University of Strathclyde

Department of Bioengineering

THE USE OF ARTIFICIAL CONDUITS IN PAEDIATRIC HEART SURGERY– SCOPE OF NEED, TECHNICAL CHALLENGE AND LIMITING FACTORS

Aisling Dillon

A thesis presented as the requirements for the MSc. in Bioengineering

2011

Declaration of Authenticity and Author's Rights

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: Date:

Acknowledgements:

This project would not have been possible without the support of many people.

I would like to express my gratitude to my thesis supervisor, Prof. Terence Gourlay, for his supervision, support, knowledge and valuable guidance throughout this project.

I wish to thank Laurie Shedden for her good judgement, advice, knowledge and valuable assistance during this project.

I also want to thank Mark Danton, Consultant Cardiac Surgeon, for his advice and direction.

A special thanks to my family for their words of support and encouragement throughout the year.

And of course, to Don, without whose love, support and calming words, none of this would be possible.

Contents

Abstract:

The aim of this thesis is to review the need for artificial conduits in paediatric patients. This involved researching the various types of conditions in children that would require cardiac conduits, for example hypoplastic left heart syndrome, pulmonary artery stenosis, and bypass grafts for coronary blockages. All of these conditions and more are examined in this thesis and the history of conduit solutions will be reviewed.

The history of technologies used in paediatric cardiac conduits will be reviewed from when the first conduit was constructed and used and for what condition it was required for, to the technologies used in present day and the main conditions occurring in paediatric cardiology. The advancements in technologies will be clearly laid out to aid in further progress for future technologies, for example the benefit of tissue engineering or polymeric heart valves

In all paediatric surgeries the fact that the patient is still growing must be considered. This must be taken into account when choosing the correct materials to use when building the conduit. Most materials for conduits used in cardiology lack growth potential so it would be beneficial to have completely new technologies that can grow somatically with the paediatric patient.

Methodology:

The methodology of research involved conducting a literature search of databases for example Science Direct, Medline, Web of Knowledge and the European Association for Cardio-Thoracic Surgery, as well as the University of Strathclyde library database and other online material and relevant textbooks. A discussion with a local Paediatric Surgeon also took place to aid the direction of research.

List of Figures

List of Tables

List of Abbreviations

AO: Aorta

ASD: Atrial Septal Defect

bFGF: Basic Fibroblast Growth Factor

CHD: Congenital Heart Defect

DNA: Deoxyribonucleic acid

EACTS: European Association for Cardio-Thoracic Surgery

ECG: Echocardiogram

ePTFE: Expanded Polytetrafluoroethylene

LV: Left Ventricle

MRSA: Methicilin Resistant Staphylococcus Aureus

NIH: Neointimal Anastomotic Hyperplasia

PA/IVS: Pulmonary Atresia with Intact Ventricular Septum

PA/VSD: Pulmonary Atresia with Ventricular Septal Defect

PA: Pulmonary Artery

PCL: Poly-ε-Caprolactone

PDGF: Platelet Derived Growth Factor

PET: Polyethylene Terephthalate

PLA: Poly-Lactic Acid

PTFE: Polytetrafluoroethylene

RV: Right Ventricle

RV-PA: Right Ventricle to Pulmonary Artery

TCPC: Total Cavopulmonary Connection

VEGF: Vascular Epithelial Growth Factor

VSD: Ventricular Septal Defect

Chapter 1: Introduction

1.1 Layout of Thesis:

This dissertation begins with a brief introduction, in Chapter 1, into the objectives of artificial conduits in paediatric heart surgery. Chapter 2 details what a normal heart should develop into and where this could go wrong with regards some different anomalies that might require artificial conduits for palliation or total repair. In Chapter 3, different procedures and methods of using artificial conduits for palliative or total repair of anomalous conditions are discussed in detail. The structural aspects of artificial conduits and valves are discussed in Chapter 4 concerning how a native blood vessel or valve functions and how an artificial one tries to replicate them. It also features the different material types for the artificial devices. Chapter 5 specifies some early detection and prevention methods of congenital heart defects and the possibility of foetal cardiac repair with prenatally implanted heart valves. The technical challenges of conduits and foreign materials in the body are discussed in Chapter 6, including porosity, calcification and some concerns regarding patients who have undergone surgical repair for a congenital heart defect. Finally, in Chapter 7, the potential of tissue engineering for vascular creation is discussed as well as some new ideas in the field of congenital heart defect repairs.

1.2 Objectives of Artificial Conduits

Merriam-Webster dictionary defines a conduit as “a natural or artificial channel through which something (as a fluid) is conveyed” (Merriam-Webster 2011). A conduit is a tube or a pipe that is used to contain a substance during motion. Artificial conduits are required in cardiac surgery to redirect blood flow. They are only necessary due to an abnormal defect, which in children is usually a congenital disease, and is also more likely a disease affecting the heart and great vessels as opposed to the coronary system. Congenital heart defects occur in 8 births for every 1000. (Buskens et al 1995). An artificial conduit can be used as a complete replacement of a damaged vessel or it can be used to alter the workings of the heart in the form of a venous or arterial shunt. (Cameron et al 2004, Yuan et al 2009).

Typically in paediatrics artificial conduits are not a long lasting solution, they are only temporary cures and according to the Yorkshire and Humber Adult Congenital Heart

Disease Network before the patient reaches the age of 10 there could be at least 2 further operations to replace or repair the conduit. It also states that the majority of procedures involving artificial conduits are right ventricle to pulmonary artery or RV-PA. (Yorkshire and Humber Adult Congenital Heart Disease Network 2011).

Palliative procedures play a huge part in controlling congenital heart diseases and act as a bridge to complete correction. The Blalock-Taussig shunt is a procedure to shunt blood to the lungs as a palliative cure for cyanosis, or baby blue syndrome (Cameron et al 2004).

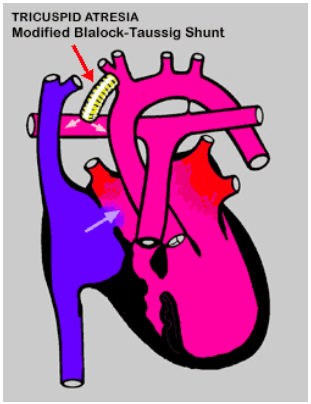

Figure 1 - Blalock-Taussig Shunt (Nursing Crib 2011)

1.3 The First Artificial Conduit

It was Alexis Carrel who first pioneered vascular surgery with the suturing of blood vessels in the early twentieth century. He worked with both heterogeneous and homogenous artery and vein graft conduits in canines in 1906. Jose Goyanes of Madrid, also in 1906, performed the first successful venous autograft. The autograft was constructed using a closely situated popliteal vein as a replacement for the diseased artery (Phifer et al (1992)). But despite the advancements in vascular surgery in general it was a while before grafts and conduits were successful in the cardiac system.

On the 19th of October 1944 the first correction of aortic coarctation was performed by Crafoord and Nylin in Sweden. It was brought about by resectioning the aorta to exclude the narrowed area and anastomosing the two functioning sections. Furthermore, Alfred Blalock successfully anastomosed the subclavian artery to the pulmonary artery on November 30th 1944 as a palliative cure for Tetralogy of Fallot (Thompson 2008).

The procedures thus far were just the joining of pre-existing native vessels. Rene Leriche, in 1923, said that "the ideal treatment of arterial thrombosis is the replacement of the obstructed segment with a vascular graft" as opposed to the previous methods of reanastomosis and ligation. It was Robert Gross, on the 24th of May 1948, who triumphantly completed the first artificial conduit replacement by implanting a preserved homogenous graft as a cure for coarctation of the aorta (Thompson 2008). Robert Gross followed this major achievement by also using a harvested and preserved homograft to create an aorta to pulmonary artery shunt as a palliative cure for Tetralogy of Fallot (Smith 1997).

Figure 2 - Robert E. Gross (Smith 1997)

Key Points:

- *Artificial conduits are required to repair abnormal cardiac defects.*
- *In paediatrics these cardiac defects are usually due to congenital heart disease.*
- *Use of the conduit can be either for palliation or total repair.*
- *The first repair of congenital heart defect was performed by Alfred Blalock in 1944 for repair of Tetralogy of Fallot.*
- *Robert Gross in 1948 successfully implanted a preserved homograft as a method of repair for coarctation of the aorta.*

Chapter 2: The Paediatric Heart

2.1 Paediatric Normal Congenital Heart

2.1.1 The Heart

The function of the heart is to pump deoxygenated blood to the lungs for gaseous exchange, and circulate oxygenated blood through the body. The heart has its own blood supply, the coronary system, which sustains the metabolic requirements of the myocardium (heart muscle). The heart is made up of 4 chambers: the left and right atria and the left and right ventricles (Seeley et al 2003). The walls of the right ventricle, which pump blood to the nearby lungs, are less muscular than the left ventricle, which has to pump blood the length of the human body. (Martini et al 2009). Figure 3 shows the structure of the heart chambers and great vessels.

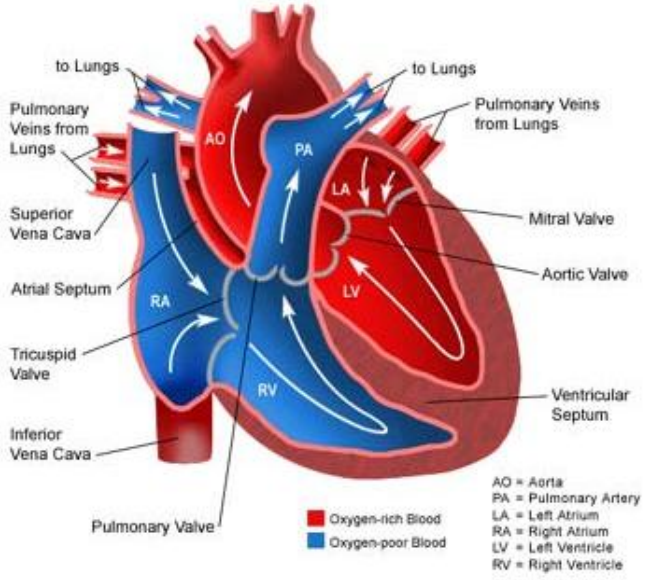

Figure 3 - Normal Human Heart (Truman Media 2010)

2.1.2 Great Vessels

There are four great vessels of the heart: the aorta, the pulmonary artery, the vena cava and the pulmonary vein. Blood leaves the right ventricle via the pulmonary trunk and then splits between the left and right pulmonary arteries in the direction of the respective lungs. As it leaves, it passes through a semilunar valve. This valve prevents backflow into the right ventricle. A similar valve is located at the aortic trunk where the blood leaves the

left side of the heart; this is also to prevent backflow. The blood leaving the heart at the aortic trunk goes into systemic blood circulation. Both the pulmonic and aortic trunks are arteries and so their predominant layer is the tunica media which is a thick muscular wall that contains a large amount of elastic connective tissue which is necessary due to the high pressures they are subjected to. (Seeley et al 2003, Martini et al 2009).

Blood enters the heart through veins. The superior vena cava and inferior vena cava deliver deoxygenated blood collected from the entire body to the heart. The pulmonary vein carries oxygenated blood from the lungs to be pumped around the body. For large veins the tunica media is thin and is made up of endothelial cells, a thin layer of collagen and a small amount of elastic fibres. The main layer of the large veins is the tunica adventitia which comprises of collagen. The reason for these thin layers is because veins are not subjected to very high blood pressure and instead transport the blood using valves (Seeley et al 2003, Martini et al 2009).

Within the chambers of the heart, there are two valves; the tricuspid valve between the right atrium and right ventricle, and the mitral valve between the left atrium and left ventricle. These atrioventricular valves ensure a one-way system of blood flow through the heart chambers which restricts backflow and therefore allows blood to keep moving forward through the pulmonic and systemic circuits. (Seeley et al 2003). Figure 4 depicts the vessels and chambers involved in the pulmonic and system circuits.

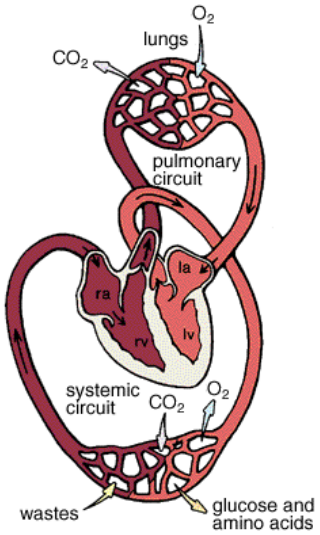

Figure 4 - The pulmonic and systemic systems (Blood Circulation 2011)

2.1.3 Development of the prenatal heart

In the prenatal development of the heart it is at approximately week 5 of embryological growth that the atrial and ventricular septa begin to develop and divide the heart into its 4 chambers, this is shown in Figure 5 below. Since the respiratory needs of the growing foetus are supplied by the mother via the placenta there is no use for the pulmonary circuit during development. To divert blood away from the pulmonary circuit during foetal growth a passage called the foramen ovale allows blood to travel from the right to left atrium but a flap of tissue prevents backflow. The foramen ovale closes at birth and the pulmonary and systemic circuits of the heart are then disassociated from each other. For the successful functioning of the heart, it is important that these two circuits are separate. (Seeley et al 2003, Martini et al 2009). Congenital heart defects as regards the inability to separate the two circuits will be discussed in a later section.

The sinus venosus illustrated in Figure 5 closes after birth; it is only present in prenatal development as a method of blood supply from the umbilical vein. A patent foramen ovale is shown in Figure 6; this is when the foramen ovale fails to close correctly. (Seeley et al 2003)

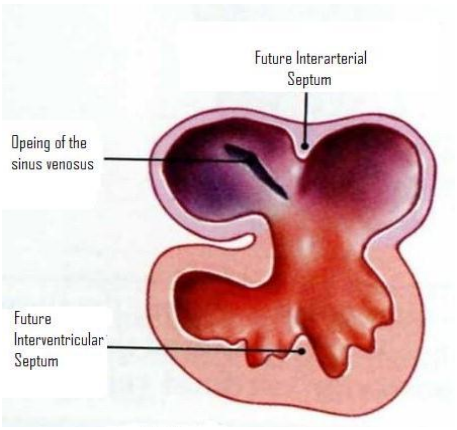

Figure 5 - Prenatal Heart Development (Martini et al 2009)

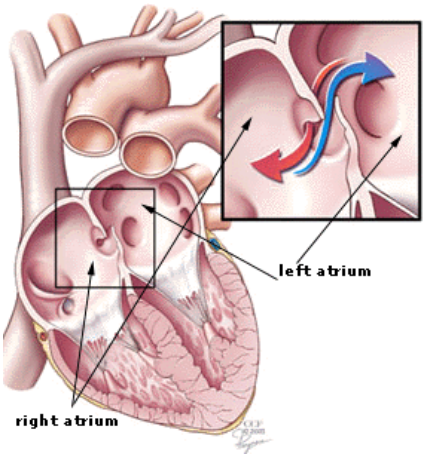

Figure 6 - Location of Foramen Ovale (Cleveland Clinic 2010)

The ductus arteriosus, which connects the pulmonary artery and the left side of the descending aorta, further short circuits the pulmonary system to the systemic system during prenatal development. The wall of the ductus arteriosus is made up of smooth muscle cells, contraction of which causes the diameter and length of the vessel to decrease, forcing blood from the pulmonary artery to the aorta. After birth the ductus should temporarily close within 18 to 24 hours. It is not for another few weeks that it will be closed completely (Gournay 2010). This closure is caused by a constriction of the artery which is stimulated by blood pressure changes. The closed ductus arteriosus is then replaced by a connective tissue called ligamentum arteriosum. A condition known as patent ductus arteriosus occurs if it does not completely close. (Seeley et al 2003). Figure 7 shows a patent ductus arteriosus connecting the pulmonary artery and the aorta.

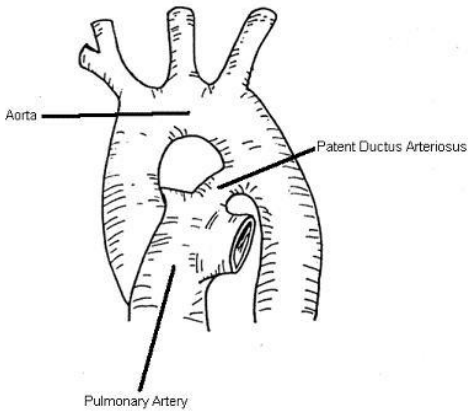

Figure 7 - Ductus Arteriosus (Virtual Medical Health 2002)

2.1.4 Coronary Vessels

As with any other organ, there is also a blood supply to support the functionality of the heart itself. The myocardium of the heart has a vast network of arteries supplying oxygenated blood to the myocardium and veins draining deoxygenated blood. This network of arteries emanate from the right and left coronary arteries which originate from the right and left Valsalva sinuses, respectively. The sinuses of Valsalva are located in the aortic root. The left and right coronary arteries then branch out into smaller arteries to distributed oxygenated blood to the heart muscle. (Anderson et al 2009). Figure 8 shows the origination of the right and left coronary arteries from the aortic root. It also shows the coronary veins illustrated in blue.

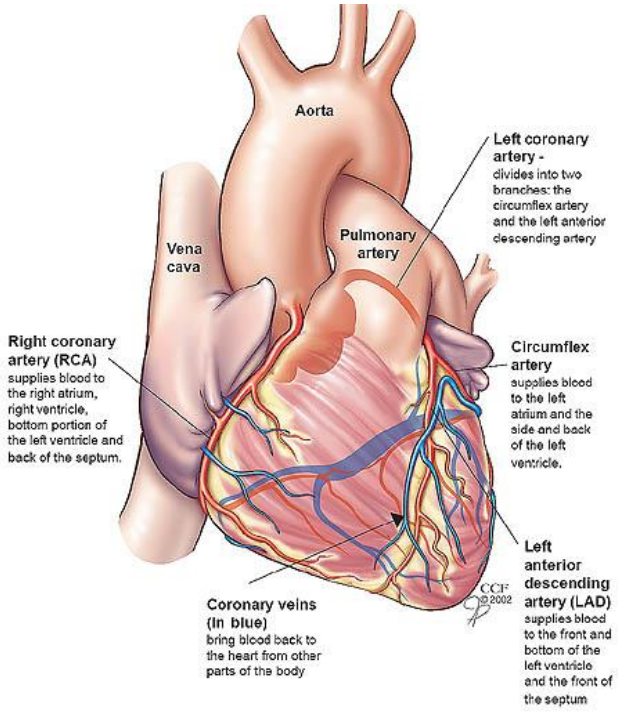

Figure 8 – Right and Left Coronary Arteries originating from aortic root (Revolution Health 2011)

The coronary sinus serves as the primary collector of venous blood from the coronary system. It is located on the posterior surface of the heart and empties its supply of deoxygenated blood into the right atrium just above the inferior vena cava. (Anderson et al 2009). Figure 9 shows the posterior view of the heart, it illustrates where the coronary veins are draining in to.

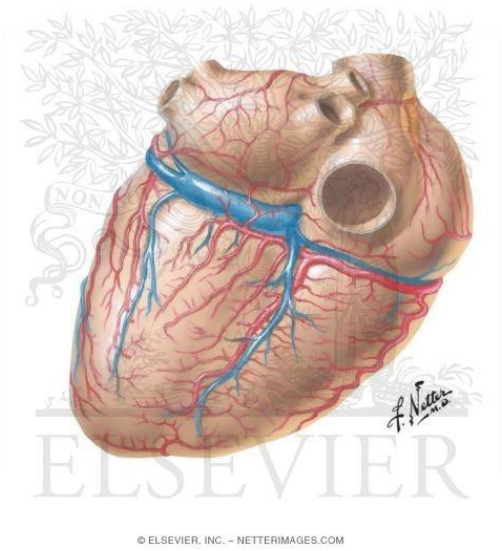

Figure 9 - Coronary Vessels Diaphragmatic View (Posterior View) (Elsevier 2005)

Key Points:

- *The heart works as two pumps: one for systemic circulation and one for pulmonic circulation.*
- *The heart has 4 chambers: 2 atria and 2 ventricles.*
- *Veins enter the heart are not under as much systemic pressure as the arteries exiting the heart.*
- *There are 4 valves associated with the heart: 2 atriopulmonary valves and 2 valves situated in the arteries exiting the ventricles.*
- *Atrial and ventricular septa begin to develop when an embryo is 5 weeks old.*
- *The foramen ovale diverts blood away from pulmonary circulation during foetal growth. It then closes at birth.*
- *The ductus arteriosus also shunts blood from the pulmonary circuit and closes shortly after birth.*
- *The heart has its own blood supply: the coronary blood vessels.*

2.2 Paediatric Heart Anomalous Anatomies

The most commonly encountered paediatric heart problems in the developed world are congenital heart defects, i.e. heart defects that the patient is born with. They are caused by insufficient or abnormal development of some part of the heart. More often the congenital heart defect is to do with the heart structure. (Woodward et al 2011). Generally congenital heart defects affect the heart chambers and great vessels. Anomalies associated with the coronary system are rare, they only occur in 0.2% to 1.2% of the general population (Mavroudis et al 2004). For many conditions that require a bypass or a replacement vessel, artificial conduits are the preferred treatment option. This section will detail the anomalous anatomies of a paediatric heart and the morbidity and mortality rates associated with them. In many cases where one congenital heart defect is present another may also occur. Studies have shown that approximately 30% of patients with one congenital heart defect will present another cardiac or extracardiac associated anomaly (Formigari et al 2008). Although there have been considerable improvements in surgical techniques, patients presenting with extracardiac anomalies still show an increased risk for death or complications (Formigari et al 2008). The occurrence of a moderate to severe congenital heart defect is 6 to 8 in 1000 births (Buskens et al 1995, Woodward 2011).

2.2.1 Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome is between 7 and 9% of all diagnosed congenital cardiac anomalies within the first year of life. It is diagnosed as a significant lack of left ventricular function and a smaller than usual ascending aorta. It occurs due to insufficient development of left ventricle, aorta, aortic valve or mitral valve (Brown et al 1971). It is a problem that develops in utero when there is not enough substantial growth of these parts of the heart. This leads to the right ventricle, which may be over developed, supplying the systemic system via a patent ductus arteriosus. (Kirshbom et al 2004). This is depicted in Figure 10.

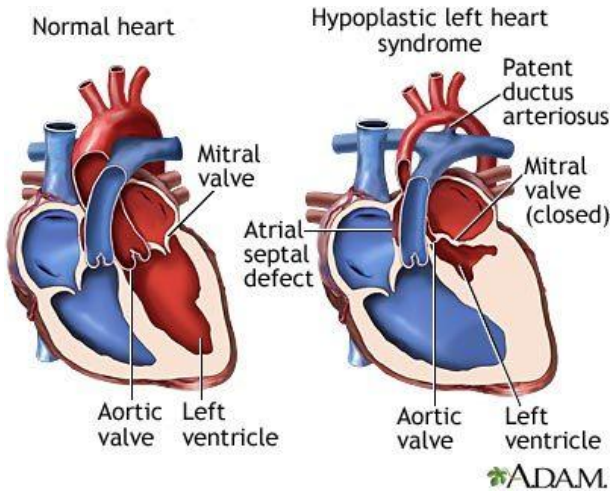

Figure 10 - Hypoplastic left ventricle (PubMed Health 2011)

2.2.2 Truncus Arteriosus

Truncus arteriosus is a rare congenital heart defect where a single blood vessel leaves both the right and left ventricles, instead of one each i.e. the pulmonary artery from the right ventricle and the aorta from the left ventricle. So in essence the two arteries are truncated or there is a common arterial trunk (Vricella et al 2004). Figure 11 below depicts truncus arteriosus. It is usually accompanied by a ventricular septal defect, an opening in the septum that separates the ventricles, which is also shown in Figure 11. The truncated artery is located above the interventricular septum or primarily over the right ventricle, but in both cases there is some form of upper ventricular septal defect. (Schnitker 1952).

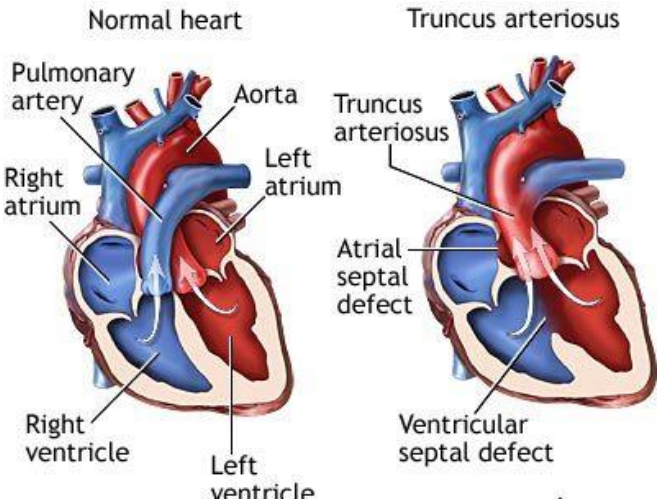

Figure 11 - Truncus Arteriosus with Ventricular Septal Defect (PubMed Health 2011)

Deoxygenated blood leaves the heart through the pulmonary artery, whilst oxygenated blood exits via the aorta, and the mixing of these two blood supplies due to truncations of the two main cardiac arteries could cause cyanosis. Various degrees of cyanosis occur due to an inability to transport a sufficient amount of deoxygenated blood to the lungs for gaseous exchange so deoxygenated blood stays within the systemic circuit. (Vricella et al 2004).

Approximately 50% of new-borns born with truncus arteriosus do not survive past their first month of life if left untreated (Vricella et al 2004). Immediate action, in the form of neonatal intervention is necessary for survival. Reintervention is usually needed in these cases because the first procedure is normally just palliative, with approximately 2.6 reinterventions in the surviving child's first 10 years (Sinzobahamvya et al 2008). The need for replacement via open heart surgery becomes less as the patient goes beyond the age of 10 and percutaneous repair can be performed due to the larger blood vessels at this later stage of growth. According to the European Association for Cardio-Thoracic Surgery (EACTS) Congenital Database, as of the beginning of 2011, 30-day mortality for Truncus Arteriosus is at 15.44%. (EACTS Congenital Database 2011)

2.2.3 Pulmonary Atresia

Pulmonary atresia is the occurrence of an underdeveloped pulmonic valve, which affects the transportation of deoxygenated blood to the lungs for oxygenation. This is usually accompanied by an underdeveloped right ventricle. These defects can result from damaged or diseased blood vessels supplying the heart during prenatal development (Lofland et al 2004). Figure 12 below shows a heart (on the right hand side of Figure 12) with a rigid and underdeveloped pulmonary valve and a hypoplastic right ventricle. This particular heart is also afflicted with patent ductus arteriosus, where the ductus arteriosus, the vessel that shunts blood away from the pulmonary circuit during prenatal development, did not close shortly after birth. A ventricular septal defect can also sometimes be found to occur with pulmonary atresia.

If pulmonary atresia is accompanied by a ventricular septal defect it is called PA/VSD (pulmonary atresia with ventricular septal defect) and it is a severe type of Tetralogy of Fallot (PubMed Health). PA/VSD amounts to about 25% of all pulmonary atresia cases (Lofland 2009)

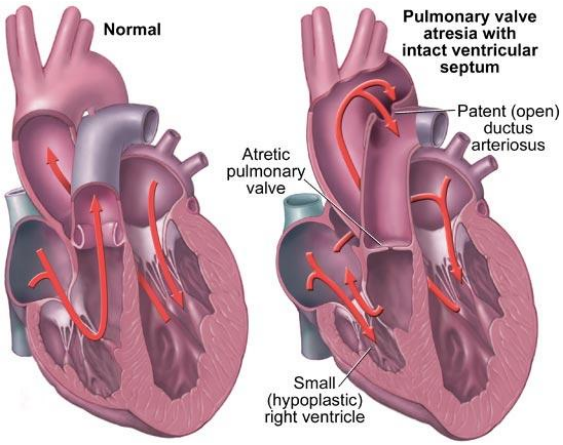

Figure 12 - Pulmonary Atresia with Patent Ductus Arteriosus (Mayo Clinic 1998)

Pulmonary atresia with intact ventricular septum (PA/IVS) is more common. Less than 10% of PA/IVS patients have a normal sized right ventricle, while the remainder suffer from a hypoplastic right ventricle, where the right ventricle has not developed properly and is almost completely absent. The EACTS congenital database reports a 6.09% 30-day mortality rate for repair of PA/VSD. (EACTS Congenital Database 2011)

2.2.4 Pulmonary Stenosis and Aortic Stenosis

One of the most common causes of right ventricular outflow tract obstruction is pulmonary stenosis with intact ventricular septum (PS/IVS). This is where the pulmonary trunk is narrowed and the flow of blood from the right ventricle to the pulmonary artery is obstructed. PS/IVS attributes 8-10% of all congenital heart defects. It is generally associated with a genetic disorder or syndromes such as Trisomy 21 (Down syndrome) and Noonan and LEOPARD syndromes. (Hillman et al 2004, Formigari et al 2008).

Pulmonary valve stenosis is another congenital heart defect that affects the pulmonic valve. In this case the valve cannot open sufficiently to release enough deoxygenated blood from the right ventricle for transportation to the lungs. Pulmonary stenosis is not only a condition affecting the pulmonary valve but the pulmonary artery itself and patients presenting pulmonary stenosis are cyanotic and have severe respiratory discomfort (Hillman et al 2004). Artery stenosis can be treated in adults by the percutaneous deployment of a stent but this treatment option is difficult in children because of the small size of the patient's blood vessels. Below in Figure 13, it can be seen

that pulmonary stenosis of the upper part of the pulmonary artery is preventing the valve from opening correctly.

It is very rare for pulmonary stenosis to occur in a patient without some other congenital heart defect. However, if it occurs alone, and there are no underlying conditions, it can be treated percutaneously with balloon valvuloplasty, once the blood vessels are large enough (Tulino et al 2009). Mortality and morbidity rates for balloon valvuloplasty are very low, less than 5% and 10%, respectively (Hillman et al 2004).

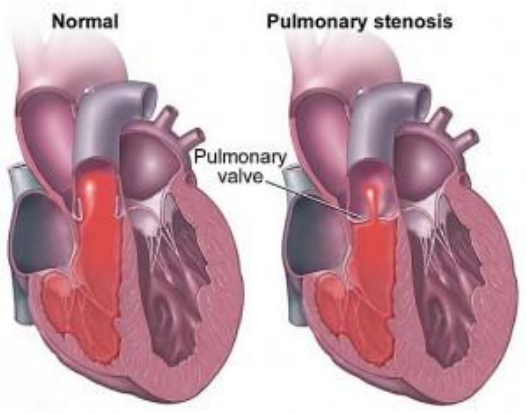

Figure 13 - Pulmonary Stenosis of upper section of pulmonary artery (Medical Blog 2008)

Aortic Stenosis is similar to pulmonary stenosis but it affects the aorta, thereby diminishing the blood supply to the entire body. Again, this condition is usually one of a number of defects. Hypertrophy of the left ventricle (thickening of the walls of the chamber) occurs in order to maintain systolic pressure and overcome the increased afterload caused by the stenotic valve (Schnitker 1952). This could eventually cause blood to distend back into the lungs through the mitral valve and through the pulmonary veins, causing damage and could lead to heart failure. (Schnitker 1952). Aortic stenosis is shown from the front (left figure) and from the top (right figure) in Figure 14.

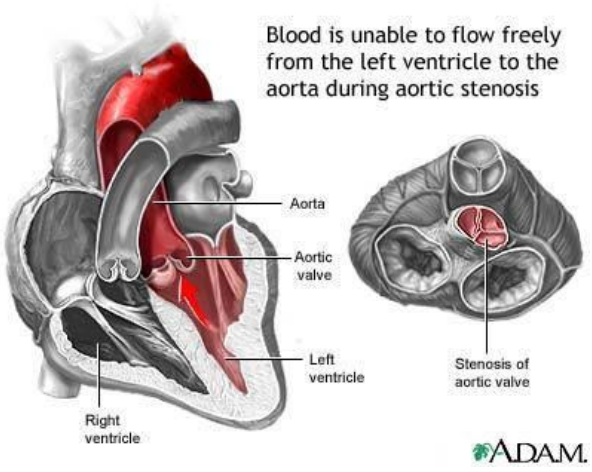

Figure 14 - Aortic Stenosis (PubMed Health 2011)

2.2.5 Tetralogy of Fallot

Tetralogy of Fallot is a congenital heart condition that consists of 4 different defects: pulmonary valve stenosis, thickening of the right ventricular wall, aortic displacement, where the aorta does not sit correctly over the left ventricle and ventricular septal defect. At least three of these defects must be present for a diagnosis of Tetralogy of Fallot. The combined defects cause a difference in oxygen saturation in the blood which can result in cyanosis, aching in the legs and dyspnoea. The patient is also at risk of heart arrhythmias and seizures. (Schnitker 1952). These are all shown in Figure 15.

It is a progressive disorder so it is best to intervene in early infancy. The pulmonary vasculature is subjected to low pressure levels due to a reduction in blood flow. Over time this causes abnormal anatomical development where the ratio of gas-exchanging capillaries in relation to the alveoli is significantly reduced. So the potential for gas exchange is reduced and this in turn leads to cyanosis (Jonas 2009).

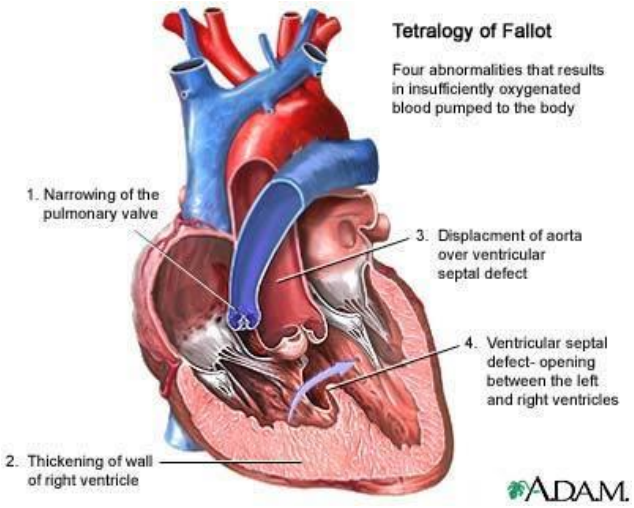

Figure 15 - Tetralogy of Fallot (PubMed Health 2011)

Tetralogy of Fallot that includes pulmonary atresia is considered one of the conotruncal heart defects, that is, it occurs as a progressive defect in the developing embryo, and may be as a result of some genetic syndromes such as conotruncal anomaly face syndrome, velo-cardio-facial syndrome and DiGeorge syndrome (Loflands 2009).

Survival from Tetralogy of Fallot due to early infancy intervention is reasonably high. A review of 49 long-term patients that presented with tetralogy of fallot at infancy showed that there was an 85% survival rate at 20years and after the age of 5years 93% of patients no longer had to be operated on for repair (Jonas 2009)

2.2.6 Ebsteins Anomaly

Ebsteins Anomaly is very rare and only accounts for less than 1% of congenital heart anomalies. It is a defect where the tricuspid valve is deformed and droops down into the inlet portion right ventricle further than normal (Pessotto et al 2004). Figure 16 shows the misshapen tricuspid valve. This causes a backflow of blood into the atrium due to the inability of the valve to close. It can lead to an enlargement of the chambers and weakening of the heart wall. Fluid may build up in the lungs or liver due to the back flow. If the anterior leaflet of this tricuspid valve is redundant it can became attached to the ventricular wall and thus obstructs the right ventricular outflow tract. Similar to all other pulmonary trunk obstructions, this could cause cyanosis, fatigue, dyspnea and heart failure (Pessotto et al 2004)

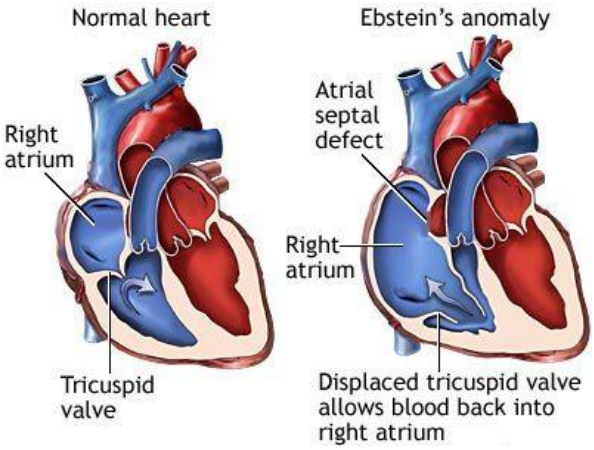

Figure 16 – Ebstein's Anomaly (PubMed Health 2011)

2.2.7 Coronary Vessels

It is very rare that the coronary arteries and veins need repair or replacement in paediatrics (Mavroudis et al 2004). Paediatric coronary artery abnormalities can be congenital or acquired. All coronary anomalies cause the patient to be at risk from myocardial ischemia and congestive heart failure. Some congenital coronary diseases are:

- Anomalous left coronary artery from the pulmonary artery: In this defect the coronary artery originates from the pulmonary artery instead of the aorta. It is extremely rare, occurring in 1:300,000 births and symptoms may not present until adult life (Mavroudis et al 2004).
- Left main coronary artery from right aortic sinus of valsalva: This has the highest rate of sudden death in coronary diseases. 30% of untreated patients leads to sudden death.
- Right coronary artery from left aortic sinus of valsalva.
- Single coronary artery. Usually the single artery supplies the left and right side equally. Figure 17 shows the two coronary artery origins.
- Congenital atresia of the left main coronary artery

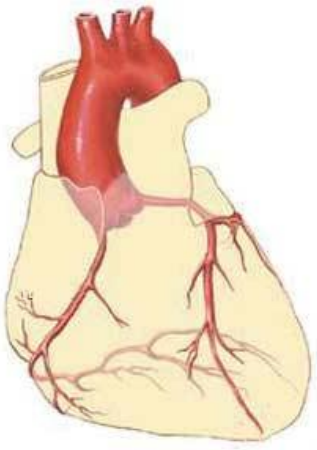

Figure 17 - Coronary Arteries Originating from Aorta (Medicine Chest 2007)

Anomalous aortic origin of a coronary artery with an interarterial course (AAOCA) is very rare, 0.1% to 0.3% of children, but there is a substantial risk for myocardial ischemia, which is failure to supply oxygen to the heart muscle, and sudden cardiac death due to over exertion (Brothers et al 2007).

Another congenital coronary heart defect is coronary ateriovenous fistulas, a condition in which there is an unusual or defective connection between one of the coronary vessels and the heart (Mavroudis et al 2004). Figure 18 below shows this. The curved vessel input may be more susceptible to blockage which results in a decreased blood supply to the heart muscle.

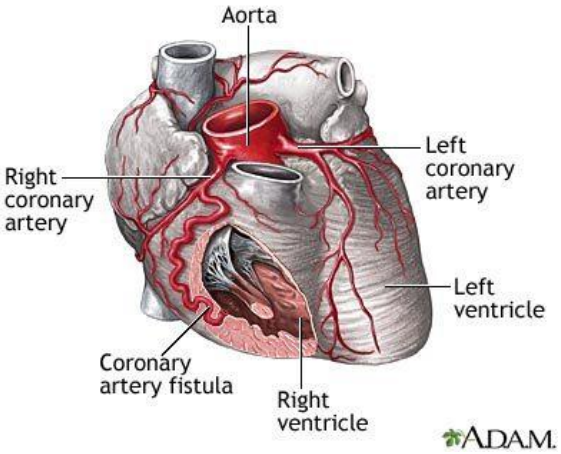

Figure 18 - Coronary Artery Fistula (PubMed Health 2011)

The build-up of plaque within the coronary arteries is not common in paediatrics and intervention or a replacement conduit is rarely needed at such a young age. This is

more of an issue in later life. However Kawasaki disease is one of the main causes of heart disease in paediatrics. It is an autoimmune disease that attacks the blood vessels and can cause coronary aneurysms in approximately 20% of patients (Takahashi et al 1997, Mavroudis et al 2004).

2.2.8 Transposition of Great Arteries

Transposition of the great arteries is a congenital heart defect where the great arteries have switched positions (Schnitker 1952). The aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. This also usually results in a displacement for coronary artery sinuses. Venous return from the systemic and pulmonic systems run in parallel with each other instead of cross-linking for transportation to the lungs for gas exchange, so blood in the systemic circulation never reaches the lungs for oxygenation, and the blood in the pulmonic circuit never goes to the rest of the body. Risks of cyanosis are very high (Duncan et al 2004). Due to the transposition this defect usually occurs with an aortic arch obstruction. An arterial switch operation is the usual procedure (Pocar et al 2005). The EACTS Congenital database lists a 16.67% 30-day mortality rate. (EACTS Congenital Database 2011). Figure 19 shows the aorta (AO) emerging from the right ventricle (RV) and the pulmonary trunk (PA) emerging from the left ventricle (LV) instead of the other way around.

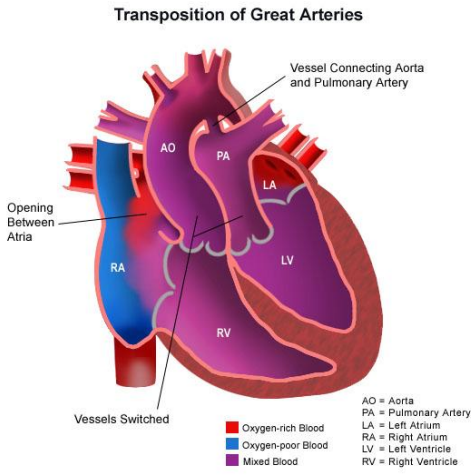

Figure 19 - Transposition of great arteries (Children's Hospital Boston 2005)

2.2.9 Coarctation of the Aorta

Coarctation of the aorta describes a condition in which the aorta is unusually narrow. Infants presenting with this defect can suffer from congestive heart failure and metabolic acidosis (Myers et al 2004). When the ductus arteriosus closes at birth for an infant with coarctation of the aorta, there is an overall increase in pulmonary artery blood flow and therefore an increase in pulmonary venous return to the left chambers of the heart. This increases the pressure in the left ventricle and causes the congestive heart failure because the left ventricle cannot pump the blood efficiently enough to the body (Myers et al 2004).

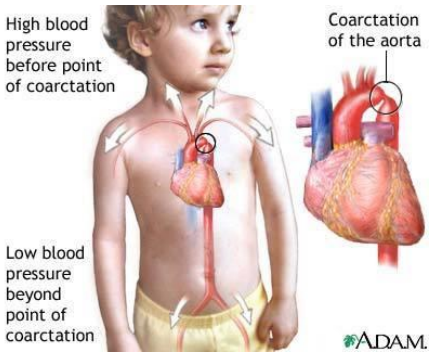

Figure 20 - Coarctation of the aorta (PubMed Health 2011)

2.2.10 Ventricular Septal Defect and Atrial Septal Defect

Ventricular septal defect (VSD) and atrial septal defect (ASD) are conditions where the walls separating the ventricles or atria have one or more holes in them or are completely missing. These are caused by insufficient foetal cardiac formation when the septum walls fail to develop fully. The consequences of these two defects are that the oxygenated and deoxygenated bloods are not kept separate within the chambers of the heart. (Bull 1986).

Key Points:

- *Congenital heart defects occur in 6 to 8 in 1000 live births.*
- *Hypoplastic left heart syndrome is an anomaly where the left ventricle has failed to develop correctly.*
- *Truncus Arteriosus is a congenital heart defect where there is only one Great Vessel exiting the heart. It is usually accompanied with Ventricular Septal Defect.*

- *Pulmonary atresia is when the pulmonic valve has not developed correctly so the right ventricular outflow tract is affected.*
- *Pulmonary and Aortic stenoses are CHD's that result in the narrowing of the outflow tracts.*
- *They are sometimes associated with genetic syndromes or disorders.*
- *They can cause thickening and overdevelopment of their associative ventricles.*
- *Tetralogy of Fallot is a CHD that consists of 3 out of the four defects:*
    - *Pulmonary valve stenosis*
    - *Thickening of the right ventricle wall*
    - *Aortic displacement*
    - *Ventricular septal defect*
- *Ebstein's anomaly is the name given to the condition where the tricuspid valve is misshapen.*
- *The coronary vessels are not usually an issue in paediatric cardiology.*
- *Misplacement of the origins of the coronary vessels can occur.*
- *Kawasaki disease can cause coronary aneurysms in paediatrics.*
- *Transposition of the great arteries is a CHD where the aorta and the pulmonary artery have switched positions with each other.*
- *Coarctation of the aorta is the narrowing of the aortic vessel.*
- *VSD and ASD are CHD's where the septum walls are not fully formed.*

Chapter 3: Repair of Lesions Procedures

3.1 Palliative or Curative

The decision of whether to perform palliative surgical procedures of total correction surgical procedures on children with congenital heart defects is a complex issue (Cameron et al 2004). There are a number of heart defects that require early palliation superseded by total correction, e.g. patent ductus arteriosus and pulmonary stenosis. There are also a number of defects, for example single ventricle conditions, that can never be completely corrected because reoperation of shunt procedures is always a factor. (Cameron et al 2004)

The post-operative management of patients who have undergone palliative procedures is more difficult than patients having undergone total correction and they are more at risk of further complications and must be continually monitored. Alfred Blalock's procedures in 1944 to shunt blood from the systemic system to the pulmonary system to prevent cyanosis lead the way for palliative procedures (Cameron et al 2004). Most palliative procedures are used to regulate the mixing of pulmonary and systemic blood circulatory systems so as to prevent further damage to the heart and lungs. Surgical procedures aspire to restore normal circulation, whether pulmonary or systemic, either by emergency palliation or total repair (Cameron et al 2004).

Palliative procedures have been classified into four sections in relation to their end goals (Yuan et al 2009). These sections are: increasing pulmonary artery blood flow; decreasing pulmonary artery blood flow; improving the mixing of blood-oxygen for systemic circulation; and finally all other procedures for stenosis or coarctation of the aorta and the hybrid procedure for palliative cure of hypoplastic left heart syndrome (Yuan et al 2009).

Total correction procedures are very patient specific. For example total repair of Tetralogy of Fallot in one patient could be quite different from total repair of Tetralogy of Fallot in another patient (Apitz et al 2009). Early total correction of congenital heart defects is the most favourable treatment, but not always immediately possible to meet the immediate needs of a functioning heart. It is more important that the intervention produces satisfactory heart function rather than providing total correction (Cameron et al 2004).

3.2 Procedures

There are a number of different procedures for repair of congenital heart defects, but only some of these require new anatomical corrections to be made. Arterial Switch, Venous Switch and the Damus-Kaye-Stansel procedure for correction of transposition of great arteries do not need artificial or tissue grafts for surgical repair. Such conduits are needed however in procedures such as the Fontan Procedure and the Norwood procedure, where venous and arterial shunts are constructed.

3.3 Shunts

Systemic to pulmonary artery shunts have been used for decades to improve pulmonary blood flow by redirecting systemic venous return to the pulmonary arteries. They are used both in procedures for palliation and total correction. Artificial conduits, of tissue or synthetic materials, can be used to create these technically simple shunts or they can be created by anastomosis of native vessels such as in the Glenn procedure. The venous shunt can only handle low pressure so it requires minimal pulmonary circulatory resistance in the lungs. There are a number of different shunt procedures, some of which use artificial conduits and some that don't. The Blalock-Taussig shunt, the Modified Blalock-Taussig shunt, the Central shunt and the Sano shunt require conduits. The Glenn shunt used in the Hemi-Fontan procedure does not require an artificial conduit, however the extra-cardiac conduit of the Fontan procedure is artificial (Cameron et al 2004, Yuan et al 2009).

3.4 Fontan Procedure

The Fontan procedure has been established as the most conclusive of palliative procedures for single ventricle congenital heart defects where there is only one pumping system for both the systemic and pulmonary circulation (Yuan et al 2009). The results of the surgery have improved throughout the years since the first one in 1971 for palliative repair of tricuspid atresia and mortality rates have lowered. Despite these improvements patients still experience anastomosis associated problems such as thrombosis or infection and a serious intolerance to overexertion due to the inability to withstand increasing pressure levels (de Leval 2005).

The Fontan procedure reorders the systemic and pulmonary circulations to change them from parallel, where the oxygenated and deoxygenated blood are intermixed, to

series where blood circulates through the pulmonary circulation, then the systemic circulation. The single ventricle is used for pumping blood around the systemic circulation, and blood circulation to the lungs is dependent on the passive filling of the pulmonary arteries (de Leval 2005). Cavopulmonary anastomosis is the term used to describe connecting the superior vena cava to the right pulmonary artery, either directly by a Glenn shunt or by use of an artificial conduit (de Leval 2005). Total cavopulmonary connection connects both the superior and inferior vena cava to the right pulmonary artery. There are two stages of the Fontan procedure: stage 1 is the Glenn procedure or Hemi-Fontan; stage 2 is Fontan completion. In stage 1 the superior vena cava's blood flow is redirected by a shunt system, usually a Hemi-Fontan procedure or a Blalock-Taussig shunt. Fontan completion re-directs the inferior vena cava blood flow to create a total cavopulmonary connection (Migliavacca et al 2003).

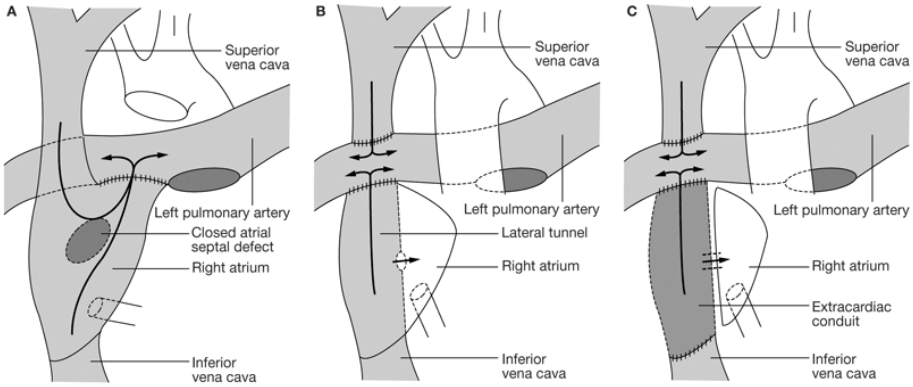

Figure 21 - A: Atriopulmonary Connection: the right atrium is used as a reservoir. B: Lateral Tunnel: the conduit to connect inferior vena cava blood flow to the pulmonary arteries goes through the right atrium. C: Extracardiac TCPC: the conduit to connect the inferior vena cava blood flow to the pulmonary arteries goes outside the heart. (Nature 2011)

The three different types of Fontan Procedures: the Atriopulmonary connection; the Lateral Tunnel or Intracardiac total cavopulmonary connection; and the extracardiac total cavopulmonary connection are shown in Figure 21 (de Leval 2005). All three types aim to redirect cavopulmonary blood flow.

In an atriopulmonary connection the blood in the right atrium is prevented from emptying into the right ventricle as it does in a normal heart, by the closure of the atrioventricular valve and of the pulmonary trunk. A direct atriopulmonary connection is made by anastomosis of the right atrium reservoir to the pulmonary artery. This is

performed with an artificial conduit as the right atrium to pulmonary artery connection (Podzolkov et al 1997). The European Association for Cardio-Thoracic Surgery Congenital Database, which was updated as of January 2011, stated that out of 8 atriopulmonary Fontan procedures performed last year, there was a 0% mortality rate. However, overexposure of the right atrium to high venous blood pressure can cause enlargement of the atrium. (de Leval 2005)

The total cavopulmonary connection (TCPC), either by lateral tunnel or extracardiac connection, involves rerouting the superior vena cava blood return into the pulmonary arteries and anastomosing the inferior vena cava to the pulmonary arteries (de Leval 2005). The lateral tunnel or intracardiac TCPC involves constructing a conduit through the atrium from the inferior vena cava to the pulmonary arteries. The extracardiac TCPC does not go through the atrium but sits outside the heart (de Leval 2005).

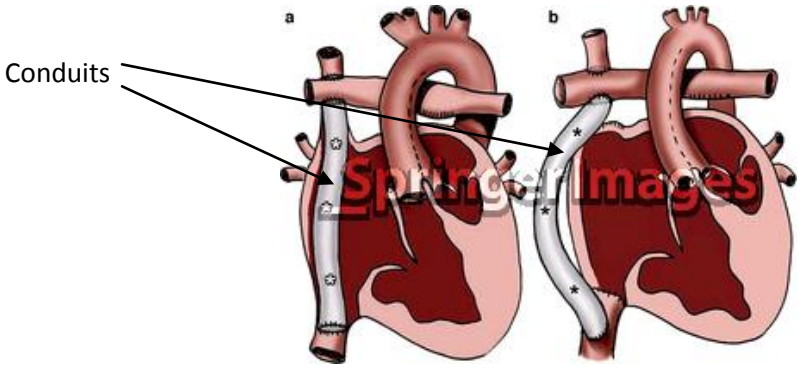

Figure 22 - A: Intracardiac (Lateral Tunnel) TCPC. B: Extracardiac TCPC (SpringerImages 2011)

Fenestration, which is the creation of miniature holes or windows in the conduit, of the venous return in both intracardiac and extracardiac TCPC's is sometimes necessary to relieve the high blood pressure; however this should be later closed to avoid a lack of oxygen supply to the body. (de Leval 2005). The EACTS Congenital Database lists the following 30 day mortality rates for the procedures mentioned:

Fontan Procedure	No. of Patients	30 day deaths	30 day mortality
External TCPC Non-Fenestrated	347	15	4.36%
External TCPC Fenestrated	268	8	3.02%
External TCPC Not Specified	29	3	10.34%
Lateral TCPC Non-Fenestrated	50	3	6.00%
Lateral TCPC Fenestrated	90	5	5.56%
Lateral TCPC Not Specified	7	0	0.00%
Fontan, other	13	3	23.08%
Fontan, not specified	13	1	7.69%

Table 1 - Fontan Mortality Rate for External and Lateral Conduits (EACTS Congenital Database 2011)

3.5 Blalock-Taussig Shunt

The classic Blalock-Taussig Shunt, which was first performed in 1945, utilised the patient's own subclavian artery, emerging from the aorta, to shunt the blood flow from the pulmonary artery for the purpose of repair of Tetralogy of Fallot. (Ullom et al 1987). The main advantage of this was that no artificial material was used for the conduit so the potential for growth was there, which was very important before total correction was a possibility. (Ullom et al 1987, Yuan et al 2009). However because this uses the artery that supplies blood to the arm it can cause arm ischemia in older children. (Cameron et al 2004). The classic Blalock-Taussig shunt has been replaced by the modified Blalock-Taussig shunt where an artificial conduit made of Gore-Tex connects the subclavian artery and the pulmonary artery. (Ullom et al 1987) This procedure can be performed either on its own or with another procedure such as the Norwood Procedure or as stage one of the Fontan Procedure. It is typically used as a bridge to total correction or palliation by temporarily redirecting blood flow to the lungs and preventing cyanosis (Cameron et al 2004, Yuan et al 2009). The European Association for Cardio-Thoracic Surgery congenital database does not have records for the Classic Blalock-Taussig shunt implying that the Modified Blalock-Taussig shunt has overtaken it. The EACTS database recorded a 30-day mortality rate of 8.09% for the Modified Blalock-Taussig shunt. (EACTS Congenital Database 2011)

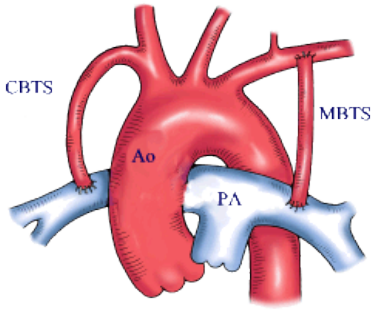

Figure 23 - Classic Blalock-Taussig Shunt and Modified Blalock-Taussig Shunt (Congenital Heart Disease Guide 2011)

3.6 Central Shunt

The Central or Mee's Shunt is an anastomosis between the pulmonary artery and the ascending aorta. It is usually used to replace a failing Blalock-Taussig shunt. (Yuan et al 2009). The mammary artery is used as the replacement conduit which allows for biocompatibility and eliminates the need for prosthetic materials to be used. Another advantage is that it avoids the need to use the subclavian artery therefore risk of arm ischemia is avoided. Synthetic material can be used instead of the mammary artery but replacement procedures as the patient's heart grows will be necessary. The central shunt allows a more even blood flow between the two arteries. It is the preferred option in very small infants, where the subclavian artery is not suitable to be used as a shunt (Yuan et al 2009). A 12.02% 30-day mortality rate was recorded by the EACTS for the Central Shunt procedure. (EACTS Congenital Database 2011)

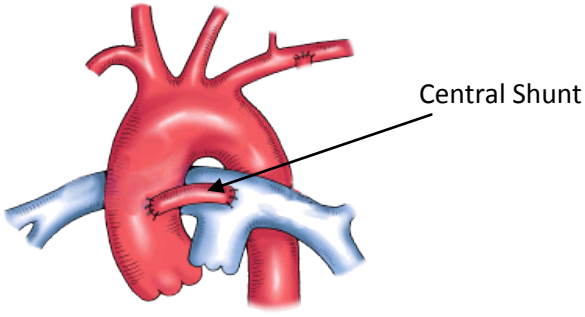

Figure 24 - Central Shunt between ascending aorta and pulmonary artery (National University of Singapore 2001)

3.7 Right Ventricle to Pulmonary Artery Conduit (Sano Shunt)

The Sano Shunt is a modification of the Norwood Procedure and is now sometimes used as the first step of a complete Norwood procedure. It is a procedure that incorporates an artificial conduit to bridge the right ventricle and the pulmonary artery, thereby utilising the pumping ability of the right ventricle to re-establish blood flow to the lungs as palliation of hypoplastic left heart syndrome (Sano et al 2004). It is a newly established, circa 2003, palliative treatment for patients with hypoplastic left heart syndrome (Sano et al 2004). The purpose of the RV-PA conduit is to connect the systemic and pulmonary circulations. Typically a 5mm diameter PTFE tube is used for the conduit, cut to an appropriate length for the patient. The use of an RV-PA conduit increases haemodynamic performance (Sano et al 2004, Migliavacca et al 2006).

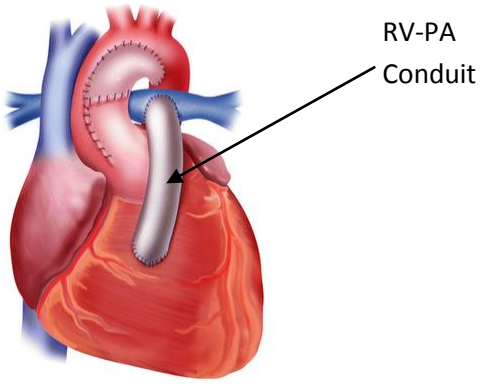

Figure 25 - Right Ventricle to Pulmonary Artery (Sano) Shunt (Blogspot 2010)

3.8 Norwood Procedure

The Norwood procedure is typically used to treat hypoplastic left heart syndrome but has been known to treat other forms of congenital heart disease that result in only one functioning ventricle. The first successful performance of the procedure was in 1981 by Norwood et al, the aim of which was to enable the systemic circulation to be pumped by the single functioning ventricle. Following this, a separate blood flow for supply to the lungs must be created. (Migliavacca et al 2006, Sano et al 2004)

The Norwood procedure is made up of three stages: Stage I; Stage II; and Stage III. Stage I is when the pulmonary artery is detached from the heart just above the pulmonary valve. The new aorta is then reconstructed by anastomosing it with the pulmonary trunk

containing the valve. This is shown in Figure 26. Stage I also involves redirecting the pulmonary blood flow from the superior vena cava to the pulmonary artery, which can be done by either a Blalock-Taussig shunt, a Central shunt or a Sano shunt. These are shown in Figure 27. (Migliavacca et al 2006, Sano et al 2004).

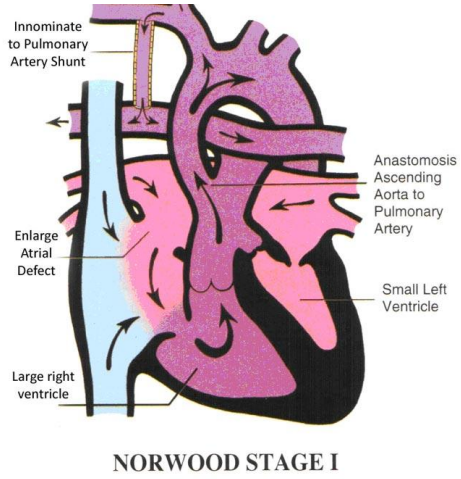

Figure 26 - Division and anastomosis of pulmonary artery to aorta (Heart Kids 2011)

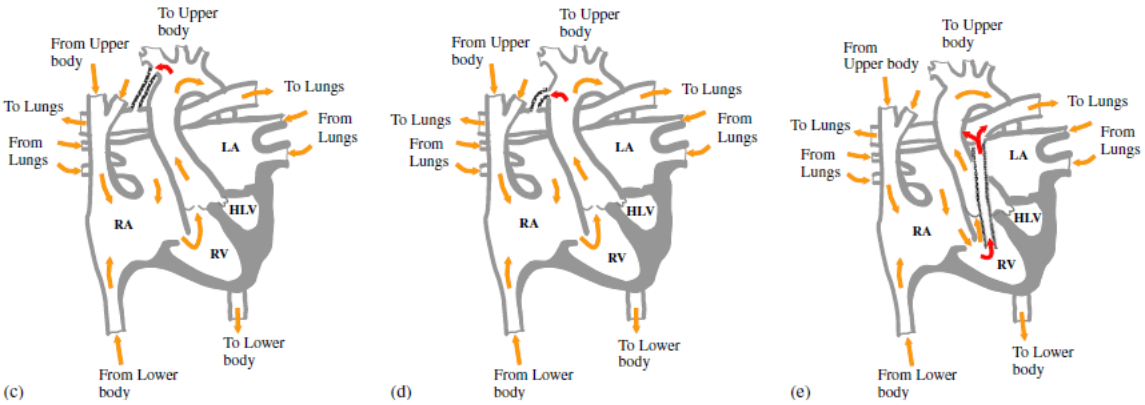

Figure 27 - (c) = Norwood Operation with Blalock Taussig shunt. (d) = Norwood Operation with Central Shunt. (e) = Norwood Operation with RV-PA (Sano) Shunt (Migliavacca et al 2006)

Norwood Stage II and Stage III are performed later in the patient's life, about age 2 to 4 years, and these are Fontan like procedures. Stage II creates an anastomosis between the superior vena cava and the pulmonary artery, while stage III completes the total cavopulmonary connection with either a lateral tunnel or an extracardiac conduit. (Website)

The EACTS Congenital Database lists the Norwood Procedure as having a 33.12% 30-day mortality rate. (EACTS Congenital Database 2011). But since the procedure has three stages the risks do increase as procedures continue.

3.9 Hybrid Procedure

The Hybrid palliative procedure is exercised in patients with one working ventricle; this is either due to hypoplastic left heart syndrome or a restrictive outflow tract due to tricuspid atresia or transposition of the great arteries. It uses a catheter deployment mechanism to stent the ductus arteriosus to shunt systemic to pulmonary blood flow. It also includes a pulmonary artery to innominate artery shunt, pulmonary artery banding and balloon atrial septostomy, which all help to decrease the restriction of blood flow to the lungs. It reports a 78.5% hospital survival rate. Using this procedure a Norwood stage I procedure can be avoided, limiting the amount of open heart surgery needed. (Yuan et al 2009)

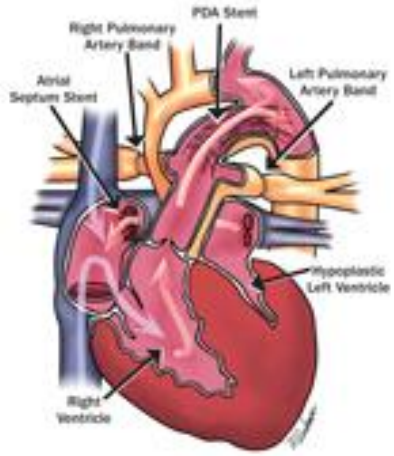

Figure 28 - Hybrid Procedure with Patent Ductus Arteriosus Stent at the top (Mayo Clinic 2001)

3.10 Rastelli Procedure

The Rastelli procedure is used as a correction of congenital heart defects such as transposition of great arteries, double outlet right ventricle, ventricular septal defect (VSD) and right ventricular outflow tract obstruction. Part of this procedure uses a Gore-Tex patch to redirect bloodflow through the VSD from the left ventricle to the aorta to bypass the obstruction. (Delius et al 1996). Figure 29 shows how a homograft and a Gore-tex tube are

anastomosed together to form this conduit. A Blalock-Taussig shunt is sometimes used as a bridge to this procedure (Delius et al 1996)

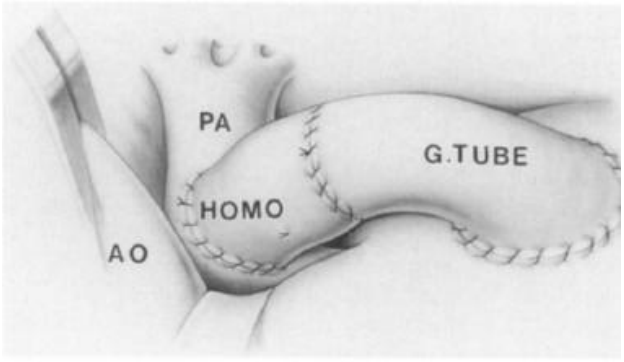

Figure 29 - Right ventricle to pulmonary artery conduit. AO – Aorta, PA – Pulmonary artery, Homo – Homograft, G.Tube – GoreTex Tube. (Delius et al 1996)

3.11 Ross Procedure

This is a two-valve operation where the native pulmonary valve is transplanted to the aortic position. The pulmonic valve itself is then replaced with another valve, usually a tissue valve. (Elkins et al 1999). The benefit of this is that the aortic valve can now grow with the child and there is no rejection of tissue at the aortic root. The new pulmonic valve could still be rejected, but this procedure is the only one to date that successfully replaces the aortic valve with a viable substitute (Riley et al 2004).

3.12 Procedures for Paediatric Coronary Defects

Whether the coronary artery disease in children is congenital or acquired, sometimes a coronary bypass either by a graft or by anastomosis of native vessels may be required (Mavroudis et al 2004). Artificial conduits are needed in the repair of some congenital coronary defects. For the condition where the left main coronary artery originates from right aortic sinus of valsalva, or the right coronary artery originates from the left aortic sinus of valsalva, a bypass needs to be created to change the origin of the artery and anastomose it to the correct position (Mavroudis et al 2004). Bypass surgery is also needed to correct such anomalies as congenital atresia of the right or left main coronary artery to bypass the obstruction (Mavroudis et al 2004). An acquired coronary artery disease in paediatrics such as coronary aneurysm caused by Kawasaki disease can also be repaired by coronary artery bypass, connecting the internal thoracic artery to the

coronary artery. The saphenous vein is sometimes used for this procedure (Mavroudis et al 2004).

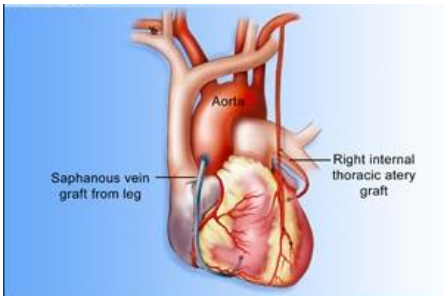

Figure 30 - Coronary artery bypass (Columbia Surgery 1999)

Key Points:

- *Early palliation followed by total correction is usually how congenital heart defects are repaired.*
- *It is more important that the child is kept alive by palliation rather than risking total repair immediately.*
- *Systemic to pulmonary artery shunts are used as palliative methods of repair in many procedures.*
- *The Fontan procedure has two stages: Stage 1 redirects superior vena cava flow. Stage 2 redirects inferior vena cave flow.*
- *There are 3 types of stage 2 Fontan completion procedures: the atriopulmonary connection; the lateral tunnel total cavopulmonary connection; and the extracardiac total cavopulmonary connection.*
- *The Blalock-Taussig shunt is a procedure to redirect blood flow from the pulmonary artery to the aorta.*
- *The classic Blalock-Taussig shunt uses the patient's subclavian artery and the modified Blalock-Taussig shunt uses a synthetic material.*
- *The Central shunt can be used to replace a failing Blalock-Taussig shunt.*
- *The RV-PA conduit connection allows use of the right ventricles pumping action to pump blood to pulmonary circuit, this is used in the case where only a single ventricle is working and the pump is needed for both circulations.*
- *The aim of the Norwood procedure is to use the single ventricles pumping action for systemic circulation.*

- *Stage 1 of the Norwood procedure involves a shunt for pulmonic circulation.*
- *The Hybrid procedure uses a catheter deployment system for repair.*
- *The Rastelli procedure uses a synthetic graft to bypass obstructions in the outflow tracts of the heart.*
- *The Ross procedure aims to correct CHD's affecting either the pulmonary or aortic root valves.*
- *Bypass grafts are used to correct coronary congenital heart defects or aneurysms.*

Chapter 4: Structural Aspects of Heart and Conduits

4.1 Mechanics of Blood Vessels and Conduits

4.1.1 Structure of Arteries and Veins

The natural blood vessel, either artery or vein, contains both muscle and elastin in their walls, the only difference is the amount of each in the two types of blood vessels. There are three distinctive layers: the tunica intima, the tunica media and the tunica externa. The amount of blood flowing through the blood vessel is regulated by vasodilation and vasoconstriction which is controlled by the amount of smooth muscle present in the tunica media. The collagen connective tissue in the tunica externa regulates how much the wall can expand (Seeley et al 2003).

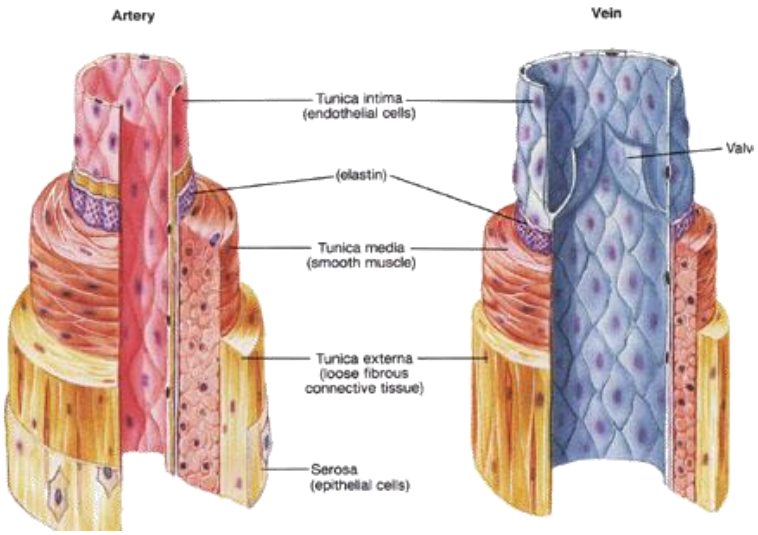

Figure 31 - Wall Structure of Artery and Vein (Cardiology in work 2008)

Pressure in the large arteries is high and varies from systolic and diastolic pressure values. This is comparative to the low pressure observed in the veins. The tunica media is much less in veins as it is not needed to transport the blood. Blood is transported using valves in large veins with diameters greater than 2mm. The valves in veins are composed of endothelial cells and prevent backflow (Seeley et al).

4.1.2 Wall Distensibility and Elastic Properties

With each diastolic and systolic movement of the heart, the blood vessels connected to the heart move both longitudinally and transversely. For the coronary vessels

transverse wall distensibility is much greater than longitudinal distensibility because the vessel is tethered to the wall, so the diameter of the vessel is more affected than the length (How 1992). Values of wall distensibility vary widely not only as the distance from the heart changes but even in a single vessel. It can vary from 2.5% to 8.5% in the thoracic aorta (How 1992).

The mechanical behaviour of the blood vessel wall is regulated by the amount of distensibility the wall can achieve. The elastin in the tunica media controls the pressure load during low pressures but the amount of collagen in the tunica externa bears the load for high pressures and restrains distortion (Van Oijin 2003). Blood vessels exhibit non-linear behaviour as shown in Figure 32. At low pressures an artery is highly distensible but becomes much stiffer and less compliant as pressure increases (How 1992).

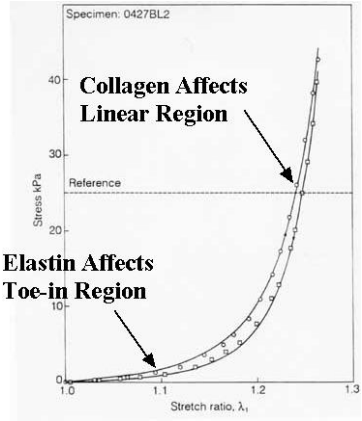

Figure 32 - Stress-Strain curve of Blood Vessel (Michigan Engineering 2011)

4.1.3 Systole and Diastole

Ventricular systole is when the right and left ventricles of the heart contract forcing blood out past the valves and through the pulmonary trunk and the aorta, respectively. This increases the pressure on the wall of the arteries. Diastole follows systole; this is the stage where the ventricles relax and so there is a decrease of pressure on the pulmonary arteries and aorta. Venous pressure is very low compared to arterial pressure and is not as affected by systolic and diastolic activity (Martini et al 2010).

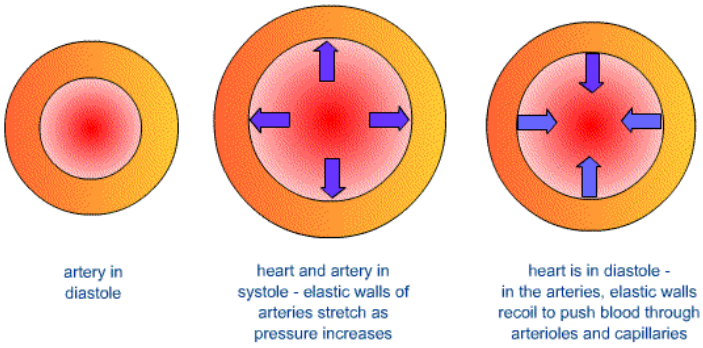

Figure 33 - Artery during diastole and systole (Birmingham City Uni. 2011)

The coronary vessels are affected by systole and diastole in much the same way as the great vessels themselves, as are all vessels in the body. But there is a difference with coronary vessels. During systole the heart contracts and so gets smaller, this relieves some pressure in the coronary vessels. Diastole has the opposite affect: relaxation of the heart causes it to fill and thus puts strain on the coronary vessels attached to the myocardium.

4.1.4 Mechanics of Flow in a Blood Vessel

Haemodynamics, or blood flow, differs between different anatomical structures and lesions. The velocity of flow increases through smaller diameters with larger velocities seen at the centre of flow and decreased velocity near the wall of the vessel (Loushin et al 2009). In large vessels, such as the ones exiting the heart, blood flow is not steady. It pulses through and is slightly out of phase with the pressure gradient. Kinetic energy is largest in the centre of the blood stream but at the wall, where shear rates are highest, the blood flow lags behind (Goldsmith et al 1992). Shear rate is the slope of the velocity profile at a certain radial position, it is a measure of the rate at which shear is applied. It can be seen in Figure 34 that the blood velocity profile through a blood vessel is parabolic (Slack et al 1992).

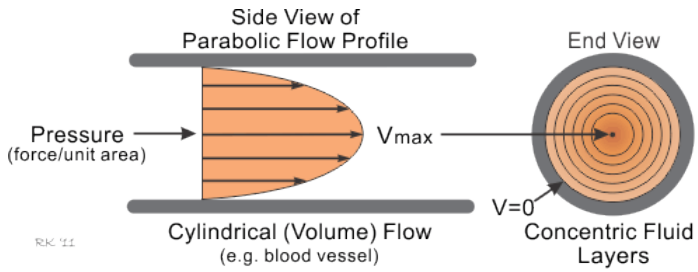

Figure 34 – Parabolic Velocity of Blood Flow (Cardiovascular Physiology Concepts 1998)

4.1.5 Blood-material Interactions

With regards the interaction of blood and materials, there is a big difference between what the natural endothelium layer of a blood vessel and what the artificial surface of an artificial conduit has to offer. The natural endothelium layer of the blood vessel offers a blood compatible layer and the various components of the blood do not stick to or bind with the surface. By this same reasoning the endothelial layer prevents the activation of clotting factors, the complement system and the formation of thrombus (Courtney et al 1992).

The problem with artificial surfaces is their lack of biocompatibility. They cannot perform like the endothelial layer of the native blood vessel. The artificial surface cannot produce the same metabolic process to discourage thrombus formation. This results in the formation of thrombus clots on the artificial surface which will affect the flow of blood through the conduit and the substance of the blood itself. The correct interaction of the blood and the material is also governed by the smoothness of the prosthesis. To prevent thrombus formation many grafts are coated with a cellular neointima which can be formed from the patient's own endothelium (Forbes et al 1978).

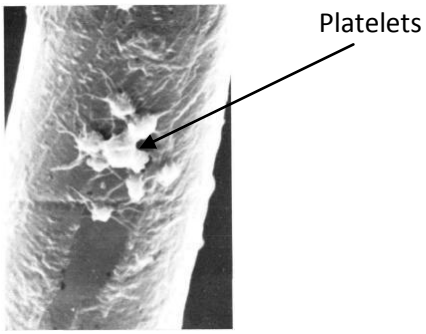

Figure 35 – Adhesion of Blood components to Dacron Wool Graft (Forbes et al 1978)

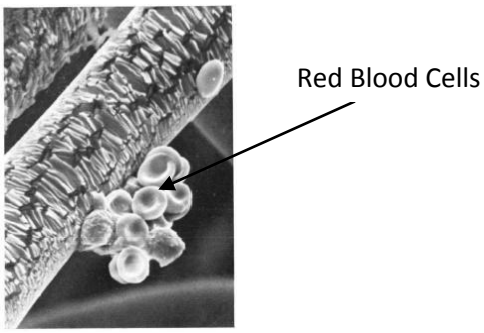

Figure 36 - Adhesion of Blood components to Dacron Wool Graft (Forbes et al 1978)

4.1.6 Anastomosis

Anastomosis between the native vessel and an artificial conduit can cause some haemodynamic issues. Anastomic intimal hyperplasia may develop particularly at the distal end of the anastomosis. This will causes problems with the flow dynamics of the graft since the intimal hyperplasia will gradually decrease the diameter of the vessel. This is shown in Figure 37 below. The anastomic site will be discussed in Section 4.2.1.1. Anastomosis using autologous vein grafts shows better results than synthetic grafts (Cole et al 2002).

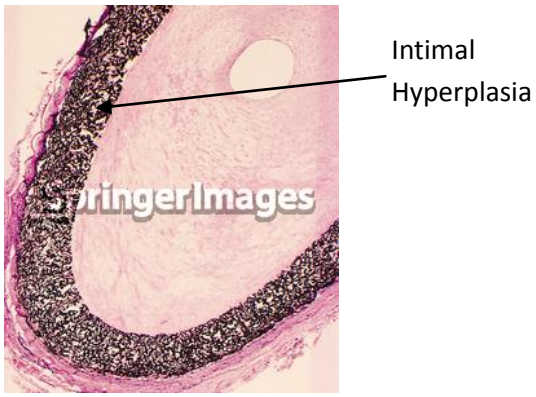

Figure 37 - Anastomotic Intimal Hyperplasia (SpringerImages 2011)

The geometry of the anastomosis between the native vessel and the artificial conduit is important in determining the flow structure along the wall of the prosthesis. Compliance mismatch can cause further endothelial affliction which adds to the possibility of thrombus formation (Phifer et al 1992). Haemolysis may also occur at this distinction where the red blood cells become damaged and release their haemoglobin.

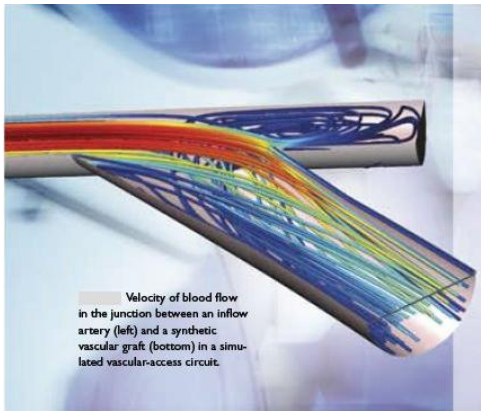

Figure 38 - Flow through junction of anastomosis (Comsol 1998)

Some repairs of lesions require a complete bypass of blood flow, not just an end-to-end anastomosis. These bypasses are shunts, e.g. the Blalock-Taussig shunt in the Norwood procedure, shown in Figure 39, for palliative treatment of hypoplastic left heart syndrome where blood flow is diverted into the pulmonary circulation. This diversion of blood could cause haemolysis and thrombosis as previously described in anastomotic issues.

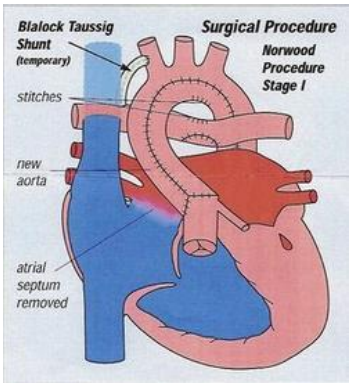

Figure 39 - Blalock-Taussig in Norwood (BabyPennington 2007)

4.1.7 Mechanics of Flow through Valves

The purpose of a valve is to prevent flow in the wrong direction. For a heart valve, when the blood pressure on the correct side of the heart is high enough, blood will be forced through the valve. When the chamber preceding the opening of the valve is full, the valve will close preventing backflow. Due to the design of the valve and the direction the leaflets point in, the valve should not open backwards. Regurgitation is when flow is reversed due to a leaky valve, leaflet prolapse or sudden change in the size of the chambers (Loushin et al 2009). There are a few different types of artificial valves available for implantation, some are mechanical and some are biological.

The mechanical valves have an advantage in that there is a low pressure gradient so the heart does not have to work as hard to pump the blood but problems such as the need for anticoagulation drugs in the long term and a high level of regurgitation are constantly present with these types of valves. Regurgitation occurs due to the incomplete closure of the leaflets to prevent it from sticking, this aids in the lower pressure gradient experienced with this type of valve.

Biological valves operate in the same way as the native human valve would. Most often a trileaflet valve would be used to replace any failing valve. They experience very little

regurgitation due to their biological structure but pressure gradients can be high and calcification could occur which makes then not altogether suitable in paediatrics.

Key Points:

- *Arteries and veins have different wall structures because they are subjected to different pressures.*
- *The blood vessels of the heart move both longitudinally and transversely with each heartbeat.*
- *Wall distensibility relates to the mechanical behaviour of the blood vessel.*
- *Blood vessel walls have non-linear stress-strain curve.*
- *Ventricular systole increases the pressure the outflow arteries are subjected to.*
- *Venous pressure is not as affected by systole or diastole.*
- *The coronary vessels are even more affected by systole and diastole because they are attached to the myocardium.*
- *Blood pulses out of the heart; it is not a steady flow.*
- *Velocity of blood flow is greater in the centre of the vessel than at the walls.*
- *The endothelial layer of the blood vessel prevents clotting and thrombosis.*
- *Haemodynamic issues may be observed at the site of anastomosis, so geometry of the anastomosis is important.*
- *Valves should open in one direction only.*
- *Pressure gradient and regurgitation have to be controlled.*

4.2 Materials Used in the Construction of Artificial Conduits

In order to perform exactly like a native blood vessel, the perfect artificial vascular graft or conduit would need to meet certain criteria. It would need to be capable of taking in and recognising signals and providing feedback, respond accordingly to haemodynamic and chemical dynamics, as well as secrete the chemicals a normal blood vessel would. Ideally, artificial blood vessels would be able to heal themselves as normal blood vessels would and they would not create any immunological reactions or difficulties. They would be long-lasting and durable, have a low resistance pathway and low compliance mismatch. The perfect artificial conduit would not cause thrombosis or infections and it would be readily available for emergency surgeries. If implanted in a child who is still growing, as most vascular grafts for congenital heart defects are, it would increase in length and diameter over time, to match the growth of the surrounding anatomy and meet the increasing circulatory needs of the child. As yet, this long list of criteria has not been completely fulfilled in any artificial conduit, and the devices that have been developed are compromising between the perfect conduit and meeting the needs of the patient, given the available materials and technology. (Kakisis et al 2005).

Creating a conduit that will move and grow with the patient is a huge challenge. It could potentially be achieved by the use of stem cells and progenitor cells in tissue engineered vasculogenesis. If a tissue engineered vascular graft was achieved, the degenerative and immunological issues would be the main problems to overcome. (Leor et al 2006). This will be discussed in more detail in Section 7.1 Vascular Cell and Tissue Engineering. However, this technology is currently not sufficiently advanced to be of clinical benefit and tissue engineered grafts are not yet widely available. Vascular grafts made of synthetic materials are still the devices of choice for the treatment of congenital heart defects requiring any repair or replacement of the great vessels. In addition, in the event that a tissue engineered graft were available, synthetic grafts would still be required. It is not feasible for a new-born to wait for a tissue engineered graft to be harvested when there are other readily available materials. Synthetic conduits will always be needed, maybe eventually just as palliation, if the end goal is to implant a tissue engineered graft.

4.2.1 Synthetic Materials

Voorhees, Jaretski and Blakemore (Dennis et al 1987, Thompson 2008) reported the use of Vinyon-N cloth tubes as artificial conduits in dogs with arterial defects in the labs of Columbia University in New York in 1952. The cloth was taken from a piece of synthetic fine-woven clothing. In 1954 Blakemore and Voorhees applied it clinically but it proved not to be effective enough. Despite this failure, this work paved the way for future developments in synthetic vascular graft technologies. (Dennis et al 1987, Thompson 2008).

Nylon, as the synthetic material of choice for artificial conduits, soon followed in 1955. The prosthesis was designed by Sterling Edwards and J.S. Tapp devised a crimping technique to prevent blockage due to bending, but Nylon did not withstand the crimping (Thompson 2008). During this time (circa 1954) DeBakey and colleagues were coming up with a new material, Dacron. Dacron is still used as a synthetic material for vascular prostheses at present. (Thompson 2008)

DeBakey and colleagues developed the first polyethylene terephthalate (PET) vascular graft, more commonly known as the Dacron graft, in 1954 using a knitting machine. (Thompson 2008). This led to the production of grafts of various sizes, shapes and porosities, with and without internal and external velour. Dacron has proven to lose very little of its tensile strength over time, with the majority of it, 20%, being lost during initial integration with the surrounding tissue. (Dennis et al 1987). A Dacron vascular prosthesis is shown below in Figure 40.

Figure 40 - Dacron vascular Prosthesis (Cleveland Clinic 1995)

Expanded polytetrafluoroethylene (ePTFE), also known as Teflon, is another polymer used in vascular grafts. It has a low level of friction on its surface and was first developed for industrial purposes, such as the sealing of pipes containing reactive uranium.

It is made up on nodules linked by fibrils, the lengths of which are controlled in the manufacturing process. It is the length of the fibrils that influences the healing of the ePTFE graft. It is quite thrombogenic, and thrombus formation can be seen on the lumen after anastomosis to the native vessel. An external ring supports the graft and prevents compression or folding. (Tomizawa et al 2003). An ePTFE graft is shown in Figure 41 below.

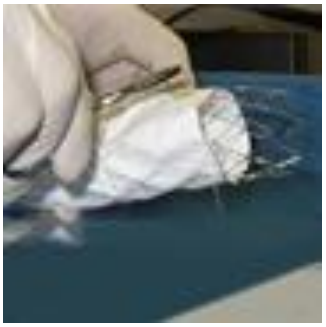

Figure 41 - ePTFE Graft (Philips Scientific 2011)

The Gore-Tex vascular graft developed by Gore Medical, shown in Figure 42 below, is made of ePTFE.

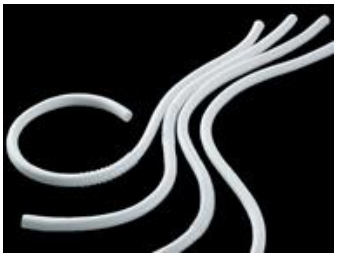

Figure 42 - Gore-Tex Vascular Graft (Gore Medical 2002)

Velour on synthetic grafts is made by knitting the grafts in a particular way to cause fabric loops on the surface. On the internal surface, this allows a greater surface area for endothelial cells to embed themselves into. On the external surface, fibres and tissue close by or touching the graft can lodge themselves between the velour fibres to give the implant more strength. (Monaghan et al 2007).

Both Dacron and ePTFE grafts are mainly used as prosthesis for large and medium sized vessels. (Kaye et al 2008). They are the most commonly used materials for vascular grafts (Yasim et al 2006). They both exhibit the strength necessary for pressure loads *in vivo*, but there have been instances in a small number of patients of aneurysms, fibre breakdown and rupture over time. (How et al 1992). Dacron and PTFE normally fail when

used as prosthesis for small diameter vessels; this is due to their low levels of wall distensibility in comparison to native blood vessels (How et al 1992) and the fact that thrombosis occurs with these materials, so the small diameter is more likely to become blocked (Monaghan et al 2007). This makes them a sufficient prosthesis for conduits in paediatric heart surgery where they could be used as material for shunts of approximately 5mm. For example a typical RV-PA conduit made of PTFE is 5mm in diameter (Sano et al 2004). This is shown in Figure 43 below.

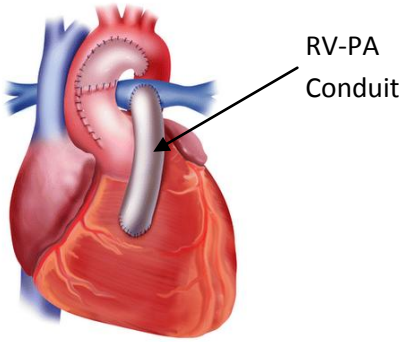

Figure 43 - RV-PA conduit made of PTFE (Blogspot 2010)

In a comparative study of the susceptibilities of gelatin-sealed Dacron prosthesis and PTFE prosthesis to infection of MRSA, it was shown that Dacron prostheses are not more susceptible to the bacterial infection (Yasim et al 2006). MRSA (methicillin-resistant Staphylococcus aureus) is a bacterium that infects cuts, so the anastomosis of a prosthesis to the native tissue can cause this bacteria to grow and an infection to occur. Vascular graft infections are not common and only occur in 0.5-6% of implantations (Yasim et al 2006). The belief, based purely on *in vitro* studies, is that Dacron grafts are more inclined to cause an infection than PTFE grafts. But this preference of PTFE grafts over Dacron is not based on clinical evidence. Yasim et al 2006 conducted an *in vivo* study on rats to compare the two materials and this study concluded that not only was Dacron not more susceptible to MRSA infection than PTFE but the new generation of gelatin-sealed Dacron proved to be less so. (Yasim et al 2006).

The extra-cardiac conduit of the complete Fontan procedure, shown in Figure 44, typically uses a Gore-Tex (PTFE) graft and has yielded positive results with a low amount of reoperations. However exercise is still a matter of concern after this procedure especially

using a synthetic graft, and also lacks the ability to grow, both longitudinally and transversely. (Ochiai et al 2010). This will be discussed in more detail in Chapter 6.

A study was conducted by Ochiai et al 2010 to determine if the growth in the autologous vessels above and below the Gore-Tex graft in this extra-cardiac procedure could compensate for the fact that the artificial conduit could not increase in length or diameter. The study was performed on 34 patients who were observed from the procedure at infancy to the age of 5.1 years. The length of the superior vena cava to the site of conduit anastomosis was seen to increase by 15% and the length of inferior vena cava to the site of anastomosis to the conduit was shown to have grown by 24%. The study concluded that the longitudinal growth above and below the artificial conduit graft was substantial enough to compensate for the lack of growth in the conduit itself. (Ochiai et al 2010).

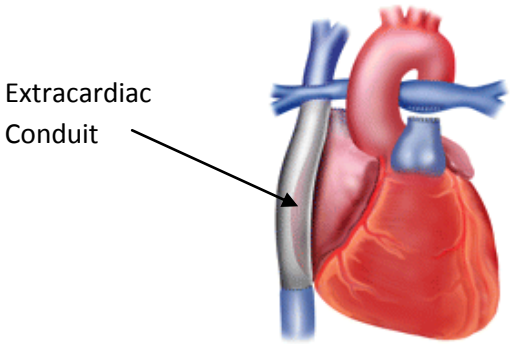

Figure 44 - Extracardiac Conduit anastomosed to superior vena cava and inferior vena cava (Radiology 2011)

4.2.1.1 Anastomic Site

Neointimal anastomotic hyperplasia (NIH) is when thrombosis, clot formation, platelet adhesion occur and growth factors are released at the site of anastomosis. It tends to be more prominent at the outflow end of the prosthesis, due to the direction of flow of blood components. (Monaghan et al 2007). One method of avoiding NIH is to use a pre-endothelialised vascular prosthesis. This ensures the surface of the graft is less thrombogenic. (Monaghan et al 2007). A graft with internal velour would be ideal to endothelialise.

Scar tissue can build up at the site of anastomosis and cause narrowing of the lumen. Scarring is a normal part of healing and is caused by the build-up of fibrous tissue around the surgical site. On account of reoperation, the fibrous build-up becomes more and

more. The use of absorbable sutures and haemostatic agents can help prevent the development of scar tissue at the site of anastomosis. (Hickey et al 2011). Scar tissue can expand into neighbouring tissue if the tissue was damaged during surgical intervention. (Hickey et al 2011)

4.2.2 Biological Materials

Biological grafts for vascular prosthesis are classed into three different types: heterografts, homografts and autografts. Autografts use autogenous materials to create the graft, for example removing the patient's own saphenous vein and using it as the replacement cardiac conduit. Homografts are of the same principle but they use a donor's vein, usually deceased, instead. The patient must remain on immunosuppressant drugs so as not to reject the donor vein. A heterograft uses material from another species for example the bovine jugular vein or bovine carotid artery, immunosuppressant drugs are also needed here. (How et al 1992). Integration of the various types of biological grafts, autografts, homografts and heterografts, will be discussed in more detail in section 3.3 Valves. Here it will be shown how one type of biological material can be used in the conduit and another type of biological material can be used in the valve.

4.2.2.1 Autografts

Autografts were first used by Alfred Blalock in 1944 when he anastomosed the left subclavian artery to the left pulmonary artery as palliation for Tetralogy of Fallot. (How et al 1992). The benefit of using the patient's own native blood vessels is that there are no immunogenicity issues, so the patient does not need to consistently take immunosuppressant drugs as there is no risk of rejecting the graft. It also has the potential to grow along with the child's own somatic growth (Elkins et al 1994). Another benefit is that there is no requirement for anticoagulation medication as there is with synthetic materials, particularly those containing metal e.g. mechanical valves or stents. (Elkins et al 1994).

The great saphenous vein has been commonly used as an autogenous graft particularly in coronary bypass surgery for example for relief of aneurysms caused by Kawasaki disease in paediatrics. (Leather et al 1987, Mavroudis et al 2004). This is due to its availability and convenient length and diameter. It is considered a standard graft that all

other grafts should ideally match (Leather et al 1987). The location of the saphenous vein is shown in Figure 45 below.

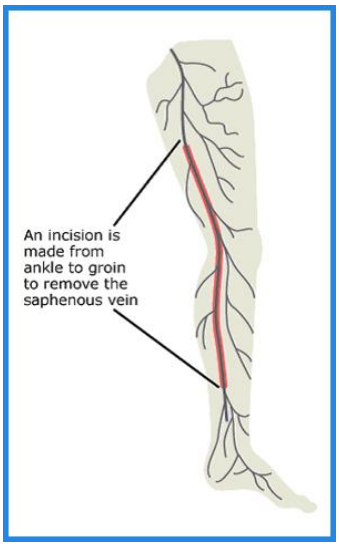

Figure 45 - Human Saphenous Vein (Heart Healthy Women 2011)

The internal iliac vein, the internal mammary artery, the radial artery and the hypogastric artery can all also be used as biological grafts. Although it is advantageous with regards degradation and immunogenicity issues to use the patient's own vessels as grafts it is not always feasible. For the child to grow up healthy, it is more beneficial to use a deceased donor vessel instead.

4.2.2.2 Homografts

Gordon Murray in 1956 reported his use of a homograft, also known as an allograft, for transplant into the descending aorta. This paved the way for developments in the use of homogenous material for artificial conduits. Allografts are grafts made from homogenous material, i.e. they come from the same species as the patient. Generally the conduit is harvested from a deceased donor and is then cryopreserved where the graft has been preserved chemically in very low temperatures to ensure no cell death. Unfortunately, however, the age groups in most need of allografts; neonates, infants and young children, showed that the durability was not adequate enough. (Elkins et al 1994).

Although it is true that allografts do not require anticoagulation drugs, they do experience a faster rate of deterioration in paediatrics due to calcification and immune rejection. This is true even for cryopreserved homografts. (Elkins et al 1994). The patient

must therefore take immunosuppressant and anticalcification drugs to delay the deteriorations.

It was once considered that cryopreserved allografts did not require immunosuppressant drugs. This was because the allografts were exposed to certain chemicals that killed off endothelial cells during cryopreservation. But this has since been disproven. (Hopkins 2006).

The human umbilical vein has been used as an allograft for vascular prosthesis. It has been extracted from an expectant mother during a planned caesarean section. The advantage of this is that the vein contains foetal tissue and therefore has the ability to grow. It is not yet proven whether the human umbilical vein can withstand the pressures it would be susceptible to when used as an arterial graft. (Hoenicka et al 2006). The human umbilical vein is shown in Figure 46.

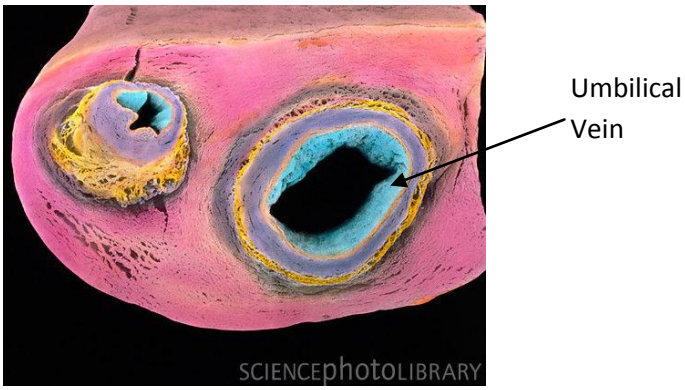

Figure 46 - Human Umbilical Vein on the right hand side. (The umbilical cord is on the left hand side) (Science Photo Library 2011)

4.2.2.3 Heterografts

Heterografts, or xenografts, are prosthetic grafts harvested from donors of another species, i.e. heterogonous material. Typically bovine or porcine biomaterial is used but it has been reported that equine pericardial tissue as a biological prosthesis was successfully implanted into a 40-day old infant for reconstruction of the right ventricular outflow tract as part of repair of Tetralogy of Fallot. (Roan et al 2006). As with allografts, xenografts are also susceptible to immunogenicity issues and calcification issues.

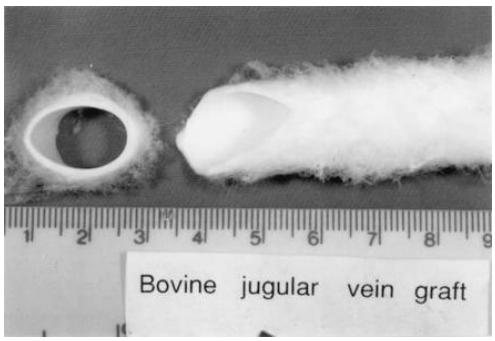

Figure 47 - Bovine Jugular Vein Graft (JTCS 2011)

The inhibition of calcification of the bovine vascular graft has been explored where it controls the release of the anticalcification agent ethanehydroxy diphosphonate. This has proven to be successful in testing in rats and sheep where pre-treated prosthesis lasted longer against calcification degeneration than prosthesis without ethanehydroxy diphosphonate (Johnston et al 1990). The Contegra graft is a bovine jugular vein graft, as shown in Figure 47, uses the internal valve of the vein in the replacement conduit. It is typically used as a replacement for outflow tracts.

Key Points:

- *The perfect artificial vascular graft needs to perform exactly like a native blood vessel.*
- *Creating a conduit to move and grow with the patient's own somatic growth is still a huge challenge.*
- *Vinyon-N cloths were the first synthetic grafts used.*
- *Crimping in nylon grafts was developed to prevent kinking.*
- *Dacron (PET) invented in 1954 is still commonly used in vascular grafts today.*
- *ePTFE is a low friction polymer used in vascular grafts.*
- *Internal and external velour help to anchor the graft.*
- *Both Dacron and ePTFE have low wall distensibility levels.*
- *Gelatin-sealed Dacron is less susceptible to MRSA infection than ePTFE.*
- *NIH and scar tissue build-up can occur at the site of anastomosis.*
- *An autograft is a graft harvested from the patient.*
- *A homograft or an allograft is a graft harvested from another human.*
- *A heterograft or xenograft is a graft harvested from another species.*

- *The bovine jugular vein graft is a xenograft that is commonly used for an RV-PA conduit.*

4.3 Valve Conduits

The purpose of a valve is to prevent flow in the wrong direction. For a heart valve, when the blood pressure on the correct side of the heart is high enough, blood will be forced through the valve. When the chamber preceding the opening of the valve is full, the valve will close preventing backflow. Due to the design of the valve and the direction the leaflets point in, the valve should not open backwards. Regurgitation is when flow is reverse due to a leaky valve, leaflet prolapse or sudden change in the size of the chambers. Prevention of regurgitation but maintenance of an acceptable pressure gradient across the valve is important in the design of valves for prosthetic use. (Loushin et al 2009).

Since the 1960's, heart valve prostheses have been successfully incorporated in cardiovascular surgery. Despite the many years of design experience since, not all problems associated with the design of viable heart valves have been eradicated. (Yoganathan et al 1992). There are a few different types of artificial valves available for implantation, some are mechanical and some are biological. Both have advantages and disadvantages which can be quite different between adults and children. The intake of drugs such as immunosuppressant, anticoagulation and anticalcification are not ideal for a growing child. Thrombosis, scar tissue overgrowth and damage to red blood cells are all problems we still face. Different valves are suitable for the four different valve replacement positions in the heart. (Husain et al 2007).

4.3.1 Mechanical Valves

Mechanical valves come in a few different designs: ball and cage; tilting discs; and bileaflet. The ball and cage design is considered the original mechanical prosthetic valve; it was developed by Hufnagel in 1952 and became available commercially in 1961 as the Starr-Edwards valve. Due to the high pressure gradients experienced across this valve, high thrombosis issues and large and awkward size it is rarely used. (Teijeira et al 1992, Yoganathan et al 1992). The Bjork-Shiley and Lillehei-Kaster tilting disk valves were introduced in 1969 and 1970, respectively. Both designs incorporate a free floating disk concept, where the disk tilts relative to the constraints it is held in. a small amount of regurgitation is allowed to reduce thrombosis. (Teijeira et al 1992, Yoganathan et al 1992).

The bileaflet valve developed by St. Jude Medical in 1978 has proven to be the most popular mechanical valve due to its appropriate revels of pressure gradient and regurgitation. (Teijeira et al 1992, Yoganathan et al 1992). It is shown below in Figure 48.

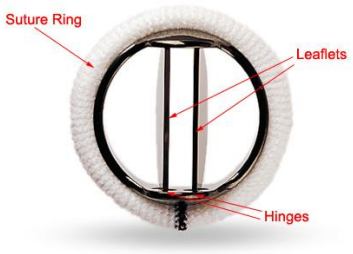

Figure 48 - St. Jude Bileaflet Mechanical Heart Valve (WegoHealth 2011)

The advantage of a low pressure gradient is that the heart does not have to work as hard to pump the blood. However, problems such as the need for anticoagulation drugs in the long term and a high level of regurgitation are constantly present with mechanical valves. (Husain et al 2007).

Bileaflet pyrolytic carbon valves are the most popular valves for mitral valve replacement. This is due to the high calcium deposits that can pass through the mitral valve position, so despite the life-long anti-coagulation therapy required by the bileaflet valve, bioprosthetic xenografts and mitral valve homografts have shown to only last 3 to 5 years in this position. (Husain et al 2007). However a failure to keep a viable level of anti-coagulation throughout life, beginning at such a young age will always be an issue in paediatrics (Elkins et al 1994).

Mechanical valves have been used in the pulmonary position for older children, however due to the high levels of anticoagulation drugs required they are usually just implantation in patients with another mechanical valve already implanted. (Husain et al 2007).

Pulmonary valve replacement is sometimes only necessary if a pulmonary autograft was used for aortic root or mitral valve replacement. This right ventricular outflow tract reconstruction has been achieved using a Gore-Tex monocusp valve. Since 1994 Husain et al 2007 have implanted Gore-Tex monocusp valves into 192 patients with 10 cases of reoperation. Freedom from reoperation of 92% has been reported at the age of 10 years. (Hussain et al 2007)

4.3.2 Biological Valves

Biological valves harvested from human or animal tissue became popular in the 1970's due to their lower incidence of thrombosis and subsequent disregard for anticoagulation drugs. (Yoganathan et al 1992). Biological valves operate in the same way as the native human semilunar valve would, that is the cusps depend on each other for support so as not to open backwards. Most often a trileaflet valve would be used to replace any failing valve. Trileaflet valves experience very little regurgitation due to their biological structure but pressure gradients can be high and calcification could occur if homogenous or heterogonous material as opposed to autogenously sourced material is used particularly in children. (Yoganthan et al 1992, Nimni et al 1992, Javadpour et al 2002).

Figure 49 - Biological Heart Valve (Heart Valve Interactive Corp. 2011)

Bioprosthetic valves proved to be more successful in the tricuspid valve position than in another position for cardiac valve replacement in paediatrics. The Mayo Clinic reported after a 25-year study of tricuspid valve replacement for repair of Ebstein's anomaly, that 97.5% of patients were free from reoperation after 5 years. (Husain et al 2007). Furthermore Guerra et al 1990 reported that 38 out of 45 patients who received porcine bioprosthetic valves in multiple cardiac valve locations showed less calcification and less degradation in the tricuspid valve position. (Husain et al 2007).

The pulmonary autograft replacement of mitral valves uses a composite structure, a structure that uses different materials for the valve and conduit, where the biological valve is sutured into a synthetic material. (Husain et al 2007). This can be seen in Figure 50 below. Husain et al 2007 reported no deaths in their study and very little regurgitation. Resizing of the Dacron graft for the support of the autograft is a necessity for autograft mitral valve replacement success.

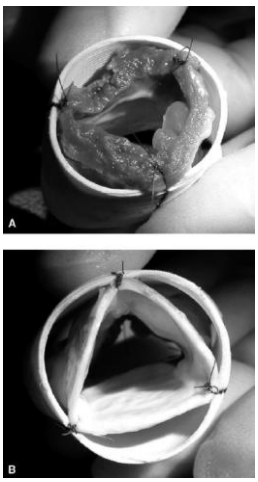

Figure 50 - Composite autograft construction. A: Proximal end of autograft valve in Dacron conduit. B: Distal end of autograft valve in Dacron conduit (Husain et al 2007)

Elkins et al 1994 reported the use composite structure of a pulmonary autograft sutured into a cryopreserved allograft for aortic root replacement in paediatrics with a 92% freedom from reoperation. The right ventricular outflow tract was reconstructed using a cryopreserved homograft of either pulmonary or aortic origin. Normal growth measurements of the aortic annulus were observed at yearly intervals. (Elkins et al 1994). The Ross procedure is used for aortic root replacement. (Husain et al 2007).

A valved saphenous vein homograft has been used for construction of an RV-PA conduit. (Reinhartz et al 2006). The saphenous vein as a conduit was spoken about in Section 4.2.2.1.

A bovine jugular vein called the Contegra bovine conduit was first used as an RV-PA conduit in the United States in 2002. No post-operation anticoagulation is necessary and it exhibits less regurgitation than a pulmonary homograft. It is also cheaper to harvest and prepare than the homograft. A study of the Contegra bovine conduit by Husain et al 2007 shown that only 1 out of 85 patients suffered a conduit related aneurysm and all other deaths were not conduit related. Also, only 7 out of the 85 patients have required reintervention to relieve stenosis of the conduit. (Husain et al 2007). The Contegra conduit is shown in Figure 51.

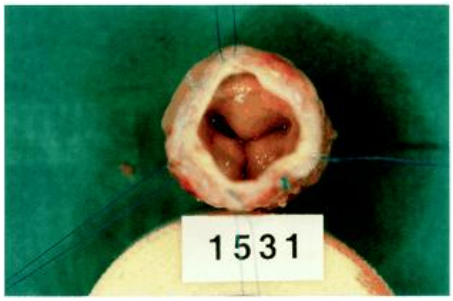

Figure 51 - A Contegra bovine conduit (JTCS 2011)

Key Points:

- *A valve should open only one direction and prevent backflow.*
- *Leaflet prolapsed causes regurgitation.*
- *Anticoagulation medication is necessary if a mechanical heart valve has been implanted.*
- *Immunosuppressant and anticalcification medication are necessary for both xenografts and allografts.*
- *Mechanical valves have a lower pressure gradient than biological valves.*
- *Biological valves have less regurgitation than mechanical valves.*
- *Mechanical valves perform better in the pulmonary position and the mitral valve position.*
- *Porcine bioprosthetic valves are used for repair of Ebsteins anomaly.*
- *A composite structure is when one type of valve is sutures into a different type of conduit.*

Chapter 5: Prenatal Detection of Congenital Heart Defects and Prevention

Due to technological advances in the fields of ultrasound imaging and foetal intervention, it is possible that the severity of congenital heart disease can be altered for certain defects through the method of intrauterine intervention. However the timing and techniques of these interventions is still debatable. (Salman et al 2009, Weber et al 2011). Despite these advancements in foetal cardiac intervention, the outcome of foetuses detected to have congenital heart defects is not always certain. (Gardiner et al 2005, Hsiao et al 2007). This is due in part to the presence of the congenital heart defects themselves and the extracardiac and chromosomal issues that frequently accompany them. (Hsiao et al 2007, Formigari et al 2009).

An example of early detection and intervention is the method used for hypoplastic left heart syndrome. The approach of intrauterine intervention in this case is the attempt to lower venous pressure by draining the venous return, thereby preventing the overdevelopment of the wall of the left ventricle. This hypoplastic left heart syndrome was diagnosed in the foetus due to a lack of communication by Doppler waves across the atrial septum. (Stoll et al 2002, Salman et al 2009).

5.1 Echocardiogram

An echocardiogram (ECG) is the method of application of Doppler ultrasound to gather data regarding size of heart, velocity of blood, absence or damage to cardiac tissue. It allows medical professionals to see if something is wrong within the foetus's heart. These results could depict issues in chamber development, valve development and great vessel development. (Stoll et al 2002, Walther et al 2005). 2-dimensional ECG can diagnose congenital heart defects by looking out for all the components of a normal heart and identifies the anatomy of stenosis or failing valves. (Tam et al 2004, Vrecella et al 2004). An ultrasound scan during the 2nd trimester of pregnancy is now carried out in most prenatal care systems. (Stoll et al 2002). Figure 52 shows an echocardiogram, the chambers of the heart are clearly visible as well as the two atrioventricular valves.

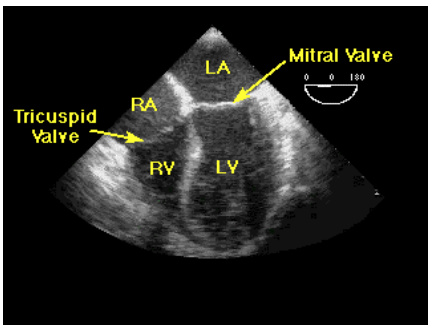

Figure 52 - Echocardiogram. RA: Right Atrium, LA: Left Atrium, RV: Right Ventricle, LV: Left Ventricle. The tricuspid and mitral valves are pointed out (Enc. Of Science 2011)

5.2 Intrauterine Foetal Intracardiac Intervention

Foetal balloon valvuloplasty has shown promise in aiding the development of the chambers of the heart. Opening any blockage or stenosis will allow more blood flow through that region and thereby improving its growth. (Gardiner et al 2005, Salman et al 2009). Despite these advancements in balloon valvuloplasty, it is not without its complications. Issues in the foetus such as bradycardia, pericardial effusion and haemorrhage have been reported as well as maternal issues with regards anaesthesia and uterine intervention. (Salman et al 2009).

After 50 days of embryonic development, the foetal heart has almost fully developed, except for minor septal formations still in progress. However it is not yet possible to image the heart by echocardiogram until the 2nd trimester. So the progression of some cardiac lesions is not feasible to intercept. Percutaneous access for foetal cardiac intervention usually involves echocardiogram guidance with the mother under anaesthetic. This is usually performed when the foetus is between 21 to 30 weeks old. (Gardiner et al 2005). The typical percutaneous administration is through the uterine wall and into the foetal chest. It is then guided directly to the site of the defect. Different equipment is needed for the different valves of the heart since the pulmonic valve is anatomically greater than the aortic valve. (Gardiner et al 2005, Weber et al 2011). A balloon catheter deployed to the mitral valve position is shown in Figure 53 below.

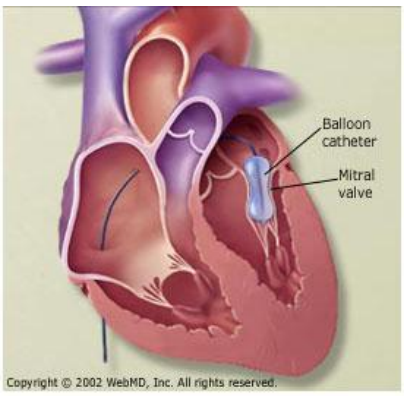

Figure 53 - Balloon catheter in Mitral Valve position (WebMD, Inc. 2002)

5.3 Prenatal Heart Valve Implantation

Whether it is technically feasible to implant a heart valve as minimally invasive as possible into a developing foetus is still under research. Prenatal cardiac intervention with the deployment of an appropriate heart valve can significantly decrease need for further neonatal intervention. These studies have thus far only been conducted on three sheep. The method of catheter deployment was by opening the foetal chest and feeding the catheter through the ductus arteriosus and into the aorta. The deployment of the stent was successful in the three sheep foetuses but the addition of the new device was not received well by any of the foetuses and blood loss was an issue. (Weber et al 2011)

The implantation of heart devices into the foetus, whether heart valve, stents or conduits is a viable area for future development. It would improve foetal heart growth and development. The main issue, assuming deployment was carried out effectively, is whether the foetus accepts the new material or not. (Weber et al 2011). Stent deployment in the pulmonary position is shown in Figure 54 below.

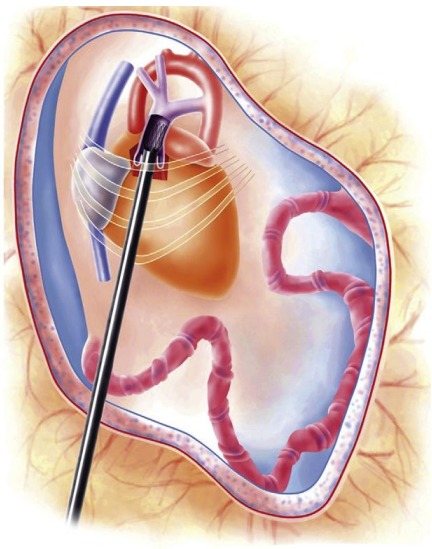

Figure 54 - Stent Deployment to the distal part of the pulmonary trunk (Weber et al in press)

Key Points:

- *Ultrasound imaging is used to detect congenital heart defects in the foetus.*
- *Intrauterine foetal intracardiac intervention is the method to attempt to repair congenital heart defects in the developing foetus.*
- *Percutaneous access is done under the guidance of an echocardiogram through the uterine wall and through the foetus's chest.*
- *Prenatal heart valve implantation attempts to remedy heart valve problems in the developing foetus.*

Chapter 6: Technical Challenges and Limiting Factors with Artificial Conduits

6.1 Porosity

The permeability or porosity of the wall of a blood vessel is important in the transfer of small molecules in and out of the conduit. This is controlled by how closely the endothelial cells lining the blood vessel are packed together. (Martini 2009). With regards to biological prosthesis, particularly of autogenous and homogenous origin, porosity is not a concern during implantation. The concern is with regards to synthetic material. If the material is too porous then too much of the content of the conduit will be lost and if it is not porous enough it could be more susceptible to infection. High porosity grafts are better at healing. (Phifer et al 1992). Ideally a pore size should be between 10µm and 45µm to ensure correct ingrowth of capillaries and binding to the surrounding tissue. Above this boundary no ingrowth will occur and below this boundary unwanted tissue will drift into the conduit. (Turner et al 1987).

When it comes to Dacron, knitted grafts are more porous than woven grafts. Dacron can come with external velour to attract more particles to it so as it adheres sufficiently to the surrounding tissue. Some knitted grafts may be pre-clotted with the patient's own blood to make them more biocompatible and more familiar to the surrounding tissue. Woven grafts are usually sealed by soaking them in albumen so as the protein binds the threads together just enough for the right size pores. (Phifer et al 1992).

PTFE grafts are not pre-clotted. Instead, the finely selected lengths of fibrils obtain a typical pore size of 30µm to ensure optimum tissue ingrowth. It has been observed that due to the lack of pre-clotting of PTFE grafts; they are less susceptible to thrombosis formation than Dacron grafts. (Turner et al 1987, Phifer et al 1992).

6.2 Repair of Damaged Conduits

If a conduit was to fail due to stenosis or rupture thereby rendering it useless, would it be more worthwhile to repair the existing conduit in as minimally invasive a procedure as possible instead of complete replacement of the conduit? (Buz et al 2008). In 1988, the death of a 22year old woman, who had received an extracardiac conduit at the

age of 7 for repair of truncus arteriosus, was reported. The conduit was made of Dacron and contained a porcine aortic valve. Five months before the patient died, she suffered trauma in a car accident that, upon autopsy, was discovered to have caused a rupture in the Dacron artificial conduit causing thrombosis and subsequent compression of the tube. This caused right ventricular obstruction leading to heart failure. (Ursell et al 1988).

Repair of a rupture if caught early enough, unlike the case reported by Ursell et al in 1988, can be treated by a stent to prevent stenosis, or by a patch deployed by a catheter and stent system. Although, in paediatrics, if the rupture happens at a very young age there still might be a need for open heart surgery instead of catheter deployment due to the small size of blood vessels.

Aggarwal et al (2007) reported successful stent placement in 90% of patients for repair of stenosis of RV-PA conduits. 29% of these patients remained free from re-intervention as the conduit stayed open. (Aggarwal et al 2007). Endovascular stent graft can be deployed without aortic clamping, although results in pigs have shown that the use of endovascular stents inhibits aortic growth, which is not suitable for children. Complete reoperation remains to be the safest method of repair of damaged conduits in paediatrics. (Buz et al 2007, Siegenthaler et al 2008).

6.3 Reoperation

Artificial conduits are not always a long lasting solution in paediatrics. Due to the growth of the child, before the age of 10 there could be approximately 3 operations to replace the conduit. These reoperations have to occur because the patient is still growing and will outgrow the conduit. Surgical replacement is often a necessity due to factors such as obstruction of the conduit, deterioration of the internal valve or growth of the patient. (Aggarwal et al 2007). After the age of 10, growth slows down considerably meaning the patients larger blood vessels allow percutaneous deployment to repair the conduits.

One of the most prevalent reasons for reintervention and reoperation is stenosis of the conduit. Endovascular stent placement, instead of replacement of the entire conduit, is suitable here provided it is possible to get there percutaneously. (Aggarwal et al 2007). Other such factors requiring reintervention are arrhythmias, regurgitation of the conduit, cyanosis, and ventricular dysfunction. (Petko et al 2003).

The European Association for Cardio-Thoracic Surgery (EACTS) Database lists a 2.8% 30-day mortality rate for conduit reoperation and also a 2.8% morbidity rate. (EACTS Congenital Database 2011). This is a low figure; however the morbidity and mortality could be caused by more damage to the site of operation and the development of scar tissue as well as infective endocarditis.

A study of 1220 consecutive children being operated on by Dr. James L. Monro between 1976 and 2001 showed that 171 patients had to have reoperations. Of these reoperations 15% were planned. The 20-year freedom from reoperation was 83%. The majority of reoperations are inevitable in children with congenital heart defects because it is known that the child suffers from a progressive disease. (Monro et al 2003).

6.4 Compression and Competition for Space

Compression of a vascular graft can also be the cause of need of reintervention. The reason compression might occur in the first place is that as the heart develops abnormally, it fills out the necessary space it needs. All surrounding tissue fills out the rest of the space; no cavity is left for the conduit so competition for space for an artificial conduit is inevitable. A method of preventing or at least resisting compression for synthetic grafts is by controlling the fibrin depth. This in turn affects either the size of the lumen or the external diameter of the conduit. (Sauvage et al 1987). The extracardiac conduit of the Fontan procedure shown in Figure 55 is more susceptible to compression than the lateral conduit of the Fontan procedure.

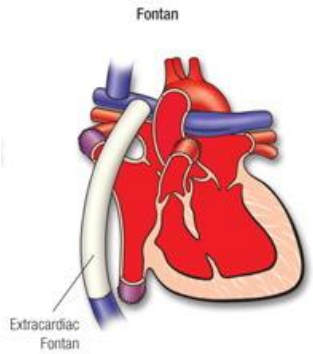

Figure 55 - Extracardiac conduit of Fontan procedure at risk of compression (American Heart Ass. 2011)

6.5 Calcification

Degradation and degeneration of a conduit, whether biological or synthetic, is inevitable. For biological conduits calcification due to degradation is a factor. The loss of elasticity of the wall and breakdown of muscular components make the vessel more at risk of calcification due to the gathering of calcium deposits. (Nimni et al 1992). The cardiovascular system is one of the most commonly affected areas of the human body by calcification. Calcification at the site of anastomosis of a conduit to native vessel is very common due to small crevices that calcium deposits can sit into. Calcification is most associated with homograft devices. Despite the popularity of cryopreserved or antibiotic preserved homograft conduits and valves due to their ease of storage and hence their availability, calcification is less prevalent in beating-heart donated homografts. This is due to their improved cellular viability, which in deceased donors has decreased by 65%, 48 hours after death. (Javadpour et al 2002). Figure 56 shows a calcified homograft valve. It is clear that the leaflets of the valve can no longer function and close correctly.

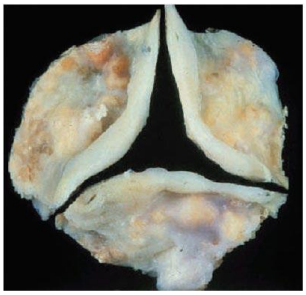

Figure 56 - Calcified Valve (Cardiogram Central 2010)

6.6 Post-operative Concerns

Repair for defects such as hypoplastic left heart syndrome requires the right ventricle to pump the blood for systemic circulation. This is not usually a problem until adulthood when exercise tolerance decreases for survivors of this procedure and the right ventricle cannot pump hard enough to meet requirements. Heart failure may result. (Woods et al 2003).

In comparing the two forms of Fontan procedures, total cavopulmonary connection and atriopulmonary anastomosis, it is beneficial to know which one will withstand exercise or exertion in later life so as the patient can lead as normal a life as possible. Podzolkov et al

1997 compared the two by a clinical study of 81 total cavopulmonary connections and 69 atriopulmonary connections. The results yielded a lower mortality rate for the total cavopulmonary connection but the atriopulmonary connection had better long-term tolerance of exercise. (Podzolkov et al 1997).

Complications concerning palliative shunt procedures may involve excessive flow through the shunt for the first few days after the procedure, which can eventually lead to congestive heart failure, due to volume overload on the heart. Post-operative intense observation of all procedures, especially these palliative shunt repairs, is extremely important. Thrombosis and infection of the shunts at the site of anastomosis is also a problem but more easily controlled. (Tsai et al 2005).

Postpericardiotomy syndrome occurs in 30% of paediatric patients who have undergone open heart surgery. It is a pericardial inflammatory response and results in fever. It may be as a result of an autoimmune response and the presence of antibodies but the reason is not entirely known. (Tsai et al 2005).

Infective endocarditis can occur on the endocardial surface at the site of anastomosis. It is as a result of increased pressure gradient and flow across the newly formed connection. Bacteria get trapped in the connection causing inflammation and infection. (Tsai et al 2005).

Key Points:

- *The transfer of molecules in and out of a blood vessel is determined by its porosity.*
- *A certain level of porosity is required for ingrowth of surrounding tissues, but too much and undesirable ingrowth occurs.*
- *Conduit repair patches or stents can be administered percutaneously.*
- *Complete reoperation is safer than repair.*
- *Due to the growth of the child, reoperation is a necessity.*
- *Stenosis and compression of the conduits also call for reinterventions.*
- *The extracardiac conduit of the Fontan procedure is susceptible to compression.*
- *Calcification of a material is due to the build-up of calcium deposits in crevices.*
- *Patients who have a redirected blood flow may suffer after over exertion.*
- *Infective endocarditis is an infection that can occur at the site of anastomosis.*

Chapter 7: Future for Artificial Conduits

7.1 Vascular Cell and Tissue Engineering

Cell and tissue engineering is an advancing technology in many medical fields. The aim of this evolving area is to create or repair tissues by the use of specialised cells and scaffolds along with growth promoting molecules or DNA to encode these molecules for growth and development (Leor et al 2006). New discoveries have indicated that stem cells are a viable source of building blood vessels and even heart muscle cells. So, in essence, an artificial conduit for replacement of a great vessel of the heart could possibly be built using stem cells along with the creation of engineered contractile cardiac tissue (Leor et al 2006).

Tissue engineering is carried out by isolating specific cells, either from the patient or a donor, and culturing them on a 3-dimensional scaffold. The scaffold, impregnated with the progenitor cells, is then implanted to the desired site in the patient's body. This scaffold acts as both a biological and mechanical support for cell and tissue growth (Leor et al 2006). An example of such a procedure was when Claudia Castillo received a bleached trachea scaffold that was seeded with her own stem cells, therefore immunosuppressant drugs were not necessary (Bessos et al 2010).

Paediatric congenital heart defects may require complete structural repair of the cardiac or coronary vessels as well as the myocardium. Although transplant and cardiovascular surgeries have proven to be viable methods of repair, the waiting lists for surgeries could be too long and morbidity and mortality remain risk factors. (Young et al 2008) Tissue engineering offers attractive prospects in the possibility of creating blood vessel substitutes by impregnating natural or synthetic scaffolds with autologous vascular cells and then transplanting the seeded tubular scaffold *in vivo*. This would be greatly appreciated in the field of paediatric cardiology since tissue engineered conduits have the potential to grow along with the patient. This would eliminate the need for anti-coagulation drugs, immunosuppressant drugs and reoperations due to synthetic materials that are otherwise used. But whether the tissue engineered construct can withstand vascular conditions is yet to be proven (Ju et al 2010).

7.1.1 Stem Cells

Stem cells are undifferentiated cells found in a living organism. They can be induced to become specialised cells of many different variations and they are capable of long term self-renewal. When a stem cell divides, the daughter cell has a choice: it can remain a stem cell or it can become a terminally differentiated cell. Stem cells are found either in an embryo or as undifferentiated cells in differentiated tissue in a developed human, these are somatic stem cells.

Somatic stem cells renew throughout the lifetime of the organism. Their main function is the regeneration of dying or damaged tissue. There are a number of different types of somatic cells for example haematopoietic stem cells found in bone marrow that give rise to new blood cells and neural stem cells found in the brain that regenerate damaged neurons. Endothelial stem cells are found in the bone marrow and have the ability to differentiate into endothelial cells for lining of blood vessel walls. (Alberts et al 2004)

Stem cells can be totipotent, pluripotent or unipotent. Totipotent stem cells are only found in the zygote, they can be manipulated to form any cell in the human body. Pluripotent stem cells are found in the inner cell mass of the blastocyst of an embryo. They can differentiate into many different cells like fat cells, neurons, smooth muscle cells etc. They have the potential to become all the cell types of a living organism. Unipotent stem cells only have the ability to produce a single cell type, an example are hepatocytes found in the liver. (Tuch 2006)

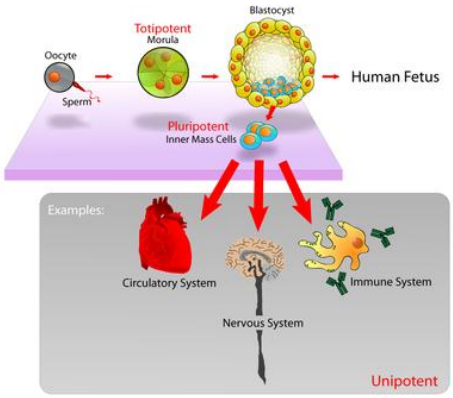

Figure 57 - Stem Cell Differentiation (Wikipedia 2011)

7.1.2 Progenitor Cells

Progenitor cells can be likened to adult stem cells because they are already pre-differentiated. Vascular stem cells are progenitor cells that have the potential to become either endothelial cells or smooth muscle cells. They are the main focus of study with regards cell and tissue engineering for blood vessels. The method of growth of blood vessels from endothelial progenitor cells is vasculogenesis. Angiogenesis is the growth of new blood vessels from already existing tissue. (Kane et al 2011). Both are depicted in Figure 58 below.

7.1.3 Vasculogenesis and Angiogenesis

Haematopoietic cells are found in the bone marrow and produce all blood cells. They also produce the vascular epithelial growth factor (VEGF) that causes vasculogenesis and angiogenesis. (Strunk et al 2006). There are two possible areas where vasculogenesis and angiogenesis can spring from: bone-marrow derived endothelial progenitor cells; and heart-originated cardiac progenitor cells. Both of these sources are being researched as possibilities for building blood vessels for use as artificial conduits. They can cause the growth of all cardiac tissue, like cardiomyocytes, endothelial cells and smooth muscle cells. Most of the research to date has focused on the regeneration of diseased adult cardiovascular systems, but the same principles could be applied to vasculogenesis for paediatrics. One of the latest advancements in stem cell engineering is the advent of induced pluripotent stem cells; this is where somatic cells are pumped with certain growth factors, including VEGF, to make them pluripotent (Kane et al 2011).

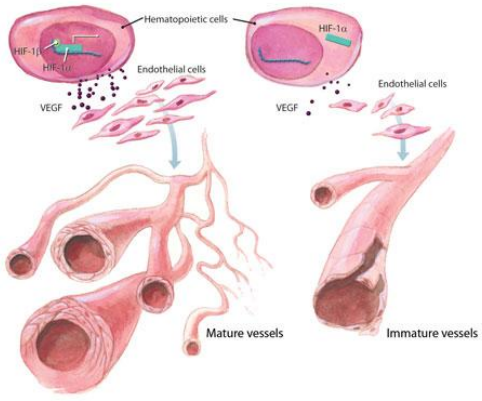

Figure 58 - Vascular Epithelial Growth Factor stimulates Vasculogenesis and Angiogenesis (R&D Systems 2011)

7.1.4 Growth Factors

Vascular epithelial growth factor (VEGF), platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) all influence the growth and development of blood vessels. These growth factors stimulate endothelial cell proliferation for the formation of new blood vessels. Both VEGF and bFGF have been injected into the myocardium of patients suffering from myocardium ischemia and subsequently the formation of new blood vessels and the perfusion of tissue was witnessed (Leor et al 2006). VEGF bound to a scaffold matrix induces the formation of new blood vessels from a transplanted tissue engineered blood vessel. Furthermore, crosslinking heparin with the scaffold assists in the release of the VEGF thereby increasing the potential of angiogenesis. (Singh et al 2011). VEGF and VEGF receptors are the first pathways to be signalled in the process for vasculogenesis and angiogenesis. Without the presence of VEGF an embryo will die after 8 or 9 days because the formation of a vascular system cannot occur. (Ribatti et al 2001 and Stegemann et al 2011)

7.1.5 Therapeutic Potential

Blood vessel growth occurs by vasculogenesis, angiogenesis and arteriogenesis (Valarmathi et al 2009). It is the hope that stem and progenitor cells can be used to initiate all three processes. In the last decade or so the proposition for the use of vascular progenitor cells for use in postnatal patients has been reported (Valarmathi et al 2009). By the use of animal models the use of pro-vasculogenic and pro-angiogenic cells has proven to be capable of therapeutic neovascularisation and re-endothelialisation of blood vessels (Kane et al 2011). Embryonic, foetal and somatic stem cells as well as endothelial progenitor cells of various origins can be considered for postnatal vascular engineering. The amount of growth factors and proteins and the physical structure of the scaffold matrix all have strong influences on the potential for vasculogenesis and angiogenesis of these engineered blood vessels. (Valarmathi et al 2009)

Engineered heart tissue has been investigated with promising results in rats and mice but experimentation is on-going. One such investigation is the implantation of neonatal rat heart cells into the myocardium of immune-suppressed rats by Zimmermann et al in 2006. 28 days after the implantation of the engineered heart tissue into the immune-suppressed rats improved cardiac function was observed. Vascularization and

differentiation of engineered heart tissue was observed. (Zimmermann et al 2006). Another area of study is the injection of embryonic stem cells and growth-factor free Matrigel into the mouse myocardium for repair of septal defects or ventricular defects. This study is being carried out by Kofidis et al since 2005. Both these research areas have yielded promising results in rodents. (Young et al 2008)

Autologous bone marrow derived stem cells have been implanted onto scaffolds for use in patches and conduits for children suffering from congenital heart defects. The study was carried out by Shin'oka et al and concluded in 2005. They tested the process in 42 patients born with congenital heart defects from the age of 1 to 24 years and followed the patients for 32 months. The tissue engineered conduits were used as the extracardiac conduit in Fontan completion and the tissue engineered patches were for repair of wall defects such as VSD. The results yielded no evidence of thrombosis or other blood clotting issues and calcification was not an issue. Growth results were neither positive nor negative; the diameter of some conduits increased and the diameter of other conduits decreased. It was surmised that the amount of blood flow through the conduits, relative to the intitial diameter, affected the growth; therefore larger vessels decreased transversely. (Shin'oka et al 2005). Some studies have identified problems with such tissue engineered grafts, where the strength of the material produced cannot withstand cardiac pressures. (Young et al 2008, Ju et al 2010)

For congenital defects that affect the heart valves, stem cells could be a method of improving the longevity of the implanted valve. They could grow and develop along with the patient and the need for mechanical valve replacements would be obsolete. The overall concept is that the valve is created *in vitro* and the stem cells are placed onto the valve scaffold and allowed to culture before implantation. (Young et al 2008) Sutherland et al 2005 have created a biodegradable synthetic scaffold seeded with bone marrow derived stem cells and implanted them in the pulmonary valve position in sheep. Over a 4 month period the sheep did not experience pressure gradient problems between both sides of the valve. 8 months after the implantation the valves showed promise of growing with the sheep's heart. (Sutherland et al 2005). Figure 59 shows a valve scaffold, it was a bovine valve that was bleached of its cells and is now ready for implantation of stem cells.

Figure 59 - Valve Scaffold (Wayne State Uni. 2010)

Bioengineered vascular prostheses have the potential to eliminate thrombosis and coagulation problems which lead to neointimal anastomotic hyperplasia regarding synthetic grafts. Endothelial cells grown in tissue culture can be used to pre-treat the internal surface of the synthetic graft. So far, this has not been successful, with only 10% of the cultured endothelial cells adhering to the synthetic surface during haemodynamic conditions. (Monaghan et al 2007). Precoating the synthetic graft with fibrin glue before attempting to attach the endothelial cells has shown improved results, but the majority of the endothelial cells are still lost during flow conditions. (Monaghan et al 2007).

7.1.6 Scaffolds

Tissue engineering requires a scaffold to bind the implanted cells together and physically support them so they can grow efficiently. The scaffold should be biocompatible, biodegradable, porous and durable (Valarmathi et al 2009). Various three-dimensional scaffolds that meet these requirements have been developed.

A tubular scaffold made of collagen type 1 was seeded with bone-marrow-derived mesenchymal stem cells and cultured for microvascular morphogenesis in the presence of the necessary growth factors. This particular scaffold met the conditions necessary for cell growth and development (Valarmathi et al 2009).

One method of building a scaffold is to de-cellularise the human saphenous vein by placing it in a solution of 0.075% SDS at 37^{o}C for 15 hours and then washing the vein with phosphate-buffered saline solution. (Harris et al 2009). This is called a “Ghost Vein”, which can be seen in Figure 60; it is completely free of cells. This removes the donor’s cells from the vein and allows implantation of the patient’s cells so as the need for immunosuppressant drugs is eliminated and there is a possibility of growth. The vein is then impregnated with the stem cells necessary for growth of a blood vessel. Ideally the stem

cells used would be the patient's own bone-marrow derived endothelial progenitor cells or cardiac progenitor cells. (Harris et al 2009).

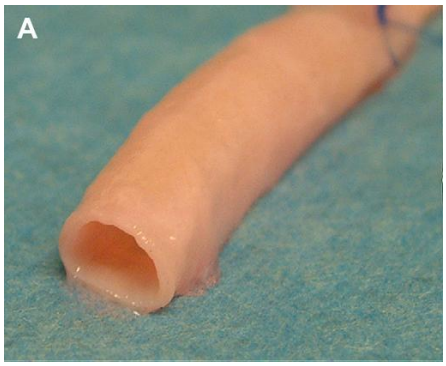

Figure 60 - Decellularised Human Saphenous Vein (Harris et al 2011)

A Multi-layer electrospinning technique has been used to create scaffolds that have the same tensile strength and mechanical properties as a native blood vessel would have (Vaz et al 2005). A biodegradable synthetic polymer based structure exhibits the necessary mechanical structure. Polymers such as poly-ε-caprolactone (PCL) and poly-lactic acid (PLA) have been used either on their own or in a bilayered structure, with PLA as the outer layer and PCL as the inner layer. The tensile properties observed showed that the bilayer scaffold was able to withstand up to 10% more of the tensile stress and strain experienced by a typical blood vessel. (Vaz et al 2005, Ju et al 2010).

Scaffolds can be mediated with vascular epithelial growth factor (VEGF) to encourage angiogenesis after implantation. Heperin-polcaprolactone scaffolds impregnated with VEGF have shown ingrowth of tissue through the scaffold and subsequent angiogenesis when implanted into mice by Singh et al 2010. The level of angiogenesis is dependent on the amount of VEGF implanted into the scaffold. (Stegemann et al 2007, Singh et al 2010).

7.2 Revolutionary Ideas

7.2.1 OptiFlo

The total cavopulmonary connection (TCPC) has its disadvantages with regards fluid dynamics and the flow of the blood through the conduit. The OptiFlo TCPC design connects both vena cava to both pulmonary arteries. It was developed with the aim of reducing the fluid mechanical power loss as blood flows through the TCPC. It was studied in comparison to a normal, unidirectional Fontan completion total cavopulmonary connection and it showed significant improvements in hydrodynamics. OptiFlo proved to be more tolerant of flow rate changes between all the connections than that of a unidirectional TCPC. (Soerensen et al 2007). The new OptiFlow configuration for TCPC can be seen in Figure 61.

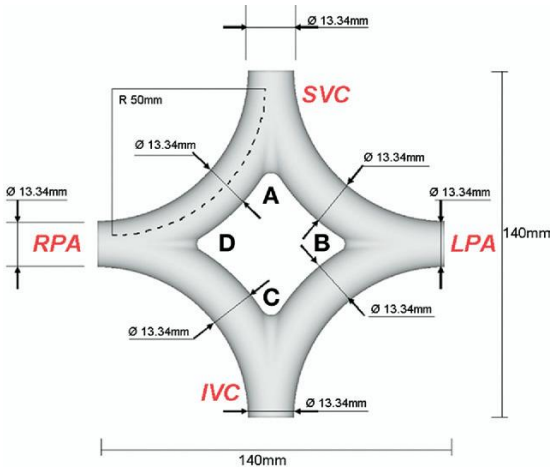

Figure 61 - OptiFlo Configuration for TCPC (Soerensen et al 2007)

7.2.2 Polymeric Heart Valves

Despite the use of mechanical and bioprosthetic valves for many decades, no substantial improvements in factors such as calcification, coagulation, durability or immunogenicity have been achieved with the use of these materials. (Kidane et al 2009, Ghanbari et al 2009). Prosthetic heart valves made with polymeric materials have the promise to avoid most of these issues (Ghanbari et al 2009). Polymers can be moulded and chemically softened to have the same flow characteristics as tissue valves, but in choosing which polymer, durability must be taken into account. Silicone and polyolefin rubber are not durable enough and PTFE is subjected to thrombosis and calcification. (Kidane et al

2009). Shown in Figure 62 is a polymeric valve sutured into a Dacron ring (Ghanbari et al 2009). Polyurethane heart valves have shown the most promising results, conquering issues such as biocompatibility, durability, flow dynamics and also function very well mechanically. However in the long term oxidation and hydrolysis cause degradation problems with these types of polymeric heart valve. (Kidane et al 2009). Whether the correct polymer to defy all issues regarding heart valves will ever be discovered is yet to be seen. (Kidane et al 2009, Ghanbari et al 2009).

Figure 62 - Polymeric Heart Valve (Ghanbari et al 2009)

Key Points:

- *Cell and tissue engineering has the potential to create completely biocompatible blood vessels.*
- *A scaffold can be seeded with the patient's own stem or progenitor cells so as it can grow along with the patient's own somatic growth.*
- *Embryonic stem cells can be induced to become any type of cell.*
- *Somatic cells are more differentiated.*
- *Vasculogenesis is the growth of blood vessels from progenitor cells.*
- *Angiogenesis is the growth of blood vessels from pre-existing tissue.*
- *VEGF causes both vasculogenesis and angiogenesis by influencing the growth and development of blood vessels.*
- *Embryonic, foetal and somatic stem cells all have the potential for use in vascular engineering.*
- *Autologous bone marrow derived stem cells have been used in clinical studies but the material created does not withstand the level of blood pressure as required.*

- *Transverse growth has been observed in tissue engineered vascular grafts, but not longitudinal growth.*
- *Endothelial cells grown in tissue culture can be used to pre-treat a synthetic vascular graft.*
- *Scaffolds are needed as structural support and biological support for developing stem cells.*
- *A de-cellularised human saphenous vein has been used as a scaffold.*
- *Electrospinning is used to build scaffolds.*
- *OptiFlo is a new TCPC design aiming to improve haemodynamics.*
- *Polymeric heart valves have the potential to avoid issues such as calcification, coagulation, durability and immunogenicity.*

Conclusion/Discussion:

The aim of this thesis was to review all the potential conditions in paediatrics that require the use of conduits for repair and evaluate the different types of conduits used and why. It also aimed to detail the different examples of surgical procedures for applications of these conduits in paediatrics.

It became evident during investigation that total correction of a heart defect is rarely the first and last procedure. More often than not palliative procedures must take place before total correction can be achieved, these palliative procedures can be seen as the first stage of a total corrective surgery. However, even after success of these "total corrections" reoperation or reintervention is inevitable due to outgrowth from the conduit or damage to the conduit from degradation, compression or stenosis.

In many cases where artificial conduits are needed for paediatrics, artificial heart valves are also required. It became evident during research for this project that the area of artificial heart valves should also be explored and researched with attention to their mechanical properties, placement and relevant materials to use. Other determinants affect the material of choice for valves because factors such as regurgitation, pressure gradient across the valves and the haemodynamic compliance of the structure are all significant.

Before setting out researching the various types of artificial conduits and valves used in paediatrics, I assumed autografts would be the material of choice in most situations, this is not so. I have discovered that in most cases, due to time constraints for early palliation to save the child's life, synthetic materials are the most prevalent.

I presumed tissue engineering was closer to the goal of harvesting a viable vascular graft from the patient's own material so it can grow and move with the child's own somatic growth; however, technology is still a long way off from this. Although a lot of research and development has gone in to the search for a viable scaffold and stem or progenitor cell combination for tissue engineered vascular autografts; results have not been steady enough to call it a success. On the positive end of the scale, neovascularisation and re-endothelialisation has been achieved in animal models and it has been proven that blood clotting issues are avoided when bone-marrow derived stem cells were used for conduits implanted into neonatal humans, along with the obvious biocompatibility of these devices.

Growth has been seen in these tissue-engineered grafts, however it is only transverse growth; longitudinal growth is necessary in paediatrics to be completely free from reintervention. Thus far, no combination of cell and scaffold has been found that can withstand the pressure blood vessels are subjected to.

It is my opinion that the field of tissue engineering for vascular grafts has a future if decellularised homografts of heterografts are used for the scaffold. However, despite the use of the human saphenous vein, bovine jugular graft and the human umbilical vein as scaffold potentials, they do not have the structural capabilities that, for example, an aorta needs to be able to withstand. Decellularised xenograft aortas, suitable in size to the patient's own aorta, impregnated with stem cells capable of smooth muscle cell and endothelial cell differentiation is the way forward in my opinion.

Even if it is possible to create a tissue engineered blood vessel that meets all the necessary requirements, it is not feasible for a patient to wait the necessary amount of time. Palliative procedures will always precede total correction unless it can be achieved prior to birth. This is why early foetal intervention is so important.

Thus far, foetal intracardiac intervention has yielded mixed results. Trauma, as a result of the intervention, can be detrimental to the developing foetus or the maternal uterus; however there is the possibility that the intervention using balloon valvuloplasty can help the developing heart to grow sufficiently. Since trauma during balloon valvuloplasty is a risk, implantation of a conduit for repair is not possible in the near future. This is by virtue of many considerations, for example the possibility of added trauma from reinterventions due to the various stages in most procedures for total repair, risk of infection in anastomotic sites, and the fact that work must be carried out percutaneously which is not feasible for the foetus's small heart and blood vessels.

The limitations and requirements in vascular prosthesis engineering are so many, that not all are possible to overcome. In paediatric cardiology there are even a greater number of considerations. Compensations must be made with the use of any material or procedure.

References:

Aggarwal, S., Garekar, S., Forbes, T.J., Turner, D.R. (2007) 'Is stent placement effective for palliation of Right Ventricle to Pulmonary Artery Conduit Stenosis?' *Journal of the American College of Cardiology Vol. 7 (4):480-484*

Alberts, B et al. (2004) *Essential Cell Biology 2nd Edition.* New York, USA: Garland Science.

American Heart Association (2011) *Single Ventricle Defects* [image online], available: http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/AboutCongenitalHeartDefects/Single-Ventricle-Defects_UCM_307037_Article.jsp [accessed 8 Aug 2011]

Anderson, S.A. et al (2009) 'The Coronary Vascular System and Associated Medical Devices'. In: Iaizzo, P.A. ed. *Handbook of Cardiac Anatomy, Physiology, and Devices 2nd Edition.* USA: Springer.

Apitz, C., Webb, G., Redington, A.N. (2009) 'Tetralogy of Fallot'. *Lancet 2009;374:1462-1471*

BabyPennington (2007) *Norwood Procedure* [image online], available: http://www.babypennington.com/?m=200708&paged=3 [accessed 8 Aug 2011]

Bessos, H., Fraser, R., Seghatchian, J. (2009) 'Scotblood 2009: The quest for understanding vCJD; Claudia's Trachea Implantation; Transfusion Triggers; Scottish Histocompatibility and Immunogenetics Network; and Islet Cell Transplantation'. *Transfusion and Aspheresis Science 42 (2010) 89-95*

Birmingham City Uni. (2011) *Systole and diastole in the arteries* [image online], available: http://www.hcc.uce.ac.uk/physiology/circulation02.htm [accessed 8 Aug 2011]

Blogspot (2010) *Sano Shunt* [image online], available: http://lillianboer.blogspot.com/2010/11/norwood-lillians-first-open-heart.html [accessed 8 Aug 2011]

Blood Circulation (2011) *Pulmonary and Systemic Circulation* [image online], available: http://www.bcb.uwc.ac.za/SCI_ED/grade10/manphys/circulation.htm [accessed 8 Aug 2011]

Brothers, J.A., McBride, M.G., Seliem, M.A., Marino, B.S., Tomlinson, R.S., Pampaloni, M.H., Gaynor, J.W., Spray, T.L., Paridon, S.M. (2007) 'Evaluation of myocardial Ischemia After Surgical Repair of Anomalous Aortic Origin of a Coronary Artery in a Series of Pediatric Patients'. *Journal of the American College of Cardiology Vol. 50 (21):2078-2082*

Brown, R.J.K (1971) 'Abnormalities in the Cardiothoracic System'. In Norman, A.P. ed. *Congenital Abnormalities in Infancy.* Pennsylvania: Blackwell Scientific Publications.

Bull, C. (1986) 'Atrial and ventricular dependant circulations'. In Macartney, F.J. ed. *Congenital Heart Disease.* UK and Europe: MTP Press Ltd.

Buskens, E., Grobbee, D.E., Hess, J., and Wladimiroff, J.W. (1995) 'Prenatal Diagnosis of Congenital Heart Disease; Prospect and Problems'. *European Journal of Obstetrics & Gynecology and Reproductive Biology 60 (1995):5-11*

Buz, S., Zipfel, B., Mulahasanovic, S., Pasic, M., Weng, Y., Hetzer, R. (2008) 'Conventional surgical repair and endovascular treatment of acute traumatic aortic rupture'. *European Journal of Cardio-thoracic surgery 33 (2008):143-151*

Cameron, D. and Vricella, L.A. (2004) 'Palliative Operations for Congenital Heart Disease'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Cardiogram Central (2010) *Heart Valve Calcification* [image online], available: http://www.cardiogram.org/heart-valve-calcification/ [accessed 8 Aug 2011]

Cardiology in work (2008) *Wall Structure of Artery and Vein* [image online], available: http://www.coryi.org/cardiology/index.htm [accessed 8 Aug 2011]

Cardiovascular Physiology Concepts (1998) *Parabolic Flow Profile* [image online], available: http://www.cvphysiology.com/Hemodynamics/H006%20parabolic%20flow%20profile.gif [accessed 8 Aug 2011]

Children's Hospital Boston (2005) *Transposition of Great Arteries* [image online], available: http://www.childrenshospital.org/az/Site511/Images/ei_0423.jpg [accessed 8 Aug 2011]

Cleveland Clinic (1995) *Dacron Graft* [image online], available: http://my.clevelandclinic.org/PublishingImages/heart/actual2_graft.jpg [accessed 8 Aug 2011]

Cleveland Clinic (2010) *Foramen Ovale* [image online], available: http://my.clevelandclinic.org/PublishingImages/HIC/heart%20w-pfo%2011626.gif [accessed 8 Aug 2011]

Cole, J.S., Watterson, J.K., O'Reilly, M.J.G. (2002) 'Numerical investigation of the haemodynamics at a patched arterial bypass anastomosis'. *Medical Engineering and Physics 24 (2002):393-401*

Columbia Surgery (1999) *Coronary Artery Bypass Grafting* [image online], available: http://www.columbiasurgery.org/pat/cardiac/cabg.html [accessed 8 Aug 2011]

Comsol (1998) *Figure 1* [image online], available: http://www.comsol.com/stories/conrad_hemodialysis/full/ [accessed 8 Aug 2011]

Congenital Heart Disease Guide (2011) *Blalock-Taussig Shunt* [image online], available: http://www.crkirk.com/chdguide/surgery/shunt.htm [accessed 8 Aug 2011]

Courtney, J.M. et al (1992) 'Blood Compatibility in Cardiopulmonary Bypass'. In: Hastings, G.W. ed. *Cardiovascular Biomaterials.* New York, USA: Springer-Verlag.

de Leval, M.R. (2005) 'The Fontan circulation: a challenge to William Harvey?'. *Nature Clinic Practice Cardiovascular Medicine Vol.2 (4):202-208*

Delius, R.E. and Stark, J. (1996) 'Combined Rastelli and atrial switch procedure: anatomic and physiologic correction of discordant atrioventricular connection associated with ventricular septal defect and left ventricular outflow tract obstruction'. *Eur J Cardio-thorac Surg (1996) 10:551-555*

Dennis, C. (1987) 'Brief History of Development of Vascular Grafts'. In: Sawyer, P.N. ed. *Modern Vascular Grafts.* USA: McGraw-Hill.

Duncan, B.W. and Mee, R.B.B. (2004) 'Transposition of the great arteries'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Elkins, R.C. et al (1999) 'The Ross operations and aortic annulus reduction'. In: Huysmans, H.A. et al eds. *Stentless Bioprosthesis 2nd Edition*. Oxford, UK: Isis Medical Media.

Elkins, R.C., Knott-Craig, C.J., Ward, K.E., McCue, C., Lane, M.M. (1994) 'Pulmonary autograft in children: realized growth potential'. *Ann Thorac Surg 1994;57:1387-1394*

Elsevier (2005) *Coronary Vessels: Diaphragmatic Surface* [image online], available: http://www.netterimages.com/image/7849.htm [accessed 8 Aug 2011]

Enc. Of Science (2011) *Echocardiogram* [image online], available: http://www.daviddarling.info/encyclopedia/E/echocardiogram.html [accessed 8 Aug 2011]

European Association for Cardio-Thoracic Surgery Congenital Database (2004) **EACTS Congenital Database** [Internet] Available from:< http://www.eactscongenitaldb.org/db/public-reports.py?fnc=r42&dbname=database> [Accessed July 2011]

Forbes, C.D. and Prentice C.R.M. (1978) 'Thrombus Formation and Artificial Surfaces'. *British Medical Bulletin Vol. 34 (2):201-207*

Formigari, R., Michielon, G., Digilo, M.C., Piacentini, G., Carotti, A., Giardini, A., Di Donoto, R.M., Marino, B. (2009) 'Genetic syndromes and congenital heart defects: how is surgical management affected?'. *European Journal of Cardio-thoracic Surgery 35 (2009) 606-614*

Gardiner, H.M. (2005) 'Progression of fetal heart disease and rationale for fetal intracardiac interventions'. *Seminars in Fetal & Neonatal Medicine (2005) 10, 578-585*

Ghanbari, H., Viatge, H., Kidane, A.G., Burriesci, G., Tavakoli, M., Seifalian, A.M. (2009) 'Polymeric Heart Valves: new materials, emerging hopes'. *Trends in Biotechnology Vol.27 (6):359-367*

Goldsmith H.L. and Karino, T. (1992) 'Flow and Vascular Geometry'. In: Hwang N.H.C et al. eds. *Advances in Cardiovascular Engineering.* New York: Plenum Press.

Gore Medical (2002) *Gore-Tex Vascular Graft* [image online], available: http://www.goremedical.com/vg/ [accessed 8 Aug 2011]

Gournay, V. in press, 'The ductus arteriosus: Physiology, regulation, and functional and congenital anomalies', *Archives of Cardiovascular Disease,* viewed 4 July 2011, Science Direct.

Harris, L.J., Abdollahi, H., Zhang, P., McIlhenny, S., Tulenko, T.N., DiMuzio, P.J. (2011) 'Differentiation of Adult Stem Cells into Smooth Muscle for Vascular Tissue Engineering'. *Journal of Surgical Research 168, 306-314 (2011)*

Heart Healthy Women (2011) *Saphenous Vein* [image online], available: http://www.hearthealthywomen.org/images/heart3.jpg [accessed 8 Aug 2011]

Heart Kids (2011) *Norwood Stage 1* [image online], available: http://www.heartkids.org.au/index.php/state/heart_defects_item/18_hypoplastic_left_heart_syndrome/ [accessed 8 Aug 2011]

Heart Valve Interactive Corp. (2011) *Biological Heart Valve Replacement* [image online], available: http://www.heart-valve-surgery.com/biological-heart-valve-replacement.php [accessed 8 Aug 2011]

Heinrichs, J., Sinzobahamvya, N., Arenz, C., Kallikourdis, A., Photiadis, J., Schindler, E., Hraska, V., Asfour, B., (2010) 'Surgical Management of congenital heart disease: evaluation according to the Aristotle score'. *European Journal of Cardio-Thoracic Surgery 2010;37:210-217*

Hickey, E.J. and Caldarone, C.A. (2011) 'Surgical Management of Post-repair Pulmonary Vein Stenosis'. *Pediatric Cardiac Surgery Annual 14:101-108*

Hillman, N. and Hawkins, J. (2004) 'Pulmonary Valve and Infundibular Stenosis'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Hoenicka, M., Jacobs, V.R., Huber, G., Schmid, F., Birnbaum, D.E. (2008) 'Advantages of human umbilical vein scaffolds derived from caesarean section vs. vaginal delivery for vascular tissue engineering'. *Biomaterials 29 (2008):1075-1084*

Hopkins, R. (2006) 'From cadaver harvested homograft valves to tissue-engineered valve conduits'. *Progress in Pediatric Cardiology 21 (2006):137-152*

How, T.V. (1992) 'Mechanical Properties of Arteries and Arterial Grafts'. In: Hastings, G.W. ed. *Cardiovascular Biomaterials.* New York, USA: Springer-Verlag.

Hsiao, S., Wu, M., Jou, H., Lee, C., Shyu, M., Shih, J., Hsieh, F. (2007) 'Outcome for foetuses with prenatally detected congenital heart disease and cardiac arrhythmias in Taiwan'. *J Formos Med Assoc 2007 Vol 106 (6):423-431*

Husain, S.A., Brown, J.W. (2007) 'When Reconstruction Fails or is Not Feasible: Valve Replacement Options in the Pediatric Population'. *Pediatric Cardiac Surgery Annual 10:117-124*

Javadpour, H., Veerasingam, D., Wood, A.E. (2002) 'Calcification of homograft valves in the pulmonary circulation – is it device or donation related?' *European Journal of Cardiothoracic Surgery 22 (2002):78-81*

Johnston, T.P., Boyd, J.A., Ciesliga, B.L., Schoen, F.J., Amidon, G., Levy, R.J. (1990) 'Controlled release of ethanehyddroxy diphosphonate from polyurethane reservoirs to inhibit calcification of bovine pericardium used in bioprosthetic heart valves'. *International Journal of Pharmaceutics , 59 (1990):95-104*

Jonas, R.A. (2009) 'Early Primary Repair of Tetralogy of Fallot'. *Pediatric Cardiac Surgery Annual 12:39-47*

JTCS (2011) *Bovine Jugular Vein Graft* [image online], available: http://jtcs.ctsnetjournals.org/cgi/content/full/114/2/224/F022603X [accessed 8 Aug 2011]

JTCS (2011) *Contegra Conduit* [image online], available: http://jtcs.ctsnetjournals.org/cgi/content/full/124/4/798/F121043002 [accessed 8 Aug 2011]

Ju, Y.M., Choi, J.S., Atala, A., Yoo, J.J., Lee, S.J. (2010) 'Bilayered scaffold for engineering cellularized blood vessels'. *Biomaterials 31 (2010) 4313-4321*

Kakisis, J.D., Liapis, C.D., Breuer, C., Sumpio, B.E. (2005) 'Artificial Blood Vessel: The Holy Grail of Peripheral Vascular Surgery'. *J Vasc Surg 2005;41:349-354*

Kane, N.M., Xiao, Q., Baker, A.H., Luo, Z., Xu, Q., Emanueli, C. (2011) 'Pluripotent stem cell differentiation into vascular cells: A novel technology with promises for vascular re(generation)'. *Pharmacology & Therapeutics 129 (2011) 29-49*

Kaye, A.J., Slemp, A.E., Chang, B., Mattei, P., Fairman, R., Velazquez, O.C. (2008) 'Complex Vascular reconstruction of the abdominal aorta and its branches in the pediatric population'. *Journal of Pediatric Surgery (2008) 43:1082-1088*

Kidane, A.G., Burriesci, G., Edirisinghe, M., Ghanbari, H., Bonhoeffer, P., Seifalian, A.M. (2009) 'A novel nanocomposite polymer for development of synthetic heart valve leaflets'. *Acta Biomaterialia 5 (2009) 2409-2417*

Kirshbom, P.M. and Spray, T.L. (2004) 'Hypoplastic Left Heart Syndrome'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Kofidis, T., Lebl, D.R., Martinez, E.C., Hoyt, G., Tanaka, M., Robbins, R.C. (2005) 'Novel injectable bioartificial tissue facilitates targeted, less invasive, large-scale tissue restoration on the beating heart after myocardial injury'. *Circulation 2005;112:I173–177*

Leather, R.P. et al (1987) 'The Saphenous Vein as a Graft and as an in Situ Aterial Bypass'. In: Sawyer, P.N. ed. *Modern Vascular Grafts.* USA: McGraw-Hill.

Leor, J. et al (2006) 'Renovation of the Injured Heart with Myocardial Tissue Engineering'. In: Battler, A. and Leor, J. eds. *Stem Cell and Gene-Based Therapy: Frontiers in Regenerative Medicine.* London, UK: Springer-Verlag.

Lofland, G.K. (2004) 'Palliative Pulmonary Atresia with intact ventricular septum'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Lofland, G.K. (2009) 'An overview of pulmonary atresia, ventricular septal defect, and multiple aorta pulmonary collateral arteries'. *Progress in Pediatric Cardiology 26 (2009) 65-70*

Loushin, M.K. et al (2009) 'The Mechanical Aspects of Cardiac Performance'. In: Iaizzo, P.A. ed. *Handbook of Cardiac Anatomy, Physiology, and Devices 2nd Edition.* USA: Springer.

Martini, F.H. and Nath, J.L. (2009) *Fundamentalsof Anatomy and Physiology 8th Edition.* USA: Pearson International

Mavroudis, C. and Backer, C.L. (2004) 'Coronary Artery Disease in Children'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Mayo Clinic (1998) *Pulmonary Valve Atresia* [image online], available: http://www.mayoclinic.org/images/pulmonary-valve-atresia-lg-enlg.jpg [accessed 8 Aug 2011]
Mayo Clinic (2001) *Hybrid Procedure Elements for HLHS* [image online], available: http://www.mayoclinic.org/medicalprofs/hybrid-procedures-congenital-heart.html [accessed 8 Aug 2011]

Medical Blog (2008) *Pulmonary Stenosis* [image online], available: http://odlarmed.com/wp-content/uploads/2009/02/pulmonary-stenosis-lg-300x233.jpg [accessed 8 Aug 2011]

Medicine Chest (2007) *Pulmonary Atresia* [image online], available: http://www.cheapmedicinechest.com/wp-content/uploads/2011/04/Myocardial-Ischemia.jpg [accessed 8 Aug 2011]

Merriam-Webster, Inc. (2011) **Merriam-Webster Dictionary** [Internet] Available from:<http://www.merriam-webster.com/dictionary/conduit [Accessed 11 August 2011]

Michigan Engineering (2011) *Non-Linear Blood Vessel* [image online], available: http://www.engin.umich.edu/class/bme456/bloodves/nonlinestres.jpg [accessed 8 Aug 2011]

Migliavacca, F., Balossino, R., Pennati, G., Dubini, G., Hsia, T., de Leval, M.R., Bove, E.L. (2005) 'Multiscale modelling in biofluidynamics: Application to reconstructive paediatric cardiac surgery'. *Journal of Biomechanics 39 (2006) 1010-1020*

Migliavacca, F., Dubini, G., Bove, E.L., de Leval, M.R. (2003) 'Computational Fluid Dynamics Simulations in Realistic 3-D Geometrics of the Total Cavopulmonary Anastomosis: The Influence of the Inferior Caval Anastomosis'. *Journal of Biomechanical Engineering Vol. 125: 806-813*

Monahan, T.S. and LoGerfo, F.W. (2007) 'Endothelialization of Prosthetic Vascular Grafts'. In: Aird, W.C. ed. *Endothelial Biomedicine*. New York, USA: Cambridge University Press.

Monro, J.L., Alexiou, C., Salmon, A.P., Keeton, B.R. (2003) 'Reoperations and survival after primary repair of congenital heart defects in children'. *J Thorac Cardiovasc Surg 2003;126:511-520*

Myers, J.L. and Stephenson, E.R. (2004) 'Coarctation of the aorta'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

National University of Singapore (2001) *Central Shunt* [image online], available: http://www.med.nus.edu.sg/paed/resources/cardiac_thumbnail/surgery/shunts.htm#Central [accessed 8 Aug 2011]

Nature (2011) *The Different Types of Fontan Circulation* [image online], available: http://www.nature.com/nrcardio/journal/v2/n4/fig_tab/ncpcardio0157_F1.html [accessed 8 Aug 2011]

Nimni M.E. (1992) 'Collagen in Cardiovascular Tissues'. In: Hastings, G.W. ed. *Cardiovascular Biomaterials.* New York, USA: Springer-Verlag.

Nursing Crib (2011) *Blalock-Taussig Shunt* [image online], available: http://cdn.nursingcrib.com/wp-content/uploads/blalock-taussig1.gif [accessed 8 Aug 2011]

Ochiai, Y., Imoto, Y., Sakamoto, M., Sese, A., Tsukuda, M., Watanabe, M., Ohno, T., Joo, K. (2010) 'Longitudinal growth of the autologous vessels above and below the Gore-Tex graft after the extracardiac conduit Fontan procedure'. *European Journal of Cardio-thoracic Surgery 37 (2010):996-1001*

Pessotto, R. and Starnes, V.A. (2004) 'Ebstein's Anomaly'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Petko, M., Myung, R.J., Wernovsky, G., Cohen, M.I., Rychik, J., Nicolson, S.C., Gaynor, J.M., Spray, T.L. (2003) 'Surgical reinterventions following the Fontan procedure'. *European Journal of Cardio-thoracic Surgery 24 (2003) 255-259*

Phifer, T.J. and Hwang, N.H.C. (1992) 'Vascular Grafts: Clinical and Hemodynamic Applications'. In: Hwang N.H.C et al. eds. *Advances in Cardiovascular Engineering.* New York: Plenum Press.

Philips Scientific (2011) ePTFE Graft Cover [image online], available: http://www.egotex2.com/product_development.html [accessed 8 Aug 2011]

Pocar, M., Villa, E., Degandt, A., Mauriat, P., Pouard, P., Vouhe, P.R. (2005) 'Long-Term Results After Primary One-Stage Repair of Transposition of the Great Arteries and the Aortic Arch Obstruction'. *Journal of the American College of Cardiology Vol. 46 (7):1331-1338*

Podzolkov, V.P., Zaets, S.B., Chiaureli, M.R., Alekyan, B.G., Zotova, L.M., Chernikh, I.G. (1996) 'Comparative assessment of Fontan operation in modifications of atriopulmonary and total cavopulmonary anastomoses'. *European Journal of Cardio-thoracic Surgery 11 (1997):458-465*

PubMed Health (2011) *Aortic Stenosis* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001230/ [accessed 8 Aug 2011]

PubMed Health (2011) *Coarctation of the aorta* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001242/ [accessed 8 Aug 2011]

PubMed Health (2011) *Coronary Artery Fistula* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004568/ [accessed 8 Aug 2011]

PubMed Health (2011) *Ebstein's anomaly* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004574/ [accessed 8 Aug 2011]

PubMed Health (2011) *Hypoplastic Left Heart Syndrome* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002096/ [accessed 8 Aug 2011]

PubMed Health (2011) *Tetralogy of Fallot* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002534/ [accessed 8 Aug 2011]
PubMed Health (2011) *Truncus Arteriosus* [image online], available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002101/ [accessed 8 Aug 2011]

R&D Systems (2011) *Hematopoietic cells* [image online], available: http://www.rndsystems.com/DAM_public/5940.jpg [accessed 8 Aug 2011]

Radiology (2011) *Extracardiac Conduit* [image online], available: http://www.radiology.rsna.org [accessed 8 Aug 2011]

Reinhartz, O., Reddy, V.M., Petrossian, E., MacDonald, M., Lamberti, J.J, Roth, S.J., Wright, G.E., Perry, S.B., Suleman, S., Hanley, F.L. (2006) 'Homograft valved Right Ventricle to Pulmonary Artery Conduit as a modification of the Norwood Procedure'. *Journal of the American Heart Association 2006 (114):I-594-I-599*

Revolution Health (2011) *Coronary Arteries* [image online], available: http://content.revolutionhealth.com/contentimages/cc-coronaryarteriesnew.jpg [accessed 8 Aug 2011]

Ribatti, D., Vacca, A., Nico, B., Roncali, L., Dammacco, F. (2001) 'Postnatal vasculogenesis'. *Mechanisms of Development 100 (2001) 157-163*

Riley, R.D. and Kon, N.D. (2004) 'Palliative Selection of a Cardiac Valve Prosthesis'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Salman, M.S.M.A., James, D.K., Bugg, G.J. (2009) 'Advances in Foetal Therapy'. *Obstetrics, Gynaecology and Reproductive Medicine 19:11*

Sano, S., Ishino, K., Kawada, M., Honjo, O. (2004) 'Right Ventricle-Pulmonary Artery Shunt in First-Stage Palliation of Hypoplastic Left Heart Syndrome'. *Pediatric Cardiac Surgery Annual of the Seminars in Thoracic and Cardiovascular Surgery, Vol. 7 (2004):22-31*

Sauvage, L.R. et al (1987) 'Development and Clinical Use of Porous Dacron Arterial Prosthesis'. In: Sawyer, P.N. ed. *Modern Vascular Grafts.* USA: McGraw-Hill.

Schnitker, M.A. (1952) *Congenital Anomalies of the Heart and Great Vessels.* New York: Oxford University Press.

Science Photo Library (2011) *Colour SEM of cut human umbilical cord and vessels* [image online], available: http://www.sciencephoto.com/image/311767/530wm/P6160154-Colour_SEM_of_cut_human_umbilical_cord_and_vessels-SPL.jpg [accessed 8 Aug 2011]

Seeley R.R. et al (2003) *Anatomy and Physiology 6th Edition.* New York, USA: McGraw-Hill

Shin'oka, T., Matsumura, G., Hibino, N., et al. (2005) 'Midterm clinical result of tissue engineered vascular autografts seeded with autologous bone marrow cells'. *J Thorac Cardiovasc Surg 2005;129:1330–1338*

Siegenthaler M.P., Celik, R., Haberstroh, J., Bajona, P., Goebel, H., Brehm, K., Euringer, W., Beyersdorf, F. (2008) 'Thoracic Endovascular stent grafting inhibits aortic growth: an experimental study'. *European Journal of Cardio-thoracic Surgery 34 (2008) 17-25*

Singh, S., Wu, B.M., Dunn, J.C.Y. (2011) 'The enhancement of VEGF-mediated angiogenesis by polycaprolactone scaffolds with surface cross-linked heparin'. *Biomaterials 32 (2011) 2059-2069*

Sinzobahamvya, N., Boscheinen, M., Blaschczok, H.C., Kallenberg, R., Photiadis, J., Haun, C., Hraska, V. and Asfour, B. (2008) 'Survival and reintervention after neonatal repair of truncus arteriosus with valved conduit'. *European Journal of Cardio-thoracic Surgery 34 (2008) 732-737*

Slack, S.M. et al (1992) 'Fluid Dynamics and Thrombosis'. In: Hwang N.H.C et al. eds. *Advances in Cardiovascular Engineering.* New York: Plenum Press.

Smith, R.B., MD (1998) 'Presidential address: The foundations of modern aortic surgery'. *J Vasc Surg, 1998 (27):7-15.*

Soerensen, D.D., Pekkan, K., de Zelicourt, D., Sharma, S., Kanter, K., Fogel, M., Yoganathan, A.P. (2007) 'Introduction to a New Optimized Total Cavopulmonary Connection'. *Ann Thorac Surg 2007;83:2182-2190*

SpringerImages (2011) *Anastomotic Intimal Hyperplasia* [image online], available: http://img.springerimages.com/Images/ImagesMD/ACVPC/01/14/WATER_ACVPC01-14-022B.jpg [accessed 8 Aug 2011]

SpringerImages (2011) *Fontan Procedures* [image online], available: http://www.springerimages.com/Images/MedicineAndPublicHealth/1-10.1007_s00247-009-1473-5-5 [accessed 8 Aug 2011]

Stegemann, J.P., Kaszuba, S.N., Rowe, S.L. (2007) 'Review: Advances in Vascular Tissue Engineering using protein based biomaterials'. *Tissue Eng. 2007 November; 13(11): 2601-2613*

Stoll, C., Dott, B., Alembik, Y., De Geeter, B. (2002) 'Evaluation and evolution during time of prenatal diagnosis of congenital heart diseases by routine fetal ultrasonographic examination'. *Annales de Genetique 45 (2002) 21-27*

Strunk, D. and Stamm, C. (2006) 'Adult Stem Cells for Myocardial Tissue Repair'. In: Battler, A. and Leor, J. eds. *Stem Cell and Gene-Based Therapy: Frontiers in Regenerative Medicine.* London, UK: Springer-Verlag.

Sutherland, F.W., Perry, T.E.,Yu, Y., et al. (2005) 'From stem cells to viable autologous semilunar heart valve'. *Circulation 2005;111:2783–2791*

Takahashi, M. and Mason, W.H. (1997) 'Long-term follow-up of patients with Kawasaki disease'. *Progress in Pediatric Cardiology 6 (1997):227-236*

Tam, V. (2004) 'Total Anomalous Pulmonary Venous Connection'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Teijeira, F.J. and Mikhail, A.A. (1992) 'Cardiac Valve Replacement with Mechanical Prostheses: Current Status and Trends'. In: Hwang N.H.C et al. eds. *Advances in Cardiovascular Engineering.* New York: Plenum Press.

Thompson, J.E. (2008) 'History of Vascular Surgery'. In: Norton, J.A. et al. eds. *Surgery: Basic Science and Clinical Evidence 2nd Edition.* New York, USA: Springer.

Tomizawa, Y. (2003) 'Vascular Grafts: Basic Research and Clinical Applications'. In: Tura, A. ed. *Vascular Grafts: Experiments and Modelling.* UK: WIT Press.

Truman Media (2010) *Normal Heart* [image online], available: http://truman-media.blogspot.com/2010/10/human-heart-aminatou.html [accessed 8 Aug 2011]
Tsai, W. and Klein, B.L. (2005) 'The Postoperative Cardiac Patient'. *Clinical Paediatric Emergency Medicine 6:216-221*

Tuch, B.E. (2006) 'Stem cells: A clinical update'. *Australian Family Physician Vol. 35 (9):719-721*

Tulino, V., Dattilo, G., Tulino, D., Marte, F., Patane, S. (2009) 'An occasional diagnosis of isolated pulmonary stenosis'. *International Journal of Cardiology 146 (2011) e61-e62*

Turner, R.J. (1987) 'Vascular Graft Development: An Industrial Perspective'. In: Sawyer, P.N. ed. *Modern Vascular Grafts.* USA: McGraw-Hill.

Ullom, R.L., Sade, R.M., Crawford, F.A., Ross, B.A., Spinale, F. (1987) 'The Blalock-Taussig Shunt in Infants: Standard versus Modified'. *Ann Thorac Surg 1987 (44):539-543*

Ursell, P.C., Griffiths, S.P., Bowman, Jr., F.O. (1988) 'Traumatic rupture of extracardiac valved conduit: unusual late complication producing outflow tract obstruction'. *Ann Thorac Surg 1988;46:351-352*

Valarmathi, M.T., Davis, J.M., Yost, M.J., Goodwin, R.L., Potts, J.D. (2009) 'A three-dimensional model of vasculogenesis'. *Biomaterials 30 (2009) 1098-1112*

Van Oijen, C.H.G.A. (2003) *Mechanics and Design of Fiber-Reinforced Vascular Prosthesis.* Eindhoven, The Netherlands: Technische Universiteit Eindhoven.

Vaz, C.M., van Tuiji, S., Bouten, C.V.C., Baaijens, F.P.T. (2005) 'Design of scaffolds for blood vessel tissue engineering using a multi-layering electrospinning technique'. *Acta Biomaterialia 1 (2005):575-582*

Virtual Medical Centre (2002) *Patent Ductus Arteriosus* [image online], available: http://www.virtualmedicalcentre.com/uploads/VMC/DiseaseImages/836_Patent_Ductus_Arteriosus.JPG [accessed 8 Aug 2011]
Vricella, L.A. and Tsang, V.T. (2004) 'Truncus Arteriosus'. In: Yang S. C. and Cameron D. E. eds. *Current Therapy in Thoracic and Cardiovascular Surgery*. Pennsylvania, USA: Mosby.

Walther, T. and Falk, V. (2005) 'Models on Left Ventricle Hypertrophy (LVH)'. In: Dhein, S. et al eds. *Practical Methods in Cardiovascular Research.* Germany: Springer-Verlag.

Wayne State Uni. (2010) *Tissue Eng Heart Valve* [image online], available: http://www.tissue.eng.wayne.edu/Current%20Research.html [accessed 8 Aug 2011]

Weber, B., Emmert, M.Y., Behr, L., Brokopp, C., Frauenfelder, T., Kretschmar, O., Falk, V., Hoerstrup, S.P. in press, 'Fetal trans-apical stent delivery into the pulmonary artery: Prospects for prenatal heart valve implantation'. *European Journal of Cardiothoracic Surgery,* viewed 10 July 2011, Science Direct.

WebMD, Inc. (2002) *Balloon Valvuloplasty* [image online], available: http://www.katycardiology.com/procedures/ [accessed 8 Aug 2011]

WegoHealth (2011) *St. Jude Medical Mechanical Heart Valve* [image online], available: http://www.mechanicalheartvalve.co.uk/ [accessed 8 Aug 2011]

Wikipedia (2011) *Stem Cells Diagram* [image online], available: http://en.wikipedia.org/wiki/File:Stem_cells_diagram.png [accessed 8 Aug 2011]

Woods, W.A., Schutte, D.A., McCulloch, M.A. (2003) 'Care of Children who have had Surgery for Congenital Heart Disease'. *Am J Emerg Med 2003;21:318-327*

Woodward, C.S. in press, 'Keeping children with congenital heart disease healthy'. *J Pediatr Health Care,* viewed 15 June 2011, Science Direct.

Yasim, A., Gul, M., Ciralik, H., Ergun, Y. (2006) 'Gelatin-Sealed Dacron Graft is not more susceptible to MRSA infection than PTFE Graft'. *Eur J Vasc Endovasc Surg 32:425-430*

Yoganathan, A.P. et al (1992) 'Heart Valve Replacements: Problems and Developments'. In: Hastings, G.W. ed. *Cardiovascular Biomaterials.* New York, USA: Springer-Verlag.

Yorkshire and Humber Adult Congenital Heart Disease Network (2011) **Yorkshire and Humber Adult Congenital Heart Disease Network** (NHS) [Internet] Available from:<http://www.yorksandhumberhearts.nhs.uk/templates/Page.aspx?id=422 > [Accessed 6th July 2011]

Young, K. and Hare, J.M. (2008) 'Stem Cells in cardiopulmonary development: implications for novel approaches to therapy for pediatric cardiopulmonary disease'. *Progress in Pediatric Cardiology 25 (2008) 37-49*

Yuan, S. and Jing, H. (2009) 'Palliative procedures for congenital heart defects'. *Archives of Cardiovascular Disease (2009) 102, 549-557*

Zimmermann, W.H., Melnychenko, I., Wasmeier, G., et al. (2006) 'Engineered heart tissue grafts improve systolic and diastolic function in infarcted rat hearts'. *Nat Med 2006; 12:452–458*