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Thirty years of experience with the Ross operation in children with aortic valve disease and complex LVOT obstruction: Results of a multi-center study

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To my family and to Klajdi

Thirty years of experience with the Ross operation in children with aortic valve disease and complex LVOT obstruction: Results of a multi-center study

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Aortic Valve Disease and Complex LVOTO

1. Introduction.

The left ventricular outflow tract is a complex anatomic structure which includes subvalvular, valvular, and supravalvular components. It lies centrally deep within the heart immediately adjacent to the two atrioventricular valves. Obstruction of the left ventricular outflow tract (LVOTO) at one or more levels increases impedance to ejection from the left ventricle and promotes development of hypertrophy [1-4]. In many instances obstruction occurs at multiple levels and although the degree of obstruction in any one area may not be severe, the combined effect of obstruction at multiple levels is clinically important. At one end of the spectrum there are patients with isolated aortic valve stenosis, normal-sized left heart structures and a normal aortic arch and isthmus. For these patients, relief of obstruction at the aortic valve level is all that is necessary to achieve a biventricular circulation. At the other end of the spectrum are patients with multiple sequential obstructive lesions that merge into the spectrum of hypoplastic left heart syndrome and severe Shone's anomaly. For these patients, a single ventricle approach commencing with a Norwood procedure may be the optimal approach. Instead for patients, especially infants, with simple aortic valve lesion which is not suitable for repair, and or with multi-level left heart obstruction in the presence a two well developed ventricles a Ross/Ross-Konno operation is the best option to offer [6].

2. Embriology.

The aortic valve develops simultaneously with the pulmonary valve. Both semilunar valves appear as swellings of subendothelial tissue when

septation of the bulbus cordis, the outflow tube from the embryonic heart, is completed by the spiral aortopulmonary septum. This process begins in the 6 mm embryo with the appearance of the two truncal bearings, upper right bearing and lower left bearing. These pads rapidly enlarge until they touch along the ever-increasing surface and merge to form the septum of the trunk, thus dividing the trunk into an aortic and a pulmonary canal [1-2]. The separation of the aortic trunk area is completed when the aortic-pulmonary septum is also formed from the dorsal part of the aortic trunk, resulting in the complete separation of the pulmonary trunk from the ascending aorta. Each trunk cushion has a tubercle at the end of its distal end. Each pair will form the pulmonary and aortic canal, respectively. A third small cushion appears on the walls of the aortic and pulmonary canals, opposite the fused cushions of the trunk [1-2]. These two intercalated valve pads form the third tubercle of each arterial valve stem. Starting from the tubercles, the flaps of the semilunar valve and the sinuses of Valsalva are formed by a process of excavation, in the proximal direction, of the trunk and of the intercalated valve cushions. Complete formation of the aortic and pulmonary valve is achieved when the embryo measures 40 mm. Both aortic and pulmonary roots, arise from the trunk and the intercalated valve cushions [1-2].

3. Anatomy.

The aortic valve is part of a complex anatomical-functional structure, which includes the aortic outflow and the aortic root [2-5]. Continence and the harmonious function of the aortic valve depends not only on the diastolic coaptation capacity of the cusps, but also on the optimal ratio between the dimensions of the various segments and / or components of the aortic root. The aortic root extends from the upper edge of the anulus of the mitral valve to the sino-tubular junction (the meeting between the

sinuses of Valsalva and the ascending aorta). For reasons of convenience, the aortic aoutflow and the aortic root can be divided into a sub-valvular region (LVOT) and a supravalvular region (aortic root) [7]. The LVOT has the shape of a fibromuscular tube consisting of two main walls: the anterior wall, formed by the muscular and membranous part of the interventricular septum, and the posterior wall formed by the anterior leaflet of the mitral valve. In anatomical continuity, above the anterior wall of the LVOT is the right fibrous trigone and above the posterior wall of the LVOT is the left fibrous trigone, which act with a hinged mechanism that allows the posterior wall of the LVOT to move backwards and forward during the cardiac cycle (Figure 1). The supravalvular region (aortic root) consists of the aortic annulus, the aortic cusps, the commissures, the sinuses of Valsalva, and the sinotubular junction. The aortic annulus can be considered the base of the aortic root. Although it is called a ring and is imagined with a rectangular shape, in reality the aortic annulus is a diamond-shaped crown with three points. It is a well-defined fibrous structure, it attaches distally to the medial tunic of the aortic sinuses, instead it attaches proximally to the membranous and muscular part of the interventricular septum (anteriorly), to the fibrous trigones (laterally) and to the upper part of the anterior mitral leaflet (posteriorly). So proximally and posteriorly we have the mitro-aortic continuity, the two valves share the same fibrous ring (Figure 2). The aortic cusps in normal anatomy are three, smooth, thin, and have the shape of a swallow's nest and in the center of the free edge of each cusp there is a small nodule called Aranzio's nodule. On each side of the Aranzio nodule, along the entire edge of the cusp, there is a very thin semilunar area, the lunula, which has fine striae parallel to the edge. When the valve is closured, the entire surfaces of the adjacent lunulae lay to each other [1-5]. Macroscopically in each cusp we can distinguish

three elements: the hinge, the belly and the coaptant surface. Microscopically, the valve cusps consist of three layers:

- Ventricularis - represents the continuation of the endocardium and consists of elastic fibers oriented perpendicular to the free edge of the cusps;
- Spongiosa - middle layer, consists of collagen fibers and fibroblasts;
- Fibrosa - layer of the arterial side, consists of collagen, fibroblasts and elastic fibers.

On the ventricular and arterial side, the outer layers are lined with endothelial cells. The aortic valve commissures (meeting point between two valve leaflets) are three fibrous structures that suspend the valve cusps, they are located over three triangular areas of the LVOT. The triangular area under the commissure between the right coronary cusp and the non-coronary cusp is fibrous and continues proximally as a membranous interventricular septum. The triangular area under the inter-coronary commissure is at the apex fibrous and at the base muscle, this area is fixed in 50% of cases to the pulmonary artery by means of the infundibular ligament. The triangular area under the commissure between the left coronary cusp and the non-coronary cusp is fibrous, corresponding to the mitro-aortic continuity (Figure 2). The spaces that each cusp encloses are called the valvular sinuses of Valsalva, symmetrical and are three small bulging of the aortic root. The sinuses extend from the aortic valve annulus to the sino-tubular junction and are called:

- right coronary sinus (origin of the right coronary artery)
- left coronary sinus (origin of the left coronary artery)
- non-coronary sinus (does not give rise to coronary arteries)

The peculiarity of the structure of the coronary sinuses of Valsalva is that they have a medial tunic that is firmly fixed to the aortic valve ring and as it rises towards the sino-tubular junction, the thickness of the medial tunic increases progressively [5].

The sino-tubular junction, that is, the junction between the valvular sinuses of Valsalva and the ascending aorta, is represented by a thin circular crest, clearly visible in the aorta. The diameter of the aorta at this level is slightly smaller than the aortic diameter at the lowest point of the root [7].

3.1 Aortic root function and aortic valve opening

The main function of the aortic root is the transmission of huge amounts of blood volumes pumped intermittently by our heart and the maintenance of laminar flow during the cardiac cycle [5]. Equally important are the following functions, such as: low resistance in the root, optimal coronary flow, and less tissue damage during the frequent and variable adaptations of the heart pump to the needs of the body. These functions have very important implications on the performance of the left ventricle and its structural integrity, as well as on the patient's well-being and quality of life. The amount of blood pumped from the left ventricle into the aortic root in humans varies from 0.3 to over 20 L / min depending on the age, body surface and physiological or pathological conditions in which we find ourselves. The aortic root as an entity is a dynamic structure, it moves in space by changing its size and shape during the cardiac cycle. The entire aortic root moves downwards towards the ventricle in systole and upwards in diastole [5].

The most dynamic structure of the root is certainly the aortic valve, with its cusps that have many properties that allow it to substantially modify

the shape and size, in a more radial than circumferential way due to their elastic properties. The interstitial cells of the cusps have been shown to contain smooth muscle α-actin (Figure 3), nerve fibers and various nerve endings that release various neurotransmitters and neuropeptides in the synapses (Figure 4) [5]. Furthermore, recent studies have shown that the aortic valve cusps contract in response to various pharmacological agents in a dose-dependent manner [5].

The mild and physiological dilation of the aortic root at the level of the sino-tubular junction during the cardiac cycle causes the separation of the upper parts of the aortic commeasures which in turn results in the displacement of the free margins of the cusps with progressive opening of the valve in a triangular orifice (Figure 5) without flexural deformities of the cusps [5]. A similar mechanism causes the partial closure of the valve at the end of systole.

The mechanism of opening and closing of the aortic valve is also partly due to the formation of blood vortices at the level of the Valsalva sinuses and the sino-tubular junction. The vortices that are formed in the aortic root are very important for maintaining coronary flow, especially during the systolic phase. The importance of the Valsalva sinuses and the sino-tubular junction in creating the vortices was first described by Leonardo da Vinci [5,7] (Figure 6).

The movements of the entire root together with the anatomical-structural composition of the valve and the formation of vortices, have very important hemodynamic effects and may be responsible for the early opening of the aortic valve, before the blood volume has moved from the left ventricle [5]. Undoubtedly, the main role in valve opening and closing is played by the pressure differences existing between the left ventricle and the aortic root.

4. Congenital aortic valve stenosis

Congenital stenosis of the aortic valve is the most frequent congenital valve defect and accounts for approximately 3-5% of all congenital heart disease [1,8]. The pathology is much more frequent in males, with a sex ratio of 4: 1. Up to 20% of patients have associated cardiovascular abnormalities; anomalies of the mitral valve, left ventricle, the LVOT, ascending aorta and of the aortic arch (aortic coarctation and hypoplasia) [1,7]. All these anomalies described can be found associated in the same patient, and in this is the case of Shone's Syndrome [1-4].

The basic malformation affecting the valve consists in the thickening of the valve tissue with varying degrees of commissural fusion. In most cases, the valve is bicuspid. In some patients it can be tricuspid or unicuspid and in this case has the shape of a dome without an implant or a lateral implant attached to the aorta at the level of the central orifice (Figure 7) [7,8]. In many patients presenting with neonatal critical aortic stenosis, the valve leaflets are poorly delimited and cannot be classified as either bicuspid or unicuspid valves. The valve tissue in neonatal age is a primitive, gelatinous or myxomatous tissue, not well developed and the valve and the ascending aorta can be severely hypoplastic (5-6mm). This pathology forms a continuum with hypoplastic left heart syndrome and aortic atresia and hypoplasia [1, 8]. When aortic stenosis is appreciated after the neonatal period, we can clearly distinguish the valve anatomical parts and thus classify the valve in tricuspid or bicuspid, but rarely is seen the presence of a unicuspid valve. In fact, in patients who have such a stenosis that they have to undergo surgery in childhood, it has been seen that in 64% of cases the aortic valve is bicuspid [1,7,8].

5. Pathophysiology and clinical presentation.

Aortic valve stenosis increases impedance to LV ejection and produces a pressure gradient across the valve such that peak intraventricular pressure exceeds aortic systolic pressure. Under these circumstances, LV wall stress (which equals Pr/2h, where P = peak intraventricular pressure, r = ventricular radius, and h = LV wall thickness) is greatly elevated [1-4]. This provides stimulus for LV concentric hypertrophy or wall thickening. The degree of thickening parallels the increase in ventricular pressure such that LV wall stress is normalized despite greatly elevated peak intraventricular pressure. This normalization of wall stress allows LV ejection fraction (EF) to be maintained despite increasing impedance to ejection. As the severity of aortic stenosis progresses, eventually the valve orifice narrows to the point where stroke volume and EF can no longer be maintained. The development of LV concentric hypertrophy places the subendocardium at risk for hypoperfusion and the development of ischemia for a number of reasons [1-4]:

- elevated LV end-diastolic pressure secondary to the diminished compliance which accompanies concentric hypertrophy
- an aortic diastolic blood pressure which is low relative to the elevated LV end-diastolic pressure
- compression of subendocardial vessels by the hypertrophied myocardium
- absence of any systolic coronary perfusion because the LV systolic pressure greatly exceeds aortic systolic pressure.

Endocardial fibroelastosis may develop as a consequence of chronic *in utero* subendocardial ischemia and infarction. The extent of fibrosis can be quite dramatic. A smooth, extremely thick layer can be seen to line the LV cavity and to encase the papillary muscles. As myocardium is lost and

replaced by fibrous tissue systolic function will deteriorate. This process also severely impairs LV diastolic function and reduces compliance. When fibrosis is severe, LV end-diastolic pressure is likely to be markedly elevated even if complete relief of valvar stenosis is achieved. The severity of stenosis at the time of birth largely determines the subsequent pathophysiologic course. In neonates with mild stenosis there will be gradual development of hypertrophy over the course of years with essentially no fibrosis. In neonates with more severe stenosis there will have been development of *in utero* hypertrophy and there may be some degree of fibrosis. Over the course of days to months it will become clear that hypertrophy has not progressed to the point of normalizing wall stress. This is a state of afterload mismatch, defined as the point where for a given level of contractility progressive increases in afterload result in progressive decreases in stroke volume. This point is reached when preload reserve is exhausted, when the sarcomeres are at their optimal length and there is no further preload recruitable stroke work. As a result, LV end-diastolic pressure and left atrial pressure will be markedly elevated predisposing to pulmonary edema. In the neonate with critical aortic stenosis there will be severe afterload mismatch and very little antegrade ejection across the aortic valve. There will almost certainly be some degree of endocardial fibrosis. As a result, the left ventricle will be more dilated than hypertrophied. The child will be dependent on right to left ductal blood flow to provide the majority of proximal and distal aortic blood flow, that is, the right ventricle is supporting the pulmonary and systemic circulation. The brain and heart are thus dependent on retrograde aortic blood flow. If ductal closure occurs the child will sustain ischemic injury to the myocardium, brain, kidneys, and splanchnic bed. Unless prostaglandin E1 is rapidly instituted the child will not survive [1-4].

Beyond the neonatal period the pathophysiology of aortic valve stenosis primarily reflects the impact of LV hypertrophy. There may be subendocardial ischemia during exercise causing angina and a risk of acute ventricular fibrillation. There also may be an ineffective increase in cardiac output with exercise leading to syncope.

Because there is often associated underdevelopment of left heart structures, critical neonatal aortic valve stenosis is frequently diagnosed prenatally by ultrasound. In this case prostaglandin can be begun immediately following birth. This will permit maintenance of systemic perfusion via the ductus during the first few days of life while pulmonary vascular resistance remains elevated. As pulmonary vascular resistance falls the tendency for Qp:Qs to increase will jeopardize ductal-dependent systemic perfusion. Neonates not diagnosed prenatally may present with signs of poor perfusion, cyanosis, and lethargy as the ductus begins to close. These children are often mistakenly evaluated for sepsis. The presence of a murmur leads to an echocardiographic examination and the correct diagnosis. Occasionally, a neonate will present with circulatory collapse following ductal closure. The extent of end organ damage will depend on the duration and severity of the systemic hypoperfusion as indicated by the degree of metabolic acidosis [1]. Neonates with severe, noncritical aortic stenosis in whom ductal blood flow is not essential for systemic perfusion are likely to present within weeks with respiratory distress secondary to pulmonary edema. Neonates with less severe aortic stenosis will be asymptomatic. Beyond infancy presentation may be similar to the adult with aortic valve stenosis including the classic symptoms of angina and syncope. A harsh systolic ejection murmur is noted on physical examination.

6. Diagnostic studies.

The echocardiogram is diagnostic. It is important, however, to understand that in the neonatal period when the ductus is patent, assessment of a gradient across the aortic valve either by catheter or Doppler-derived methods will underestimate the severity of the stenosis due to the low flow across the valve. Depressed contractility, high grade obstruction to transaortic flow, and ductal blood flow into the aorta all contribute to low flow across the aortic valve. It is particularly important for the echocardiographer to measure all left heart structures in two planes. Cavity and valve dimensions should be measured and a Z score for each calculated [1-4]. Assessment of the mitral valve size and mobility is just as important as for the aortic valve. The long axis length of the left ventricle as a percentage of the total long axis length of the heart (atrioventricular valve annulus to apex) is also a valuable measurement. The decision whether to pursue a two ventricle or a one-ventricle approach will be guided by these calculations [1]. An assessment of the extent and severity of endocardial fibroelastosis should be made as well. In the older patient who is being followed for aortic valve stenosis serial echo studies should document the Doppler-derived valve gradient, indexed valve area, LV wall thickness and LV volume. Calculations of LV wall stress and other echocardiographic- derived methods for assessing LV contractility allow informed decisions regarding the timing of intervention.

7. Medical and interventional therapy.

For the medical management of neonatal critical aortic stenosis it is essential to achieve secure intravenous access and delivery of prostaglandin E1, which was introduced in 1976 and revolutionized the management of these patients and arch pathologies [1-4]. Before this

time, which also predated the introduction of two-dimensional echocardiography, it was necessary to manage acidotic neonates symptomatically as they underwent emergency cardiac catheterization and were then rushed from the catheterization laboratory to the OR. Not surprisingly, few survived this sequence. Prostaglandin E1 must be infused through a secure intravenous line. If ductal patency does not become apparent in any neonate less than 1 week of age within 1 hour, it should be assumed until proven otherwise that there is a technical problem with delivery of the medication into the central bloodstream. Establishing ductal patency represents just the first step in medically resuscitating the neonate with severe aortic stenosis. Because the lower half of the body is dependent on perfusion through the ductus and because blood in the ductus also has the choice of passing into the pulmonary circulation, it is important that pulmonary resistance be maximized. This can be achieved by avoiding a high level of inspired oxygen (usually room air is appropriate), as well as avoiding respiratory alkalosis caused by hyperventilation. Sometimes control of ventilation may need to be achieved by anesthetizing and intubating the neonate and inducing paralysis. Because myocardial function is likely to be depressed at the time of presentation and it may be necessary for the heart to handle a moderate volume load (dependent on the success with which pulmonary resistance is maximized), an inotropic agent such as dopamine is usually employed. Dopamine has the added advantage of maximizing renal perfusion in this setting of an ischemic renal insult. It should be very unusual that a child is taken to the OR with any abnormalities of acid/base, renal, or hepatic indices.

Balloon dilation is the method of choice for management of critical neonatal aortic valve stenosis [1]. The procedure should be undertaken by a highly skilled team with excellent imaging facilities. Surgical backup

should be readily available throughout the procedure although in skilled hands complications such as acute severe aortic valve regurgitation or injury to the mitral valve are exceedingly rare. Balloon dilation is also the preferred primary mode of therapy in the infant and child with aortic valve stenosis. Care must be taken to avoid oversizing the balloon which can lead to an unacceptable degree of valvar regurgitation.

8. Surgical management

a) History of Surgery

In 1910, Alexis Carrel performed experimental surgery using a conduit from the apex of the left ventricle to the aorta as a means of addressing LV outflow obstruction. In 1912, Tuffier approached the lesion directly, performing successful transaortic digital dilation in a young man with aortic stenosis. More than 40 years passed before any additional significant advance occurred. In 1953, Larzelere and Bailey performed a closed surgical commissurotomy. In 1955, Marquis and Logan performed closed surgical dilation of a stenotic aortic valve using antegrade introduction of dilators via an incision in the LV apex. Inflow occlusion with open valvotomy was reported in 1956 by both Lewis and Swan and their associates. Also in 1956, Lillehei and colleagues performed an aortic valvotomy using cardiopulmonary bypass. All of these milestones were achieved in patients well beyond infancy [1-4]. In 1969, Coran and Bernhard, at Children’s Hospital Boston, reported surgical relief of critical aortic stenosis in neonates and infants, with cases dating back to 1960. Various surgical procedures have been described for enlargement of the hypoplastic aortic annulus (Figure 8). Posterior annular enlargement was the first of these techniques. It was reported by Nicks and colleagues from Sydney, Australia in 1970. A similar but more

extensive technique was described in 1979 by Manougian, although there has been controversy regarding who should be credited with the original concept for the procedure. Anterior enlargement of the hypoplastic annulus was described in 1975 by Konno from Tokyo, Japan [11]. Successful replacement of the aortic valve with a mechanical device was pioneered by Harken at the Brigham Hospital in Boston in 1960.

In 1962, Ross in London [9,10] and Barratt-Boyes in New Zealand described successful implantation of an aortic allograft for replacement of the aortic valve. Ross later introduced the pulmonary autograft procedure [9,10] which has subsequently been combined with the Konno procedure [11] for patients with annular hypoplasia and particularly those with associated tunnel subaortic stenosis. Percutaneous balloon aortic valvuloplasty in adults was described in 1984 by Lababidi and coworkers. Use of this technique in infants was reported in 1985 by Rupprath and Neuhaus and by Sanchez and associates. Shortly thereafter, use of the technique in neonates with critical aortic stenosis was described by Lababidi and Weinhaus. Balloon dilation of the aortic valve in the fetus *in utero* was first described by Maxwell et al. from Guy's Hospital, London, UK in 1991.

Although there are many surgical operations to address the critical aortic stenosis and complex or simple LVOTO in the pediatric population, in our opinion the Ross/Ross-Konno operation represents the best option to offer to these patents [9,10,11]. Thus, here described is this fascinating operation.

b) ROSS/Ross-Konno Operation

The first successful clinical application of the Ross procedure was carried out by Donald Ross on 6 August 1967 at Guy's Hospital in London [10]. The idea of the operation arises from the need to have a natural and ideal

substitute for the native aortic valve, given the long-term results of the aortic Homograts [12]. The pulmonary valve is an autologous, living tissue with a structure very similar to that of the aortic valve, which is why D. Ross had the brilliant idea and the great courage in using the native pulmonary valve as the ideal replacement for the aortic valve. The first patients who received the pulmonary autograft in the aortic position were young adults with disease of the aortic valve only and with a life expectancy greater than 40 years [12].

The original technique used for the first time by Ross is the sub-coronary implantation of the autograft. The complexity and technical difficulties in having a perfect coaptation between the flaps of the neo-aorta again led Ross in 1982 to change the autograft implant technique, including the autograft ("inclusion technique") as a cylinder inside the aorta. In this way, the valve apparatus is implanted as a single unit, maintaining a good geometry.

In 1986, again Ross evolved the technique and described the total aortic root replacement with pulmonary autograft, which is the technique of choice in the pediatric population. This technique is currently the most used by many centers, for its simplicity, safety, and for the excellent geometry and excellent results of freedom from re-intervention obtained. Another anatomical reason for the choice of the aortic root replacement technique is represented by the fact that the pulmonary valve does not have a natural and well-formed ring like the aortic one, therefore the underlying infundibular muscle acts as a true pulmonary ring/neo-annulus. In cases (especially in newborns and infants) where there is valvular aortic disease and hypoplasia of the aortic annulus there’s a need to replace the aortic valve and simultaneously enlarge the LVOT. Among the various options that exist, the favorite technique in many Institution’s is to perform a Ross-Konno operation. The principle consists in applying

the Konno incision in the LVOT to enlarge the outflow and then implant the pulmonary autograft. The defect in the inter-ventricular septum that results from the Konno incision to enlarge the outflow can be closed with a pericardial or Dacron patch or utilizing a lip of autograft tissue harvested from the right ventricular outflow tract (RVOT).

The operation is performed in median sternotomy and with the use of the cardio-pulmonary bypass machine in moderate hypothermia (26-28 °C). The technique of cannulation is standard and consist in the usage of two right angle caval cannulas with caval tapes and arterial cannulation of the ascending aorta. An LV vent is inserted through the right superior pulmonary vein. Multiple infusions of blood cardioplegia or single dose of crystalloid cardioplegia are given throughout this relatively lengthy procedure. After CPB initiation the aorta is cross-clamped and the aortic root excised living the non-coronary sinus intact to support the neo-aortic root. The aortic valve is completely excised and The coronary arteries are mobilized with generous “U-shaped” buttons of aortic wall attached (the shape correct orientation during reimplantation; Figure 9 a). The pulmonary autograft is harvested before the Konno septal incision is made.

It is important to understand that the incision used to harvest the autograft is different from the incision used to enlarge the LV outflow tract. It is the support of the pulmonary valve by a ring of muscle, the subpulmonary conus, that makes the autograft procedure possible. The subpulmonary conus that is divided to harvest the autograft is subsequently used as the sewing ring to implant the pulmonary root (Figure 9 b). The main pulmonary artery is divided just proximal to its bifurcation. The pulmonary valve is examined to be sure that it is suitable for the procedure. A right-angle instrument is passed down through the

valve and acts as a guide for the initial incision in the anterior wall of the infundibulum of the right ventricle. Failure to do this can result in placing the incision too close to the pulmonary valve. Consideration should be given to harvesting a little more infundibulum than for a standard Ross procedure if a Konno procedure is to be added as well. A large infundibular patch however should be avoided as it may become aneurysmal when exposed to LV pressure. Following the initial incision in the anterior wall of the infundibulum the autograft is harvested with particular care being taken at the leftward extent of the incision which is always very close to the first septal perforator branch of the left anterior descending coronary artery. As a result, it is very common to expose the first septal perforator. If the septal perforator is injured it is very important that it be repaired or at least oversewn. Failure to repair an injured perforator is likely to result in a steal of blood from the entire left coronary system. This has potential to cause considerably more ischemic injury than would be expected from injury to the perforator alone. The autograft is stored in a bowl which is clearly marked and separated from the pulmonary homograft which should be undergoing thawing and rinsing at this stage. The aortic annulus is enlarged by incising the LV outflow tract in a leftward direction rather than toward the apex. This will keep the incision well above the conduction area. The incision should not be extended too far into the anterior trabeculated ventricular septum as this will complicate closure of this end of the incision.

The pulmonary autograft is sutured into the aortic annulus and ventricular septal incision (Figure 9 c). If necessary, a bullet-shaped patch of Gore-Tex can be used to close the Konno incision. In general, however, the pulmonary annulus is quite a bit larger than the aortic annulus and in conjunction with a small amount of supplementary infundibular muscle is adequate for closure of the entire outflow tract without a patch. It is

important that the autograft be sutured to the Konno incision with an external row of supporting pledgetted sutures following an initial running suture to ensure that a ventricular septal defect is created. The autograft is implanted as a full root technique with single multiple interrupted sutures which are ligated over three streps of pericardium just to further support the autograft and the hemostasis. The left coronary button is implanted. At this point an appropriate-sized pulmonary homograft is anastomosed distally to the pulmonary bifurcation area. The ascending aortic anastomosis is performed subsequently (Figure 9 d) followed by reimplantation of the right coronary artery. The pulmonary homograft is anastomosed proximally to the right ventricular outflow tract, usually with continuous 4/0 Prolene. Because this suture line passes very close to the left main coronary artery and the left anterior descending coronary artery most of this anastomosis should be performed with the aortic cross-clamp still in place (Figure 9 e). Toward the end of the suture line the left heart is allowed to fill with blood and air is vented through a site in the ascending aorta. The aortic cross-clamp is released with the aortic vent site bleeding freely [1-4, 9,10,11,12]. During warming the usual monitoring lines are placed. It is a reasonable precaution to use TEE or to place a pulmonary artery monitoring line to check for any left to right shunt at the ventricular level. This will occur if there is breakdown of the suture line between the ventricular septum and the pulmonary autograft. Figure ten (a, b, c, d) in the appendix shows intra-operative photos of a Ross operation performed with a root technique in a teenager pediatric patient.

Aim of the Study

The aim of the study is to document the outcomes into the third decade after the Ross operation in infants and children.

The primary objective is to analyze the survival rate and re-operation rate on the left and right heart. The secondary objective is to identify risk factors for autograft and homograft failure.

To address those issues a multi-center study was conducted.

Results of the Ross operation, a multi-center study

1. Material and methods.

a) Study population

The present study is a multi-center study that includes data from ten pediatric cardiac surgery units. The total number of patients that were qualified for the study are 325 and data were retrospectively collected. Local institutional board review approval was asked for the study and the boards waived the need for patient consent. Patients were enrolled from January 1990 to December 2020.

Indications for the primary operation were in accordance with American College of Cardiology/American Heart Association guidelines. The responsible surgeon at each center determined the surgical technique, including root replacement, root replacement with aorto-ventriculoplasty (Ross–Konno), subcoronary grafting and cylinder inclusion. The median number of procedures done at each center was 21 (IQR 20-27).

Primary outcomes of the study were: hospital (prior to or within 30 days of discharge) and late survival, freedom from reoperation on the autograft, freedom from reintervention on the homograft, freedom from replacement of the homograft and freedom from any reoperation. Secondary outcomes were prevalence of cardiovascular events, clinical and functional status at follow-up.

b) Clinical follow-up

In the present cross-sectional follow-up study, all 325 late survivors (100%) were assessed by means of direct examination at local clinic, by the referring cardiologist or primary care physician between January and February 2020-2020. Major adverse cardiovascular events were reported

according international guidelines. Criteria for reoperation included: moderate or greater autograft valve regurgitation; severe autograft root dilation (>5 cm or 2.6 cm/m2); severe homograft stenosis (mean Δp>30 mm Hg) or regurgitation and not suitable for trans-catheter approach.

c) Statistical analysis

Categorical variables were reported as absolute numbers and percentage. Continuous variables were expressed as median ± IQR. Comparison between categorical variables was performed using the χ^2 test. Time-related events were described using the Kaplan–Meier estimate and compared using the log-rank test. The Cox proportional hazards regression analysis was used to evaluate the following variables as predictors for mortality and reoperation over time: age, year of surgery, indication to Ross procedure (aortic regurgitation, stenosis, mixed), prior aortic procedure, prior aortic balloon dilation, operative technique (subcoronary cylinder, root, Ross–Konno), associated procedure and centre experience (patients per centre). First, all variables were entered into a univariate analysis. Next, all variables that were significant on univariate analysis or showed tendency toward significance ($p < 0.20$) were forced into the multivariate Cox regression analysis (enter method). The proportional hazards assumption was assessed for each variable through graphic inspection of the log minus log survival and the linearity assumption for continuous variables though the partial residuals. No indication was seen of a violation of the assumptions. All testing was performed two-sided. For all data analysis, the Statistical Package for Social Sciences, V.25.0.0 (SPSS, Chicago, Illinois, USA) was used.

2. Results

a) Study population

Patients' characteristics and operative data are showed in Table 1. Median follow-up time was 11 years (IQR: 4,2-17).

b) Early and late survival

There were 7 (2,1%) hospital deaths, all due to cardiac events. Early mortality was greater in the neonatal/infant population (5/32, 15.6% in neonates/infant's vs 2/291, 0.7% in children, p=0.0001). During follow-up, 14 late deaths were recorded due to cardiac cause in five patients, infection in three, thromboembolism in two and cardiac transplantation in one. Late mortality was also greater in infants (2/27, 7,4% infants vs 14/289, 4,8% children, p=0.58). Cumulative overall survival (including early mortality) was 96 ±1,6%, 95±2%, 93±2,5%, 91,6±3,3% and 86% ±7% at 5, 10, 15, 20 and 25 years, respectively (Figure 11). Multivariate analysis showed that age less than 1 year (p=0.01) and associated congenital cardiac defects (p=0.001) were correlated with an increase in the overall mortality (Table 2).

c) Autograft reoperation

From the overall cohort, there were only 39 (12%) patients who underwent autograft reoperations. Indication to first reoperation was isolated valve regurgitation in 10 patients, isolated autograft dilatation in 14, combined lesion in 14 and 1 patient needed a heart transplant. Reoperation consisted in valve replacement in 10 patients, root replacement in 14, root replacement with valve preservation in 8, ascending aortic replacement in 2 and valve repair in 5. Among these,

there were ten patients (25.6%) who had simultaneous homograft replacement. Median time to autograft reoperation was 8,3 years (range 6,3–11,5). In general, autograft reoperation was similar between infants and the rest of population (3/32, 9,3% vs 36/291, 12.5%, p=0.6). There was only one hospital mortality after autograft reoperation. In three patients who had an autograft reoperation, cardiac transplantation was needed due to persistent left ventricular failure early after the operation, one of whom died. Actuarial freedom from autograft reoperation was 97±1,4%, 89±3,3%, 82±4,8%, 75±8% and 70%±11% at 5, 10, 15, 20 and 25 years, respectively (Figure 12). Multivariate analysis showed that use of subcoronary technique (p=0.03) was associated with increased risk of autograft reoperation (Table 2).

d) Homograft reintervention

There were 58 (17,8%) overall procedures regarding homograft reintervention. The reintervention consisted in balloon dilation in 6 patients, trans-catheter pulmonary valve implantation in 25 and surgical pulmonary homograft valve replacement in 26. Median time to homograft reintervention was 9 years (IQR 5,3-14). Neither hospital mortality nor second reoperation after isolated right heart reoperation was observed. Therefore, actuarial freedom from any homograft reintervention was 94±2%, 86±4%, 75±5,6%, 65± 8 and 60±10% at 5, 10, 15, 20 and 25 years, respectively (Figure 13). Multivariate analysis showed that age less than 1 year (p=0.001), aortic stenosis as indication to Ross procedure (p=0.049), use of root technique (p=0.045) and associated lesion (p=0.002) were associated with increased risk of homograft reoperation (Table 2).

e) Valve-related morbidity and function status

Valve-related morbidity and functional status Major morbidity due to either autograft or homograft reoperation was calculated in a composite end-point as freedom from any reintervention, which was 94±2%, 82±4%, 68,4±6%, 56±10% and 44±13% at 5, 10, 15, 20 and 25 years, respectively (Figure 14). Other non-fatal valve-related events requiring hospitalization at follow-up included homograft endocaridits resolved by intravenous antibiotic therapy in two patients, thromboembolic events causing transient cerebral ischemia in two and need for permanent pacemaker implantation in six, all having Ross– Konno operation. No hemorrhagic event was observed. Functional status at follow-up echocardiographic examination showed absent to mild autograft regurgitation in 194 (60%) patients and moderate or greater in 28 (8%), while absent to mild homograft regurgitation was found in 144 (44%) patients and moderate or greater in 3 (1%). Mean age of 304 late surviving patients was 12 years (IQR 4.6-17) and functional status satisfactory, with 213 (70%) in NYHA class I and 234 (76%) free from any medication, including aspirin or warfarin.

3. Discussion.

The Ross procedure is a very attractive operation for the surgical therapy of the aortic valve disease, as it provides a replacement that does not require anticoagulation and has a growth potential equal to the native valve. The indications for the intervention are increasingly widespread, thanks to the low mortality rates (1.5%-3.5%) recorded in large published series [13-16] and thanks to the excellent quality of life especially in young adults [17,18]. Nowadays the operation is being offered not only to the pediatric patents where most of the times is the only bail-out

operation in neonates and infants but also to teenagers, adolescents and young adults with superb results and quality of life [12, 17, 18].

The present study is an Italian national multi-center study investigating the results of the Ross operation in the pediatric population into the third decade of life. The previous survey which dates back in 2012 showed overall low hospital risk and satisfactory early and late survival, despite the fact that pediatric Ross operation bears substantial valve-related morbidity in the first two decades. The rate for autograft reoperation was more common than homograft in the previous study [13]. Also given the fact that the Ross/Ross-Konno operation is a technically demanding operation, the study clearly showed that centre experience had a weak influence on hospital survival, as the median number of procedures per unit was 20, thus, on average, no more than one procedure per year [13].

In the current report there were only 7 (2.1%) hospital deaths due to cardiac events, mainly low cardiac out syndrome. The majority of deaths occurred in neonates/infants (5/32 Neonats/infants Vs 2/291 0.7% in children and adolescents) so bringing mortality rate up to 15.6% in this category. Late deaths occurred in 14 patients and due to cardiac cause only in 5. Also, late mortality was greater in neonates and infants. Overall survival was greater than 93% and 91% at 15 and 20 years respectively while at 25 86+-7% but with only one patient at risk. This results which are excellent correlated to the severity and complexity of the pathology correlate well with other studies present in literature.

In fact, in a recent study Bovè at al [19] analyzed the results of the Ross/Ross-Konno operation in a pediatric series of 110 patients. Early mortality occurred in 15 (11%) patients, significantly more in Ross-Konno than in Ross patients (n =9 [33%] vs n= 6 [6%]; P < .001). The overall survival was 88.9% +-2.7%, 86.8% +- 3.0%, and 85.4% _+-3.3% at 1 year, 10 years, and 20 years, respectively, revealing a significant

survival difference at the cost of the Ross-Konno group (P < .001). The authors, despite age and associated congenital cardiac defects, found a strong correlation for mortality the need of a Konno incision in addition to the Ross Operation. In ours study, performing a Ross-Konno was not associated with and increase in mortality. Only age at Ross and associated cardiac defects were risk factors for mortality at multivariate analysis.

Thus, age is a strong factor for mortality and this is confirmed by different study in literature, that report a high rate of mortality that varies from 10 to 20% in neonates and infants [14, 19]. The high mortality when performing Ross operation before 12 months of age could be explained with the severity of the aortic pathology, complex LVOTO and impaired LV (sometimes small LV). Also, the immature myocardium may play a role, given the complexity of the operation, especially when Ross operation is performed as a bail-out after severe aortic insufficiency due to aortic valve ballon dilation.

To overcome such a complication some Institution have adopted a strategy of primary surgical aortic valve valvulotomy with associated repair techniques. Another recent report from Buratto at al. [20] described their result of 140 consecutive Ross divided into two groups, 72 primary Ross and 68 secondary Ross operations after previous aortic valve surgery. Their results in non-matched patients were comparable between the two groups in terms of survival and rate of operation which correlates well with our findings in the present study. After matching the two groups with 50 patients respectively the only significative finding was survival. At 10 and 15 years was 90.0% (95% CI: 77.5% to 95.7%) and 82.6% (95% CI: 65.7% to 91.7%) in the primary Ross procedure group, respectively, compared with 96.8% (95% CI: 79.2% to 99.5%) at both 10 and 15 years in the secondary Ross procedure group. This represented a statistically significant difference (p = 0.04). The rate of re-operation in

right heart and left heart did non differ, there wasn't a statistically significative difference despite the others observed a trend of higher autograft reoperation. Freedom from autograft reoperation at 10 and 15 years was 82% (95% CI: 64.1% to 91.5%) and 74.1% (95% CI: 54.2% to 86.3%) in the primary Ross procedure group, respectively, compared with 97.0% (95% CI: 80.4% to 99.6%) at both 10 and 15 years in the secondary Ross procedure group. The authors concluded that performing a delayed Ross procedure after initial aortic valve repair can provide better results than those achieved with primary Ross procedure. The approach of performing before and aortic valve conservative surgery using different technique of surgical valvuloplasty may seem reasonable whenever possible. Given the high mortality rate of the neonatal/infant Ross, this should be a strategy to pursuit always at list to go out form infant age (> 12 months). In fact, in the study the median time from aortic valve surgery to Ross operation was 4.2 years. Similar results are observed also by other groups [21]. We agree with such strategy, although we were not able to address directly this issue in the present study, given the fact that Ross operation was performed after previous heart surgery in 116 patients (34%). Further investigation is needed to properly address this aspect of delayed Ross operation after aortic valve surgery.

In our cohort of patient there were only 39 (12%) who underwent autograft reoperation. Valve sparing root surgery with valve preservation was possible in 8 patients and valve repair alone in 5 and ascending aorta replacement in 2. So, in 38,5 % of the cases it was possible to save the neo-aortic valve. Freedom from left heart reoperation at 15, and 20 years was 82+-4,8% and 75+-8% respectively. Similar results are reported by other studies in literature which were mentioned above [15,1619-21].

From our study and also evidence in literature evidence that autograft dilatates with time is strong and a current issue to deal with. In fact, evidence exists showing that pulmonary autograft in pediatric patients dilates with time disproportionately to somatic growth. Certainly, freedom from autograft reoperation 25 years after Ross procedure in childhood is somewhat disappointing and not dissimilar to data in adults (70.5 %). [12, 17,18]. Mean time to reoperation is nearly 8.3 years (IQR 6,3-11,5) in our series, discrepancy with prior studies may be explained by longer follow up herein. Certainly, protective strategies such as root reinforcement or support such as inclusion of the autograft in a Dacron tube, shown to be effective in delaying autograft reoperation in adults, are not suitable in a growing patient population. Therefore, strategies to support the root technique other than inclusion in a Dacron tube may be effective in protecting from time-related dilation [17]. For this reason, supporting the autograft with pericardium and the remaining aortic wall posteriorly and with pericardium in the aortic suture line may pa a role. Further studies are needed to address this issue.

In this study multivariate analysis found that the use of sub-coronary technique was strongly associated with left heart re-operation. This may be explained with the learning curve given the fact that the sub-coronary implant is technically more difficult to perform compared to the root technique. Evidence exists from previous studies that also age may influence the rate of left heart reoperation [22, 23]

In addition, infant age per se may be a surrogate for concomitant need for right heart reintervention in children carrying smaller homografts and this was identified at multi-variate analysis. Other factors were identified but with a less strong evidence than age. Re-intervention on the right heart were more frequent in this study. There were 58 (17,8%) overall procedures in the right and 51 patents needed a valve in the RVOT (26

undergone surgery) with a median time to homograft re-interventions of 9 years (IQR 5,3-14). More than half of the patients were managed exclusively by trans-catheter approach, be it dilatation or replacement, thus reducing significatively morbidity. The rate of right heart reoperation correlates with other reports in literature and is similar to that on the left heart. This finding is different from our previous study where the rate of any right heart intervention was lower than the left heart. With time the need for right heart operation increases significatively and this is strongly correlated with age at implant. The need for concomitant surgery on the left and right heart was necessary in 10 patients in the series, with no mortality occurred.

When looking at freedom from any valve-related reintervention as a composite end-point, present estimates of 68.4+-6% at 15 years and 56+-10%% at 20 years and match closely with observations made by Burato, Bovè and other pediatric Ross series [15, 19, 20]. Data provide evidence that after 20 years from initial Ross operation, nearly 50% of the patients get a reoperation, either on the left side, right heart or both. In pediatric patient's reintervention/reoperation tend to be more frequent on the right heart and age at Ross was a strong risk factor for reoperation. The issue of treating a single-valve disease by including potentially a double-valve problem is pertinent at long term-follow up and is consistent after 20 years from Ross procedure. Similar to prior studies [24, 25] morbidity of reoperation, be it on left heart, right heart or combined, was quite low, with the only casualty or need for transplant listing due to persistent left ventricular failure in complex anatomic substrates. Also, experience with reoperation on the left heart has proven evidence in nearly half of the patents is possible to preserve the neo-aortic valve by performing ether simple valve repair or aortic root surgery (Yacoub/David operation) [24]. Based on the low prevalence of valve-related events requiring

hospitalization, other than reoperation, on the functional status in terms of NYHA class (70% NYHA Class I), autograft and homograft performance at follow-up echocardiography and freedom from medication (76% of patients), and also on the ability of fertile women to carry on term pregnancies, it may be surmised that quality of life was satisfactory and compatible with lifestyle of a teenage and young adult population. Although, we didn't address directly quality of life in patients throughout a questionnaire, data provided here-in and from literature [25] clearly shows evidence that it is superb.

The rate of operation from any cause at 20 years of follow up is acceptable considering the lack of alternatives in this difficult series of patients with pediatric aortic valve disease. In our opinion, there isn't another heart valve operation that matches the results of the Ross operation in terms of survival, freedom from reoperation and quality of life. In facts experience with biological aortic valve replacement (aortic homograft) in pediatric patients is limited and has high reoperation rate as it is expected with most reoperations occurring 6-12 years after valve implant [26]. A "recent" total valve replacement utilizing three symmetric neo-cusps with pericardial patch was developed (Ozaki operation) and originally performed in adult patients. The initial results were satisfactory and attractive, so the method and operation were adopted also in pediatric patents. A recent study form Polito at al [27] compared the results of the Ross operation with the Ozaki operation in pediatric patents. The authors compared 16 Ross with 22 Ozaki patents. Freedom from reintervention or death at 24 months was 89.4% (64–97) and 93.5% (63–99) in Ozaki and Ross group, respectively (p = 0.2, not significative). While the median follow-up time was significantly longer in Ross group compared to the Ozaki group [38.9 (13.8–52.8) months vs. 11.3 (4.7–21) months, p = 0.02] and so its premature to put out definitive conclusions regarding the

superiority of the Ozaki. In our opinion with time pericardium tends to retract and calcify and thus the neo-valve becomes stenotic or insufficient and this operation with time is not comparable to the results of the Ross operation and should not be used routinely to address the aortic valve disease in children but used only in rare and selected cases where aortic valve repair and Ross operation can't be performed. At present and with all data in literature, the Ozaki operation is miles away compared to the results of the Ross operation in the pediatric population.

Interesting observation's come from another recent study performed by Alsoufi at Al [28], which compared the results of mechanical aortic valves with Ross operation in children's less than 6 years of age at surgery. In this study mechanical prothesis (MP) were associated with comparable operative mortality and survival up to 15 years, although the higher re-intervention rate. On the longer follow-up, after 15 years, survival diverged with increased attrition in MP group, likely due to late valve and reoperation-related complications. The study demonstrates that, in a selected group of small children when the Ross procedure is not possible or desired, the use of MP, with or without annular enlargement, provided remarkably good survival for at least 15 years following AVR, followed by a decline compared to the Ross procedure. This study further demonstrates the long-term benefits of the Ross procedure in terms of survival, acceptable reoperation rate and superb quality of life.

4. Limitations.

Limitations of the present study are inherent with the retrospective nature, including incompleteness of information on baseline and follow-up z-scores for the aortic root and variability in indications to the Ross reoperations among units, possibly leading to underestimate true prevalence of autograft dilatation and dysfunction. Furthermore, only

valve-related events requiring hospital admission could be registered. In addition, the registry covers over three decades of surgical experience during which indications and techniques of the Ross procedure have evolved, as attested by the increasing frequency with which congenital aortic regurgitation is managed by valve repair in some units.

5. Conclusion.

In conclusion, the present study validates the Ross procedure as low risk operation for isolated aortic valve or complex left heart obstruction in children, as satisfactory early and late survival is achieved at the expense of significant valve-related reoperation. Based on the data herein provided and confirmed from multiple studies present in the literature, we believe that the Ross operation is the procedure of choice in the pediatric population when dealing with aortic valve disease. When possible, the Ross operation should be avoided in infants and post-pond after 12 months of age due to the high mortality rate in infants. In such patients an initial strategy of aortic surgical valvulotomy associated with valve repair should be performed if possible.

Appendix

1. Iconography

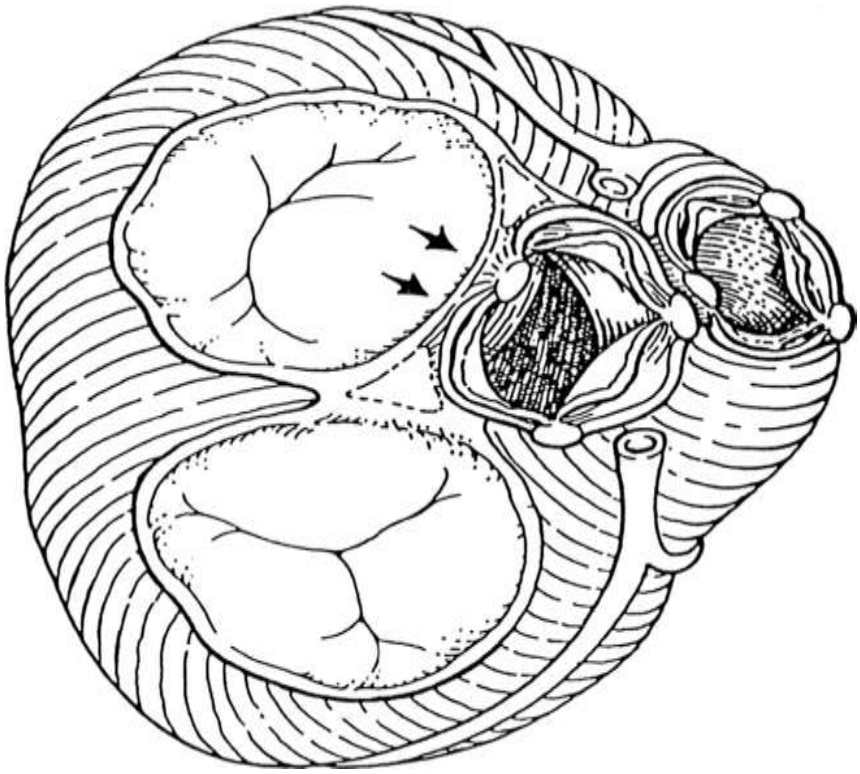


Figure 1. Diagram showing the fibrous trigons of the heart. To note the mitro-aortic continuity (arrows) and the right and left trigons. (*Magdi H. Yacoub et al.[4])*

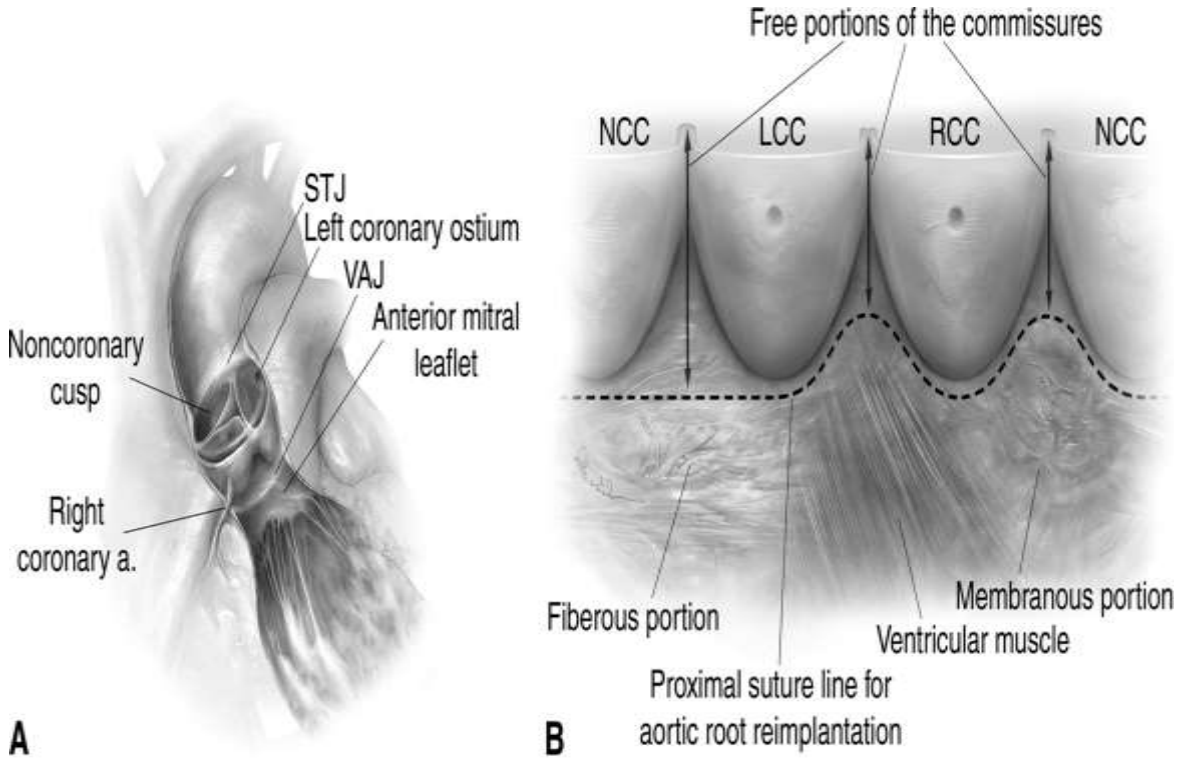
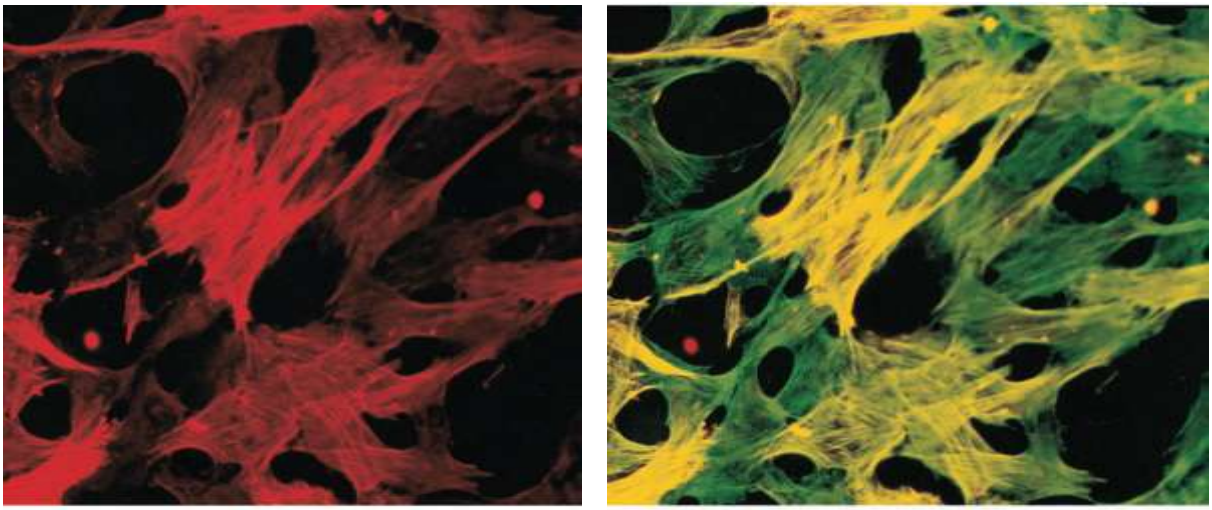


Figure 2 (A) Like the mitral valve, aortic valve function involves an important interaction between the valve annulus and leaflets. Importantly, however, the annulus of the aortic valve is not a single structure but rather consists of three different components, namely, the sinotubular junction, the ventriculo-aortic junction, and the anatomic crown-shaped annulus, which serves as the insertion point of the aortic valve cusps. These components work together to facilitate normal valve function and together are termed the "functional aortic annulus." (B) The anatomy of the subvalvular region of the aortic valve and its surrounding structures also has important implications for aortic valve repair. The first observation is that external dissection of the aortic root from its surrounding structures is limited by the membranous septum (at the junction of the noncoronary and right coronary cusps) and by ventricular muscle (at the junction of the left and right coronary cusps), whereas, at all other points, external dissection down to the level of the anatomic valve annulus is possible and necessary when valve-sparing root replacement is performed using the reimplantation technique. Thus, the proximal suture line for the aortic valve reimplantation procedure follows these external limitations in a curvilinear fashion (dotted line). Legend: a, artery; LCC, left coronary commissure; NCC, non-coronary commissure; RCC, right coronary commissure; STJ, sino-tubular junction; VAJ, ventriculo-aortic junction.*(Boodhwani et al.[12])*



A B

Figure 3. Photomicrographs (3500) of interstitial cells cultured from a human aortic valve stained with (A) antibody against smooth muscle a-actin (characteristic of myofibroblasts) tagged with Texas red: myofibroblasts appear red and (B) double exposure of cells stained with Oregon green phalloidin which irreversibly binds to filamentous actin (present in all cells) and antibody against smooth muscle a-actin tagged with Texas red: myofibroblasts expressing smooth muscle a-actin appear yellow, undifferentiated fibroblasts appear green. Cells were fixed and permeabilized with ice-cold acetone. *(Magdi H. Yacoub et al. [4])*

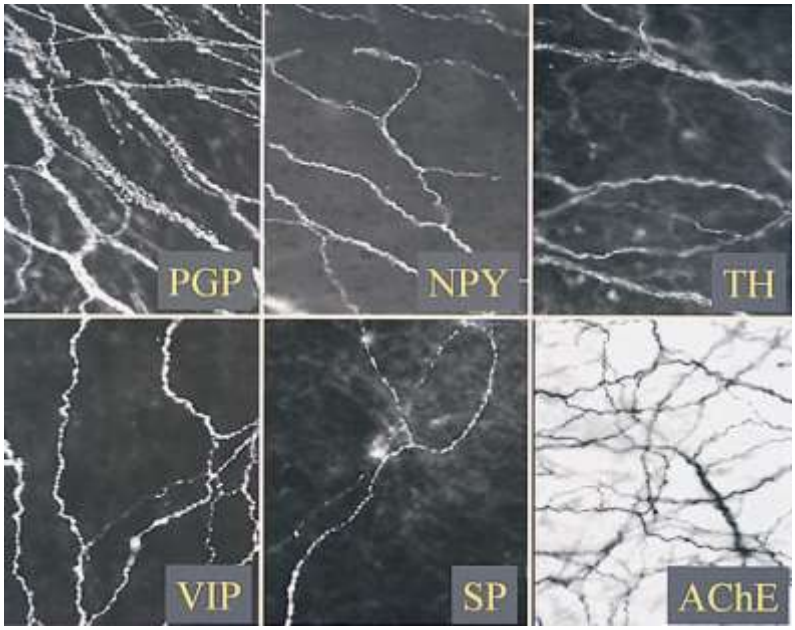


Figure 4. Photomicrograph showing nerve fibers and fascicles in the atrial layer of the valve (PGP 5 protein gene product, NPY 5 neuropeptide Y, TH 5 tyrosine hydroxylase, VIP 5 vasoactive intestinal polypeptide, SP 5 substance P, AChE 5 acetylcholine). *(Magdi H. Yacoub et al. [4])*

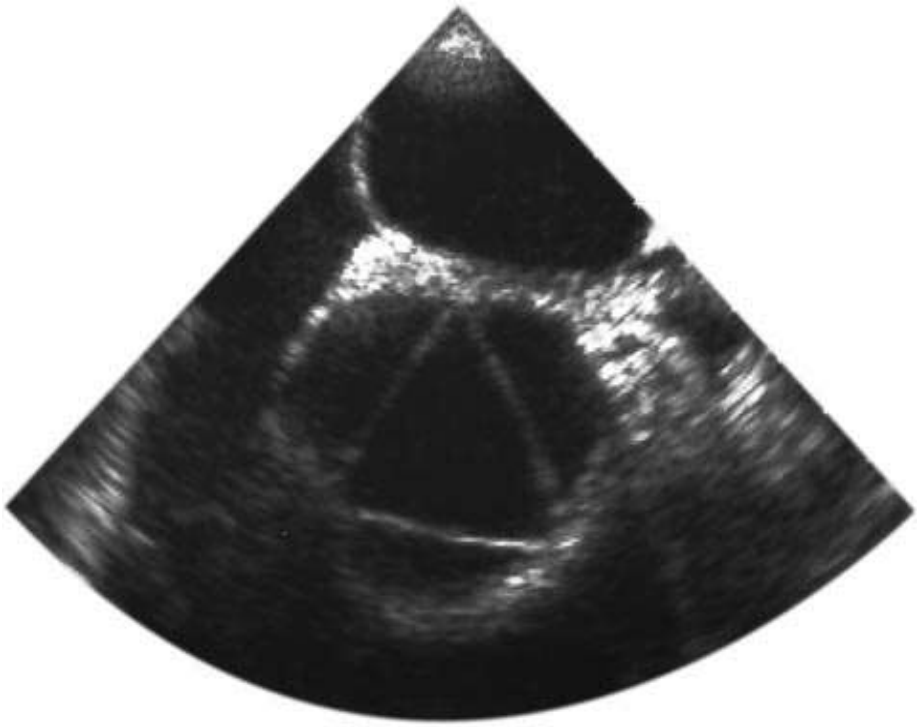


Figure 5. Transesophageal echocardiography across the aortic valve demonstrating the triangular shape of the open leaflets. Short-axis, basal view, 40 degree angle (*Magdi H. Yacoub et al. [4])*

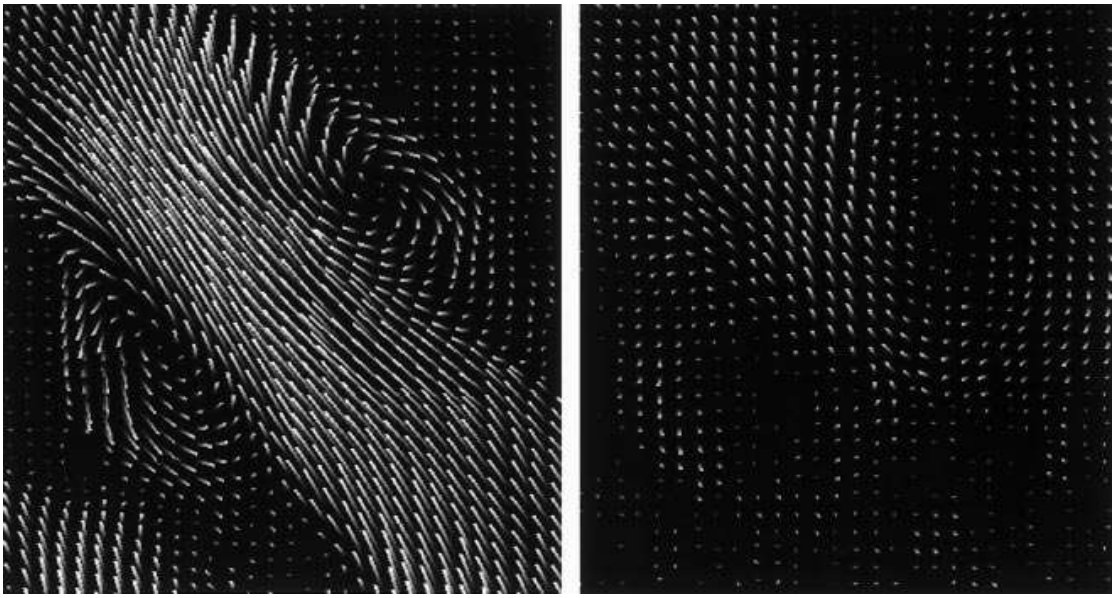


Figure 6. Late systolic and end-systolic patterns of flow in the aortic root. The direction of outflow runs obliquely up and left. Flow vectors (thick-end pointing in the direction of flow) are derived from magnetic resonance velocity data in a healthy volunteer. Vortices are accommodated by two of the sinuses, contributing to valve closure without regurgitation at end-systole. *(Magdi H. Yacoub et al. [4])*

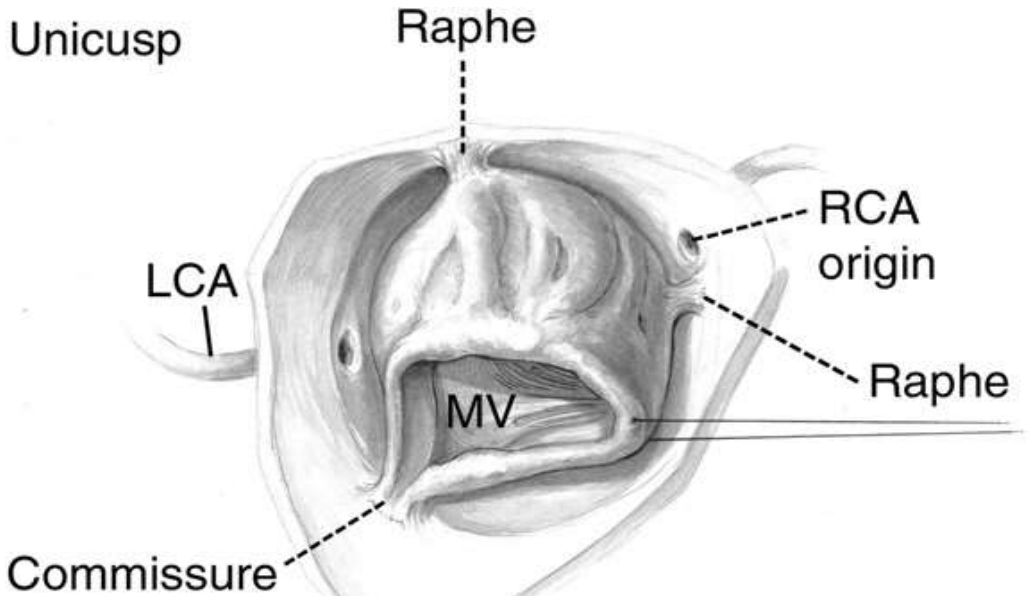


Figure 7. Unicuspidal aortic valve, the so called " Toilet Seat Valve ". We can notice the primitive aspect of the valve, with a single true commissure and two abortive commissures, a fibrotic raphe not supported by a real commissure. Legend: LCA, left coronary artery; MV, mitral valve; RCA, right coronary artery. *(Christopher W. Baird et al. [9])*

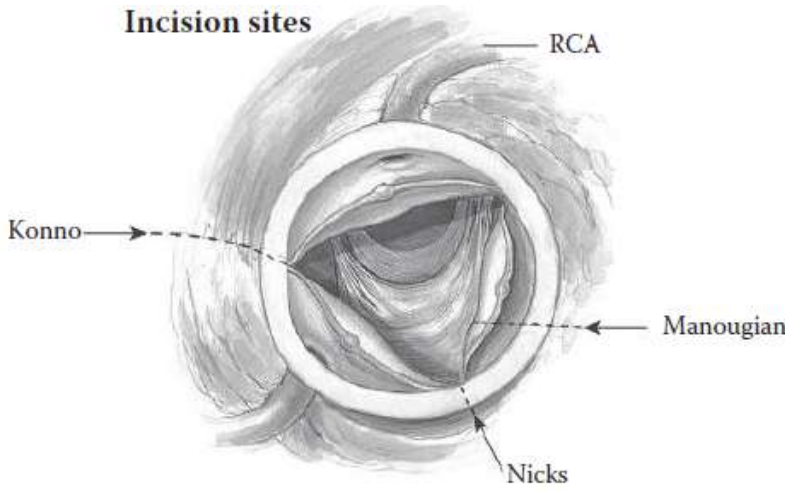


Figure 8. The aortic annulus can be enlarged posteriorly by either a Nicks or Manougian incision. Anteriorly the annulus can be enlarged with a Konno incision which extends between the right and left coronary cusps of the aortic valve. If the subaortic area is to be enlarged the Konno incision is extended into the ventricular septum.

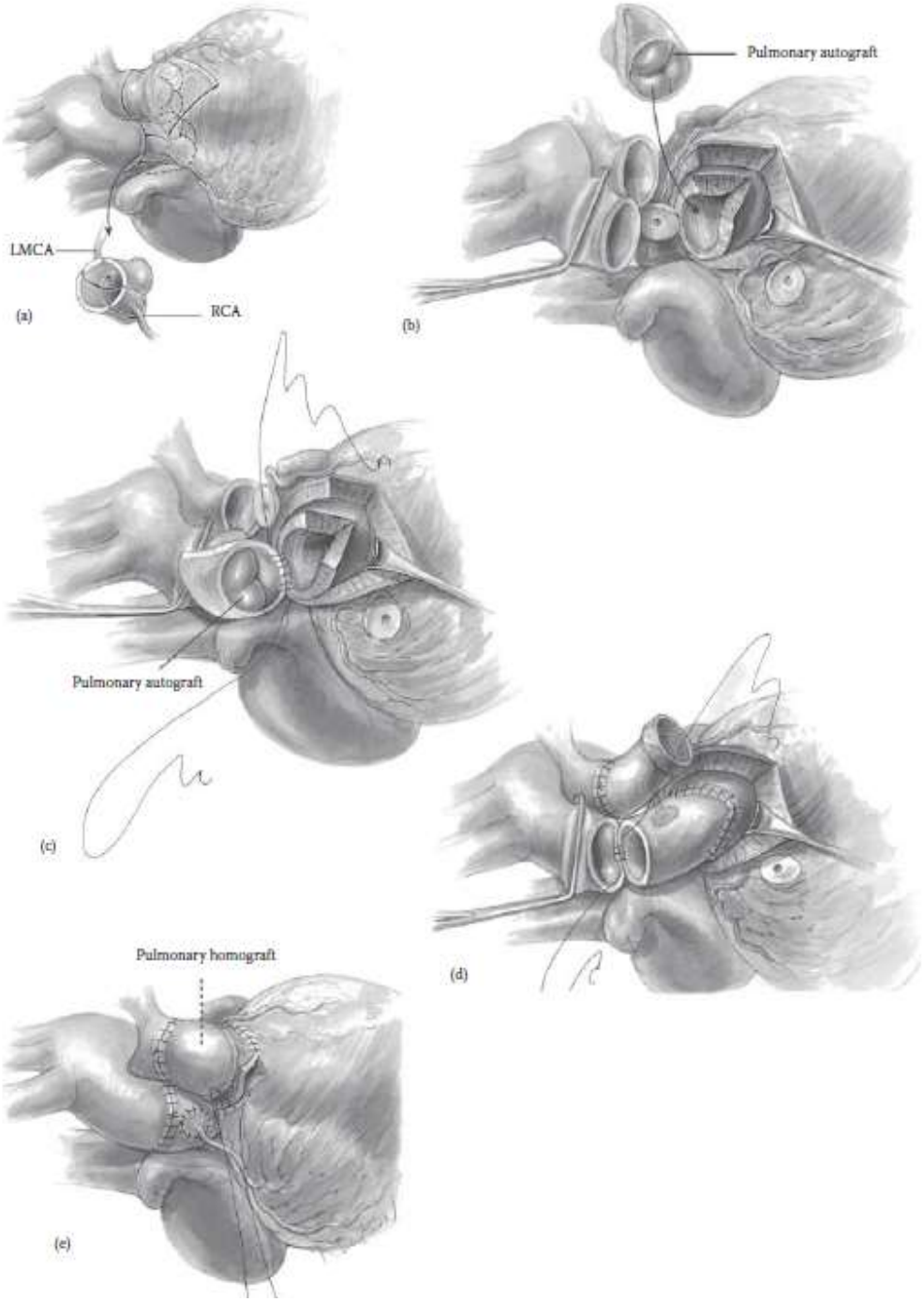
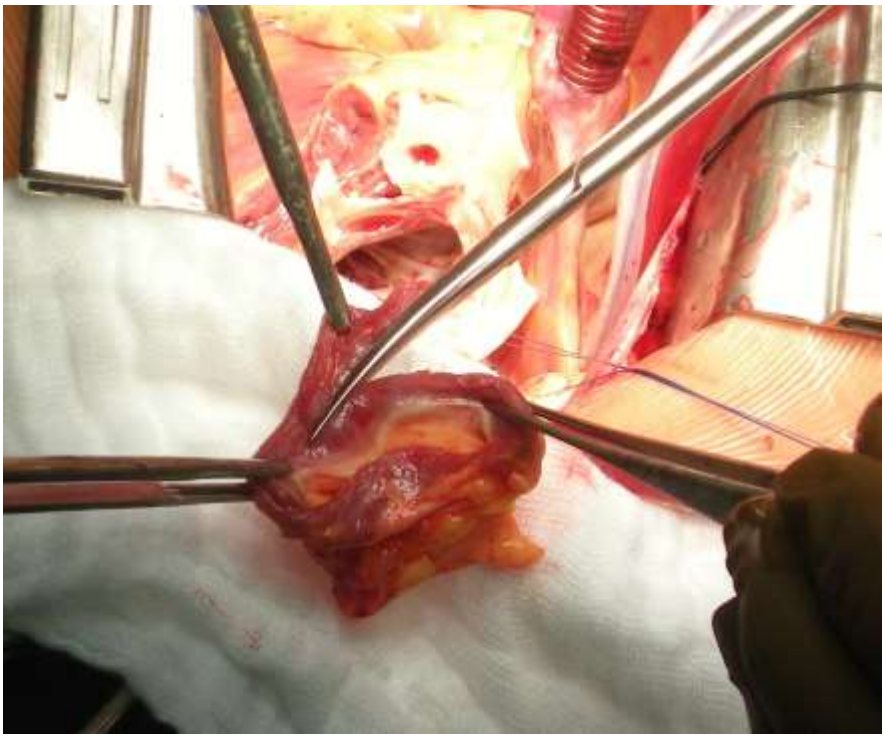
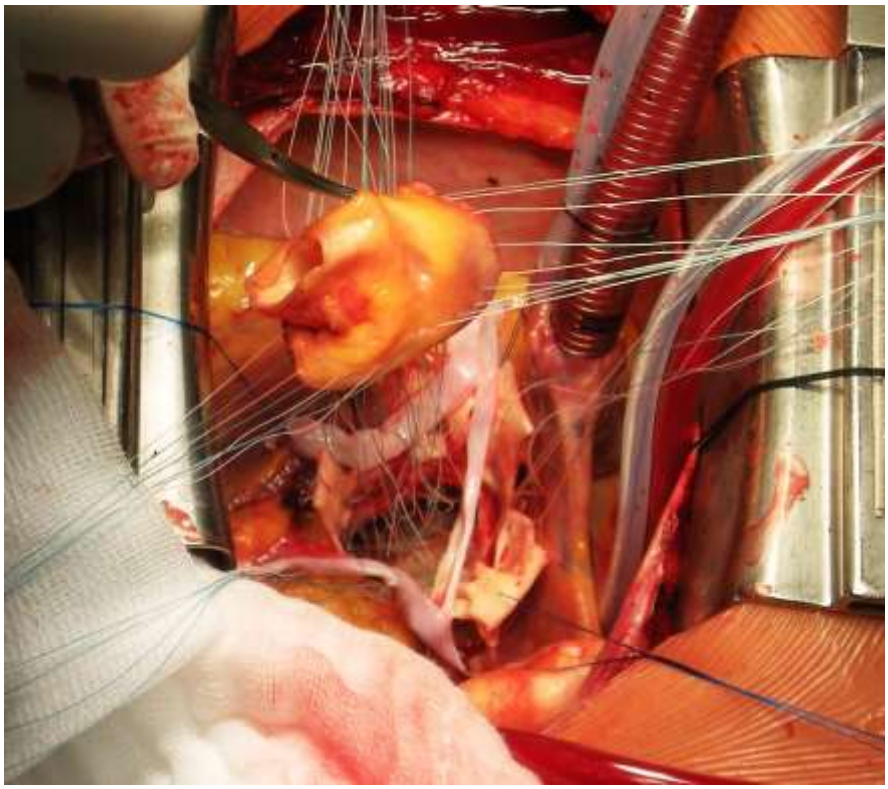


Figure 9. Ross/Konno procedure. (a) The aortic root and aortic valve are completely excised. The coronary arteries are mobilized with generous buttons of aortic wall attached. The pulmonary autograft is harvested. (b) An incision has been made in the ventricular septum thereby opening the subaortic area and aortic annulus as described by Konno. (c) The pulmonary autograft is sutured to the base of the left ventricle using a continuous 4/0 Prolene suture reinforced externally with pledgetted interrupted sutures. (d) The left coronary artery has been implanted. The distal pulmonary homograft anastomosis has been fashioned to begin reconstruction of the right ventricular outflow tract. The distal aortic anastomosis is fashioned before reimplantation of the right coronary artery. (e) The right coronary artery has been implanted following distention of the aortic root with cardioplegia to obtain the site for reimplantation. The proximal anastomosis of the pulmonary homograft to the right ventricular infundibulum is undertaken.

A



B



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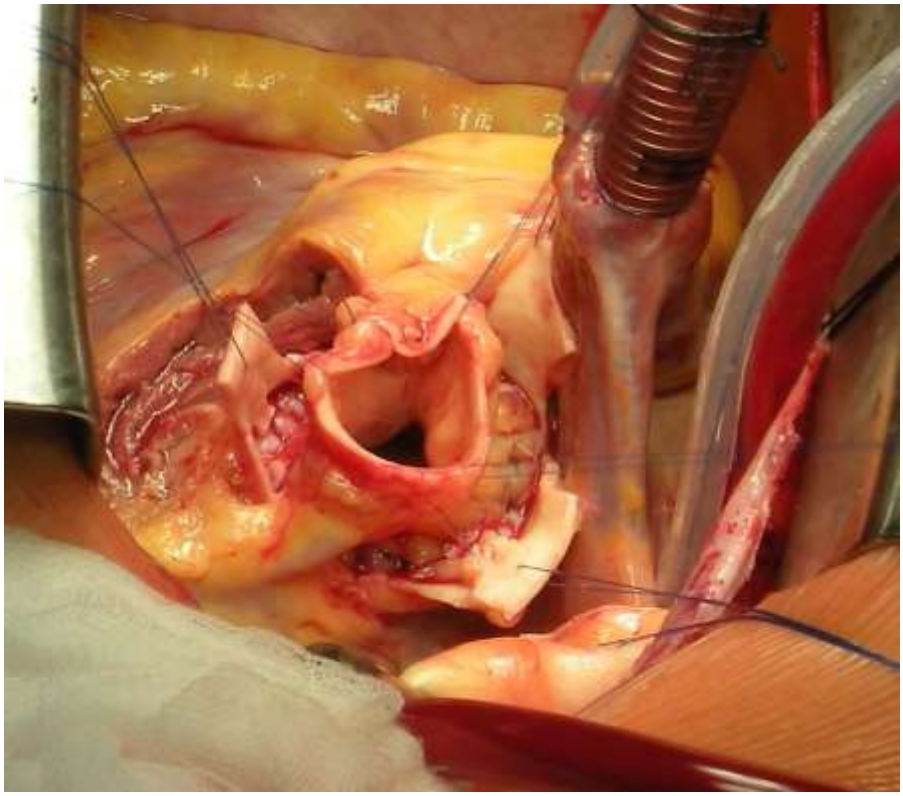

D

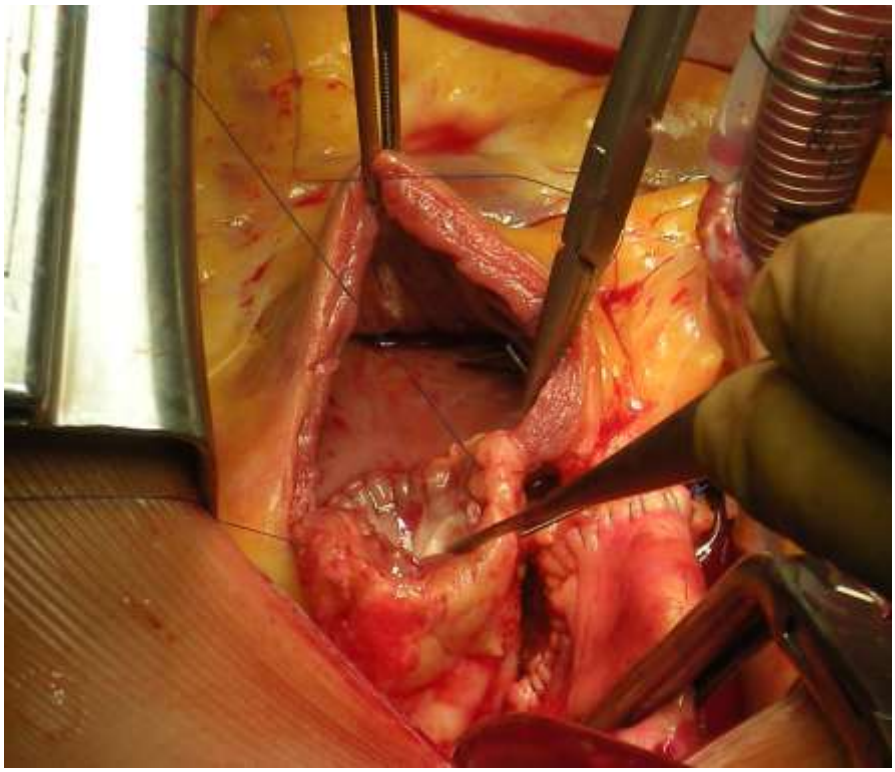

Figure 10. Ross/Konno procedure. (a) Pulmonary autograft explanted from the RVOT and remodeling of muscle tissue, leaving 2-3 mm of muscle tissue under the valve. Muscle tissue acts as a ring to the pulmonary valve as it is not supplied by a true natural ring. (b) Implantation of the pulmonary autograft in the aortic root with single interrupted sutures that are tied to 3 strips of autologous pericardium to further support the root and improve hemostasis (c) Autograft implanted in the aortic root together with the two coronary buttons. (d) Reconstruction of the RVOT with a pulmonary homograft, proximal anastomosis

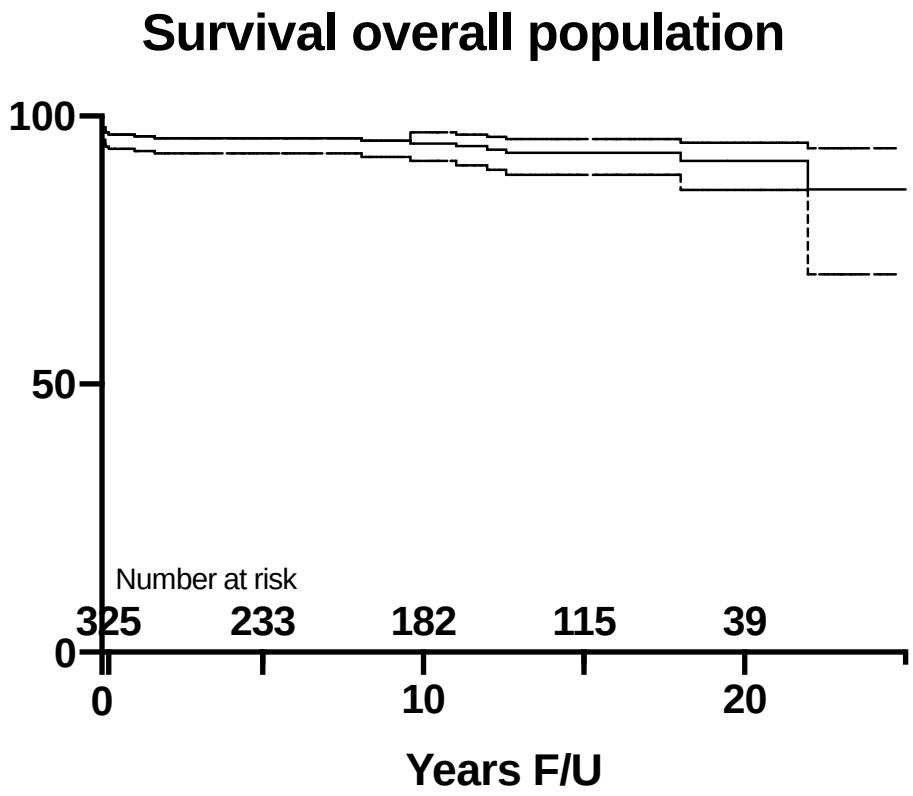

Figure 11. Kaplan-Meier estimates actuarial survival in 325 children after Ross procedure.

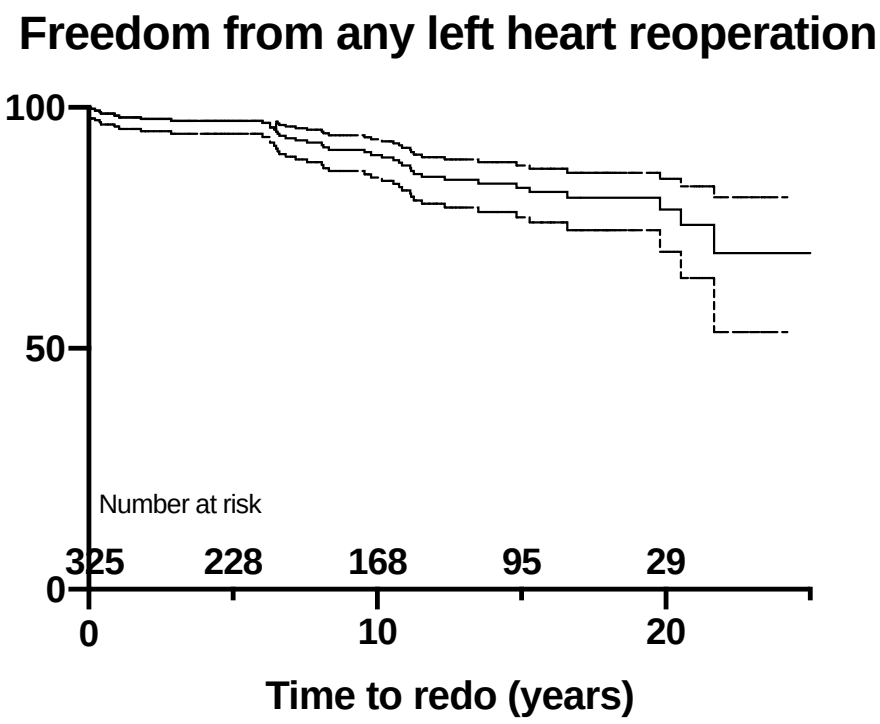

Figure 12 Actuarial freedom from autograft reoperation in 325 children after Ross procedure

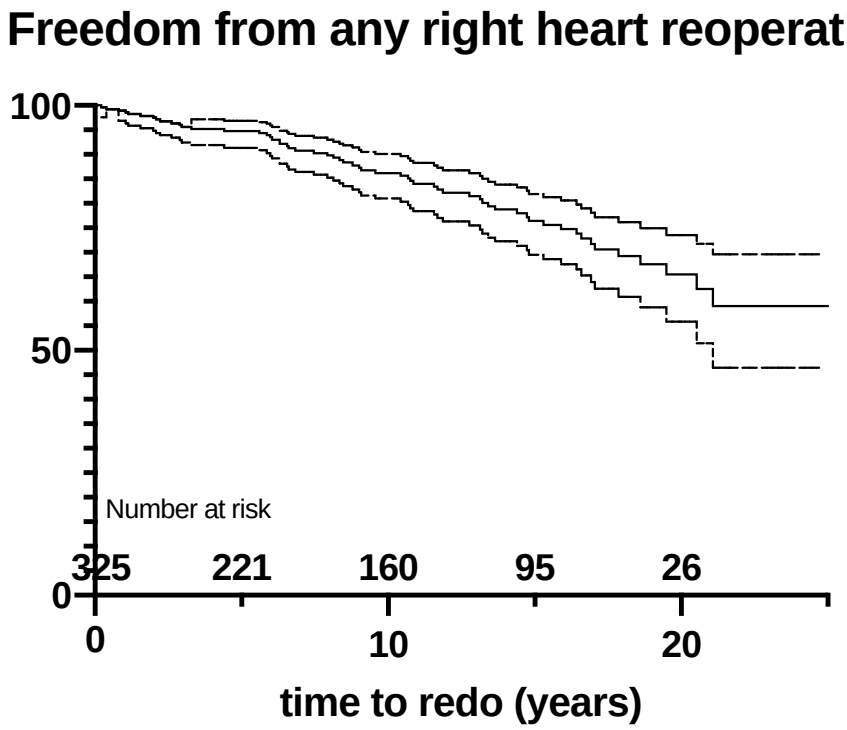

Figure 13 Freedom from autograft reoperation in children after Ross procedure

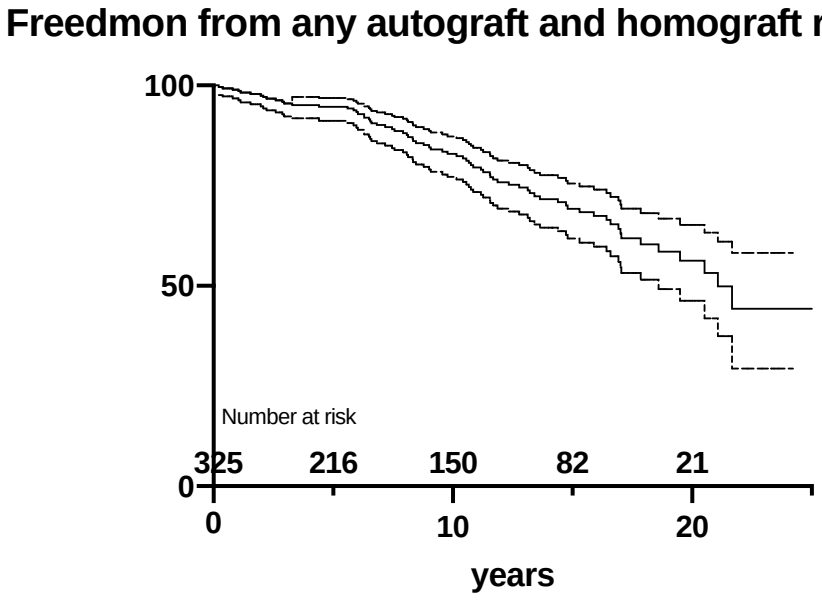

Figure 14. Kaplan-Meier estimates actuarial freedom from any reoperation (left and right heart) in 325 children after Ross procedure.

2. Tables

Table 1. Demographic data

	N (%)	0-12 months	1-12 years	12-18 years
N	325	32 (10)	183 (56)	110 (34)
Median F/U (IQR)	11 (4,2-17)	8,8 (1,7-16,6)	10,5 (3,3-16)	13 (7,3-18)
Median age (IQR)	10 (6-15) years	3.5 (0-8) months	8 (5-10) years	16 (14-17) years
Indications				
Aortic Stenosis	114 (34)	14(44)	59 (32)	35 (32)
Aortic regurgitation	116 (34)	2 (6)	66 (36)	45 (41)
Mixed lesion	109 (32)	16 (50)	58 (32)	30 (27)
Associated lesion	52 (15)	12 (38)	34 (19)	6 (5)
Prior cardiac surgery	116 (34)	13 (41)	75 (41)	26 (24)
Emergent surgery	5 (1)	2 (6)	2 (1)	1 (1)
Techniques				
Root replacement	223 (66)	10 (31)	127 (69)	79 (72)
Ross-Konno	63 (19)	20 (63)	36 (20)	6 (5)
Subcoronary	20 (6)	1 (3)	7 (4)	12 (11)
Inclusion	33 (10)	1 (3)	13 (7)	13 (12)
Associated procedures	37 (11)	11 (34)	20 (11)	5 (5)
Alive	305 (93)	25 (78)	172 (94)	107 (97)

Table 2. Risk Factors for mortality, autograft and homograft reoperation

Mortality	HR	IC 95%	P value
Age <1 year	6	2-15	0.01
Indications			
Aortic Stenosis	1.4	0.6-3.5	0.4
Associated lesion	4.8	2-12	0.001
Prior cardiac surgery	2	0.8-5	0.11
Emergent surgery	3.7	0.5-27	0.2
Associated procedures	10	4-25	0.001
Autograft reintervention			
Age <1 year	0.6	0.14-2.5	0.5
Techniques			
Root replacement	1.3	0.6-2.6	0.5
Ross-Konno	1	0.4-2.5	0.9
Subcoronary	0.4	0.05-2.7	0.03
Inclusion	0.9	0.3-2.9	0.8
Indications			
Aortic stenosis	0.5	0.2-1	0.6
Aortic regurgitation	0.8	0.4-2.3	0.6
Mixed lesion	1.5	0.8-3	0.2
Homograft reintervention			
Age <1 year	3.2	1.6-6	0.001
Indications			
Aortic stenosis	0.5	0.26-1	0.049
Associated lesion	2.5	1.4-4.7	0.002
Techniques			
Root replacement	0.6	0.3-1	0.045

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