -- patient weight and age, for example. Clinical variables were then assessed by a univariable logistic regression analysis in which

conduit type was the dependent variable. Variables which were predictive of conduit type (P-value of < 0.15) were selected for use in the propensity score creation. This score (probability) was created by a multivariable logistic regression analysis using appropriate clinical variables. A pair of patients (one for each conduit type) closest to a given probability within a certain range (known as *caliper width*; we used a width of 0.1, or 10%) was selected for as many patients as possible so that the subgroup contained equal numbers of patients for each conduit. This subgroup was then subjected to analysis by familiar statistic techniques.

Clinical values were represented as counts, percents, means, standard deviations, medians, and interquartile ranges, as appropriate. Between-group differences were assessed by analysis of variance (ANOVA) and Mann-Whitney tests for quantitative variables and Fischer's exact test for qualitative variables. Survival analyses were produced using the Kaplan-Meier method; between-group comparisons were performed using the log rank sums test. Univariable Cox regression analysis was performed to investigate risk factors for conduit replacement. Non-correlated variables with a P-value of less than 0.20 were included in the multivariable Cox regression analysis. Missing data were imputed using mean values. An appropriate model was selected after multiple regression models were fitted using a retrograde, stepwise approach. P-values less than 0.05 were used to ascribe statistical significance. All analyses were performed using SPSS version 24.

Paper 3

This was a retrospective study of patients from 1993 to 2020 who underwent patch augmentation of their pulmonary arterial tree. An illustrative example of one such diagnostic group that often requires such augmentation are patients with pulmonary atresia, VSD, and major aortopulmonary collateral arteries (PA/VSD/MAPCAs, see Figure 8). The two main groups of patch materials used were pulmonary homograft and autologous pericardium.
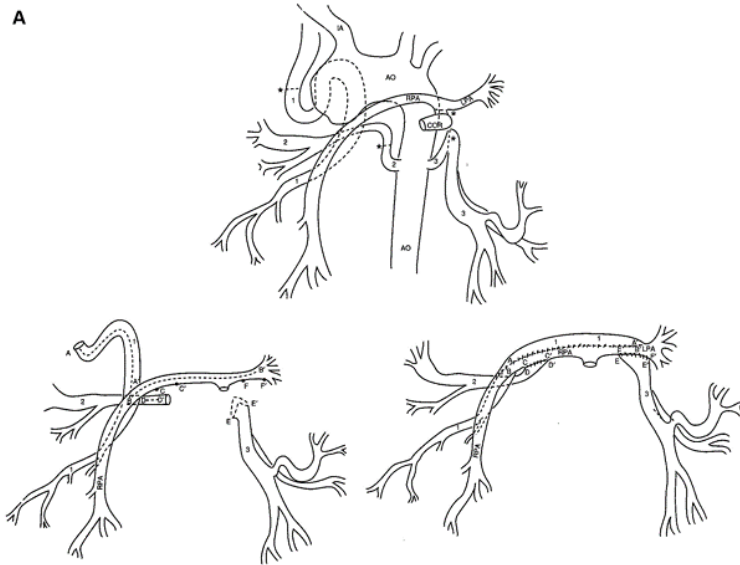
Figure 8 – Pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries (PA/VSD/MAPCA)
Unifocalization procedure for PA/VSD/MAPCA. *Illustration used with permission from Soquet et al., Ann Thorac Surg. 2019, https://doi.org/10.1016/j.athoracsur.2019.01.046, https://creativecommons.org/licenses/by/4.0/*

Pulmonary artery patching is a common procedure – by itself but often in combination with other procedures – in pediatric heart surgery. It is often performed in small children, and is often subject to repeat intervention, both in the form of reoperation and catheter-based intervention. In addition to comparing patch types, additional factors were analyzed to help understand risk for reintervention. Patient factors (e.g., diagnosis and age), operative factors (e.g., patch type and prior operative strategy), and pulmonary artery pathology descriptors (e.g., stenosis location and size) were assessed and evaluated.

Statistics

Data were reported as counts, percents, means, standard deviations, medians, and interquartile ranges, as appropriate. Between-group differences were assessed by ANOVA or Mann-Whitney tests for quantitative variables and Chi square or Fischer's exact test for qualitative variables. Survival analyses were produced using the Kaplan-Meier method; between-group comparisons were performed using the log rank sums test. Univariable Cox regression analysis was performed to investigate risk factors for reintervention. Those variables that were neither correlated with another variable nor had a P-value greater than 0.20 were included in the multivariable Cox regression analysis. Missing data were imputed using mean values. SPSS version 25 and R version 4.2.2 were used to conduct the analysis.

Paper 4

This was a retrospective study of patients from 1993 to 2022 who underwent pulmonary valve insertion, either with a valved conduit (as described in Paper 2) or by PPVI. The focus of this paper was to assess and compare the incidence of prosthetic pulmonary valve endocarditis (PPVIE) between these two modes of PV implantation.

PPVIE is, first and foremost, a morbidity with significant treatment implication for the involved patients. It can also lead to need for valve replacement acutely (rarely in our study) or semi-electively after a period of antibiotics (more often the case in our patients). It can also be ameliorated with antibiotics alone; however, the infection itself or the conditions that made the valve susceptible to infection often persist, leading to eventual need for replacement of the PV prosthesis.

As mentioned in the introduction, the first percutaneous pulmonary valve available for implantation was the Melody valve. This valve is delivered via access in the groin or jugular vessels as opposed to requiring the resternotomy and cardiopulmonary bypass that a surgical conduit exchange entails. Given the size limitations of the Melody valve and the manufacturer`s recommendations, it is typically delivered to a previously placed surgical conduit. The valve sits within a laser-welded platinum-iridium stent which is placed and, if needed, dilated to an appropriate size (the smallest size diameter available is 18 mm).

Many reports in the literature have shown an increased incidence of endocarditis with the Melody valve compared to surgically placed conduits. Different surgical

conduits themselves have different reported rates of infectious endocarditis (IE). As can be surmised, an evaluation and analysis of factors that can lead to an increased risk of PPVIE was called for.

Statistics

Data were reported as counts, percentages, means, and standard deviations, as appropriate. Between-group differences were assessed by Chi square or Fisher's exact test for qualitative variables and ANOVA for continuous variables. Survival analyses were produced using the Kaplan-Meier method; between-group differences were assessed using the log rank sums test. Univariable Cox regression analysis was performed to investigate risk factors for PPVIE. Those that were neither strongly correlated with other variables nor had a p-value > 0.20 were included in the multivariable Cox proportional hazards model. No imputation methods were required for missing data. Statistical analyses were performed using SPSS version 28.

Results

Paper 1

Long-term results of aortic arch reconstruction with branch pulmonary artery homograft patches

The aim of this study was to evaluate the long-term performance of pulmonary homograft tissue used to augment the aortic arch.

Study population and patient characteristics

After exclusion of five patients living in another country at the time of the study, 124 patients were included in this study. The median age and weight at the time of operation was 5.0 days (range 0 to 693 days) and 3.4 kg (range 1.1 – 11.2 kg), respectively. There were 119 patients in the group that had patch augmentation as their first operation; five patients had patch placement after another primary intervention.

Of those who had patch placed at their primary operation, 68 underwent a Norwood operation, with 62 patients having a diagnosis of HLHS; 42 underwent aortic arch reconstruction, 40 of whom had a diagnosis of hypoplastic aortic arch with or without aortic coarctation; and nine underwent repair for IAA.

Overall survival

For all patients, 15-year OS (including OHT) was 83.9%. Of the 20 mortalities that did occur, none were attributable to complications that occurred in the area of patch reconstruction. Patients with a patch placed at their first operation had a 15-year OS of 84.0%, while those with a patch placed after another primary intervention had a 5-year OS of 80.0%. In the group of patients who had patch placed at primary intervention, the Norwood operation group had a 15-year OS of 76.5% (the HLHS patients had a 15-year survival of 75.8%); the aortic arch reconstruction group had a 10-year OS of 92.9% (the patients without co-existing TGA had a 10-year OS of 92.5%); and the IAA group had a 5-year OS of 100.0% (see Figure 9). These survival estimates were different from each other (log rank p-value = 0.03).
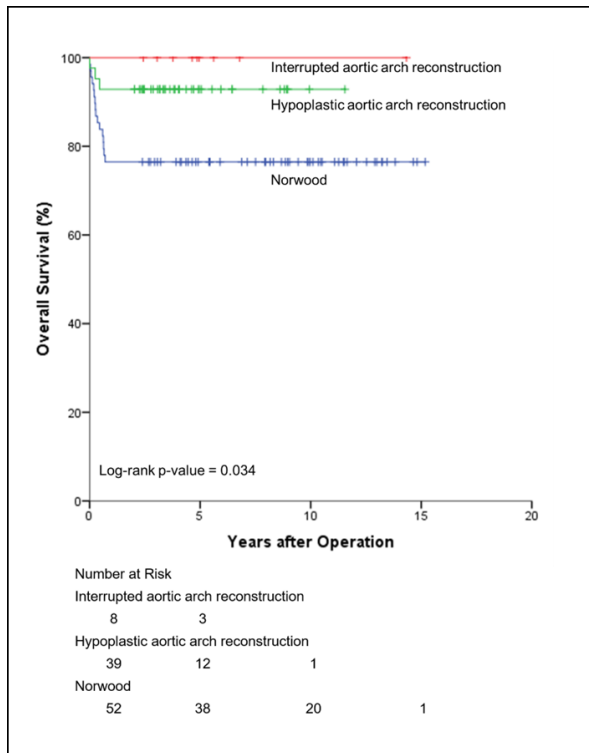
Figure 9 – Overall survival (OS) for patients undergoing aortic arch reconstruction with pulmonary homograft patches, grouped by type of operative repair.

Freedom from reintervention

Only one (0.8%) patient received a reoperation due to complication in the area of prior patch reconstruction. Catheter-based reintervention of prior patch reconstruction was performed in 12 (9.7%) patients, the majority of which were balloon dilations for stenosis formation. No reintervention was performed for subsequent aneurysm formation, nor was aneurysm formation appreciated on patient follow-up evaluation. For the entire patient group, 15-year FFR was 89.2%. The Norwood operation group had a 15-year FFR of 96.4% (the HLHS patients had a 15-year FFR of 96.1%); the aortic arch reconstruction group had a 10-year FFR of 82.7% (the patients without co-existing TGA had a 10-year FFR of 82.2%); and the IAA group had a 10-year FFR of 66.7% (see Figure 10). These FFR estimates were different from each other (log-rank p-value < 0.01).
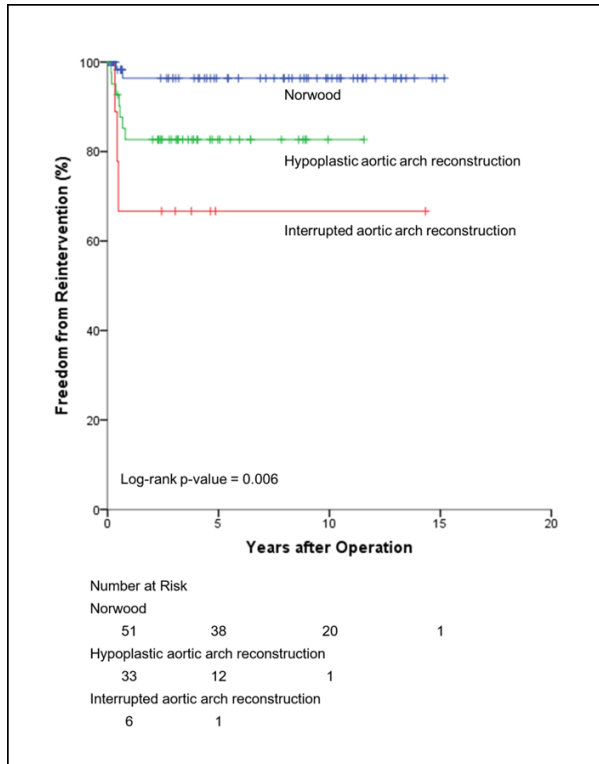
Figure 10 – Freedom from reintervention (FFR) for patients undergoing aortic arch reconstruction with pulmonary homograft patches, grouped by type of operative repair

Paper 2

Long-term follow-up of right ventricle to pulmonary artery biologic valved conduits used in pediatric congenital heart surgery

The aim of this study was to evaluate the performance of valved homografts used to reconstruct the RVOT and to compare them with other biologic valved conduits.

Study population and patient characteristics

Twenty patients (4.2%, who received a total of 22 RV-PA conduits, 3.4%) were excluded because they were living in another country at the time of the study; 455 patients (who received a total of 625 conduits) were included. There were 145 aortic homografts (23.2%), 288 pulmonary homografts (46.1%), and 192 Contegra grafts (23.3%) used. Initial RV-PA conduit placement was performed in 430 operations (68.8%) with 195 conduit exchanges (31.2%) performed. Kaplan-Meier curves were created on this unadjusted data, showing superior performance of pulmonary homografts for both FCR and FFR (see Discussion for details).

There were seven diagnostic groups of patients (see article text for details). For ease of comparison, one group consisted of several diagnoses with smaller numbers of patients. The group with the largest number of patients was TOF (121, 26.6%); the group with the largest number of conduits used was pulmonary atresia with ventricular septal defect (PA/VSD, 146, 25.6%). Patient and conduit characteristics at the time of the 625 conduit operations are listed in Table 1. Conduits are listed first by conduit number and further by conduit type. As could be expected, patient age, patient weight, and conduit diameter all increased with conduit number (percentage of male patients remained unchanged). Furthermore, consistently shown throughout all conduit number subgroups, age, weight, and conduit size were all different from each other (percentage of male patients was again the same). This confirms the suspicion of treatment bias; certain conduits were used preferentially in certain patients. Given the number of possible variables and clinical questions, a table listing all potential patient and conduit characteristics quickly becomes untenable.

Table 1. Patient and conduit characteristics for patients undergoing right ventricle-pulmonary artery (RV-PA) conduit insertion or replacement, listed by conduit number and type

Conduit Number	Conduit Type			Mean Age at Operation ± SD		Mean Weight at Operation ± SD		Male		Mean Conduit Diameter ± SD	
		N	%	y	P-value	kg	P-value	%	P-value	mm	P-value
Total		625	100.0	6.4 ± 5.8	--	23.3 ± 19.4	--	54.9	--	18.0 ± 4.0	--
1st conduit		430	68.8	5.2 ± 5.6	--	19.8 ± 18.8	--	54.2	--	17.2 ± 4.2	--
	Aortic homograft	109	25.3	2.3 ± 3.2		9.5 ± 6.9		53.2		15.0 ± 3.0	
	Pulmonary homograft	190	44.2	8.7 ± 5.8	< 0.001	30.9 ± 20.9	< 0.001	55.8	0.85	19.9 ± 4.3	< 0.001
	BJV graft	131	30.5	2.6 ± 4.0		11.8 ± 11.7		52.7		15.3 ± 2.5	
2nd conduit		157	25.1	8.2 ± 5.1	--	27.7 ± 17.6	--	54.8	--	19.3 ± 2.6	--
	Aortic homograft	33	21.0	6.6 ± 4.0		22.8 ± 11.5		51.5		18.4 ± 1.6	
	Pulmonary homograft	74	47.2	9.7 ± 4.7	0.002	31.8 ± 17.9	0.023	59.5	0.58	20.8 ± 2.7	< 0.001
	BJV graft	50	31.8	7.0 ± 5.7		24.6 ± 18.9		50.0		17.7 ± 1.8	
3rd or 4th conduit		38	6.1	12.6 ± 3.8	--	45.3 ± 15.7	--	63.2	--	21.1 ± 2.2	--
	Aortic homograft	3	7.9	10.2 ± 6.6		44.0 ± 1.4		100.0		19.3 ± 2.1	
	Pulmonary homograft	24	63.2	13.0 ± 3.2	0.47	45.9 ± 15.3	0.96	33.3	0.20	22.1 ± 2.0	0.001
	BJV graft	11	28.9	12.3 ± 4.2		44.4 ± 18.5		54.5		19.5 ± 1.3	

BJV bovine jugular vein, SD standard deviation

Many modern studies focus on the performance characteristic differences between pulmonary homografts and Contegra conduits. That was both the major clinical question for us and made for a tidy comparison between two groups, as mandated in the propensity score-matched subgroup analysis. However, we had no data to show that performance of aortic homografts was any different from the other two conduit types. An algorithm was created in SPSS to select conduits and compare the parameters listed in Table 1. This resulted in 425 conduits being selected from the original patient population, 200 less than the original 625. A Kaplan-Meier curve describing FCR was produced between these three adjusted subgroups (see Discussion for details). What could be seen was that the aortic homografts had worse FCR compared with the other two conduit types, and that pulmonary homografts and Contegra grafts performed similarly. Rather than drawing distinct clinical conclusions from this analysis, this served as the reasoning behind further statistical analysis.

As will be described subsequently in risk factor analysis, many clinical variables were assessed in this study. As discussed in Patients and Methods, all suitable variables were used to create a propensity score, which was used to select similar pairs of patients who received either a pulmonary homograft or a Contegra graft. This necessarily results in a loss of data, with 184 conduits (92 pairs) being selected, 441 less than the original 625. As a whole, this subgroup had younger, smaller patients with smaller conduits compared with the original cohort: mean age of 5.2 years vs. 6.4 years, mean weight of 18.8 kg vs. 23.3 kg, and mean conduit diameter of 17.1 mm vs. 18.0 mm (see article text for details). Logical data trends remained in the subgroup as in the original group: age, weight, and conduit diameter increased with conduit number. Most importantly, within each conduit number subgroup, the clinical parameters were not different from each other. In other words, the two groups were now suitable for comparison.

A Kaplan-Meier survival curve describing FCR was then created between the two groups (see Figure 11). The two curves appear quite similar and are deemed not to differ from each other via the log-rank p-value of 0.26. Similar findings were found for FFR (see article figures for details).
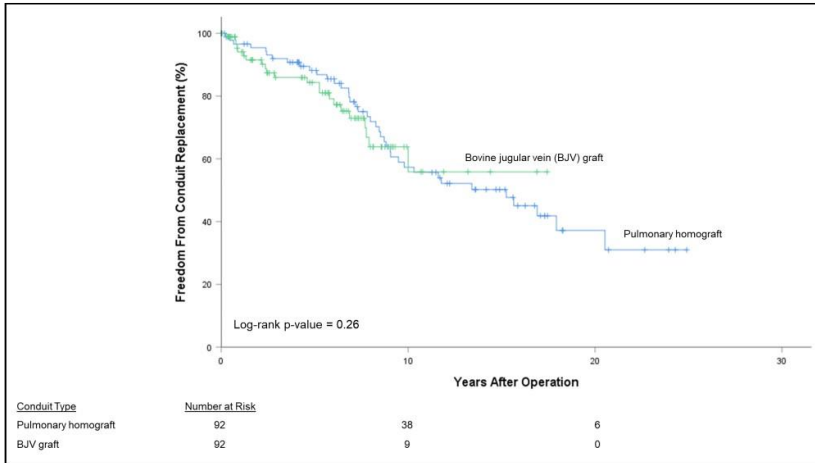
Figure 11 – Freedom from conduit replacement (FCR) for the propensity score-matched subgroup of patients undergoing right ventricle-pulmonary artery (RV-PA) conduit insertion or replacement, listed by conduit type

Risk factor analysis

An analysis of risk factors for conduit replacement was performed (see Table 2). The variables listed in Table 1 were included, as were conduit type, conduit number, and diagnosis. Additional factors studied included: whether a patient had undergone previous cardiac surgery and number thereof; graft Z-score, based on the patient's expected PV annulus size; RV systolic pressure measured directly intraoperatively after conduit insertion or replacement; the presence of narrowed branch pulmonary arteries (defined as either the left PA [LPA] or right PA [RPA] being more than two standard deviations smaller than expected diameter); whether a proximal hood was used to augment the proximal RV to conduit anastomosis and type of material used; whether the conduit lay in an anatomic location (as opposed to extra-anatomic); and, whether the patient had had a previous homograft or BJV conduit.

Table 2. Univariable and multivariable Cox proportional hazards regression analysis for risk factors for conduit replacement in patients undergoing right ventricle-pulmonary artery (RV-PA) conduit insertion or replacement

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Female	Reference			
Male	1.15 (0.86-1.51)	0.35		
Weight (kg)	0.95 (0.93-0.96)	< 0.001	*	
Age at operation (y)	0.87 (0.84-0.89)	< 0.001	*	
Conduit type				0.21
Pulmonary homograft	Reference		Reference	
Aorta homograft	3.17 (2.30-4.37)	< 0.001	1.43 (0.95-2.16)	0.09
BJV graft	2.04 (1.36-3.05)	0.001	1.27 (0.79-2.04)	0.33
Conduit number				0.03
First	Reference		Reference	
Second	0.63 (0.44-0.90)	0.01	0.49 (0.28-0.85)	0.01
Third / Fourth	0.53 (0.23-1.20)	0.13	0.29 (0.08-1.00)	> 0.05
Diagnosis				0.005
PA / VSD	Reference		Reference	
TOF	0.48 (0.29-0.78)	0.003	1.44 (0.50-4.17)	0.50
TA	1.91 (1.31-2.79)	0.001	2.17 (1.24-3.83)	0.01
TGA/VSD/PS	1.87 (1.17-3.00)	0.009	3.31 (1.88-5.82)	< 0.001
PS, PI, PA/IVS	0.36 (0.14-0.90)	0.03	1.61 (0.40-6.44)	0.50
AS, AI	0.28 (0.10-0.77)	0.01	1.26 (0.32-5.04)	0.74
All others *****	1.11 (0.68-1.80)	0.67	1.91 (1.10-3.30)	0.02
Previous cardiac operation	0.35 (0.26-0.48)	< 0.001	0.48 (0.28-0.83)	0.01
Number of previous cardiac operations	1.76 (1.54-2.01)	< 0.001	2.32 (1.88-2.87)	< 0.001
Conduit diameter (mm)	0.80 (0.77-0.83)	< 0.001	0.87 (0.80-0.95)	0.001
Graft Z-Score	1.28 (1.09-1.52)	0.003	1.02 (0.83-1.25)	0.84
RV systolic pressure after repair (mmHg)	1.01 (1.00-1.02)	0.02	0.99 (0.98-1.01)	0.33
RV / systemic pressure after repair	5.09 (2.64-9.78)	< 0.001	**	
Narrow pulmonary artery	1.29 (0.81-2.05)	0.28		
Proximal hood	2.15 (1.60-2.89)	< 0.001	0.87 (0.56-1.34)	0.53
Proximal hood type			***	
Ascending aorta	Reference			
Pulmonary homograft patch	0.45 (0.24-0.85)	0.01		
BJV graft patch	0.58 (0.21-1.60)	0.29		
PTFE patch	0.43 (0.16-1.18)	0.10		
Autologous pericardial patch	2.02 (0.92-4.44)	0.08		
Dacron patch	0.69 (0.40-1.18)	0.18		
Bovine pericardial patch	0.00 (0.00-inf)	0.96		
Anatomic graft position	0.31 (0.22-0.45)	< 0.001	1.11 (0.42-2.90)	0.83
Previous homograft	0.61 (0.42-0.89)	0.01	****	
Previous BJV graft	0.71 (0.26-1.93)	0.51		

* Correlated with graft size
** Correlated with RV systolic pressure after repair
*** Removed due to small number of operations (n=199)
**** Correlated with conduit number
***** Included diagnoses: ALCAPA, CCTGA, DORV, IAA, TGA

AI aortic insufficiency, ALCAPA anomolous left coronary artery from the pulmonary artery, AS aortic stenosis, BJV bovine jugular vein, CCTGA congenitally-corrected transposition of the great arteries, CI confidence interval, DORV double outlet right ventricle, HR hazard ratio, IAA interrupted aortic arch, IVS intact ventricular septum, PA pulmonary atresia, PI pulmonary insufficiency, PS pulmonary stenosis, PTFE polytetrafluoroethylene, RV right ventricle, TA truncus arteriosus, TGA transposition of the great arteries, TOF tetralogy of Fallot, VSD ventricular septal defect

Univariable analysis for all factors was performed first. Those found to be associated with conduit replacement (p-value less than 0.05) were: lower weight; younger age; either aortic homograft or Contegra graft (when compared to pulmonary homograft); first conduits (when compared with second conduits); certain diagnoses (pulmonary atresia with ventricular septal defect [PA/VSD] was the reference group and all diagnoses except for the heterogeneous diagnostic group differed from it); patients who had not had a prior cardiac operation; increased number of cardiac operations; smaller conduit diameter; increased graft Z-score; increased RV pressure after conduit insertion; presence of a proximal hood; hood material other than pulmonary homograft; non-anatomic conduit position; and not having had a prior homograft conduit.

This calls for some further analysis. Multivariable regression analysis adds numerical heft to the pleasing graphical depictions of Kaplan-Meier curves. Putting it another way, through significant prior statistical manipulations (choosing and creating matched-pair subgroups for survival curve analysis), one factor was evaluated quite closely (type of conduit). With multivariable regression analysis, all chosen factors can be evaluated on their own merits: After controlling for the effects of variables x and y (*ad nauseum*) what effect does variable z have on the outcome (here risk for conduit replacement)? There are a few caveats. Too many variables are bad (it makes the analysis very sensitive to small changes) as are variables that are closely associated (*correlated*) with each other (termed *collinearity*). Incomplete patient information is bad; lack of information for one variable results in all other variables for that instance (here, a specific conduit) being omitted from the analysis, causing significant data loss.

All the aforementioned variables were chosen because they make clinical sense to study and have been evaluated in prior studies. Indeed, most of them had a significant association with conduit intervention on univariable regression analysis. Ultimately, young patients who weighed less received smaller conduits. As this was a study focused on the behavior of conduits, conduit size was selected for the multivariable analysis in lieu of patient age and weight. Whether the patient had a prior homograft was correlated with conduit number; similarly, conduit number was selected for the multivariable analysis. There were too few patients that received a proximal hood; thus, hood type was removed from the multivariable analysis.

The results of the multivariable analysis showed the following to have significant association with conduit replacement: first conduits (compared with second conduits), diagnoses of truncus arteriosus (TA) and transposition of the great arteries with ventricular septal defect and pulmonary stenosis (TGA/VSD/PS), not having had a prior cardiac operation at the time of conduit insertion, increasing number of cardiac operations, and smaller conduit diameters.

Incidence of conduit infectious endocarditis

While not the primary outcome of interest in this study, infection of the conduit and / or the valve contained within it (*conduit endocarditis*) is, indeed, a clinically interesting outcome. As the focus of this study was conduit replacement, we chose to assess those patients who ultimately required replacement of their conduit due to infection. Pulmonary homografts required replacement due to endocarditis in 1.4% (4 of 288) of cases, which was less than the 4.7% (9/192) of BJV graft cases. This was a finding consistent with the literature, and provided the stimulus for further, more extensive study in Paper 4.

Paper 3

Evaluation and comparison of patch materials used for pulmonary arterioplasty in pediatric congenital heart surgery

The aim of this study was to evaluate branch pulmonary homograft patches used to augment the pulmonary arterial circulation and to compare them with other commonly used materials.

Study population and patient characteristics

Ten (4.4%) of the 227 patients eligible for enrollment in the study were excluded because they were living in another country at the time of the study. The remaining 217 patients underwent 280 operations (217 primary operations and 63 reoperations) with 313 patches used for augmentation of the pulmonary arterial tree. Operations were performed in neonates (N = 37, 17.1%), infants (N = 74, 34.1%), and children (N = 106, 48.8%). There were three comparison groups: autologous pericardium (N = 166, 53.0%), pulmonary homograft (N = 126, 40.3%), and a smaller group of heterogenous materials (N = 21, 6.7%). Single ventricle patients were included in the study, encompassing 29.5% (N = 64) of the study population.

The diagnostic groups with the largest number of patches used were HLHS (N = 55, 17.6%) and PA/VSD/MAPCA (N = 55, 17.6%). Patch usage did not differ by gender, weight, or age, though it did differ according to diagnosis. A careful characterization of the stenoses was performed, describing their anatomy and etiologic origin (see Table 3). Analyzing without taking into account time to reintervention, bilateral stenoses required more intervention than unilateral stenoses

(28.9% vs. 15.7%), as did single (long [26.1%] or short [23.9%]) stenoses compared with diffuse / combined stenoses (5.9%).

Table 3. Rate of reintervention for patients undergoing pulmonary arterioplasty, listed by characteristics of the native lesion

Factor	Patches N (column %)	Reintervention N (row %)	p-value
Location	312 (100.0) *	69 (22.1)	
Proximal	223 (71.5)	46 (20.6)	
Distal	10 (3.2)	2 (20.0)	0.54
Both	79 (25.3)	21 (26.6)	
Etiology	312 (100.0)	69 (22.1)	
Congenital	68 (21.8)	19 (27.9)	
Acquired	191 (61.2)	41 (21.5)	0.33
Combined	53 (17.0)	9 (17.0)	
Laterality	312 (100.0)	69 (22.1)	
Unilateral	153 (49.0)	23 (15.0)	< 0.01
Bilateral	159 (51.0)	46 (28.9)	
Size	312 (100.0)	69 (22.1)	
Short	186 (59.6)	43 (23.1)	
Long	92 (29.5)	24 (26.1)	0.046
Diffuse / Combined	34 (10.9)	2 (5.9)	

* One patch of 313 lacked significant anatomic description to be included

Freedom from reintervention

Kaplan-Meier curves were created to assess OS, freedom from reoperation (FRO) and FFR, which included both reoperation and catheter-based intervention in the area of patch arterioplasty. OS was 86.2% and FRO was 81.0% at 27 years after initial operation. FFR was 70.6% at 27 years after initial operation and did not differ among patch groups (Figure 12).
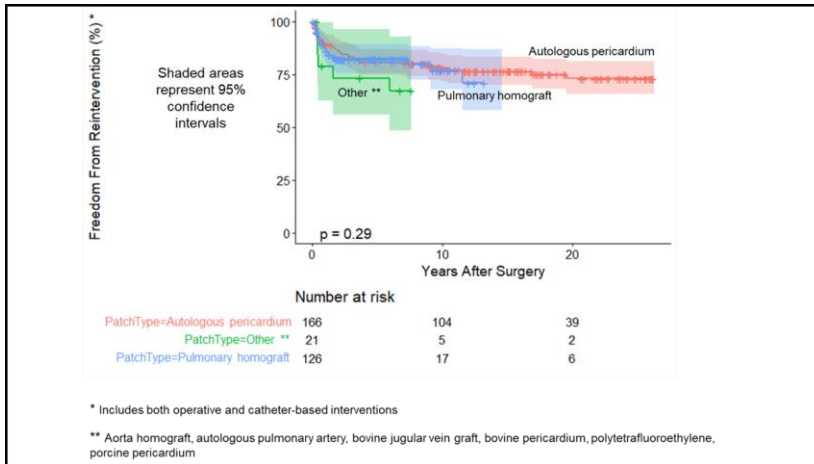
Figure 12 – Freedom from reintervention (FFR) for patients undergoing pulmonary arterioplasty, grouped by patch type

Risk factor analysis

Univariable and multivariable Cox proportional hazards analyses were performed in a manner akin to that described in Paper 2 (see Table 4). On univariable analysis, the following patient and operative factors were found to be associated with reintervention: male gender, younger age, lower weight, a diagnosis of either PA/VSD/MAPCA or HLHS, a patch that was placed at a patient's first cardiac operation, and fewer prior cardiac operations. With respect to stenosis characteristics, bilateral and single (long or short) stenoses were associated with reintervention.

On multivariable analysis, none of the stenosis-specific variables were associated with reintervention. Of the patient-specific variables, a diagnosis of either PA/VSD/MAPCA or HLHS remained associated with reintervention. Of the operation-specific variables, a patch placed at first cardiac operation and increasing number of cardiac operations were associated with reintervention. Notably, both on univariable and multivariable analysis, patch type was not associated with reintervention.

Table 4. Multivariable Cox proportional hazards regression analysis for risk factors for reintervention in patients undergoing pulmonary arterioplasty, listed by characteristics of the native lesion

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Female	Reference			
Male	1.15 (0.86-1.51)	0.35		
Weight (kg)	0.95 (0.93-0.96)	< 0.001	*	
Age at operation (y)	0.87 (0.84-0.89)	< 0.001	*	
Conduit type				0.21
Pulmonary homograft	Reference		Reference	
Aorta homograft	3.17 (2.30-4.37)	< 0.001	1.43 (0.95-2.16)	0.09
BJV graft	2.04 (1.36-3.05)	0.001	1.27 (0.79-2.04)	0.33
Conduit number				0.03
First	Reference		Reference	
Second	0.63 (0.44-0.90)	0.01	0.49 (0.28-0.85)	0.01
Third / Fourth	0.53 (0.23-1.20)	0.13	0.29 (0.08-1.00)	> 0.05
Diagnosis				0.005
PA / VSD	Reference		Reference	
TOF	0.48 (0.29-0.78)	0.003	1.44 (0.50-4.17)	0.50
TA	1.91 (1.31-2.79)	0.001	2.17 (1.24-3.83)	0.01
TGA/VSD/PS	1.87 (1.17-3.00)	0.009	3.31 (1.88-5.82)	< 0.001
PS, PI, PA/IVS	0.36 (0.14-0.90)	0.03	1.61 (0.40-6.44)	0.50
AS, AI	0.28 (0.10-0.77)	0.01	1.26 (0.32-5.04)	0.74
All others *****	1.11 (0.68-1.80)	0.67	1.91 (1.10-3.30)	0.02
Previous cardiac operation	0.35 (0.26-0.48)	< 0.001	0.48 (0.28-0.83)	0.01
Number of previous cardiac operations	1.76 (1.54-2.01)	< 0.001	2.32 (1.88-2.87)	< 0.001
Conduit diameter (mm)	0.80 (0.77-0.83)	< 0.001	0.87 (0.80-0.95)	0.001
Graft Z-Score	1.28 (1.09-1.52)	0.003	1.02 (0.83-1.25)	0.84
RV systolic pressure after repair (mmHg)	1.01 (1.00-1.02)	0.02	0.99 (0.98-1.01)	0.33
RV / systemic pressure after repair	5.09 (2.64-9.78)	< 0.001	**	
Narrow pulmonary artery	1.29 (0.81-2.05)	0.28		
Proximal hood	2.15 (1.60-2.89)	< 0.001	0.87 (0.56-1.34)	0.53
Proximal hood type			***	
Ascending aorta	Reference			
Pulmonary homograft patch	0.45 (0.24-0.85)	0.01		
BJV graft patch	0.58 (0.21-1.60)	0.29		
PTFE patch	0.43 (0.16-1.18)	0.10		
Autologous pericardial patch	2.02 (0.92-4.44)	0.08		
Dacron patch	0.69 (0.40-1.18)	0.18		
Bovine pericardial patch	0.00 (0.00-inf)	0.96		
Anatomic graft position	0.31 (0.22-0.45)	< 0.001	1.11 (0.42-2.90)	0.83
Previous homograft	0.61 (0.42-0.89)	0.01	****	
Previous BJV graft	0.71 (0.26-1.93)	0.51		

* Correlated with graft size
** Correlated with RV systolic pressure after repair
*** Removed due to small number of operations (n=199)
**** Correlated with conduit number
***** Included diagnoses: ALCAPA, CCTGA, DORV, IAA, TGA

AI aortic insufficiency, ALCAPA anomolous left coronary artery from the pulmonary artery, AS aortic stenosis, BJV bovine jugular vein, CCTGA congenitally-corrected transposition of the great arteries, CI confidence interval, DORV double outlet right ventricle, HR hazard ratio, IAA interrupted aortic arch, IVS intact ventricular septum, PA pulmonary atresia, PI pulmonary insufficiency, PS pulmonary stenosis, PTFE polytetrafluoroethylene, RV right ventricle, TA truncus arteriosus, TGA transposition of the great arteries, TOF tetralogy of Fallot, VSD ventricular septal defect

Prosthetic pulmonary valve infective endocarditis in pediatric congenital heart disease patients

The aim of this study was to evaluate the occurrence of infectious endocarditis in valved homografts used to reconstruct the RVOT and to compare them with both other biologic valved conduits and percutaneously placed PV prostheses.

Study population and patient characteristics

Twenty (4.1%) of the 489 patients (22 [3.1%] of the 711 pulmonary valves) eligible for enrollment in the study were excluded because they were living in another country at the time of the study. The remaining 469 patients received 689 pulmonary valve implantations (PVIs). There were 668 surgical pulmonary valve implantations (SPVIs) accounting for 97% of the PVIs, while 21 PPVIs accounted for 3% of the PVIs.

There have been a few trends in the literature with respect to rates of PPVIE: it appears to be higher in PPVI versus SPVI, and higher in BJV conduits versus homografts. BJV grafts are components of both the SPVI (Contegra) and PPVI (Melody) groups. Therefore, this must be accounted for in the analysis to be able to draw appropriate conclusions. Of the 668 SPVIs, 432 (64.7%) were homografts (120 aortic and 312 pulmonary) and 235 (35.2%) were Contegra. All the 21 PPVIs were Melody valves. Of the 689 PVIs, 432 (62.7%) were homografts and 256 (37.2%) were BJV valves.

The diagnostic group with the largest number of PVIs was PA/VSD (N = 174, 25.3%). The SPVI group had PVI performed in younger, smaller patients compared with the PPVI group; there were no differences between the groups with respect to gender. Given both the multiple possible permutations within this data set and the disparity in size between the two main comparison groups, no effort was made at selecting subgroups of patients with similar baseline variables. This was instead left for the regression analysis.

Incidence of PPVIE

PPVIE occurred in 5.1% (31/689) of the PVIs. The incidence of PPVIE was higher in PPVI (23.8%) versus SPVI (4.5%). Of clinical interest, mean times to onset of PPVIE were calculated. The mean time from PVI to onset of PPVI was 6.3 years in all patients; 6.9 years in the SPVI group (11.4 years in the homograft group and 4.6 years in the Contegra group); and, 2.5 years in the in the PPVI group. A more robust comparison of rates of PPVIE was addressed using Kaplan-Meier analysis.

Staphylococcus (N = 9) and *Streptococcus* (N = 8) species were responsible for 48.6% (17/35) of the cases of PPVIE. *S. aureus* (N = 5, 14.3%) was the single organism responsible for most cases of PPVIE. Number that required valve replacement…

Freedom from PPVIE (FPI)

Within the entire cohort, FPI was 97.7, 95.6, and 89.0% at 5, 10, and 30.9 years, respectively, for all prostheses and all methods of intervention. FPI for each PV type was as follows, from highest to lowest (p<0.01): aortic homografts (100.0, 100.0, and 98.0% at 5, 10, and 30.6 years, respectively), pulmonary homografts (99.7, 98.9, and 95.5% at 5, 10, and 30.9 years, respectively), Contegra (94.3, 89.9, 74.1% at 5, 10, and 21.2 years, respectively), and Melody (85.4, 74.1, and 74.1% at 5, 10, and 16.1 years, respectively) (Figure 13). FPI was higher (p<0.01) for homografts (99.8, 99.2, and 96.4% at 5, 10, and 30.9 years, respectively) compared with BJV grafts (94.1, 88.5, and 62.9% at 5, 10, and 30.9 years, respectively). FPI was higher (p<0.01) for SPVI (98.1, 96.3, and 92.8% at 5, 10, and 30.9 years, respectively) versus PPVI (85.4, 74.1, and 74.1% at 5, 10, and 16.1 years, respectively).

Figure 13 – Freedom for prosthetic pulmonary valve infective endocarditis (FPI) in patients undergoing pulmonary valve implantation (PVI), listed by type of prosthetic pulmonary valve (PV)

Risk factor analysis

Univariable and multivariable Cox proportional hazard analyses were performed (Table 5). On univariable analysis, the following variables were found to be associated with PPVIE: third pulmonary valve placed, Contegra or Melody PV, a valve placed in a Contegra conduit (in cases of PPVI), younger age at initial PVI, presence of infection (other than PPVIE) after PVI, prior Melody valve, BJV PV (compared with homograft), and PPVI (compared with SPVI). As can be imagined, many of these variables were correlated with each other and the variables for the multivariable model were chosen with the main study aims in mind. In the multivariable model, the following variables were associated with PPVIE: Contegra or Melody valve and presence of infection after PVI.

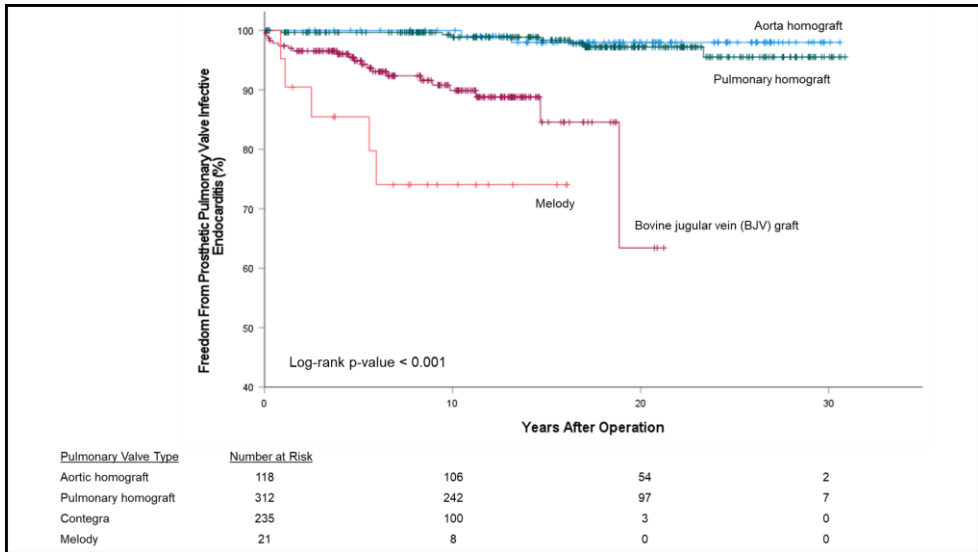**Table 5. Univariable and multivariable Cox proportional hazards regression analysis for risk factors for prosthetic pulmonary valve infective endocarditis (PPVIE) in patients undergoing pulmonary valve implantation (PVI)**

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Male gender	1.12 (0.57 - 2.19)	0.74		
Presence of genetic syndrome	1.87 (0.88 - 4.00)	0.11	1.37 (0.61 - 3.09)	0.45
Type of genetic syndrome *	****	0.60		
Diagnosis **	****	0.93		
Pulmonary valve diameter	1.00 (0.92 - 1.09)	0.97		
Pulmonary valve number				
1		Reference		Reference
2	1.28 (0.60 - 2.76)	0.53	1.30 (0.58 - 2.93)	0.52
3 or 4	1.38 (1.38 - 8.79)	0.01	2.94 (1.01 - 8.56)	<0.05
Pulmonary valve type				
Aorta homograft		Reference		Reference
Pulmonary homograft	1.58 (0.33 - 7.64)	0.57	1.62 (0.33 - 7.88)	0.55
Contegra	14.51 (3.14 - 67.09)	<0.01	12.47 (2.66 - 58.44)	<0.01
Melody	40.15 (7.19 - 224.28)	<0.01	28.32 (4.56 - 175.82)	<0.01
Conduit type				
Aorta homograft		Reference	*****	
Pulmonary homograft	1.37 (0.37 - 5.06)	0.64		
Contegra	9.47 (2.68 - 33.51)	<0.01		
Age at intervention	1.01 (0.98 - 1.05)	0.50		
Weight at intervention	1.01 (0.99 - 1.02)	0.27		
Presence of infection after intervention	5.26 (2.57 - 10.75)	<0.01	4.77 (2.27 - 10.02)	<0.01
Number of infections after intervention	1.20 (1.10 - 1.31)	<0.01	******	
Thrombosis prophylaxis, periprocedural	1.76 (0.79 - 3.96)	0.17		
Prior pulmonary valve type				
Aorta homograft		Reference	*****	
Pulmonary Homograft	0.86 (0.25 - 2.96)	0.82		
Contegra	1.32 (0.37 - 4.72)	0.68		
Melody	17.91 (2.00 - 160.83)	0.01		
Surgical PVI ***	0.13 (0.05 - 0.33)	<0.01	0.45 (0.14 - 1.39)	0.16
Homograft PVI ***	0.09 (0.04 - 0.20)	<0.01	0.12 (0.05 - 0.29)	<0.01

* Syndromes not listed due to lack of significant association with the model: Alagielle's, Catch-22, CHARGE, Chromosome 1 deletion, DiGeorge, Noonan's, Partial Trisomy 4, Trisomy 5p deletion, Trisomy 5q, Trisomy 21, VACTERL, 17q12 deletion

** Diagnoses not listed due to lack of significant association with the model: ALCAPA, AS/AI, CCTGA, DORV, IAA, PA/IVS, PA/VSD, PI, PS, TA, TGA, TGA/VSD/PS, TOF

*** Correlated with PV type; parallel models created exchanging for PV type

**** HR and CI not included due to large number of variables

***** Correlated with PV type, not included in the multivariable model

****** Correlated with presence of infection after intervention, not included in the multivariable model

ALCAPA anomalous origin of left coronary artery from pulmonary artery, AI aortic insufficiency, AS aortic stenosis, Catch-22 (cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia), CCTGA congenitally corrected transposition of the great arteries, CHARGE (coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities), CI confidence interval, DORV double-outlet right ventricle, HR hazard ratio, IAA interrupted aortic arch, IVS intact ventricular septum, PA pulmonary atresia, PI pulmonary insufficiency, PS pulmonary stenosis, PV pulmonary valve, TA truncus arteriosus, TGA transposition of the great arteries, TOF tetralogy of Fallot, VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities), VSD ventricular septal defect

Discussion

All pediatric heart centers are ultimately evaluated on how well the children it treats do. National benchmarks can compare length of intensive care stay, frequency of urinary tract infections, and number of cardiology clinic visits. Single- and multi-institutional studies can show 3D heart model utilization and socioeconomic status of patients served. With the plethora of available variables to study, it can be easy to lose sight of the forest for the trees.

Both the forest *and* the trees are important. While modern-day clinicians and scientists may have (at best) been born too late to experience the renown of inventing the heart-lung machine, we have our own groves to tend to. Not to be lost in the focus of this thesis is the fact that children in Lund with congenital heart disease have been very well cared for. And the operative results have followed course. Dissemination of knowledge from every corner of the forest has and will continue to drive forward the care of children with congenital heart disease. Furthermore, children in Lund have received such care over a relatively long period of time. The sole focus on children is somewhat unique among centers that perform similar work; many studies with long experience report on a mix of children and adults.

When it comes to an analysis of those trees, it makes a difference which forest they come from. Relatively standard statistical techniques have been used throughout this thesis, techniques that have also been utilized in the bulk of the available similar literature. Newer techniques that take into account the individual nature of study subjects (multiple interventions on a single patient, multiple patients from a single center, etc.) have started appearing in the literature (51) and are an intriguing method of analyzing the data in this thesis. The complexity of these so-called *mixed models* prohibited their application in this thesis.

This study assessed the long-term performance of pulmonary homograft patches taken from branch pulmonary arteries, which were then used to patch augment the thoracic aorta children with common congenital heart disease diagnoses. 124 patients were assessed over a 15-year period from 2001 to 2016. Three groups of patients were studied, divided into common types of operative repair. Given the unique challenges associated with each operative group, it was not surprising that the first primary outcome – operative survival – differed among diagnostic groups. Investigating why is perhaps a suitable discussion point of departure.

The group written about most in the literature is the group with the worst OS – the patients receiving a Norwood procedure, most often due to a diagnosis of HLHS [52-61]. Incredible strides have been made since Norwood elucidated the details of his repair. Data are maturing on how well these patients fare later in life after the third and final stage of their final single ventricle palliation. Some parents will choose not to carry to term a pregnancy with a fetus with a diagnosis of HLHS. Some studies advocate for earlier heart transplantation. In some countries zero HLHS babies are born.

The Norwood operation was given a polish of reproducibility thanks to the work of James Tweddell [62]. It is this description on which Lund's operative technique is based. And it produced excellent results. While designed to test other components of operative repair, the Single Ventricle Reconstruction (SVR) Trial – multicenter, prospective, and randomized -- is the most significant study of HLHS patients to date [31, 63]. The transplant-free survival reported in the SVR was 59% to 64% at six years after operation. Patients in Lund had a nearly 76% OS at 15 years.

Gaynor and colleagues reported their large, single-center experience with patients with hypoplastic arch with or without aortic coarctation, citing an overall mortality of 96% at three years after operation [64], similar to that of other studies [65,66]. Patients in Lund had a 92.5% overall mortality at 10 years after operation. Quoted survival estimates for patients with IAA have varied widely depending on follow-up, from 94% two years after operation [67] to 59% at 16 years [68]. One recent study reports 91.7% survival 20 years after operation [69]. Again, excellent results were reported from Lund, with 100% overall survival at five years after operation.

While the number of patients in the IAA group (N = 9) may have precluded drawing robust conclusions from its survival curve, the shape of the curve is in one important way similar to that of the other two groups. Namely a long, flat portion after a sharp descent during the first year (of course, no descent was seen with 100% survival in the IAA group). This suggests that after a critical first year, all components of care that the patients receive in the course of remedying their heart defect lead to a durable result. Mortalities did occur, 20 in total. Though data were not available in

all cases (9 of the 20), no death could be attributed to a complication in the area of patch reconstruction.

FFR was the second primary endpoint. The appearance of the Kaplan-Meier curves was similar to that of the OS curve: different values for the three different groups and all with a flat, chronic portion after an initial, short descent. During this first year, whatever characteristics that led to increased mortality also put the patients at risk for reintervention. After this time, essentially no intervention was needed in the area of patch reconstruction.

The patient groups are inverted in the FFR curve compared with the OS curve, which was somewhat surprising. Norwood patients – who received the largest reconstructive patch -- required very little reintervention. A tempting hypothesis in that a larger patch provides more complete relief of obstruction than a smaller one. While small numbers may again preclude drawing robust conclusions in the IAA group, the hypoplastic arch group perhaps offers more opportunity for insight. A spectrum of operative strategies is used at different centers for its repair, from a large Norwood-type patch to a direct anastomosis without the need for patch material at all. Such variations in operative technique could be the basis for multi-center collaboration.

While taken now somewhat for granted, it may not have once been so clear that a patch consisting of tissue from a vessel (PA) different than the vessel it is used to reconstruct (the aorta) would work. The low operative mortality (3.2% for all patients) indicates the patients left the operating room without complication secondary to the patch (e.g., bleeding or kinking). While there was a need for reintervention in the long-term, nearly all reinterventions performed (12 of 13) were catheter-based and nearly all for stenosis in the area of patch reconstruction. No aneurysmal dilatation of the patch material was appreciated clinically or on follow-up imaging, again indicating the suitability and durability of pulmonary patches in the aortic position.

Paper 2

The operative techniques used to place and replace RV-PA conduits have been stable for a number of years, both specifically in Lund and in general in the field of congenital heart surgery. This study aimed to assess long-term outcomes after RV-PA conduit placement, and to investigate differences between conduit types. 455 patients – 625 conduits – were evaluated over a 30-year period from 1990 to 2019. Operative results in Lund, again, compared favorably with a 10-year operative survival rate of 95.3%, compared with 10-year survival rates of from 87% to 96% quoted in the literature [70-80]. There were few studies that could report similar length of follow-up to 30 years which we reported. Patient groups were similar to those in

the literature, with the largest patient groups in Lund consisting of the diagnoses TOF, PA/VSD, and TA.

Compared with many studies of pediatric heart surgery patients, there was much data in this study. Opportunities to draw conclusions – and assess their quality – were possible at multiple stages of data manipulation throughout its analysis. From the original pool of data a preference was clear: 288 of the 625 conduits – 46.1% -- were pulmonary homografts. And a glance at the survival curve from that data confirmed the suspicion that they performed better than both aortic homografts and BJV grafts (see Figure 14).
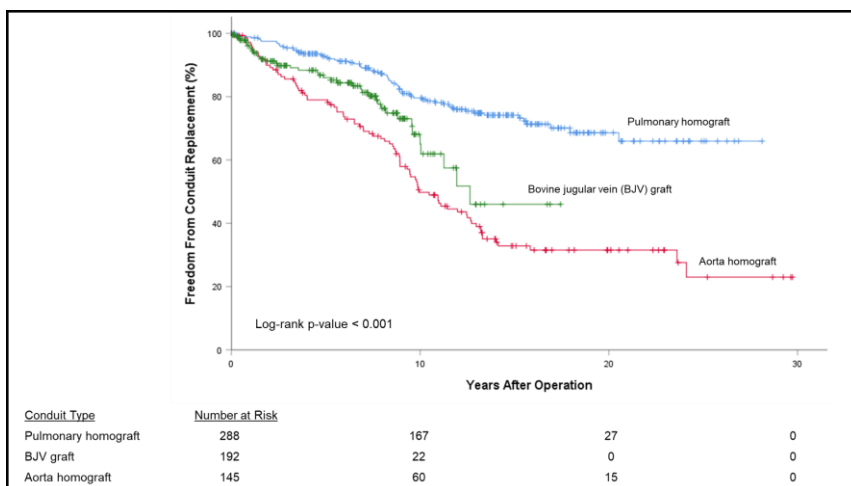

Figure 14 – Freedom from conduit replacement (FCR) for patients undergoing right ventricle-pulmonary artery (RV-PA) conduit insertion or replacement, listed by conduit type; unadjusted data

However, both clinical experience and prior studies had shown that smaller conduits inserted in younger, smaller patients tended to require replacement faster. Reviewing the baseline data, it was clear that for pulmonary homografts, larger (for all conduit numbers) conduits were inserted in older, larger patients (statistically significantly so in initial and second conduits). Manual selection of patients was done so that the baseline variables were similar; the Kaplan-Meier curves produced had some noticeable differences: aortic homografts – while less dramatically than before – still performed worse than their counterparts; and the difference between pulmonary homografts and BJV grafts was less clear (see Figure 15).
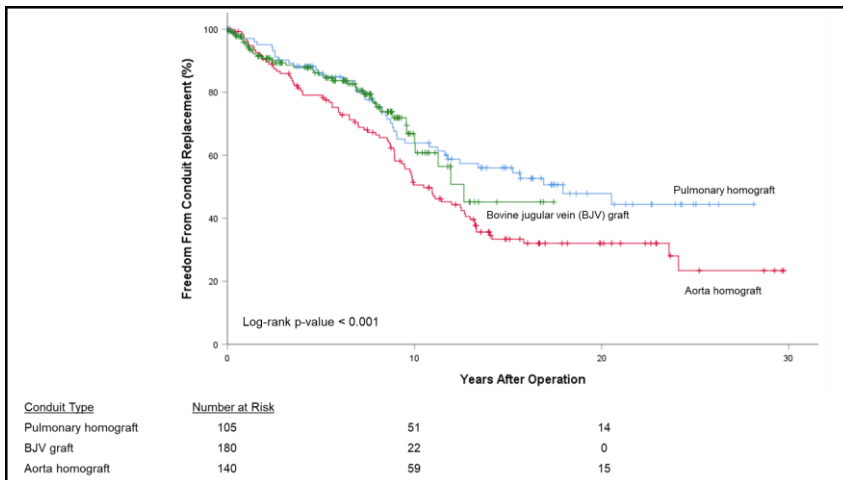
Figure 15 – Freedom from conduit replacement (FCR) for patients undergoing right ventricle-pulmonary artery (RV-PA) conduit insertion or replacement, listed by conduit type; conduits manually selected with respect to similar baseline patient and conduit characteristics

The stage was now set for a closer comparison between pulmonary homografts and BJV grafts; this time equal-sized groups with similar baseline variables were selected based on a calculated propensity score. The result (Figure 11) confirmed what was hinted at in Figure 15, that their long-term performance was quite similar. As this message runs contrary to the conclusions drawn initially from the pool of all 625 conduits, further investigation was clearly called for.

Do first (i.e., initial) conduits wear out faster than subsequent ones (i.e., conduit replacements) [81]? Could that be confounding the analysis? The question was worth investigating. Again, taking all 625 conduits into consideration, earlier-placed conduits degenerated faster than their replacements (Figure 16). Just like the analysis for conduit type, controlling for baseline variables (i.e., size and weight) would be needed to further clarify this conclusion. Instead of going through a similar process as was done for the different conduit types for all possible comparison groups, a regression analysis was performed.
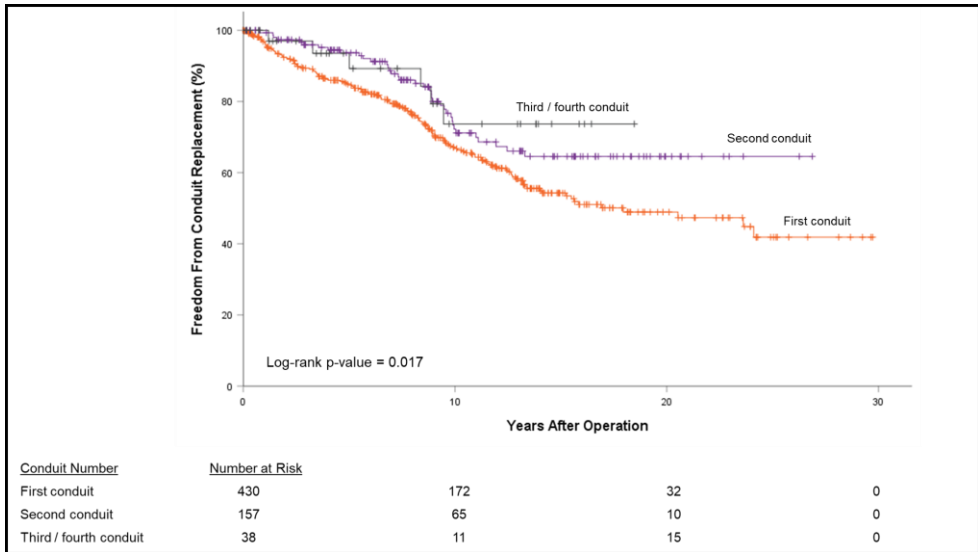
Figure 16 – Freedom from conduit replacement (FCR) for patients undergoing right ventricle-pulmonary artery (RV-PA) conduit insertion or replacement, listed by conduit number; unadjusted data

Controlling for the effects of other variables on the outcome in question is the heart of regression analysis. As should be evident, addressing the simple question *Which conduit is better?* can and must be attacked from several different perspectives. The variables we took into account were numerous, and there existed a number of variables that had been proposed and evaluated in the existing literature, which also were included. Only the factors found to be significantly associated with conduit replacement on multivariable analysis are discussed below.

There was no difference with respect to conduit type. Not only did pulmonary homografts and BJV grafts perform similarly, there was no difference when compared with aortic homografts. The difference trended towards statistical significance for aortic homografts, and as there was no propensity score-matched subgroup analysis performed, ascribing to them similar performance as the other conduit types would perhaps be premature. At the very least, the performance difference seen from the original data of 625 conduits was less than appreciated, and under certain circumstances aortic homografts could serve as an appropriate conduit. The similar performance of pulmonary homografts and BJV grafts reinforced similar findings from other centers [82-84], but not all [85].

Weight and age were correlated with conduit diameter, and smaller conduit diameters were associated with conduit replacement. This is a consistent finding in similar studies [86-89] which is due, in part at least, to patients outgrowing their

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conduits. Heightened immune and inflammatory responses in the infant have been proposed as further explanatory mechanisms [90], but data are lacking at this time.

Diagnoses of TA and TGA/VSD/PS were associated with conduit replacement. TA patients typically have their conduits inserted very early in life. That TA is still associated with conduit replacement after controlling for the effects of other factors (young age, low weight, small conduit diameter, etc.) suggests that some other process is at work. For instance, TA patients have an association with DiGeorge syndrome; presence of a syndrome was not included in the multivariable model. TGA/VSD/PS is often associated with a non-anatomic conduit position, which refers to a conduit that lies in a position markedly different than under normal anatomic circumstances. However, conduit position was also accounted for in the multivariable model, suggesting this alone was not fully explanatory. Perhaps certain aspects of conduit geometry or neighboring by other structures not measured in this study play a role.

Increasing conduit number was found to be protective against conduit replacement, with second conduits (and a trend for third and fourth conduits) performing better than first conduits [81]. Additionally, *not* having had a cardiac operation prior to conduit insertion (e.g., VSD closure) presented an increased risk. This is further evidence that conduits implanted early [90-93] – in actual time and in relation to other procedures – are predisposed to early replacement. However, the more cardiac procedures a patient had was also associated with conduit replacement. While increased number of prior homografts has been shown to correlate with anti-HLA antibodies [94] (which could affect candidacy for future cardiac transplant), the deleterious, additive effects of prior cardiac surgery on conduit degeneration require further study.

The risk of conduit endocarditis requiring conduit exchange was higher in BJV grafts compared with pulmonary homografts, a phenomenon noted in other studies [95-98]. However, as demonstrated, this did not lead to an overall worse FFR of BJV grafts. In this study we did not account for medically treated cases of conduit endocarditis, which are still a significant source of resource utilization for healthcare systems and morbidity for patients.

Paper 3

Pulmonary arterioplasty is a commonly performed procedure in children with heart defects, yet there are relatively few studies which have examined the performance of the involved patch materials. The aim of our study was to do just that, and to investigate possible differences among the commonly used patch types. Over a 28-

year period from 1993 to 2020, 217 patients were assessed who underwent 280 operations ultimately receiving 313 patches.

The mix of patient diagnoses was similar to the few reports that did exist in the literature [99-101], while single ventricle patients were also included in our study. Having demonstrated excellent patient survival in the Papers 1 and 2, the primary focus turned to FFR (freedom from either reoperation or catheter-based intervention) in this study. Reported rates of FFR in the literature ranged from 46% to 80% 10 years after operation. Our 10-year FFR compared favorably at 76.6%. At 27 years of follow-up, FFR was 70.6% for all patches. We could not find similar lengths of follow-up for comparison in the available literature.

Our primary outcome showed that pulmonary homograft and autologous pericardium patches performed similarly. This was confirmed by both Kaplan-Meier curve analysis and multiple variable Cox regression analysis. Furthermore, among the existing studies available for comparison, this was a common finding. Additionally, a third heterogeneous group of patch materials trended towards an increased risk for reintervention. It is possible – even likely – that with an increased number of patches this group would have shown worse FFR than the other two groups.

Characteristics of the lesions themselves were investigated as risk factors for reintervention. Neither stenosis location nor presumed etiology were found to be significant risk factors by any of the measures we used for assessment. On comparison of gross rates of reintervention and on univariable analysis, bilateral lesions appeared more at risk than unilateral lesions. This echoed findings by Cresalia and colleagues in a similar study [99]. However, no increased risk was demonstrated in our multivariable analysis. Further study will help to clarify this discrepancy. Size was investigated, with no obvious difference seen between short (less than 2 cm) and long stenoses. A smaller group of patients whose stenoses were not so easily defined were allocated into a 'Diffuse/Combined' group that appeared to be protective for reintervention; this did not persist through multiple variable analysis, however.

Patient characteristics were also assessed. Interestingly, younger, smaller patients did not prove to be a risk factor for reintervention, as they did in our study on conduit longevity. Two diagnoses – PA/VSD/MAPCA and HLHS – proved to be risk factors for reintervention through multivariable analysis. PA/VSD/MAPCA patients often require repeat interventions in the catheterization lab. Their operative repair alone often involves complex rerouting of vessels to the pulmonary circulation with multiple patches, known as *unifocalization* [102,103]. However, the effects of this were controlled for in the multivariable model, so perhaps the increased risk in this diagnostic group had more to do with the native pulmonary vessels and collaterals themselves, which are prone to recurrent multilevel stenosis formation. As data has matured in the treatment of HLHS patients (from the

aforementioned SVR trial, for example), a larger RV-PA shunt has been preferred over a smaller modified BT shunt. While favorable from a (short-term, at least) mortality standpoint, perhaps variations in shunt technique predisposed this patient group to reintervention.

Aspects of operative repair were assessed, but none were shown to be risk factors for reintervention. This included single- versus two-ventricle repair (with or without unifocalization) and whether a prior pulmonary patch arterioplasty had been performed. As addressed in our study on conduit longevity, timing of patch placement in the patient's surgical history as well as the cumulative effects of prior cardiac surgeries were assessed. A patch arterioplasty performed as the patient's first cardiac surgery was a risk factor for reintervention, as was increasing number of prior cardiac interventions preceding patch arterioplasty. This was similar to our findings in our second study which assessed conduit longevity. The immune and inflammatory interaction of an infant's early exposure to foreign bodies is one yet to be clearly delineated and requires further study.

Paper 4

PPVIE is not uncommon in children with treated congenital heart disease. As percutaneous options become more prevalent, it is important to be aware of how their infection risk profile compares with surgical options, which we sought to investigate. Our study spanned 30 years from 1993 to 2022, ultimately enrolling 469 patients and 689 PVIs. Analysis was possible along several lines: each individual valve type; surgical versus percutaneous valve prosthesis; and homograft PVs versus BJV PVs.

Our patient population and choice of prosthesis were similar to those seen in the literature [104-111]. Preference for SPVI reflected both the historical nature of PVI and an institutional preference. SPVI was discussed in Paper 2, with Contegra gaining clinical use some years after sole use of homografts. PPVI were solely Melody valves, as these were the first percutaneously inserted PVs available for implantation. Their use continues in the adult population but has largely been supplanted by the Sapien valve in recent years [112,113], which is constructed from bovine pericardium.

Not unexpectedly, patient weight and age differed among all four primary PV prosthesis types (though there was no difference in gender). This reflects findings reported elsewhere in this thesis detailing treatment preference, or bias. This is often the case in clinical studies and makes clear the need for further analysis past the raw data.

Time-to-event phenomena is best illustrated with Kaplan-Meier curves and compared using the log-rank sums test. There is some clinical value, however, in

approaching the subject from another angle, which was done by calculating mean times to onset of PPVIE. Mean time to PPVIE was almost 7 years for SPVI (around 11.5 years for homografts and 4.5 years for Contegra) and 2.5 years for PPVI. Strictly speaking it cannot be demonstrated which values are statistically different from each other, but the trend towards shorter time to PPVIE was evident in both BJV grafts and in PPVI. The etiology of PPVIE was staphylococcal or streptococcal in the majority of cases, on par with similar reports in the literature [114].

As presented in the results section, risk factors for PPVIE were assessed by both univariable and multivariable Cox regression analysis. Some pertinent negatives were not unexpected, like gender status. It was somewhat surprising that neither presence of genetic syndrome nor syndrome type were found to be risk factors. DiGeorge syndrome is often associated with this patient population and has potential negative immune consequences; however, no associated increased risk for PPVIE was demonstrated. Likewise, it was somewhat surprising that no particular diagnosis was more associated with PPVIE than another. In both Papers 2 and 3, certain diagnoses were found to be more associated with risk for reoperation or reintervention; this was not the case for risk for infection. While smaller conduits implanted in young, small patients have been shown to be at risk for earlier degeneration, this did not extend to increased risk for PPVIE. Thrombosis prophylaxis after PVI was not shown to be associated with PPVIE.

Conduit type (excluding the type of PV) was investigated as an independent risk factor for PPVIE. Since exclusively valved biologic conduits were used in this study, the type of valve was the same as the type of conduit for all SPVIs. This was not necessarily the case for PPVI, and Contegra conduits were found to be associated with PPVIE on univariable analysis. Conduit type was correlated with PV type and was not included in the multivariable analysis. In a similar fashion, prior Melody valve was found to be associated with PPVIE, but was also correlated with PV type and therefore not included in the multivariable analysis.

Non-PPVIE infections were noted. Both presence of a single infection and increasing number of such infections were found to be associated with increased risk for PPVIE. These two variables were correlated with each other, so only presence of infection was included in the multivariable model, where it again was shown to be associated with increased risk for PPVIE. This underscores the heightened vigilance for infection that all members of the care team for such patients must maintain.

There did appear to be an association of PPVIE with increasing number of PVI. Third and fourth PVs were associated with PPVIE on univariable analysis which carried through to the multivariable analysis. This is logical, with the question remaining as to why second PVs were not at increased risk compared with initial PVs. Perhaps further studies with a larger number of implanted valves (both SPVI and PPVI) would help to clarify this.

Three different Kaplan-Meier curves were produced, showing the following: from highest to lowest, FPI in each PV type were aortic homograft, pulmonary homograft, Contegra, and Melody; SPVI had a higher FPI compared with PPVI; and homograft PVs had a higher FPI compared with BJV PVs. These variables were also subjected to regression analysis, and the differences seen on Kaplan-Meier curve analysis were again demonstrated in the univariable regression analysis.

Multivariable analysis required some thoughtful consideration. There was some correlation among these three variables: surgical (versus percutaneous) PVI was not correlated with homograft (versus BJV) PV, and both of these were correlated with PV type. As each variable addressed important clinical questions, two parallel multivariable analyses were performed. The results showed: Contegra and Melody PVs were risk factors for PPVIE compared with homografts, similar to the findings of other studies (115-118); BJV PVs were risk factors for PPVIE compared with homografts; and there was no difference in risk for PPVIE between SPVI and PPVI. In the first analysis, the two valve types constructed from BJV graft were risk factors, even if type of intervention could not be accounted for. In the second analysis, there was no risk difference between type of intervention, even if some of the granularity in the valve data was sacrificed.

It appears that valves constructed from BJV run a higher risk for PPVIE than those made from homograft, and the higher rate of PPVIE seen in PPVI compared to SPVI is likely because only valves constructed from BJV (as of the writing of this study) were used. Indeed, the high rates of PPVIE in PPVI has led to a reevaluation of many variables at our catheterization lab, including choice of antibiotic prophylaxis, room air flow analysis, and implantation of Sapien valves in favor of Melody valves. Careful analysis will help to show which factors are important to decrease risk of PPVIE.

Conclusions

This thesis contributes to the body of knowledge of children with surgically repaired congenital heart disease. Reconstructive materials are needed in many such operative repairs, and homograft tissue has been and continues to be one such material of utmost importance.

In the first paper, we showed that many branch pulmonary homograft tissue works well for aortic arch reconstruction, both acutely and in the long-term. Despite the different operative strategies that the different diagnostic groups required, the common denominator of pulmonary patch material in the aortic position was shown to be of durable benefit in small children. Almost without exception, catheter-based reintervention alone was successful in treating patch stenosis.

In the second paper, we evaluated valved biologic conduits used to reconstruct the RVOT. Trends were seen in actual usage of aortic homograft, pulmonary homograft, and BJV graft; namely, that pulmonary homograft had better FCR and FFR. However, when usage characteristics were controlled for that performance advantage was less dramatic. Aortic homografts appeared to perform worse than their counterparts, but even that performance deficit was less obvious when controlling for other factors. When accounting for the effects of all the variables in our study, pulmonary homograft and BJV graft had similar FCR and FFR, despite a higher rate of endocarditis in BJV graft. Smaller-caliber conduits implanted in smaller children required earlier conduit replacement, as were conduits implanted in patients with diagnoses of TA and PA/VSD/MAPCA. There appeared to be an important component of timing of conduit placement, as first conduits and not having had prior cardiac surgery were risk factors for conduit replacement, as was increasing number of previous cardiac operations.

In the third paper, patch materials used in pulmonary arterioplasty were evaluated and compared, both in single and two ventricle patients. We found no difference in FFR between pulmonary homograft and autologous pericardium. None of the variables we assessed describing the initial stenosis proved to be risk factors for reintervention. PA/VSD/MAPCA and HLHS patients were at risk for reintervention. Similar to the second article, timing of patch arterioplasty in a patient's surgical history revealed certain trends: not having had a prior cardiac surgery was a risk factor for reintervention; however, somewhat in contradistinction to that, so was increasing number of previous cardiac operations. Whether this represents – as mentioned before – a manifestation of interacting inflammatory processes early in a patient's life, a phenomenon not accounted for by the statistics used in this study, or something else requires further attention.

In the fourth paper, we evaluated incidence of endocarditis in prosthetic pulmonary valves including both SPVI and PPVI. The primary finding was that homografts

were less susceptible to endocarditis than BJV grafts. Aortic and pulmonary homografts had similar risk profiles. BJV grafts are used as both surgical (Contegra) and catheter-based (Melody) PVs. The inherent characteristics of the BJV seemed to be a more important risk factor for endocarditis than method (surgical versus catheter-based) of PV implantation. In all valve types, any serious infection after implantation put the valve at risk for endocarditis development.

Future Perspectives

The care of children with congenital heart disease marches on. The thoughtful, innovative spirit that has characterized those who provide that care throughout history will continue. The ways we collaborate with others in the field and appreciate their contributions will be of utmost importance.

Homograft tissue has been used since the beginning of reconstructive heart surgery and shows no signs of being less important in the coming years. Characterizing with increasing detail how it performs has many important ramifications. First, is the analysis of our data sufficiently nuanced? Analyses which take into account the sameness of the center providing treatment or of the patient receiving treatment have begun appearing in the literature. The sophistication of these tests is often beyond that of even capable researchers. This will likely improve in the coming years. Second, opportunities exist to compare operative approaches. Certain operations utilizing patch material at one center are different than those at another center, sometimes not utilizing patch material at all. Multi-center trials -- comparing operative repair techniques for hypoplastic aortic arch, for example -- would be ideal. And third, there is and will continue to be a need to evaluate and innovate the reconstructive materials we use. The donation and use of homograft tissue, for instance, is not performed in Japan. They have found solutions through synthetic materials that have produced clinical outcomes similar to those of the Western world. And finally, the continued work of tissue banks to secure, process, and store homograft tissue for use remains as important as it ever was. Cardiovascular homografts are often a scarce resource and a continued efforts to promote donation are paramount. The need for cooperation among tissue banks to concentrate and share knowledge and expertise is as important as similar needs have been in the field of cardiac surgery.

Caring for complicated patients is dependent upon coordinated efforts across multiple fronts. Improving that care requires focusing intently on any one small component of that apparatus. Entwined within these written words is the hope that this thesis will do just that.

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