Heart Valve Repair in Children

MYERS, Patrick Olivier

Abstract

With improvements in the management of complex congenital heart disease and in valve repair techniques, infants and children are increasingly being referred for valve repair. Surgical management of heart valve disease in children must take into account the specificities of this patient population: (1) the very long expected survival and durability of a repair, (2) allow for growth of the patient, (3) implants calcify much quicker in children, (4) mechanical heart valves and their anticoagulation carry a prohibitive risk of thrombo-embolism and bleeding, as well as panus formation. The present thesis reviews recent advances in valve repair in children, which avoids anticoagulation and its complications and improves survival. Aortic cusp extension valvuloplasty has excellent long-term freedom from reoperation or significant aortic valve regurgitation, although failure is mainly linked to extension patch materials. Mitral and tricuspid valve operations are feasible with good long-term clinical outcomes. Annuloplasty with a biodegradable annuloplasty ring, implanted intra-annularly, provides durable remodeling of the mitral […]

Reference


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"Heart Valve Repair in Children"

Thesis submitted to the Medical School of the University of Geneva

for the degree of Privat-Docent

by

Dr Patrick Olivier MYERS

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Abstract
With improvements in the management of complex congenital heart disease and in valve repair techniques, infants and children are increasingly being referred for valve repair. Surgical management of heart valve disease in children must take into account the specificities of this patient population: (1) the very long expected survival and durability of a repair, (2) allow for growth of the patient, (3) implants calcify much quicker in children, (4) mechanical heart valves and their anticoagulation carry a prohibitive risk of thrombo-embolism and bleeding, as well as panus formation.

The present thesis reviews recent advances in valve repair in children, which avoids anticoagulation and its complications and improves survival. Aortic cusp extension valvuloplasty has excellent long-term freedom from reoperation or significant aortic valve regurgitation, although failure is mainly linked to extension patch materials. Mitral and tricuspid valve operations are feasible with good long-term clinical outcomes. Annuloplasty with a biodegradable annuloplasty ring, implanted intra-annularly, provides durable remodeling of the mitral and tricuspid annulus, while allowing for growth in children. Leaflet tethering is an important mechanism of regurgitation in children, and both leaflet suspension and right ventricular papillary muscle to the ventricular septum have been shown to be safe and effective as an additional tool in the surgical armamentarium. Multiple valve repair is feasible with good early- and mid-term results, although this is only a palliative approach to delay valve replacement. Using the techniques describes above to relieve inflow (mitral) and outflow (aortic) obstruction, as well as resection of endocardial fibro-elastosis and restriction of the atrial septal communication, it is feasible to bring selected patients with hypoplastic left heart syndrome to a biventricular repair with excellent results.

These strategies will help improve the long-term outcomes for children with heart valve disease.
Introduction

Definitions of Heart Valve Functional Lesions

Heart valves can be affected by regurgitation, stenosis or mixed disease. In regurgitation or insufficiency, the valve leaflets abnormally allow blood to flow through them at a time point in the cardiac cycle, which normally requires them to be closed and prevent blood flow through the valve. In stenosis, the valve opening is insufficient for the blood flow, either from leaflet mobility restriction, commissural fusion or dysplasia, or from hypoplasia of the valve annulus, creating obstruction. Mixed valve disease shows a combination of regurgitation and insufficiency.

Carpentier divided the mechanism of valvular regurgitation depending on leaflet mobility (see Table 1) in his seminal description (1). Although first described for the mitral valve, this classification has been applied to the tricuspid and aortic valve (see Table 1) (2).

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Normal leaflet motion." /></td>
<td><img src="image" alt="Enhanced leaflet motion." /></td>
<td><img src="image" alt="Restricted leaflet motion." /></td>
</tr>
<tr>
<td>Regurgitation is due to leaflet perforation or annular dilatation</td>
<td>Regurgitation is due to leaflet prolapse with lack of coaptation.</td>
<td>Leaflets do not have enough mobility to reach the coaptation plane.</td>
</tr>
</tbody>
</table>

Table 1 – Carpentier physiopathological classification of mechanism of regurgitation for the mitral valve. Leaflet position is depicted in systole (solid lines), with leaflet position in diastole in dotted lines and leaflet excursion in pale blue.
Table 1 – Repair-oriented functional classification of aortic insufficiency (AI). FAA, Functional aortic annulus. Reproduced from Boodhwani et al. (2)

**Treatment Options for Heart Valve Disease in Children**

In adults with heart valve disease, medical management in well-tolerated heart valve disease is the first line of treatment. Surgical intervention to repair the hemodynamic lesion created by severe heart valve disease is required when symptoms appear, either through replacement of the heart valve with a prosthetic valve, or through valve repair (3). The timing of surgery is of paramount importance, as offering surgery too early needlessly exposes patients to the risks of an open heart procedure, and offering it too late may increase the operative risk. Current guidelines are increasingly recommending intervention at an earlier stage in asymptomatic patients who have shown decrease in the systolic ventricular function, or significant dilation of the ventricle (3), to prevent irreversible ventricular dysfunction and heart failure.

Since the pioneering work by Alain Carpentier in developing surgical techniques to repair the aortic, mitral and tricuspid heart valves (1), valve repair has become the standard in managing disease of the mitral valve, with excellent long-term survival and freedom from reoperation (4), including in complex lesions such as anterior and bileaflet prolapse (5). Mitral valve repair has been shown to have long-term survival, freedom from reoperation, freedom major adverse cardiovascular events and cost-effectiveness superior to mitral valve replacement (1, 6-10). This
has lead to a near 100% rate of mitral valve repair rather than replacement in adults treated in selected reference centers (11). Standardized, reproducible, and stable long-term results of mitral valve repair are three key factors that have encouraged surgeons to apply this conservative approach on the aortic (2, 12, 13) and tricuspid valves, although both the results and adoption have been much less dramatic than for the mitral valve.

Children are increasingly being referred for valve repair (see figure 1), which likely results from the improving survival for complex congenital heart disease (14) and the focus on the development of valve repair and complex reconstruction rather than replacement (15).
Figure 1 – Mitral and aortic valve operations at Boston Children’s Hospital, 2005-2010.

Upper panel reproduced with permission from (16); lower panel reproduced with permission from (15). Canal: atrioventricular canal repair with mitral cleft closure; MV: mitral valve.

Compared to the data available on valvular heart disease in adults, there is a relative paucity of data on valvular heart disease in children, coming mostly from single center retrospective reviews. The indications for intervention are essentially clinically guided, based on
clinical assessment and application of adult valvular heart disease management guidelines. Valve repair has been shown to provide a clear survival advantage over valve replacement in children (16, 17) (see figure 2).

![Image](image_url)

**Figure 2 – Kaplan–Meier survival analysis of postoperative long-term survival in patients undergoing mitral valve repair versus mitral valve replacement.** Reproduced with permission from (16). MV: mitral valve.

**Specificities of Valve Repair and Replacement in Children**

Valve surgery in a growing child must take into consideration the specifics of this patient population: firstly that a child, depending on associated lesions, is expected (or at least hoped) to survive a very long time, much longer than typical adults undergoing cardiac surgery for acquired heart disease. This increases considerably the requirements on durability of the repair or replacement.

Secondly, any procedure should allow for growth of the valve being operated on, proportional to somatic growth of the patient. As with all other cardiac structures, heart valves
grow during the somatic growth of the child (see Figure 3). Off-the-shelf prosthetic valves don’t grow, meaning that small children who require valve replacement will invariably require a reoperation to replace a prosthetic valve which has become too small, sometimes requiring supra-annular placement to be able to fit a sufficiently large prosthesis (18-20) or annular enlargement at re-replacement (21). Standard annuloplasty rings used in adults for mitral or tricuspid valve repair, which ensure stable long-term results of repair by remodeling the annulus, also don’t grow, and aren’t used in small children (14). Alternative techniques of annuloplasty, such as the Kay-Wooler commissural reduction annuloplasty (22), Paneth-type suture annuloplasty (23), partial or interrupted ring of autologous pericardium or expanded polytetrafluoroethylene (ePTFE) patches (24), are used to stabilize the annulus. More recently, our group has developed a biodegradable annuloplasty ring (25, 26), in the hopes to provide the long-term benefits of an annuloplasty ring to children while allowing for growth potential.
Figure 3 – Growth of the mitral and tricuspid annulus during normal somatic growth in children. (A) Growth curve for the mitral annulus antero-posterior dimension. (B) Growth curve for the lateral dimension of the mitral annulus. (C) Growth curve for the lateral dimension of the tricuspid annulus. Solid lines indicate mean values, dotted lines indicate 95% confidence interval. Reproduced with permission from King et al. (27)

Thirdly, implants don’t behave the same way in children as in adults. Bioprosthetic valves, which include treated bovine pericardium or treated porcine aortic tissue for their leaflets,
or allogenic homografts, degrade with time by calcification. Treated patch materials used to augment or extend leaflets also calcify with time. Children have an increased calcium metabolism compared to adults, and calcify much quicker any material prone to calcification.

Fourthly, mechanical prosthetic valves, although engineered to last as long or longer than the life expectancy of the patient the valve is being implanted in, require life-long anticoagulation to avoid thrombo-embolism. Anticoagulation is not without risk (28): frequent blood testing is required, and being off target (over- or under-dosed anticoagulation) exposes patients to the risks of thrombo-embolism and bleeding. Patients on anticoagulation are restricted in their physical activities and any activities with a risk of injury, such as contact sports, due to the increased risk of bleeding. Coumadin also carries significant risks of bleeding during pregnancy and giving birth; childbearing is thus usually considered contra-indicated in patients with mechanical heart valves. On optimal management, anticoagulation for a mechanical prosthetic heart valve is considered to carry a risk of bleeding or thrombo-embolism of approximately 2% per year. In a young child, with a life expectancy beyond 30-60 years, the cumulative risk becomes very high, if not prohibitive. Alternatives to valve replacement, which don’t require anticoagulation and avoid implanting tissue at risk of early calcification, are desirable.

The present thesis intends to review recent advances in surgical repair of valvular heart disease in children. The first chapter will review recent contributions on aortic valve repair in children, focus on cusp extension valvuloplasty and illustrate a subset of patients with aortic valve disease concomitant with truncus arteriosus communis (e.g. truncal valve repair). The second chapter will review recent contributions on mitral and tricuspid valve repair in children, with a particular attention on annuloplasty using a biodegradable annuloplasty ring developed for pediatric valve repair, and techniques to relieve leaflet restriction or tethering, a major cause of mitral or tricuspid regurgitation in children. The third chapter will review recent contributions on multiple valve repair in children. The fourth and final chapter will review how, by applying the valve repair techniques outlined above, the surgical management of borderline hypoplastic left
heart syndrome is changing from the Norwood paradigm of single ventricle palliation to a paradigm of biventricular repair through staged left ventricular recruitment.

References


Chapter 1 - Aortic Valve Repair

Aortic Valve Reconstruction in the Young Infants and Children


Abstract

Considering the structure and function of the aortic root, changes in the aortic valve leaflets and changes in the geometry of the aortic root are the two primary causes of aortic valve dysfunction. In adults, aortic valve sparing reconstruction has a long history beginning in the 1970s, where tensor fascia was used for leaflet repair in patients with isolated aortic regurgitation and ascending aortic replacement was used in patients with ascending aortic aneurysms or aortic ectasia. Subsequent progress in the 1980s and 1990s led to pericardial leaflet replacement and aortic root re-implantation and remodeling. However, it has not been until the last decade that these concepts and techniques have been applied in younger patients focusing on the conotruncus, valvar apparatus, sino-tubular junction, and ascending aorta.
Introduction

The timing of surgical intervention for aortic valve disease in infants and children is often difficult because of the potential need for replacement. However, over the past 5 years at Children’s Hospital Boston, we have seen a significant increase in the number of referrals of patients at an earlier stage of the disease than previously, for surgical aortic valve repair (Fig. 1). This likely results from the focus on reconstructive rather than replacement techniques.

The most common congenital heart defect is a bicuspid aortic valve (BAV); infants and young children presenting for intervention often have congenital aortic stenosis (AS), with leaflet deformity being the most common indication. Historically, young infants with congenital AS have presented in the neonatal period for surgical valvotomy. However, because of its success, balloon aortic valvuloplasty has now become the preferred treatment for neonates and infants with congenital AS at most centers. Between 1984 and 2008, 563 patients with congenital AS underwent balloon aortic valvuloplasty at Children’s Hospital Boston. Peak AS gradients were significantly decreased and neonates had significantly lower residual gradients. However, surgical
intervention was ultimately required in 28% of patients at 5 years. In this subset of patients, aortic valve reconstruction has generally focused on leaflet reconstruction. In older children, aortic dilatation leading to aortic regurgitation (AR) has generally been recognized with conotruncal congenital heart defects, including tetralogy of Fallot, pulmonary atresia with ventricular septal defect (VSD), truncus arteriosus, and double outlet right ventricle. We have begun to focus on aortic root remodeling techniques along with leaflet repair as needed in these patients.

**Advantages of Aortic Valve Reconstruction**

Historically, options in neonates and small infants have been limited to pulmonary autografts (Ross Procedure) or aortic homografts, while larger infants and children often received oversized mechanical prosthesis. In patients undergoing the Ross procedure, a number of studies have demonstrated that both the neoaortic root and sino-tubular junction (STJ) diameters increase out of proportion to somatic growth ultimately resulting in neo-AR. Furthermore, Kadner et al reported an overall reoperation rate of 43% at 10 years with a hospital mortality for the reoperation of 10%. Pasquali et al reported a re-intervention rate on right and left ventricular outflow tracts of 19% and 17%, respectively, at 8 years, with smaller homograft size (ie, infants and young children) being the strongest predictor of right ventricular outflow tract re-intervention.

While there are ongoing controversies surrounding conversion of single valve disease to two valve disease, the unreliable nature of homografts associated with the Ross procedure, and the management, poor compliance, and complications associated with anticoagulation for mechanical prosthesis; clearly freedom from hemodynamic compromise and the avoidance of anticoagulation are agreed upon and can be achieved with reconstruction rather than replacement. Potential advantages of aortic valve repair include: low incidences of thrombo-embolism and endocarditis, no need for conduit replacements, the maintenance of aortic root growth potential, and improved quality of life by avoiding anticoagulation. Over the last decade, aortic valve
repair has emerged as an attractive technique and is being applied more commonly in infants and young children.\textsuperscript{12,13}

**Anatomy and Classification**

A reconstructive approach to the aortic valve requires a complete understanding of valve anatomy, valve function, assessment, and classification of pathologic lesions.\textsuperscript{1} The annulus of the aortic valve consists of three separate components, including the sinotubular junction, the ventriculo-aortic junction, and the annulus, which work together to facilitate normal valve function. As Boodhwani and El Khoury elegantly outline in Figure 2, the repair techniques and classification of aortic valve disease are best defined by the mechanism of dysfunction. Although it is important to consider each of the potential mechanisms, it is particularly important to consider conotruncal and leaflet abnormalities (including Type II-cusp prolapse and Type III-cusp restriction) in infants and young children.\textsuperscript{14}
Figure 2 - Classification of aortic insufficiency (AI) encompasses all the mechanisms of aortic insufficiency, provides a common language for discussion among clinicians, and guides the repair techniques. In this classification (as in the mitral valve), AI associated with normal leaflet motion is designated as Type I and further divided into subtypes based on the specific pathologic condition. Type 2 AI is caused by excessive cusp motion (ie, cusp prolapse), and Type 3 AI is due to restrictive cusp motion as seen in rheumatic disease and in BAVs. a, artery; AI, aortic insufficiency; FAA, functional aortic annulus; SCA, sub-commissural annuloplasty; STJ, sinotubular junction. (Reprinted with permission.14)

Imaging of the Aortic Valve Complex

To provide optimal treatment of the entire affected valve complex, it is important that systematic examination begins early. We often obtain preoperative 3-dimensional echocardiography (3D-echo), which improves our ability to access more anatomic features.15 It
allows a detailed assessment of the entire aortic valve complex, including the subvalvar area, annulus, leaflets, sinuses, and STJ. Dimensions of the annulus, sinus, STJ, and ascending aorta are important measurements because they facilitate remodeling of the aortic root on the arrested heart. For example, in the case of thickened leaflets, 3D-echo helps to plan appropriate solutions to achieve the optimal coaptation surface. It potentially facilitates the measurement of the area of the aortic cusps and/or the deficient leaflets. Figures 3 and 4 demonstrate 3D-echo images of the aortic valve in a patient with severe congenital AR before and after surgical aortic valvuloplasty.¹⁶

**Figure 3** - This represents a patient with a deficient left coronary leaflet (LCL): 3D intraoperative quantification of leaflets areas and deficiencies. NCL, noncoronary leaflet; RCL, right coronary leaflet. (Reprinted with permission.¹⁵)

**Figure 4** - Matrix array 3D-echo images of aortic valve in a patient with severe congenital AR before (Pre) and after (Post) surgical aortic valvuloplasty. The image before surgical aortic valvuloplasty (top) demonstrates partial left-right leaflet fusion, large central deficiency in fused left-right leaflet, and thickening of all leaflets. The image after surgical aortic valvuloplasty
(bottom) demonstrates three well-formed leaflets that have excellent coaptation. There was no AR after surgical aortic valvuloplasty. R, right leaflet; L, left leaflet; N, noncoronary leaflet. (Reprinted with permission.4)

**Disease Primarily Involving Aortic Valve Leaflets**

Generally, infants and young children presenting for surgical aortic valve reconstruction started off with severe congenital AS with a bicuspid or unicuspid aortic valve (Fig. 2.5A and B), which later evolved to mixed stenosis and regurgitation or primarily regurgitation, particularly late after initial interventions as neonates and young infants. Analysis of BAV morphology is also of additional clinical and prognostic relevance. Fusion of the right coronary and non-coronary leaflets is associated with more significant valve pathology, whereas fusion of the right and left coronary leaflets has been shown to be associated with aortic coarctation but less aortic valve pathology.17
Figure 5 - **A**, The unicusp aortic valve has the classic “toilet seat” appearance, with two primitive unsupported thickened raphe. **B**, The BAV has two developed commissures and a single primitive unsupported thickened raphe. LCA, left coronary artery; RCA, right coronary artery. (Reprinted with permission.)

Although there are many surgical options for repairing the aortic valve, including direct repair of torn leaflets, commissurotomy (Fig. 2.6A), repair of prolapsed leaflets by resuspension (Fig. 6B), thinning of leaflets, free-edge shortening of the leaflets, closure of fenestrations, and extension of leaflets, complex repair in infants and children often requires more innovative and advanced techniques. In patients with significant cusp prolapse, usually patients in their teen years or older, Boodhwani et al report success with several techniques, including plication of the free cusp margin and triangular resection of the central portion of the cusp.
Figure 6 - Superior view of the aortic valve. A, This schematic shows an aortic commissuroplasty that is commonly used in situations with mild central regurgitation and a mildly dilated annulus. B, This schematic illustrates the classic “Trussler” repair of aortic valve insufficiency that originates from a prolapsing redundant leaflet that has had elongation of its free edge from chronic prolapse, as is often seen in outlet-type VSDs. (Reprinted with permission.17)

Infants and young children born with unicuspid or BAV (Fig. 5) have often undergone multiple catheter-based interventions that resulted in insufficiency and/or residual stenosis. As balloon aortic valvuloplasty has become the preferred treatment for neonates, infants, and young children with congenital AS, it has introduced another particularly important pathologic finding. When balloon valvuloplasty is performed, it routinely tears a portion of the fused leaflet of the right coronary sinus, which often results in a prolapsing segment of the anterior leaflet and AR.21 Although many of the reported aortic valve repair techniques have been pioneered in older patients (see Table 1), we often apply them in young infants and children.
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Age Range</th>
<th>Patients</th>
<th>Disease</th>
<th>Technique</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myers et al</td>
<td>JCTVS</td>
<td>2010</td>
<td>(12.3 ± 3.5 y) mean</td>
<td>78</td>
<td>Rheumatic</td>
<td>3 Cusp extension-Fresh auto PC, PF bov PC, Glut bov PC</td>
<td>5, 10, 15 yr FF Re-operation = 86%, 81%, 75%</td>
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<td>Polimenakos et al</td>
<td>JCTVS</td>
<td>2010</td>
<td>&lt;19 y</td>
<td>142</td>
<td>Congenital AS, Rheu, etc.</td>
<td>3 Cusp extension-glut (.625%), 3 m auto PC</td>
<td>18 yr FF Any Intervention = 50%; 1.5,10,18 yr FF AVR = 98%, 80%, 72%, 60%</td>
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<td>Schäfers et al</td>
<td>ATS</td>
<td>2008</td>
<td>4-39 y</td>
<td>21</td>
<td>Assoc VSD, Rheu, endo</td>
<td>1 Cusp - bovine PC</td>
<td>1 yr FF Re-operation = 100%</td>
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<td>Bacha et al</td>
<td>JCTVS</td>
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<td>&lt;19 y</td>
<td>81</td>
<td>Multiple</td>
<td>Multiple techniques</td>
<td>4 yr FF Re-operation = 67%, 4 yr FF AVR = 100%</td>
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<td>Aicher et al</td>
<td>JCTVS</td>
<td>2007</td>
<td>3-86 y</td>
<td>427</td>
<td>Congenital AS, Rheu, etc.</td>
<td>3,2,1 Cusp extension - glut (1%, 2-3 m auto PC)</td>
<td>5 yr FF Re-operation = 94%, 5 yr FF AVR = 98%</td>
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<td>Hawkins et al</td>
<td>JCTVS</td>
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<td>2d-18 y</td>
<td>54</td>
<td>Congenital</td>
<td>Multiple techniques</td>
<td>FF Re-intervention: 1 y = 91%, 5 y = 63%,7.5 y = 41%; FF AVR: 5 y = 72%,10 y = 54%</td>
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<td>Alsoufi et al</td>
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<td>5-18 y</td>
<td>22</td>
<td>Congenital AS</td>
<td>3 Cusp extension-glut (.625%), 5 m auto PC</td>
<td>2.5 yr FF Re-operation = 80%, 5 yr FF AVR = 75%</td>
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<td>Leusberg et al</td>
<td>EJCTS</td>
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<td>(52 ± 19 y) mean</td>
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<td>Single patch - glut (0.2%, 1.2 m) auto PC</td>
<td>5 yr FF Re-operation = 97%</td>
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<td>Prêtre et al</td>
<td>EJCTS</td>
<td>2006</td>
<td>10-27 y</td>
<td>12</td>
<td>Congenital bicuspid AoV</td>
<td>Single patch - glut (0.2%, 1.2 m) auto PC</td>
<td>Follow-up 3-46 months; “remained stable”</td>
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<td>Odim et al</td>
<td>ATS</td>
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<td>10d-81 y</td>
<td>62</td>
<td>Congenital</td>
<td>2.3 Cusp extension-glut (.625%), 9 m auto PC</td>
<td>2 yr FF Re-operation = 90% (trileaflet), 70% (bileaflet)</td>
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<tr>
<td>Al Halsees et al</td>
<td>EJCTS</td>
<td>2005</td>
<td>12-68 y</td>
<td>92</td>
<td>Rheumatic</td>
<td>3 Cusp extension-glut (0.5%, 10 m) auto PC</td>
<td>10, 16 yr FF Re-operation = 68%, 47%</td>
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<td>Tweddell et al</td>
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<td>2005</td>
<td>11d-36 y</td>
<td>**57</td>
<td>Congenital AS, Rheu, Endo</td>
<td>Multiple techniques, (<strong>complex</strong>)</td>
<td>FF Re-intervention: 1 y = 94%, 5 y = 85%,10 y = 44%; FF AVR: 1 y = 96%, 5 y = 77%,10 y = 77%</td>
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<td>Bezbuga et al</td>
<td>ATS</td>
<td>2004</td>
<td>15-58 y</td>
<td>46</td>
<td>Rheumatic</td>
<td>3 Cusp extension-glut (.62%, 5 m) auto PC</td>
<td>7.5 yr FF Re-operation = 76%</td>
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<td>Aln et al</td>
<td>EJCTS</td>
<td>2002</td>
<td>16-68 y</td>
<td>34</td>
<td>Not specified</td>
<td>3 Cusp extension-glut (.625%), 15 m auto PC</td>
<td>1, 5 yr FF Re-operation = 94%, 94%</td>
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<td>ATS</td>
<td>2002</td>
<td>6-32 y</td>
<td>89</td>
<td>Rheumatic</td>
<td>3 Cusp extension-glut (.62%, 8 m) auto PC</td>
<td>5 yr FF Re-operation = 92%</td>
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<td>(11.5 ± 2.7 y) mean</td>
<td>41</td>
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<td>Duran et al</td>
<td>ATS</td>
<td>1998</td>
<td>12-68 y</td>
<td>91</td>
<td>Congenital AS, Rheu, etc.</td>
<td>3 Cusp extension-glut auto PC (.5%, 10 m, bovine PC)</td>
<td>8 yr FF Re-operation = 70% (bovine), 76% (autologous)</td>
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</tbody>
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Abbreviations: AoV, aortic valve; AS, aortic stenosis; AVR, aortic valve replacement; Endo, endocarditis; FF, freedom from; glut bov, gluteraldehyde bovine; PF, photofix; PC, pericardium; Re-intervention, Re-interventionrevention; Rheu, rheumatic; VSD, ventricular septal defect.

**This manuscript was an update to Kalangos' paper from 1988 and included all of these prior patients.**

*Represents studies including infants and children.
**Aortic valve leaflet repair techniques.** Pericardium is generally harvested and fixed in 0.6% gluteraldehyde for a short period of time (2 to 3 minutes). After establishing mildly hypothermic cardiopulmonary bypass, aortic cross-clamping, and cardioplegic arrest, each part of the aortic valve complex is examined from the leaflet edges to the aortic root. Commonly, there is preserved coaptation between the left and non-coronary leaflet with a tear in the anterior leaflet and resultant prolapse. The leaflet edges are extensively debrided of any fibrotic membrane that often extends into the subaortic area. Generally, the unsupported commissure (or raphe) between the relatively preserved left and deficient right coronary leaflet is sutured to the aortic wall, creating a neo-commissure. When there is at least one relatively normal leaflet, we have commonly used a Prêtre technique (Fig. 7), where by the fused leaflet is removed from the annulus creating a more normal non-coronary leaflet with the creation of a right coronary leaflet from autologous pericardium. In our early experience, we then simply replaced a triangular portion of the very deficient right coronary leaflet with autologous pericardium. However, more recently we have paid particular attention to the height of the commissures and attempted to use the residual right leaflet to augment the non-coronary leaflet (labeled R2 in Fig. 8A) and commissural height, followed by replacement of the entire right coronary leaflet (Fig. 8B). This allows more precise commissural apposition and improved coaptation, while creating a more native appearing tri-leaflet valve (Fig. 8B).
Figure 7 – Superior view of a BAV. Prêtre’s technique involves sharply incising the aortic valve leaflet at the annulus. The fused leaflet is then trimmed and reconstructed into an acceptable non-coronary leaflet. The right coronary leaflet is created with a patch of pericardium. R, right coronary sinus; L, left coronary sinus; NC, non-coronary sinus. (Reprinted with permission.21)

Figure 8 - A, Schematic of a BAV where the right leaflet has been previously torn at a prior aortic balloon valvuloplasty. Portions of the right leaflet are used to support the raphe and to
extend the height of the non- and left coronary leaflets. B, The right leaflet is then replaced with lightly tanned autologous pericardium. L, left coronary leaflet; R, right coronary leaflet; MV, ant leaflet of mitral valve; R1 and R2, divided raphe; N, non-coronary leaflet. (Reprinted with permission.)

When there is extensive and more complex disease involving all leaflets, bicuspidization or tricuspidization using autologous pericardium as leaflet extensions can be considered (Fig. 9). Following extensive debridement, the treated autologous pericardium is fashioned to precise measurements and customized (Fig. 3). Each of the leaflets are sewn to the residual leaflet or root. The commissures are then created by sewing each of the two leaflets and the aortic wall together upwards, toward the new sinotubular junction (Fig. 10).

Figure 9 - A, Schematic showing measurements being taken using a silk tie. It is particularly important to take the measurements on a “stretched” leaflet so not to foreshorten the leaflet extension, which can lead to stenosis and/or regurgitation. B, The height of the leaflet extension(s) should be equal to optimize coaptation. L, left coronary leaflet; R, right coronary leaflet; N, non-coronary leaflet. (Re-printed with permission.)
Figure 10 - Schematic showing completed repairs after (A) 3-leaflet and (B) 2-leaflet extensions. (Reprinted with permission.)

**Results of aortic valve leaflet repair.** Outcomes from complex aortic valve repair in infants and small children are limited and difficult to ascertain. However, based on multiple studies (Table 1), \(^4,12,23\) using many of the techniques described, 5- and 10-year freedom from re-intervention is between 65%-85% and 45%-60%, respectively; while 5- and 10-year freedom from aortic valve replacement is between 70%-80% and 55%-75%, respectively. Table 1 summarizes these results. In our earlier experience, outcomes were slightly better with pure AR compared with mixed AR/AS disease. Estimated freedom from aortic valve replacement was 72% ± 6% at 5 years and 54% ± 9% at 7.5 years, and was shorter in patients with moderate or severe AS before surgical aortic valvuloplasty (Fig. 11). \(^4,24-27\)
**Figure 11** - Children’s Hospital Boston data 1989-2005. Kaplan–Meier graph demonstrating freedom from aortic valve replacement (AVR) among patients with moderate or greater aortic stenosis (AS) before surgical aortic valvuloplasty and those with less than moderate AS. Numbers of patients at risk at 0, 1, 3, 5, 7, 9, and 11 years are listed. (Reprinted with permission.)

**Disease Primarily Involving the Conotruncus**

Aortic dilatation and AR has generally been recognized in older children and young adult patients with conotruncal congenital heart defects, including tetralogy of Fallot, pulmonary atresia/VSD, truncus arteriosus, and double outlet right ventricle. There have been a number of reports correlating definitive late repair with increased amounts of aortic root dilation and AR. Dodds et al\(^3\) first reported progressive AR and aortic root dilatation (Fig. 12) after complete, uncomplicated repair of tetralogy of Fallot or pulmonary atresia/VSD. When Niwa\(^2\) examined aortic specimens from patients with conotruncal anomalies, all patients (despite early or late complete repair) had significant medial wall abnormalities like that of Marfan’s patients, suggesting that the progression of aortic root dilation is associated with an intrinsic aortopathy. Thus, the pathology of aortic root dilatation and AR in conotruncal abnormalities is likely a
combination of increased aortic blood flow before complete repair and intrinsic vascular structural abnormalities in the aortic wall. In addition to secondary AR from aortic root dilation, it is important to consider other etiologies of AR in these patients. Many of these patients also appeared to have AR related to prior aortic valve injury at the time of complete repair, secondary to endocarditis, or residual VSD requiring other valve repair techniques.

Figure 12 - Schematic illustrations showing external fibrous annulus reduction. The annulus was reduced with specially designed strips along the luminal and adventitial aspect of the fibrous portion of the left ventricular outflow tract. R, right coronary leaflet; L, left coronary leaflet; N, non-coronary leaflet. (Reprinted with permission.36)

Subcommissural aortic valve annuloplasty. During the last decade, valve sparing operations have become an attractive alternative in older patients. Advances in anatomic and physiologic understanding of the aortic valve complex resulted in two different procedures being described. Yacoub’s “remodeling” technique reduces the diameter at the sinotubular junction and creates three neo-sinuses of valsalva32 and David’s “re-implantation” technique reduces the annulus and abolishes the sinuses.33 Others have since combined the advantages of both procedures by adding an external (Fig. 12)34 or internal (Fig. 13)35 subvalvular prosthetic partial/full ring annuloplasty to the physiological reconstruction of the fibrous portion of the aortic root. Recently, we have begun to apply these principles in children with conotruncal disease, whereby subcommissural annuloplasty allows us to address subvalvar dilation at the
aorto-ventricular junction. If placing a complete ring, particular care must be taken above the comissure between the non-coronary and right coronary sinuses of Valsalva to avoid damage to the bundle of His. In smaller infants and children where annular growth is necessary, an absorbable suture tightened over a dilator based on a predicted annular size can be used (Fig. 14).

**Figure 13** – Schematic illustrations showing internal fibrous annulus reduction. (Reprinted with permission.³⁵)

**Figure 14** – Schematic illustrations showing an absorbable suture in an infant to reduce the internal fibrous annulus. (Reprinted with permission.¹⁸)
Disease Involving Aortic Sinuses, STJ and Ascending Aorta

There is often associated aortic root and ascending aortic pathology with or without leaflet disease. In older patients, Hahm et al\textsuperscript{36} has advocated addressing each of the three component lesions whereby the fibrous annulus and STJ are reduced and the leaflets are reconstructed (Fig. 15). With this approach, as opposed to the re-implantation and/or remodeling techniques, aortic sinus function is maintained while not completely restricting the aortic annulus during systole and maintaining growth potential.

Figure 15 – Schematic illustration of sinotubular and subannular reduction. (Reprinted with permission.\textsuperscript{36})

In younger patients where there is an enlarged aortic sinus and/or STJ dilation, “stretching” of the leaflet can occur, resulting in poor leaflet mobility that can lead to stenosis and/or regurgitation. This can be addressed by resecting a triangular portion of the aortic wall from the non-coronary sinus through the STJ with primary closure. In effect, this decreases the aortic diameter, resulting in more leaflet mobility with improved coaptation (Fig. 16A and B). A small aortic root and STJ can have the opposite effect, whereby the leaflet “folds or buckles” with resultant regurgitation (Fig. 16C and D). There is often concomitant aortic root and ascending aortic pathology. Ascending aortic dilation can be addressed by aortoplasty (Fig. 17) or ascending aortic replacement.
Figure 16 – A, Schematic of an enlarged aortic sinus can cause stretching of the leaflet, resulting in poor leaflet mobility. B, A triangular resection of the aortic wall from the non-coronary sinus with primary closure will decrease the aortic diameter, allowing more leaflet mobility and improved coaptation. C, A small aortic sinus can have the opposite effect whereby the leaflet “folds or buckles.” D, Enlarging the sinus and sinotubular junction allows improved coaptation by stretching the leaflet. (Reprinted with permission.¹⁹)

Figure 17 – Ascending aortoplasty. (Reprinted with permission.¹⁹)
Innovative Strategies

At times there are more innovative strategies of repair that can be used in patients with complex disease involving the leaflets, annulus, and subannular outflow tract. For example, in patients with hypoplastic aortic annuli, insufficient and stenotic aortic valves, and with poorly functioning pulmonary valves, one can consider aortic root enlargement and pericardial leaflet extension or reconstruction. Although technically, surgical strategies such as these are feasible with excellent early results, the longer-term outcomes are yet to be determined.

Future

There are a number of groups interested in optimizing the future of aortic valve reconstruction in younger children and infants. Our research and clinical interest has been focused in three areas: imaging, modeling, and leaflet reconstructive materials. In experimental imaging work, Perrin (D. Perrin, personal communication) have been able to describe methods to increase 3D ultrasound frame rates, through post-processing, for clinical evaluation of pediatric heart valve pathology. These methods re-order images of the moving valve leaflets taken at a large number of instances over several periods to reconstruct a higher-frame rate sequence than the imaging system could produce on its own in a single period, which significantly enhances the ability to understand structural detail.

Computational modeling is allowing us to understand the complex geometry and function of the moving aortic valve and different properties of native leaflets compared with other materials, such as pericardium. Structural finite element models of the aortic valve are being used to explore the effect of pericardial leaflet graft size on the closed, loaded state of the repaired
valve. This computational modeling environment can be rapid and flexible, which could be extended to patient-specific surgical planning (P. Hammer, personal communication, 2011).

The “Achilles heel” of aortic valve reconstruction remains the type of reconstructive material used. While for the last decade autologous pericardium has been the “gold standard,” it remains less than optimal. There is no growth potential, it has different biomechanical properties than native leaflets, and is unpredictable with regard to calcification. Although tissue fixation technique has been shown to have a differential impact on durability of the repair, a better reconstruction material remains to be found. There has been increasing interest in the remodeling characteristics of extracellular matrix scaffolds when used as leaflet reconstructive material. In other tissue types it has been shown that naturally occurring biologic extracellular matrix scaffolds are completely degraded following host remodeling responses. The potential for seeding extracellular matrix scaffolds with mesenchymal stem cells, which could differentiate into valve leaflets, appears to be very attractive but is yet unproven.

Conclusions

Over the last two decades many cardiologists and surgeons have contributed to the imaging and technical advances in complex aortic valve repair. However, despite evolving and favorable outcomes with a subset of surgeons, aortic valve reconstruction in young infants and children continues to be underutilized because of the complexity and lack of optimal reconstructive materials.

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Aortic valve repair by cusp extension for rheumatic aortic insufficiency in children: long-term results and impact of extension material

A portion of this chapter has been published in J Thorac Cardiovasc Surg 2010;140(4):836-44, by Patrick O. Myers, Cécile Tissot, Jan T. Christenson, Mustafa Cikirikcioglu, Yacine Aggoun, Afksendiyos Kalangos.

Aortic valvuloplasty by cusp extension is one of the oldest techniques described for valve repair for aortic insufficiency. In this section, a study of 78 children having with rheumatic aortic insufficiency having undergone cusp extension valvuloplasty reviews the long-term results, with follow-up up to 15 years, and analyzes the outcomes stratified by cusp extension material used. This study showed that this technique is an alternative to valve replacement in older children, with excellent long-term results allowing to delay valve replacement as long as possible (freedom from reoperation 80% at 10 years, 75% at 15 years), and that glutaraldehyde-treated bovine pericardium had worse outcomes compared to untreated autologous pericardium and photo-oxidized bovine pericardium.
Abstract

Objective: Aortic valve repair has encouraging mid term results in selected patients. However, neither the long-term results of cusp extension nor the durability of different pericardial fixation techniques have been reported. Our goal was to address these issues.

Patients and methods: Seventy-eight children with severe rheumatic aortic regurgitation (mean age 12±3.5 years) underwent aortic valve repair using cusp extension over a 15 year period, with fresh autologous pericardium in 53 (67.9%), glutaraldehyde-fixed bovine pericardium in 9 (11.5%) and Photofix bovine pericardium in 16 (20.5%). Fifty-seven (73.1%) underwent concomitant mitral valve repair, and 8 (10.3%) underwent tricuspid valve repair.

Results: There was one operative death from left ventricular failure. During a median follow-up of 10.7 years (range 1 month – 16.4 years), 1 late death occurred and 15 patients (19.7%) required reoperation at a mean of 43±33.7 months (range 1 month - 9 years), 9 within the autologous pericardium group (18%), 3 within the bovine pericardium group (33%) and 3 within the Photofix pericardium group (19%). Freedom from reoperation was 96±2.3% at 1 year, 87.5±3.9% at 5 years, 80.7±4.9% at 10 years and 75.3±6% at 15 years, and was significantly decreased in the bovine pericardium group (p=0.039). On multivariable analysis, greater age (hazard ratio 1.25, p<0.001) and acute rheumatic carditis (hazard ratio 8.15, p=0.001) at operation were significant predictors of reoperation.

Conclusions: aortic cusp extension provides adequate valve repair in a large proportion of children with rheumatic aortic regurgitation. Fresh autologuous and Photofix pericardium trended towards better durability than glutaraldehyde-fixed bovine pericardium.
Introduction

Surgical management of aortic regurgitation in the young is problematic, because of the lack of an ideal valve substitute within this age group. Prosthetic valves carry significant drawbacks, such as difficult lifelong anticoagulation and panus formation for mechanical valves, and rapid deterioration and calcification for biological valves (1). Alternate surgical approaches have been used, such as aortic homo- or autograft (Ross procedure) valvular replacement (2), however they have not demonstrated their superiority in rheumatic valvular disease (3). Rheumatic mitral valve (MV) repair has been shown to be feasible and have good midterm results (4). This has stimulated the development of techniques for aortic valve (AV) repair, which could theoretically result in optimal hemodynamic conditions, avoiding anticoagulation, and potentially allowing normal aortic annulus growth. Efforts have been focused on patient selection and subgroups amenable to repair. Duran et al. developed the cusp extension technique for aortic regurgitation due to cusp retraction (5), the most common lesion in rheumatic aortic disease. We previously reported our midterm results with a highly standardized and reproducible modification to the technique (6), with actuarial survival of 97% at 1 and 3 years, exacerbation of aortic regurgitation from grade I to grade II in only 2.5% of patients, no significant increase in peak systolic transaortic gradient and no reoperations for relapsing aortic regurgitation during follow-up. Several midterm reports on the same technique have reported similar results in children, with a mean follow-up of 5.2 and 4.6 years respectively (7, 8), but no long-term results to this date. Furthermore, differently fixed pericardium has been used, and the results of these different forms of pericardium have not been reported. The aim of this study was to update our cohort to report the long-term results of the cusp extension technique for repair of rheumatic aortic regurgitation in children, assess the relative durability of different materials for cusp extension and identify risk factors for reoperations.
Patients and Methods

The study was reviewed and approved by the local Ethics Committee, and patient consent was waived.

Demographics. From March 1993 through July 2007, 78 consecutive children underwent cusp extension aortic valve repair for rheumatic aortic regurgitation due to cusp retraction. Indications for operation included the presence of grade III or IV aortic insufficiency (AI) resulting in progressive increase in left ventricular dimensions. Eight patients had peak systolic AV gradients higher than 20 mm Hg. Patient demographics are summarized in Table 1. All of the patients were from African and Asian countries and had a well-documented history of rheumatic fever determined by the revised Jones’ criteria (9).
<table>
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<tr>
<th>Variable</th>
<th>Entire study population</th>
<th>Fresh autologous pericardium</th>
<th>Glutaraldehyde-fixed bovine pericardium</th>
<th>Photofix bovine pericardium</th>
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<td>N = 78</td>
<td>n = 53</td>
<td>n = 9</td>
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<tr>
<td>Age (years)</td>
<td>12.3±3.5</td>
<td>11.9±2.7</td>
<td>14.5±8.9</td>
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<td>Male</td>
<td>49 (63%)</td>
<td>33 (62%)</td>
<td>5 (56%)</td>
<td>11 (69%)</td>
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<td>Weight</td>
<td>33.4±9.6 kg</td>
<td>33.1±10.0 kg</td>
<td>47.0±12.5 kg</td>
<td>32.4±7.6 kg</td>
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<td>Acute rheumatic carditis*</td>
<td>4 (5%)</td>
<td>2 (3.8%)</td>
<td>1 (11.1%)</td>
<td>1 (6.3%)</td>
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<tr>
<td>NYHA functional class</td>
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<td></td>
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<tr>
<td>I or II</td>
<td>5 (6.4%)</td>
<td>3 (5.7%)</td>
<td>1 (11.1%)</td>
<td>1 (6.3%)</td>
<td>0.83§</td>
</tr>
<tr>
<td>III or IV</td>
<td>73 (93.6%)</td>
<td>50 (94.3%)</td>
<td>8 (88.9%)</td>
<td>15 (93.8%)</td>
<td>0.83§</td>
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<td>Concomitant surgery</td>
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<tr>
<td>Mitral valve repair</td>
<td>57 (73%)</td>
<td>40 (75.5%)</td>
<td>5 (55.6%)</td>
<td>12 (75%)</td>
<td>0.45§</td>
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<tr>
<td>Tricuspid valve repair</td>
<td>8 (10%)</td>
<td>5 (9.4%)</td>
<td>0 (0%)</td>
<td>3 (18.8%)</td>
<td>0.31§</td>
</tr>
</tbody>
</table>

**Table 1 – Patient characteristics.** NYHA: New York Heart Association. *Active rheumatic carditis was based on clinical examination, serologic criteria, and surgical macroscopic evaluation. ° One-way ANOVA; § χ² test.

**Operative procedure.** Cardiopulmonary bypass with systemic hypothermia to 28°C was used in all patients between March 1993 and December 1999. Since 2000, all patients were operated upon at normothermia. A transverse aortotomy was made 2 cm above the right coronary artery, and extended downward toward the noncoronary sinus. Myocardial protection consisted of hyperkalemic crystalloid solution selectively infused into both coronary ostia, at intervals of 30 minutes throughout the operation.
In 57 patients, concomitant MV repair consisted of annuloplasty and various techniques as reported previously (4). After exposing the AV, the cusps were inspected and measured with particular regard to the length of the free edge, the height of the cusps and commissures, and the appearance of the sinuses of Valsalva, the aortic annulus, and the sinotubular junction. In all patients, tricuspid morphology of the AV was confirmed. No patients had aortic cusp calcification. In 32 patients, a variable degree of cusp thickening and retraction was found with no evidence of cusp prolapse, 17 of whom needed cusp shaving. Nine patients underwent concomitant aortic commissurotomy before proceeding to aortic cusp extension. Among the 46 remaining patients, 31 had one aortic cusp prolapse with elongation of the free edge and retraction in the height of the cuspal tissue: in 17 of them, the noncoronary cusp was prolapsed, in 11, the right coronary cusp was prolapsed and in 3, the left coronary cusp prolapsed. 12 patients had associated right and noncoronary cusp prolapse, 1 had right and left coronary cusp prolapse, and one had prolapse of all three cusps.

In 53 patients (67.9%), autologous pericardium was used as the cusp extension material. A large rectangular piece of anterior autologous pericardium was cut and applied on a Dacron patch with its mesothelial surface upward. Subsequently, the shape of each pericardial patch was traced onto the Dacron patch, which served as a template for sizing, trimming, and handling of the attached pericardium according to the established dimensions, as described previously (6). We used Photofix© bovine pericardium (CardioFix©, Sorin Carbomedics, Milano, Italy) in 16 patients (20.5%), and then glutaryldehdye-fixed bovine pericardium (St Jude Medical Inc. St. Paul, Minnesota) in 9 patients (11.5%) when Cardiofix© was discontinued, in patients who had pericardial adhesions generated by repeated episodes of rheumatic fever and pancarditis. The use of autologous pericardium already affected by inflammatory reaction and fibrosis in these patients was not deemed suitable because of the risk of accelerated structural deterioration (8).

The cusps were first thinned if their mobility was restricted, maintaining a leathery consistency at cuspal free edges to better hold the sutures. A 5-0 polypropylene suture (Cardionyl,
Péters Pharm Lab, Bobigny, France) was passed through the midpoint of the pericardial patch and the corresponding cusp and tied with the knot on the aortic side. Two vertical 5-0 polypropylene “U” stitches were then passed through both commissural extensions of the pericardial patch and aortic wall above both commissures, passed through pericardial pledgets and tied outside the aorta. This was done to facilitate the next step of cusp extension, which consisted of running one of the arms of the tied suture from the midpoint of the cusp, up the commissures, to the end point of pericardial extension on the aortic wall. A similar procedure was followed for the other half of the cusp’s free edge with the use of the second arm of the suture. The suture was then brought out through the aortic wall and kept tense. The running sutures of the neighboring cusps brought out through the aortic wall at the same commissural extension level were then tied together over a pericardial pledget outside the aorta. The Dacron patch was then removed. The same procedure was repeated for each cusp with each specifically corresponding scalloped pericardial patch. The mesothelial surface of the pericardium was thus placed so as to correspond to the aortic aspects of the cusps. We added two commissural extensions on each pericardial patch to ensure better balanced tension, especially concentrated on the commissural regions during systole when flexion of the free edges of the extended cusps is minimal. In this geometric configuration, the length of the free edge of each cusp, which is equivalent to 2 times the radius of the sinotubular junction plus 15%, is equal to the diameter of the aortic orifice and remains constant whether the valve is open or closed. The combined surface of the three cusps is approximately 15% larger than that of the sinotubular junction, assuring coaptation.

When required, tricuspid annuloplasty was performed on a beating heart after other valvar procedures were finished. Intraoperative transesophageal echocardiography examinations were performed in all patients before skin incision and after termination of cardiopulmonary bypass.
Follow-up. Transthoracic echocardiography was carried out in all patients before surgery, before discharge from the hospital, and at 3 and 6 weeks postoperatively in the outpatient clinic of our institution before returning to their countries of origin.

Doppler echocardiographic grade of AI was measured with color Doppler flow and graded from the width and length of the regurgitant jet in the left ventricle (grade 0-IV) according to previously described criteria (10). Peak gradient across the AV was estimated by measuring peak systolic velocity from Doppler studies in the transthoracic 5-chamber or suprasternal notch sagittal view. Left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD) and left ventricular shortening fraction were measured at midpapillary level in the standardized parasternal transthoracic long-axis or short-axis position. Z-scores were calculated using the latest formulas (11). Seventy-six of the 78 patients (97%) were thereafter followed in outpatient clinics by cardiologists in their country of origin, who periodically informed us of the patients’ evolution by filling out a questionnaire including clinical, echocardiographic, and medication information. Follow-up in this study was achieved until July 2009. We followed published guidelines in reporting freedom from valve-related events (12).

Statistical analysis. Statistical analyses were performed with SPSS software (SPSS Inc, Chicago, IL). Data are presented as mean±SD. Continuous variables were analyzed with the Student t test, or the related samples Wilcoxon signed rank test when appropriate, and categorical variables using the χ2 test. Differences between cusp extension material group continuous variables were analyzed with ANOVA with Bonferroni post hoc correction. Actuarial estimates were calculated using the Kaplan-Meier method and differences between curves assessed by the log-rank test. Univariate and stepwise Cox multivariable regression analyses were used to identify the independent predictors of late outcomes. Preoperative and operative variables with a univariate p < 0.1 or those judged to be clinically important were entered into the Cox models. Hazards ratios for reoperation of risk factors were calculated using univariate and multivariable Cox proportional hazards estimates. All statistical tests were two-tailed and p values < 0.05 were
taken as significant. Methodological support was provided by the Clinical Research Center, University of Geneva and Geneva University Hospitals.

**Results**

**Early outcome.** The mean aortic crossclamping time was 73.9±35.2 minutes (range 33-144 minutes) for 21 children undergoing isolated AV repair and 112.1±34.7 minutes (range 58-195 minutes) for 57 children undergoing concomitant MV and AV repair. There was one operative death from left ventricular failure. Two patients presented intraoperative suspected dynamic coronary ostia occlusion by the extension patches after cross-clamp removal (evidenced by intractable ventricular fibrillation), requiring cardioplegic arrest, valve repair exploration and shortening of each cusp extension patch by 1 mm. Both patients subsequently regained normal sinus rhythm and had an uneventful postoperative course.

**Late outcome.** Follow-up was complete in 98.7% of the patients (76 of 77). The patient lost to follow-up was from the early part of the series. Mean and median follow-up was 115.5±61.4 months and 128 months, respectively, ranging from 1 to 16.4 years overall. The median follow-up for the fresh autologous pericardium group was 163 months (mean 142±54.9 months), 22 months for the bovine pericardium group (mean 43±38 months) and 75.5 months for the Photofix pericardium group (mean 71.7±21.3 months). One patient died in the 55th postoperative month of sudden cardiac arrhythmia at home, with apparently competent aortic and mitral valves. In all patients, anticoagulation with warfarin began on the second postoperative day and was stopped during the third postoperative month until 1999; since then, patients did not receive any anticoagulation unless another indication required it. No thromboembolic or hemorrhagic events were observed up to the most recent follow-up examinations. A total of 15 patients (19.7%) underwent reoperation for severe aortic valve dysfunction after a mean period of 42.9±33.7 months (range, 1.2 to 108) from the initial aortic valve repair, 9 within the autologous
pericardium group (18%), 3 within the glutaraldehyde pericardium group (33%) and 3 within the Photofix pericardium group (19%).

The mode of failure differed depending on the extension material: glutaraldehyde-fixed bovine pericardium presented deterioration from calcification; fresh autologous pericardium undergoes inflammatory cell infiltration and a variable degree of retraction; finally, Photofix pericardium was surprisingly unaffected (see Figure 1), and repair failure was linked either to continued rheumatic degeneration of the native leaflets or to annular dilatation.

Figure 1 – Photofix© pericardium cusp extension 5 years later. Surgical view of the repaired aortic valve in a patient requiring reoperation for mitral valve repair 5 years after Photofix© cusp extension. The extensions were pliable and presented no calcifications or retraction.

Among the 15 patients requiring reoperation for aortic valve replacement, 3 required concomitant mitral valve replacement. Two more patients required non-aortic valve related reoperation during follow-up, one for mitral valve replacement and one for mitral valve repair.

Valve function. Of the 76 patients followed-up, 44 (58%) had no or trivial aortic valve regurgitation and 14 (18%) showed mild aortic regurgitation at their last follow-up
echocardiography. Eighteen patients (24%) had significant aortic regurgitation during follow-up. The aortic regurgitation was moderate to severe (grade III) in 7 patients (9%) and severe (grade IV) in 11 (15%). The 11 patients with severe aortic regurgitation and 4 patients with grade III aortic regurgitation all underwent reoperation. The remaining 3 patients with grade III regurgitation are being monitored and one is scheduled for reoperation.

Actuarial freedom from reoperation due to significant aortic regurgitation was 96±2.3% at 1 year, 87.5±3.9% at 5 years, 84.6±4.3% at 7 years, 80.7±4.9% at 10 years, 78.7±5.2% at 12 years and 75.3±6% at 15 years. For the fresh autologous pericardium group, freedom from reoperation was 98±2% at 1 year, 91.9±3.9% at 5 years, 83.5±5.4% at 10 years and 79.8±6.2% at 15 years, for glutaryldehyde-fixed bovine pericardium 88.9±10.5% at 1 year, 77.8±13.9% at 5 years and 77.8±13.9% at 8 years, and photofix pericardium 93.8±6.1% at 1 year, 81.3±9.8% at 5 years and 81.3±9.8% at 7 years. This difference was statistically significant, with a higher reoperation rate in the bovine pericardium group (log rank test, p = 0.02, see Figure 2a).
Figure 2 – Survival curves after aortic valve repair for rheumatic aortic valve regurgitation in 78 children. (A) Actuarial freedom from reoperation-free survival (B) Actuarial freedom from aortic valve related event-free survival (including early and late deaths, reoperation, moderate to severe aortic regurgitation, endocarditis and thrombo-embolism).
On univariate analysis, greater age (hazard ratio (HR) 1.24, p < 0.001), acute rheumatic carditis (HR 9.57, p < 0.001) at operation, necessity of aortic commissurotomy before cusp extension (HR 8.19, p = 0.007) and use of glutaraldehyde pericardium (HR 5.31, p = 0.02) were predictors of reoperation (see Table 2). On multivariable analysis, only greater age and acute rheumatic carditis at operation were significant independent predictors of reoperation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
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<tr>
<td></td>
<td>HR</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>1.24</td>
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</tr>
<tr>
<td>Male sex</td>
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<tr>
<td>Concomitant mitral operation</td>
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<td>Aortic commissurotomy</td>
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<td>0.007</td>
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Table 2 – Cox regression analysis of predictors for reoperation. * Reference group.
Aortic valve–related event-free survival (including death, reoperation and moderate to severe aortic regurgitation) was 85±4.2% at 5 years, 73.8±5.4% at 10 years and 68.8±6.1% at 15 years after the initial operation (see Figure 2b).

**Transvalvular gradients.** The peak gradients through the aortic valve are shown in Table 3. There was a significant increase in the peak gradient during follow-up, from a mean postoperative value of 15.6±5.7 mmHg to a mean of 21.8±9.5 mmHg at the latest follow-up (p < 0.001), regardless of the material used for cusp extension. This represented an increase of 6.3±9.3 mmHg, or 1.3±2.7 mmHg/year, during follow-up, which was markedly increased in the bovine pericardium group (3.6±3.7 mmHg/year, p = 0.02).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fresh autologous pericardium</th>
<th>Glutaryldehydrate-fixed bovine pericardium</th>
<th>Photofix pericardium</th>
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<tr>
<td>Preoperative</td>
<td>17.2±5.0</td>
<td>19.4±6.8</td>
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<td>Discharge</td>
<td>16.0±5.5</td>
<td>15.7±4.8</td>
<td>14.4±6.9</td>
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<tr>
<td>$p^a$</td>
<td>0.04</td>
<td>0.007</td>
<td>0.003</td>
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<td>Latest follow-up</td>
<td>22.1±8.6</td>
<td>19.9±5.7</td>
<td>21.9±13.7</td>
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<tr>
<td>$p^b$</td>
<td>&lt; 0.001</td>
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<td>0.009</td>
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<tr>
<td>Increase per year</td>
<td>1.0±2.4</td>
<td>3.6±3.7</td>
<td>1.1±2.4</td>
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<tr>
<td>$p^c$</td>
<td>*</td>
<td>0.02</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Table 3 – Transvalvular gradients.**

- $p^a$ value: comparison between the preoperative values versus those at discharge within each treatment group using related samples Wilcoxon signed rank test.
- $p^b$ value: comparison between the values at discharge versus those at latest follow-up within each treatment group using related samples Wilcoxon signed rank test.
- $p^c$ value: comparison between the increase in peak transvalvular gradient per year, compared to the reference group (*) using ANOVA multiple comparisons with Bonferroni post hoc comparison.
Overall ANOVA test of significance was $p = 0.02$. All values are reported as mean±SD, in mmHg unless otherwise noted.

**Left ventricular dimensions and shortening fraction.** Increased preload due to aortic regurgitation resulted in enlarged LVEDD and LVESD values preoperatively of 6.1±0.6 cm ($z$-score 4.1±1.1) and 4.0±0.5 cm ($z$-score 3.6±1.0), respectively. Mean LVEDD and LVESD were significantly ($p < 0.001$) reduced at hospital discharge, at 4.7±0.5 cm ($z$-score 1.5±1.3) and 3.6±0.6 cm ($z$-score 2.9±1.2) respectively. These values increased at latest follow-up, to 4.9±0.5 cm ($z$-score 2.3±2.2) and 3.4±0.5 ($z$-score 2.7±1.8) respectively, significantly increased when comparing discharge to follow-up LVEDD and LVESD values ($p < 0.001$ for both) and LVEDD $z$-scores ($p = 0.008$), but not when comparing discharge and follow-up values indexed to BSA ($p = 0.06$ and 0.5, respectively) and $z$-scores ($p = 0.48$). Comparing between the different cusp extension material groups, there was no significant difference between their respective preoperative ($p = 0.37$ and 0.29), discharge ($p = 0.72$ and 0.51) and follow-up ($p = 0.29$ and 0.73 respectively) LVEDD and LVESD. Comparing indexed values and $z$-scores did not find any more significant differences between groups.

The mean preoperative left ventricular shortening fraction was 34.4±3.3%, followed by a significant reduction ($p < 0.001$) at time of hospital discharge to 23.5±4.3%, followed by a significant increase ($p < 0.001$) at latest follow-up to 30.6±4.1%. There were no significant differences between cusp extension material groups at each time point ($p = 0.58$, 0.17 and 0.24 respectively).

**Discussion**

Long-term results in surgery for mitral regurgitation have demonstrated that repair is advantageous over replacement in terms of survival and incidence of thrombo-embolic and bleeding complications (13). MV repair has thus become the treatment of choice, and its
feasibility has led to the recommendation of earlier surgery, even in asymptomatic patients, to preserve ventricular geometry and function (14). Part of these advances has come from better understanding the etiologies and specific mechanisms of mitral regurgitation, and identification of patient subgroups and the optimal repair technique to be applied. A major limitation to the more generalized application of AV repair is the absence of such a common framework for valve assessment to guide the approach to valve repair. Boodhwani et al. proposed a repair-oriented functional nomenclature (15), similar to Carpentier’s pioneering classification of mitral regurgitation (16), dividing lesions into 3 types: I (mainly due to aortic dilatation), II (cusp prolapse) and III (cusp retraction). Various series have reported encouraging mid-term outcomes in heterogeneous groups of patients undergoing aortic valve repair. Aicher et al. reviewed their experience in 640 patients (mean age 56±17 years) undergoing aortic valve repair for insufficiency of all functional types and etiologies, with freedom from reoperation at 5 and 10 years of 88% and 81% for bicuspid and 97% and 93% in tricuspid valves. Similarly, Boodhwani et al. reported 264 patients (median age 55 years), with a 5 year survival of 95±3% and freedom from reoperation of 92±4% (15). However, freedom from reoperation was reduced in restricted (type III) aortic valves (88±9%, versus 94±4% in type I and II, p = 0.08), and freedom from recurrent >2 AI was significantly lower for type III lesions than for type I or II lesions (HR 2.6, 95% CI 1.1–11.6, p = 0.03). These results are encouraging for a more widespread use of AV repair. Nonetheless, specific subgroups of patients and their optimal repair strategy need to be assessed. Furthermore, these results must be confirmed in children.

We have focused our attention on patients with aortic regurgitation due to cusp retraction, the most common lesion in rheumatic aortic disease. We previously reported our short and mid-term results (6) in 49 children (mean age 11.5±2.7), with actuarial survival of 97% at 3 years and no reoperations, and showed growth of the repaired valves with no increase in peak systolic gradients during follow-up. Grinda et al. reported 89 patients (mean age 16±5 years) who underwent cusp extension for rheumatic aortic valve disease. Five-year survival and freedom
from aortic reoperation were 96% and 92%, respectively (8). Similarly, Bozbuga et al. (7) reported 46 patients with rheumatic valve disease (mean age 35±12 years) with survival of 98% at 8.6 years and freedom from reoperation of 76.1% at 7.5 years. The longest available results with this technique, with a follow-up of up to 16 years, were reported by Al Halees et al. (17) for 92 patients (mean age, 30 years) with mostly rheumatic valve disease. The survival rate was 85%. There were no episodes of thromboembolism and freedom from reoperation was 68% at 10 years and 47% at 16 years. We report significantly improved results with our tailored, highly standardized modification to triple cusp extension repair, with freedom from reoperation of 81±5% at 10 years and 75±6% at 15 years.

Various materials have been used to extend the aortic cusps, including fascia lata (18), heterologous (bovine) pericardium (17), fresh autologous (6) and glutaraldehyde-stabilized autologous pericardium (8, 19). Duran and colleagues compared the use of glutaraldehyde-fixed bovine and autologous pericardium. At the short to mid-term (5, 20), bovine pericardium appeared to have significantly worse outcomes and made them abandon this material for cusp extension. At long-term follow-up, however, there was no significant difference between the groups, with freedom from reoperation of 72±6% at 10 years and 45±8% at 16 years in the bovine pericardium group, versus 68±5% at 10 years and 47±6% at 16 years (17). We confirm the initial results of Duran and colleagues, with significantly worse results with glutaraldehyde-fixed bovine pericardium at the midterm, with freedom from reoperation of 78±14% at 7 years, compared to 85±4% for fresh autologous pericardium and 81±10% for Photofix bovine pericardium. However, these results must be mitigated, as the statistical significance of the log-rank analysis is limited by the number of events and reaches significance based on a single supplementary event in the glutaraldehyde pericardium group; furthermore, this trend was not confirmed on multivariable analysis. The multivariable models used are also limited by the number of events: there are 15 events for 8 degrees of freedom in the model (see Table 2), although 5-10 times more events than degrees of freedom are usually recommended. Finally, the comparison of the rate of increase of
transvalvular gradients between the groups is confounded by the relatively short follow-up in the glutaraldehyde pericardium group relative to the other groups.

Despite these limitations, Photofix pericardium trended to be the better alternative in patients in whom autologous tissue can’t be used. Photofix is an alternative to glutaraldehyde fixation, which uses dye-mediated photooxydation rather than chemical cross-linking. Photooxydized bovine pericardium is similar to untreated tissue in texture, pliability and shrinkage temperature, but unlike untreated tissue, it possesses chemical, enzymatic and in vivo stability. It is thus non-immunogenic, biocompatible and, unlike glutaraldehyde-treated tissues, non-calcifying and non-cytotoxic, thus allowing endothelization (21). Its use in valve reconstruction has been very limited (22), due to poor results with Photofix-based bioprostheses (23), although this was shown to be due to valve design rather than fixation technique.

This study suffers from several limitations. It is a retrospective and nonrandomized comparison of aortic cusp extension materials and represents a fifteen year period of evolving experience with aortic valve repair. As such, any inferences drawn from this data are limited by confounding variables such as extent of cusp disease, severity of preoperative AI, need for MV or TV repair and duration of follow-up that are differently distributed between study groups. Our sample size also limits our ability to perform extensive statistical adjustments for these differences.

Conclusions

Aortic cusp extension provides adequate valve repair in a large proportion of children with rheumatic aortic regurgitation. Fresh autologuous and Photofix bovine pericardium showed better durability, requiring fewer reoperations than glutaraldehyde pericardium at mid term.
References


Surgical Repair of Truncal Valve Regurgitation


Truncus arteriosus is a congenital heart malformation, in which there is a single great vessel arising from the heart instead of the aorta and pulmonary artery. There is a single ventriculo-arterial valve, the truncal valve, which, after repair of this malformation, becomes the aortic valve. Regurgitation from this valve remains a major problem in these patients, as a risk factor for mortality and reoperations. This paper reviewed the results of Boston Children’s Hospital experience in repairing and replacing the systemic semi-lunar valve in these patients, the largest series published to date.
Abstract

**Objective:** Truncal valve regurgitation remains a short and long-term risk factor for patients with truncus arteriosus. There is limited data available on techniques and outcomes of truncal valve repair. The aim of this study is to report our experience with truncal valve repair surgery in patients of all ages.

**Methods:** From 1997 to 2012, 36 patients (13 neonates, 30 children and 3 adults) underwent truncal valve repair for significant regurgitation.

**Results:** There were 3 early deaths (8%), all of which were in neonates. 22 patients had a quadricuspid, 13 a tricuspid and 1 a bicuspid truncal valve before repair. Valve repair improved regurgitation in 31 of 36 repairs. The median regurgitation decreased from moderate-severe to mild (P < 0.001). During a mean follow-up of 38.3±44.9 months (range 1 month – 15 years), there was 1 late death, 16 patients required reoperation on the truncal valve and 1 patient required a second reoperation. Freedom from reoperation was 91.4±4.8% at 1 year, 55.0±10.4% at 5 and 22.9±12.2% at 10 years. A quadricuspid valve after repair tended to worse freedom from reoperation (P = 0.15), and tricuspidization tended to improve freedom from reoperation (P = 0.19). Neonatal repair (HR 4.1, P = 0.03) and leaflet thinning (HR 22.5, P = 0.002) were independent predictors of reoperation.

**Conclusion:** Valve repair for truncal valve regurgitation is feasible with good results. Surgical creation of a tricuspid truncal valve seems to provide the best outcomes in this challenging population.
Introduction

Truncus arteriosus is a rare cardiovascular malformation that represents 2 to 4% of all congenital heart defects (1). Since the first description of successful repair by McGoon and colleagues in 1968 (2), outcomes have evolved from a fatal condition early in life in 50% of patients to one in which neonatal repair is increasingly common and successful (3). However, associated lesions such as interrupted aortic arch (IAA), coronary anomalies and truncal valve insufficiency (TVI) remain major risks factors for reoperation and survival (4).

TVI is estimated to occur in 25 to 50% of patients with truncus arteriosus (5). In this condition, the semilunar valve can be dysplastic or dysfunctional or have an abnormal number of leaflets, usually four. Moreover, associated abnormalities such as conal septum hypoplasia, VSD causing valve prolapse and relationship of the pulmonary arteries to a consistently dilated aorta may affect the truncal valve function. In addition, TVI may present in the neonatal period or throughout childhood. Therefore, the surgical management of moderate or severe TVI is challenging, especially in the neonatal period. Traditional strategies for the operative management of these patients have included temporization of this problem or attempts at valve replacement with a homograft valve or a mechanical prosthesis (5, 6). However, none of these options have been shown to be very successful or desirable. Moreover, in growing children, the ability to repair a regurgitant semilunar valve may be even more important to avoid the need to replace or up-size a prosthetic valve or allograft. Thus, repair of the regurgitant truncal valve constitutes the “ideal” surgical strategy. However, reports on technical feasibility or durability of truncal valve repair (TVR) are scarce and limited to case reports or small series of patients (7-10). No standard approach, with regards to timing and surgical technique, for the treatment of this condition currently exists.
The aim of this study is to report our recent experience with truncal valve surgery in neonates, children and young adults, focusing on the surgical strategy, timing of operation and durability of the repair.

Methods

Study design

This study is a retrospective review of all patients managed at our institution with the diagnosis of truncus arteriosus and moderate or severe truncal valve regurgitation during follow-up from 1997 to 2012. The cardiology and cardiac surgery databases were queried for patients with both these diagnoses, and all of them were included in the study. The study was approved by the Boston Children’s Hospital Institutional Review Board, and individual patient consent was waived.

The primary endpoints were truncal valve reoperation, late valve function and death. Clinical or treatment variables were recorded to determine the predictors of reoperation. All patients underwent follow-up to death or March 2012.

Operative techniques

The techniques used to repair the truncal valve were planned ahead of time with the help of 2D and 3D echocardiography and tailored to the underlying mechanism of valve dysfunction. Preoperative datapoints of interest for planning the repair included the number, size and shape, thickness and mobility of the leaflets, number and location of commissures and cusps, regurgitant jets and size of the truncal valve annulus, aortic root and sinotubular junction. Specific techniques varied according to the anatomy of the valve and the cause of insufficiency. A combination of suture closure of adjacent leaflets with resection or exclusion of rudimentary leaflets, leaflet
extension with autolo-gous pericardium, annular plasties, commissuroplasties and aor-toplasties were used to repair the truncal valve (see Fig. 1).

**Figure 1 – Truncal valve repair tricuspidization techniques.** (A) Resection of rudimentary leaflet and tricuspidization. Reproduced with permission from Imamura et al. [22]. (B) Rudimentary leaflet and sinus resection with coronary transfer. Reproduced with permission from Mavroudis and Backer [16]. (C) Leaflet approximation in a quadricuspid truncal valve. Reproduced with permission from Kaza et al. [9].

The most common surgical scenario in our series was a quad-ricuspid truncal valve with thick edges and one deficient and one flail leaflet usually separated by a raphe. These leaflets were mostly located at the left or non-coronary sinuses of Valsalva. Repair was accomplished by thinning the free edges of the leaflets, and the raphe was then taken down to improve mobility and the flail leaflet was resuspended either by suturing it to the adjacent leaflet or commissure, making the valve trileaflet [9, 11]. In patients with a dilated aortic root, the non-coronary sinus
was excised and the aortic wall sutured back together. Taking advantage of the existence of a subannular conus in truncal valves, an annuloplasty was also used, particularly in neonates [12].

In older patients, a technique of truncal valve annulus remodelling, inspired by Yacoub et al.’s technique of transaortic primary repair of subpulmonary VSD with aortic cusp prolapse [13] was used (see Fig. 2), as the truncal valve annulus below the right coronary cusp was found to balloon out and cause prolapse of the right coronary cusp. A series of interrupted pledgeted multifilament braided sutures were inserted in a transaortic approach on the left aspect of the crest of the ventricular septum, passed through the truncal valve annulus and out the aortic root wall adjacent to the infundibulum, where they were tied. As in Yacoub et al.’s technique, this results in closing the VSD, placating redundant tissues towards the media of the aortic sinus and bringing the right coronary sinus, cusp and truncal annulus down to the VSD crest, effectively remodelling the truncal annulus.
Figure 2 - Truncal annulus remodeling technique by bringing the VSD crest up to the truncal annulus. (A) View from the head of the patient (at the bottom of the image), down the barrel of the transected ascending aorta towards the truncal valve. (B) Cross-sectional representation of the truncal root and ventricular septal defect patch before repair, with a prolapsing truncal cusp. (C) View after repair, eliminating prolapse. LCA: left coronary artery; LV: left ventricle; MPA: main pulmonary artery; RA: right atrium; RCA: right coronary artery; RV: right ventricle.

Statistical methods

Statistical analyses were performed with SPSS software (version 20, SPSS Inc., Chicago, IL). Data are presented as mean±SD or median (range) where appropriate. Continuous variables were analyzed with the Student’s t test for normally distributed variables, or the related samples
Wilcoxon signed rank test for non-normally distributed variables, and categorical variables using Fisher’s exact test. Normality of continuous data was evaluated with the Kolmogorov-Smirnov test. Actuarial estimates were calculated using the Kaplan-Meier method and differences between curves assessed by the log-rank test. Univariable and stepwise Cox multivariable regression analyses were used to identify the predictors of late outcomes. Preoperative and operative variables with a univariable P < 0.1 or those judged to be clinically important were entered into the Cox models. Hazards ratios for reoperation of risk factors were calculated using univariable and multivariable Cox proportional hazards estimates. All statistical tests were two-tailed and P values < 0.05 were taken as significant.

Results

Demographics

36 patients underwent a total of 53 truncal valve procedures during the study period for moderate or severe regurgitation. 49 procedures were valve repairs, and 4 were valve replacement. The initial procedure was truncal valve repair in all 36 patients. Patient baseline characteristics are summarized in Table 1. The mean age at truncal valve repair was 6.9±6.8 years. 60% of patients had a quadricuspid truncal valve prior to repair, and 33% had associated cardiac lesions.
Table 1 – Baseline patient characteristics.

Truncal valve repair techniques

A functional tricuspid valve was accomplished in 21 31 patients (58%), quadricuspid in 11 (31%) and bicuspid in 4 7 (11%) by a combination of commissuroplasties, suture closure of adjacent leaflets, pericardial patch extension and leaflet resuspension and thinning. Surgical valve repair techniques used are detailed in Table 2. The techniques used among the 13 neonates didn’t differ significantly from the overall cohort of patients, which included commissurotomy in 2 patients (15.4%), commissuroplasty in 7 (53.8%), leaflet augmentation in 2 (15.4%), leaflet thinning in 3 (23.1%), annuloplasty in 2 (15.4%), single sinus excision in 1 patient (7.7%) and tricuspidization in 4 (30.8%).
Table 2 – Operative techniques used in truncal valve repair.

### Table 2: Operative techniques used in truncal valve repair

<table>
<thead>
<tr>
<th>Technique</th>
<th>Entire cohort (n = 36)</th>
<th>Reoperation free (n = 20)</th>
<th>Reoperations (n = 16)</th>
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<tr>
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<td>Commissuroplasty</td>
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<td>Tricuspidation</td>
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<td>7 (35.0%)</td>
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<td>Truncal annuloplasty</td>
<td>5 (13.9%)</td>
<td>4 (20.0%)</td>
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<td>Annular remodelling using VSD crest</td>
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<td>3 (15.0%)</td>
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<td>Single sinus of Valsalva reduction</td>
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<td>Subaortic resection</td>
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<td>1 (5.0%)</td>
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</table>

### Outcomes

There were four deaths (11.1%). Three neonates died in-hospital after primary repair following ECMO. The first one collapsed and was transferred to our institution with significant right ventricular dysfunction and tricuspid insufficiency that persisted after repair. The second had still significant truncal valve regurgitation after repair and areas of duskeness that precluded the patient from weaning from by-pass. Interestingly, these two patients had IAA and single coronary artery as associated lesions. The third patient had persistent significant truncal valve regurgitation, which required truncal valve re-repair. Although this improved the regurgitation to mild, weaning from cardiopulmonary bypass remained impossible and the patient was transitioned to ECMO, and subsequently developed multiorgan system failure on full flow ECMO and expired. The postmortem examination showed obstruction of left main coronary ostium. In addition, a 4.5 year-old child died from a massive stroke after reoperation for severe TVI which was unsuccessfully re-repaired and ultimately required a prosthetic replacement.

Valve repair improved regurgitation in 31 of 36 repairs (86%) and was less than moderate in 27 patients (75%) after repair. The median regurgitation decreased from moderate-severe to mild (P < 0.001). Although 9 patients (25%) presented a significant truncal valve peak gradient
prior to repair, no patient exhibited truncal valve stenosis after repair. During a mean follow-up of 38.3±44.9 months (range from 1 month to 15 years), 16 patients required a reoperation on the truncal valve, one of which required a second reoperation. No patients required more than 2 reoperations. Nine of the 13 patients who had their initial truncal valve repair as neonates required a reoperation (69%). Among reoperations, 13 were for truncal valve re-repair, 2 for prosthetic replacement after attempted re-repair and 2 for direct prosthetic replacement. Freedom from reoperation for TVI was 91.4±4.8% at 1 year, 87.2±6.1% at 2 years, 55.0±10.4% at 5 years and 22.9±12.2% at 10 years (see Figure 3).
Figure 3 – Kaplan-Meier estimates of freedom from truncal valve reoperation after truncal valve repair. (A) Entire cohort. (B). Analysis stratified by age at truncal valve repair. (C) Analysis stratified by truncal valve anatomy after truncal valve repair.
One patient required placement of a permanent pacemaker for post-operative atrio-ventricular block after reoperation for valve replacement. This patient’s initial repair included only leaflet-level repairs, and no annuloplasty or truncal root remodeling techniques.

**Predictors of truncal valve reoperation**

The Kaplan-Meier survival analysis stratified by age category showed that neonates and adults had significantly more reoperations than children (P = 0.039; see Figure 3). A quadricuspid anatomy after repair tended to have had worse freedom from reoperation, however not to a significant level (P = 0.15), and tricuspidization also trended towards better freedom from reoperation (P = 0.19). At univariable and multivariable Cox regression analysis, neonatal truncal valve repair and valve repair using leaflet thinning were significant predictors of truncal valve reoperation (see Table 3).

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*Reference group.

Table 3 – Cox regression analysis of predictors of truncal valve reoperation.
Although limited by the number of patients and not reaching statistical significance, repair techniques appeared to differ in neonates (n=13) who required a truncal valve reoperation (9/13), who had a more leaflet-level repairs (commissuroplasties 5, commissurotomies 1, pericardial patch leaflet augmentation 1) and fewer annulus-level repairs (annuloplasty, 1), compared to neonates who didn’t require a reoperation (4/13), who had more truncal root or annulus repairs (root remodeling 1, resection of nodular leaflet, annuloplasty and translocation of coronary ostium 1, and truncal annulus remodeling in 1) and fewer leaflet-level repairs (commissuroplasty 1, leaflet thinning 1).

Discussion

Despite improved surgical management of patients with truncus arteriosus, semilunar valve regurgitation remains a risk factor for early and late morbidity and mortality (8, 14). However, there is no standard surgical approach to TVI. A recent review of the STS Congenital Heart Surgery Database results (10), reporting 572 truncus arteriosus repairs from 2000 to 2009, included 27 patients with truncal valve surgeries (23 at truncus arteriosus repair, 4 later). The mortality of truncus repair with a concomitant truncal valve procedure (30%) was significantly increased compared to controls without truncal valve surgery at truncus arteriosus repair (10%, P = 0.0002), while all 4 patients who had delayed truncal valve procedures died. The association of truncus arteriosus repair, IAA repair and TVR had a mortality of 60%. Truncal valve procedures also increased the risk of mechanical support and a longer hospital stay. This study was limited to the initial neonatal admission, and provided no follow-up on late reoperations and truncal valve dysfunction after repair. Kaza et al. reviewed their single-center experience in TVR in 17 patients from 1995 to 2008 (9). This study, although on a more limited number of patients, has the advantage of including 3 non-neonatal patients and follow-up data. Three patients had 1 re-repair, and 1 patient had 2 re-repairs before undergoing a prosthetic valve replacement at age 13 years.
Freedom from truncal valve reoperation was 70% at 5 years and 50% at 7 years, with only 1 patient (6%) who required valve replacement.

Anomalies associated with truncus arteriosus, such as significant truncal valve regurgitation, IAA and/or coronary anomalies remain a risk factor for morbidity and mortality. In our series, 5 7 patients presented with IAA, 5 7 with coronary anomalies and 3 exhibited both conditions. Two of the early deaths were in patients with significant TVI IAA and single coronary artery. Those deaths seemed related to myocardial ischemia rather than the valve repair itself, because of the inability to wean from cardiopulmonary bypass and myocardial dysfunction depicted by echocardiography. In our experience, the association of TVI, IAA and coronary anomalies remains a challenging condition with high mortality.

The optimal approach to management of TVI remains controversial (8, 9, 15, 16). Previous studies have reported initial moderate or severe TVI as a risk factor for truncal valve reoperation or late development of severe insufficiency (6). Moreover, we previously reported increased mortality in neonates with significant TVI not undergoing TVR (8). Thus, our approach is not to temporize with the problem but to deal with moderate or severe TVI at the time of presentation either at neonatal repair or later on during follow-up, usually concomitantly with a conduit change or pulmonary valve replacement surgery. Timing of intervention is key because the techniques used to repair the truncal valve differ slightly based on age at repair. For neonates, we prefer to use annuloplasty, aortoplasty and commissuroplasty techniques, to minimize the risk of damaging the extremely delicate neonatal leaflets. Nevertheless, for infants and older children, thinning out of the edges of the leaflets, with suture closure or resuspension of flail leaflets and pericardial augmentation of deficient leaflets are utilized more frequently. A limitation of the present study is that we included all patients with diagnoses of truncus arteriosus and truncal valve regurgitation. This study thus didn’t aim to include patients with truncal valve stenosis, and cannot comment on the surgical management of this patient group, although 9 patients (25%) presented significant stenosis before repair.
An important application of 3D echocardiography is the understanding of the semilunar valves (17). Unlike 2D imaging, 3D echocardiography demonstrates the entire surface area of the leaflets and therefore the zones of coaptation and the extent and location of valvar deficiency and prolapse. In addition, it details the dynamic and coordinated movements of the leaflets and helps in assessing the regurgitant jets. In our experience, 3D echocardiography is key for preoperative planning of valve repair as well as for intraoperative assessment of the repair and therefore is being applied on a routine basis for surgical planning for aortic, truncal and/or mitral valve repair at our institution.

Systemic semilunar valve repair is thought to provide a better hemodynamic result and allow for growth in a neonate or child, compared to valve replacement. However, outcomes of children undergoing surgical systemic semilunar valvuloplasty are limited to few reports with small numbers and limited follow-up (7, 8, 18, 19). Moreover, little is known about the outcomes of repair of systemic semilunar valve in neonates (20) and specifically, durability of TVR is mostly unknown (9, 15, 16). McElhinney et al. reported 66% early mortality in truncal valve replacement, and 25% early mortality in truncal root replacement with a homograft, compared to 0% early mortality in truncal valvuloplasty (21). Furthermore, they found that TVI conferred a survival disadvantage, with 1- and 5-year survival of 56 and 52%. We have recently reported our experience with aortic valve repair in children (18). From 1989 to 2005, 81 patients younger then 19 years with moderate or severe aortic regurgitation underwent surgical valvuloplasty. Regurgitation improved in 77 patients (95%), was mild or less in 68 (84%) and 33 (41%) required reoperation during follow-up. Estimated freedom from reoperation was 72% at 5 years and 54% at 7.5 years. In our series of 21 patients undergoing TVR from 1997 to 2008, TVI improved in 27/30 procedures (90%) and was less than moderate in 24/30 procedures (80%). Reoperation was required in 11 patients (47%) during follow-up and estimated freedom from reoperation was 100%, 77% and 34% at 1, 5 and 10 years, respectively. Therefore, in our experience,
contemporary results of truncal valve repair are similar to those reported for the aortic valve. However, this statement is limited by the retrospective nature of our study, our single-institution approach and the relatively small series of patients. Moreover, the larger and older timeframe reported in the aortic valve repair study could also bias the comparison. However, in our present study almost 40% of the patients were neonates, in whom valve repair is generally considered less durable. Finally, it should be noted that it wasn’t always possible to improve regurgitation with truncal valve repair, as 9 patients (25%) still presented moderate regurgitation after repair. This result is sub-optimal, and perhaps reflects the fact that surgeries were included over a relatively long time-period and involved surgeons of varying expertise in valve repair. We currently wouldn’t accept more than mild regurgitation after repair.

One point of interest is the identification of leaflet thinning as an independent risk factor for reoperation after truncal valve repair. This is a classic example of statistical significance needing to be interpreted. Should leaflet thinning be eliminated from truncal valve repair? Leaflet thinning improves the mobility of thickened leaflets, which allows for more normal leaflet curvature and coaptation, increasing the coaptation height, a parameter of paramount importance for valve competence in the aortic position. We would argue that the multivariable analysis identified leaflet thinning as an independent predictor of reoperation, because this technique was used in a subgroup of patients with thickened, fused leaflets which were more difficult to repair.

In summary, we report the largest series of patients to date undergoing TVR within all age groups. Outcomes are comparable to those reported for children undergoing aortic valve repair. Neonatal repair was a significant independent predictor of reoperation, and creation of a trileaflet valve provides the most durable results in this challenging population. New techniques, such as truncal root and annulus remodeling, are promising and require further evaluation.

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Conflicts of interest: none to declare.

References


Chapter 2 - Mitral and Tricuspid Valve Repair

*Mitral valve operations at a high-volume pediatric heart center: Evolving techniques and improved survival with mitral valve repair versus replacement*

A portion of this chapter has been published in Ann Pediatr Cardiol 2012;5(1):13-20, by Christopher W. Baird, Patrick O. Myers, Gerald R. Marx and Pedro J. del Nido. This paper reviewed the last 6 years experience (2005-2010) in valve surgery at Boston Children’s Hospital, which included 778 mitral valve operations, 724 valve repairs and 54 valve replacements. The results of this study are significant, in that they show the current status and results at a single center, with a national and international reference-level.

Abstract

Mitral valve disease is quite variable and can occur as an isolated defect or in association with other complex left sided lesions. These lesions are often best described with detailed pre-operative imaging studies to define the valve anatomy and to access associated left heart disease. Depending on the type of mitral valve disease, various surgical repair techniques have led to improved survival in the recent era. We describe lesion specific approach to mitral valve repair and results.
Introduction

Mitral valve disease in the pediatric patient is quite variable and ranges from a routine cleft in the anterior leaflet of the mitral valve to complex mitral stenosis associated with Shone's complex or hypoplastic left heart syndrome (HLHS). Further complicating the management of these children are the associated concomitant cardiac lesions, which can dramatically affect clinical outcomes. Historically, mitral valve replacement (MVR) has been associated with significant morbidity[1] in the pediatric population and thus considerable attention has been directed to mitral valve reconstruction in children over the last decade.[2,3] As mitral valve reconstructive techniques have been perfected, they evolved as the preferred approach for mitral valve stenosis and/or insufficiency in the pediatric population. Because of this, referrals for mitral valve surgery have increased since the mid-2000s. This study reviews our 6-year experience in mitral valve operations and focuses on the evolving technical aspects of mitral valve reconstruction.

Methods

Imaging of the mitral valve complex

In order to provide optimal treatment of the entire affected valve complex, it is important that systematic examination begins early. We often obtain preoperative three-dimensional echocardiography (3D-echo), which improves our ability to access more anatomic features. It allows a detailed assessment of the entire mitral valve complex, including the subvalvar area, annulus, leaflets, and chords. With associated hypoplasia or borderline hypoplasia of the left ventricle, magnetic resonance imaging (MRI) is used to assess left ventricular (LV) volumes, location, and extent of LV endocardial fibroelastosis, and quantify the flow across the mitral valve for purpose of deciding on initial strategy, whether it be single-ventricle or two-ventricle.
General operative procedure

Transesophageal echocardiography (TEE) was used routinely in all cases where an echo probe could be inserted, including young infants. With the availability of smaller TEE probes, pre- and postoperative echo studies can be performed in the vast majority of patients. In patients in whom a TEE probe could not be inserted, postbypass epicardial echocardiography was performed to assess the mitral valve function. In the past 3 years, 3D TEE probes have become available. These probes were used in all children weighing over 40kg if the probe was able to pass in the esophagus.

Cardiopulmonary bypass was generally established via standard single aortic and bicaval cannulation, followed by moderate hypothermia and cardioplegic arrest. Ventricular fibrillation was used in some patients, usually for the initial assessment of anatomy and to plan the repair. The mitral valve (MV) was exposed through the atrial septum or directly though the left atrium after developing Sondergaard's groove. Multiple MV repair techniques were used depending on the associated pathology, which are outlined in the following.

Lesion specific technical considerations

Atrioventricular canal. As a routine, we close the cleft in all cases of partial or complete atrioventricular (AV) canal defects. Cleft closure is done using double running 6-0 or 7-0 monofilament polypropylene suture, which is brought down to the tips of the chords except in patients were stenosis is a concern, and tied loosely to avoid reducing the height of the neo-anterior leaflet [Figure 1]. Patients in whom we are concerned about stenosis include mostly parachute or forme fruste parachute mitral valve with a functionally single left ventricular papillary muscle and variable development of the mural leaflet. In this case, the valvar orifice is mainly the cleft, which we routinely leave mostly or partially open, as closure would lead to severe stenosis. Our approach is to close the base of the cleft in most cases, and progress with
closure towards the chordal attachments until the predetermined inflow orifice size is achieved based on the patient's body size and predicted Z-score of −2.

Figure 1 – Cleft closure in atrioventricular canal defects. (a) Atrial surface of the left atrioventricular valve after cleft closure extending down to the level of the chords. (b) and (c) Schematic representation of the forces at work on the neo-anterior leaflet. Extended closure (c) may reduce the stresses on the zone of the apposition suture line by directing some of the force inferiorly instead of laterally.

After cleft closure, central or commissural regurgitation, as detected by saline injection, were corrected by annuloplasty, either using a De Vega-type double running suture along the left lateral annulus from commissure to commissure (ie, “posterior annuloplasty”), or by commissural annuloplasties.

The AV canal repair consisted of either a double patch repair[4] or a classic single patch repair[5] in most patients. The modified single patch technique[6,7] was seldom used, mostly in patients with a small ventricular septal defect amenable to direct closure and/or patients requiring
earlier repair, usually within the neonatal period. We have not used the modified no patch
technique.[8]

**Congenital mitral stenosis.** When considering the complex mitral valve repair in small
patients with small left-sided structures and/or congenital mitral stenosis (CMS), the technical
details of proper and adequate exposure are challenging and critically important. Our approach is
generally through the right atrium and atrial septum. As Stellin points out,[9] “eversion” of the
mitral valve annulus with everting stay stitches significantly enhances exposure of the entire
valve apparatus. Once everting temporary sutures are placed around the mitral annulus, the MV
complex is thoroughly examined. Although the surgical treatment is individualized for each
patient with CMS, the initial steps often involve resection of thick fibrous supra-valvular mitral
rings [Figure 2a]. This resection begins by developing a plane sharply with subsequent stripping
of the fibrous ring. When commissural fusion is present, commissurotomy is sharply performed.
Next, the subvalvular apparatus must be optimally exposed. In order to gain adequate exposure
under the posterior leaflet, it can be detached from the annulus [Figure 2b]. This maneuver is
particularly useful in patients that have abnormal subvalvular structures such as in patients with
“parachute, hammock, and arcade mitral valves.”[10,11,12] Many secondary tethering, fused or
shortened chords are then separated, mobilized or resected [Figure 2c] or sharply divided [Figure
2d]. In patients with “parachute or hammock mitral valves” the single or two large papillary
muscles, respectively, are split/divided, whereas in patients with “arcade mitral valves,” the short
intrapapillary tendinous chords are divided. Once there is adequate mobilization, the posterior
leaflet is often reattached using a treated autologous pericardial patch [Figure 2e]. Upon
completion, the posterior leaflet has improved mobility, which allows for increased leaflet
excursion during diastole [Figure 2f]. We believe that obtaining a mobile leaflet is the only way
to obtain a sufficient coaptation height, which has been shown to be an independent predictor of
durability of valve repair in adults.[13,14]
Figure 2 – Surgical repair of congenital mitral stenosis. (a) Surgeon’s view of the mitral valve demonstrating a thick supra-annular fibrous ring. The resection is completed using sharp and blunt dissection. (b) The subvalvar area is often exposed by incising the posterior leaflet. (c) and (d) Secondary tethering chords are then separated and/or divided to improve mobility of the posterior leaflet. (e) A pericardial patch is used to augment the posterior leaflet. (f) Lateral view after complete resection and mobilization

*Mitral regurgitation.* Congenital mitral regurgitation (CMR) lesions are classified according to the leaflet motion, using Carpentier’s seminal functional classification of mitral regurgitation: (1) normal, (2) enhanced (or prolapsed), and (3) restricted leaflet motion.[15,16] This classification translates into different causes of CMR and their associated treatment, although there is sometimes overlap or association of more than one mechanism that leads to
regurgitation. Detailed analysis of the mitral complex, including the annulus, the leaflets and the subvalvar apparatus both by preoperative echocardiography and intraoperative assessment should be used.

In the first functional group, regurgitation is due to a lack of apposition of the leaflets from primary annular dilatation (extremely rare) or more frequently leaflet defects, such as a cleft or agenesis of a leaflet segment. Annular dilatation was managed by different means of annuloplasty, as outlined below. In most cases, a cleft was closed primarily, using the same technique as described in closing the left atrioventricular cleft in CAVC. We favor a double running closure, the first layer in a horizontal mattress and the second layer over-and-over, extending to the tip of the chords. It can be necessary to fill the space between the cleft edges with a pericardial patch, particularly if the annulus is dilated. Leaflet defects, such as holes or localized agenesis, can be treated by direct suturing or pericardial patch repair depending on the size of the defect, taking care that the leaflet-free edge remains adequately supported by chords.

In leaflet prolapse, the free edge of the leaflet overrides the plane of valve orifice in systole,[16] creating a regurgitation jet toward the nonprolapsing leaflet. This is most often encountered with elongated chords, such as can be seen in Barlow's disease or Marfan syndrome, and involves the anterior leaflet most often in children, although both leaflets can be involved. In this condition, the annulus is usually enlarged, and the prolapsing A2 scallop can be resected [Figure 3] and the defect edges reapproximated. Annuloplasty of the enlarged annulus adapts the size of the annulus to the size of the leaflets and ensures adequate coaptation. Chordal shortening techniques, which bury elongated chords within the papillary muscle[17] have been shown to have poor long-term results in myxomatous mitral regurgitation in adults[18] and are often impractical to perform in a small child, and has not been used in our institution. Rarely, a segment or an entire leaflet is unsupported by chords. If this absence is relatively localized and small, it can be treated by transfer of secondary or basal chords to the free edge, or leaflet triangular resection. Rarely, ePTFE neochords can be used, although it is more difficult to size the chords
adequately in a small child, and there is concern that they will not grow with the child, although there are rare reports that refute this hypothesis.[19]

Figure 3 – Repair of anterior leaflet prolapse. (a) Surgeon's view of the mitral valve demonstrating a “tall” prolapsing segment of the middle scallop of the anterior leaflet. (b) and (c) After resection of the prolapsing segment, the edges are re-approximated normalizing the height of the anterior leaflet

In restricted leaflet motion, the lesions often overlap with those described in the section on CMS. The lesions include “commissural fusion”,[11] in which the commissural area is covered by endocardial fibroelastosis, along with fused chords and hypertrophied papillary muscles adherent to the commissure, and “short chordae syndrome,” were the chords are thickened, the interchordal spaces are reduced. Van Praagh demonstrated 20 years ago that, in
these anomalies, the mitral leaflets are covered with endocardial fibroelastosis (EFE) that creeps onto the chords. By trans-illumination from the ventricular surface of the valve, one can easily make out this extra tissue between the chords, which only appear short. They are actually normal sized, but covered with this EFE. Repair consists of resection of this EFE from the valve leaflets and chords, to restore mobility and pliability to the leaflets and subvalvar apparatus. Although Carpentier et al. proposed commissurotomy, leaflet augmentation and annuloplasty to treat this type of lesion, as we eluded to above, resection of EFE and obtaining a mobile leaflet is the only way to obtain a sufficient coaptation height. Furthermore, commissurotomy in this type of lesion can create commissural regurgitation.

Annuloplasty was performed when annular dilatation was present. Multiple annuloplasty techniques were used including De Vega-type double running suture annuloplasty along the posterior annulus, commissural annuloplasties, or ring annuloplasty in older children. The biodegradable ring, which has shown promising results in children with mitral insufficiency,[20–23] was used in the mitral position in four patients with atrioventricular valve regurgitation and in one patient with mitral regurgitation after repair of atrial and ventricular septal defects at our institution (under an FDA exemption, approved). It has been shown both in animal models[24] and for annuloplasty in the tricuspid position[25] to allow for annular growth without compromising stability of the repair. Longer-term results remain unknown.

For restricted leaflet mobility, secondary chords were divided and/or leaflets were augmented with autologous pericardium. In repeat operations, prior suture and/or pledget material was removed. For residual clefts, running or interrupted cleft closure was performed.
Results

Types of mitral valve disease and operative indications

From January 1, 2005 to December 31, 2010, 1609 heart valve operations were performed at Children's Hospital Boston. Over these 6 years, there has been 45% increase in mitral valve (MV) operations, which totaled 778 MV operations on 673 patients [Figure 4]. There were 724 MV repairs (which included 360 atrioventricular canals) and 54 MVR. When stratifying by age, there were 33 operations performed on neonates (0-30 days), 362 on infants (1 month to 1 year), 343 on children (1 year to 18 years), and 40 on adults (patients greater than 18 year old).

Figure 4 – Mitral valve operations at Boston Children’s Hospital from 2005-2010.

The most common fundamental diagnoses at this center from 2005–2010 considering all 673 patients were: AV canal defects, including partial and complete (443, 67%), congenital mitral stenosis (CMS)/Shone's complex (76, 11%), HLHS with CMS (41, 6%), CMR (25, 3.7%),
VSD/TOF/DORV (18, 2.7%), rheumatic disease/endocarditis (17, 2.5%), Marfan/Ehlers Danlos syndrome (10, 1.5%), and others (33, 5%). The most common fundamental diagnoses when considered by age at first operation are outlined in Table 3.1.1.

![Table 1 – Diagnoses stratified by age group.](image)

The primary indication for operation was AV canal in 360 patients. Of the other 364 MV repair operations, the primary indication for operation was mitral regurgitation in 53% (194 of 364), mitral stenosis and regurgitation in 25% (92 of 364) and mitral stenosis in 12% (42 of 364) and another indication in 10% (37 of 364) of the operations. Of the 54 MV replacements, the primary indication for operation was mitral stenosis and regurgitation in 48% (26 of 54), mitral stenosis in 37% (20 of 54) and mitral regurgitation in 13% (7 of 54) and another indication in 2% (1 of 54) of the operations.

**Follow up**

Follow-up data were available in 628 of 673 patients, ranging from 1 day to 6.1 years. There was definitive late follow up after discharge in 377 of 673 patients up to 6.1 years. Considering all 778 mitral valve operations, the 30-day hospital discharge and overall mortalities were 1.3% (10 of 778 operations), 2.8% (22 of 778 operations), and 4.1% (32 of 778 operations), respectively. Mortalities occurred a median of 9.3 days (MM, 1–27 days), 36 days (MM, 1 day–
20.3 months), and 64 days (MM, 1 day–34.2 months) from the most recent MV surgery, respectively. When considering all 673 patients undergoing MV operations; the 1-, 3-, 6-, 12-, 18-, 24-month and 5-year survivals were 98.5%, 97.3%, 96.9%, 96.1%, 95.5%, 95.4%, and 95.2% respectively.

Excluding AV canals, Figure 5 shows survival stratified by MV repair versus MVR. Five-year survival was greater for MV repair (96.0%) versus MVR (81.1%) (log-rank P<0.0001). When considering patients undergoing MV repair; the 1-, 3-, 6-, 12-, 18-, 24-month and 5-year survivals were 98.3%, 98.3%, 98.3%, 97.6%, 97.3%, 96.6%, and 96%, respectively. When considering all patients undergoing MVR, the 1-, 3-, 6-, 12-, 18-, 24-month and 5-year survivals were 94.6%, 94.6%, 91.9%, 91.9%, 81.1%, 81.1%, and 81.1%, respectively.

Figure 5 – Kaplan-Meier survival analysis of postoperative long-term survival to 5 year in patients undergoing mitral valve repair versus replacement.

With regard to reoperation, 14% of the 673 patients had a previous cardiac operation prior to 2005 of which in 54% was a MV procedure. Eighty-six percent of all patients underwent
their first MV operation between 2005-2010 and of these patients, 11% underwent redo operations during the same period. From 2005 to 2010, definitive reoperation data were available for analysis in 11% of the 673 patients. They underwent 105 reoperations on the mitral valve. These operations occurred from 4 days up to 3.5 postoperative years with a median of 196 days from prior mitral valve operation for a total of 62.7 total patient years. Of these patients having their initial operation between 2005-2010 and undergoing reoperation, there were 48 patients that had one reoperation, 16 patients that had two reoperations, seven patients that had three reoperations, and one patient that had four reoperations. The most common fundamental diagnoses in the 72 patients undergoing MV re-operations were AV canal, HLHS- MS, and congenital mitral stenosis. When considering all 673 patients undergoing mitral valve operations, freedom from reoperation was 97.3%, 96.3%, 94.8%, 93.2%, 91.5%, 90.5% and 89.3% at 1-, 3-, 6-, 12-, 18-, 24-month and 5-years, respectively.

Discussion

This report highlights the recent surgical experience at Boston Children's Hospital and comments on several important and evolving technical considerations. There are many lesions that often co-exist with congenital mitral valve disease with certain subsets continuing to present a surgical challenge. In our most recent series, we found that mitral valve reconstruction or repair rather than replacement is associated with improved survival of patients that have underlying congenital mitral valve disease.

AV canal

Carpentier postulated that the left atrioventricular valve in repaired CAVC consisted of a trileaflet valve, and advocated leaving the “commissure” between the superior and inferior bridging leaflet open.[16] Van Praagh argued that a commissure is supported by chords and is not the cause of regurgitation, and that this is not the case in the “commissure” between the bridging
leaflets, making it a cleft.[26] Wetter et al. showed that cleft closure at primary CAVC repair improved left atrioventricular valve regurgitation, from 28% of patients with the cleft left open who presented worsening of mitral regurgitation late after repair, to 9% in those whose cleft was closed.[27]

Kanani et al. showed, in a morphological study of normal and CAVC hearts, that the neo-anterior mitral leaflet is very different from the normal mitral valve[28] with a rectangular rather than triangular shape, deficient chordal arrangement, and fewer secondary and tertiary chords. They also found that the axis of chordal attachment to the leaflet [Figures 2b and 2c] could provide the biomechanical basis for tension on the repaired cleft and encourage reopening at the tip of the newly created leaflet, and proposed that cleft closure extending below the zone of apposition may reduce the tension on the repaired cleft.

Our preferred technique for cleft closure is the double-layer running suture. The first layer is a running horizontal mattress and the second layer is a simple running over-and-over suture, which is not tightened but left loose enough to help the pliability of the unified leaflet and avoids shortening leaflet height. The leaflet edges at the cleft are frequently rolled and coapt over a small surface area. Care must be taken to preserve this degree of coaptation in closing the cleft and not to unroll the leaflet edges, because leaflet coaptation adds strength to the cleft closure, as it has been shown in mitral[29] and aortic[14] valve repair.

The left atrioventricular valve annulus is very different from a normal mitral annulus, composed of a composite of native annulus and septal defect closure material or ventricular septal crest, depending on the CAVC repair, and no fibrous trigones.[30] Over time, the degree of regurgitation increases by 1 grade in 41% of patients with repaired CAVC[31] and the annulus progressively dilates. Regurgitation could thus be seen as a two hit event, with biomechanical forces tending to pull apart the segment of neo-anterior leaflet below the cleft closure, and annular dilatation making this distal cleft functionally more important and the cause of regurgitation.
Myamiura et al. first suggested that total circular annuloplasty with an absorbable suture at the time of primary CAVC repair could help break the vicious cycle of regurgitation begetting more regurgitation in the early period after repair, without interfering with the annular growth.[32] Furthermore, Padala et al. showed in an in vitro CAVC-like valve model that 2/3 cleft closure and 20% undersizing annuloplasty decreased regurgitation and minimized the risk of stenosis.[33]

Further studies into the segmental mechanism of annular dilatation after CAVC repair, such as can be provided by three-dimensional echocardiography,[34] would be helpful. Also, if prophylactic annuloplasty is shown to be beneficial, the ideal means of annuloplasty, for example, the entire posterior annulus or only at the commissures, as well as the material used, such as a small diameter nonabsorbable suture that could be expected to break with growth but provide structural stability for an extended period, absorbable suture versus biodegradable annuloplasty rings,[8] need to be defined. As mentioned above, the cleft is completely closed in all patients in whom stenosis is not a concern. However, partial closure in patients with parachute or forme fruste parachute mitral valve has not been formally evaluated.

In patients with AV canal lesions, we have focused on the techniques of cleft closure and the utility of annuloplasty. We strongly feel that the biomechanical forces predispose the left atrioventricular valve to dysfunction that can be minimized by carrying the cleft closure down to the level of the chords. Apposition of the cleft alone sets it up so that there is maximal stress on the distal cleft closure, making it at risk for cleft dehiscence. Extending the cleft closure down to the tips of the chords may allow for distribution of this force lower down, possibly decreasing stress on the cleft closure. Following these observations, we have selectively applied a combination of complete cleft closure and under sizing suture annuloplasty at the time of primary CAVC repair. Although in this series annuloplasty consisted of a mix of De Vega-type double running posterior suture annuloplasty and commissural annuloplasty, we now routinely perform
prophylactic posterior annuloplasty in many patients undergoing repair of CAVC where mitral stenosis is not a concern.

**Congenital mitral stenosis**

Congenital mitral stenosis is a rare and morphologically heterogeneous disease.[10,17,18] As described by Ruckman and Van Praagh,[10] it can affect any one of the components of the mitral valve, from above the annulus (supramitral ring) or the annulus itself, the leaflets and/or the subvalvar apparatus. It is frequently associated with additional left heart obstruction or ventricular septal defect. Interventional management in severe mitral stenosis has been advocated,[19] as medical management entails significant morbidity and mortality.[35] Interventional balloon dilatation has been shown to effectively relieve left ventricular inflow obstruction in most infants and children with severe congenital mitral stenosis who require intervention, although with a rate of freedom from failure of bi-ventricular repair or mitral valve reintervention of 76% at 1 month, 55% at 1 year and 39% at 5 years.[19] Surgical mitral valve repair for CMS may relieve inflow obstruction, but the success of these procedures may vary according to the pathology. Valve repair rather than replacement for congenital mitral dysplasia or CMS has been advocated, mostly because of the high rate of re-operation and heart block requiring pacemaker implantation, particularly in small children,[36,37] after valve replacement. There is relatively little data on the results of surgical repair for congenital mitral stenosis,[19,38] and criteria for patient selection and anatomical subgroups amenable to repair as of yet are not completely known.

Despite our attempts at delaying early intervention to allow for early AV valve remodeling and development in patients with congenital MS, over the last decade our tendency toward earlier mitral valve reconstruction versus replacement has increased. Mitral valve reconstruction with retention of the native subvalvular apparatus has been said to offer distinct advantages by conserving the ventricular geometry resulting in the improved long-term
ventricular function.[39] We now routinely employ conservative techniques to avoid MVR in infants and children. Despite the fact that MVR has been successfully reported in young children,[40–42] there are still persistent unavoidable problems such as heart block, endocarditis, thrombosis and stroke.[1] Several groups have also pointed out early predictors of mortality after MVR: the fundamental diagnosis, patient age, or size,[1] ventricular function and the size of prosthetic mitral valve.[43] All of that make the subset of patients with congenital mitral stenosis and/or Shone's syndrome (small left-sided structures) particularly challenging.

In addition to the technical improvements, there are many other important considerations that have led to an increase in MV reconstruction over the last decade. There have been dramatic advances in understanding the pathology[44] with preoperative imaging using two- and three-dimensional echocardiography to provide a precise delineation of the associated pathology.[45] Additionally, specific techniques for patients with complex AV canal lesions and congenital mitral stenosis have improved. We have been much more aggressive in our approach to the subvalular apparatus by dividing/splitting papillary muscles and secondary tethering chords. As timing of such interventions has been important, we will often accept “less-as-more” at the initial operation realizing multiple operations with shorter intervals will be required but avoiding the need for MVR.

Although MV repair may be associated with an increased number of reoperations, it is associated with improved 5-year survival compared to MVR in pediatric patients. At some point following multiple MV repairs, however, MVR will prove to be preferred but further follow-up and analysis is necessary to better define that time point.

References


Biodegradable Ring Annuloplasty

Valve Repair Using Biodegradable Ring Annuloplasty: From Bench To Long-Term

Clinical Results

A portion of this chapter has been published in Heart Lung Vessel 2013;5(4):213-18, by Patrick O. Myers and Afksendiyos Kalangos.

This paper reviewed the place of annuloplasty in valve repair, the history of biodegradable annuloplasty, the development, experimental and initial clinical studies of the biodegradable annuloplasty ring.

Abstract

Annulus remodeling and stabilization with a ring is a necessary step in mitral and tricuspid valve repair to maintain effective leaflet coaptation and improve long-term results. Although conventional rings meet the basic needs of adults, they do not preserve the changes in shape and size occurring during the cardiac cycle, and do not allow growth of the native annulus in children. The bioring annuloplasty ring was developed to allow for annular stabilization, while remaining biodegradable and allowing for growth. It is a curved "C" segment of poly-1,4-dioxanone polymer located on a non-degradable polyvinyl monofilament suture equipped with a stainless steel needle at each extremity. This ring is inserted subendocardially directly into the mitral or tricuspid annulus, away from blood contact. Animal model experiments have shown that it degrades within 12 months of implantation and is replaced by fibrous tissue, which stabilizes the annulus durably, while allowing for annular growth in children. We review the published data, from bench to bedside, as well as the early, mid and long-term clinical outcomes using the biodegradable ring, which shows that biodegradable rings remodel the annulus, reinforce the repair, restore the function of the atrioventricular valve and maintain the three dimensional
dynamic motion and geometry of the mitral and tricuspid valves annulus. Growth potential is preserved in children. The mid- and long-term results showed that degradation of the device occurred without negative observable consequences.

**Introduction**

Annulus remodeling and stabilization with a ring have been demonstrated to be a necessary step in mitral and tricuspid valve repair to maintain effective leaflet coaptation and improve long-term results (1). After establishing the basic tools of valve repair and annuloplasty, Professor Carpentier envisioned biodegradable annuloplasty in his pioneering review of the state of the art of valve repair in 1983 (2), predicting valvuloplasty using a “polyethyl-collagenol resorbable ring, which dissolves spontaneously in 12 months” and is “replaced by strong connective tissue by a process of creeping substitution”.

The need for such a degradable device, beyond the science-fiction vision of a pioneer, stems from two areas in which non-permanent, biodegradable annuloplasty can theoretically fill a void: (1) valve repair in infected tissues, such as endocarditis, to avoid colonization of permanent implanted materials and infection recurrence, and (2) valve repair in children, where traditional annuloplasty rings can’t be used due to the risk of acquired stenosis from lack of growth.

Following in the footsteps of Prof. Carpentier’s vision for the future, Duran et al. (3,4) and Chachques et al. (5) showed the feasibility of absorbable flexible ring or large bore suture annuloplasty in animal models, with degradation of the ring material within 1-2 months when comprised of fibrin (3), or 4 to 12 months when comprised of polydioxanone (4,5). Duran et al. completed this with a clinical study on 73 patients with functional tricuspid regurgitation, who received the first De Vega “vanishing” annuloplasty using 2-0 polydioxanone (6). They concluded that this vanishing annuloplasty resulted in annular stabilization for 4 months, and had acceptable results at 2 years follow-up.
Despite these promising laboratory and initial clinical results, little is known on the long-term outcomes of suture annuloplasty, and in particular the stability of annular remodeling after suture annuloplasty with a biodegradable suture or the risk of annular re-dilatation with degradation.

Following in these footsteps, we were encouraged to develop a new biodegradable annuloplasty ring in 1994, which received the CE mark approval in 2005. Initially marketed by Bioring (Bioring S.A., Lonay, Switzerland), it is now being produced by Parvulus Suisse (Lonay, Switzerland) with renewed CE marking since 2011, and is undergoing clinical investigation by the US Food and Drug Administration (FDA) under a “humanitarian use exemption” for orphan drug products.

**Design Of The Biodegradable Annuloplasty Ring And Initial Animal Models**

The biodegradable ring has a curved C segment comprised of a poly-1,4-dioxanone polymer, located at the middle of a non-degradable suture material equipped with stainless steel needles at each extremity. The suture material is 2-0 polyvinyl monofilament in adult sized rings, and 3-0 polyvinyl in pediatric sized rings. The suture material increases the resistance to tensile redilatory stretch of the dilated mitral or tricuspid annulus. The specific molecular weight of polydioxanone polymers ensures structural memory against subsequent deformity (contrary to biodegradable sutures), and adds three-dimensional flexibility to the ring. The ring material is degraded by hydrolysis within 6 months of implantation. The product of hydrolysis (2-hydroxyethoxy-acetic acid) triggers inflammation, such that the implanted ring will disappear in six months, inducing fibrous tissue.

As with traditional annuloplasty rings, the rings are available in various sizes, ranging from 16 to 36. The rings are sized, using a specific sizer, according to the height of the anterior leaflet. There are separate mitral and tricuspid rings, differing in shape. The mitral ring is a
symmetrically curved C shape, sized to remodel the posterior and both commissural annulus segments. The tricuspid ring is asymmetric and designed to remodel the anteroposterior annulus.

Contrary to traditional annuloplasty rings, which are implanted onto the native atrioventricular valve annuli, the biodegradable ring is inserted directly into the native annulus underneath the endocardium using the needles and suture extensions at each extremity of the ring, similarly to De Vega suture annuloplasty. For mitral annuloplasty, insertion starts at the posterior commissure, approximately 2-3 mm from the insertion of the posterior leaflet and 2-3 mm in depth, advancing the needle along the posterior annulus, as far as the needle allows. Once the needle has been advanced through and out of the tissue, the suture is pulled on, in the same direction as the exit point so as to avoid ripping the endocardium, to advance the ring into the annulus until the first exit point. Subsequent insertion of the needle is made through the previous exit point, allowing the ring to move forward into the annulus up to the next exit point. Complete insertion of the ring into the native mitral annulus is achieved by repeating the same steps in 2-3 bites past the anterior commissure. The ring is then fixed to the anterior trigone by passing the suture twice down from the anterior trigone to the anterior commissure, and tied onto itself. The posterior needle is then passed twice through the first subendocardial entry point at the posterior commissure, up to the posterior trigone twice. Care should be taken to maintain tension on the first loop on the posterior trigone before tying down the suture on itself, as this completes the annular remodeling at the desired size.

In pathologies which require complete ring annuloplasty, such as ischemic mitral regurgitation, the partial ring can be converted to a complete ring by advancing the suture extensions on each extremity to the midpoint of the mitral annulus, after tying the sutures on themselves at both trigones as explained above, and then tying both extensions together at the mid anterior annulus.

For tricuspid annuloplasty, insertion technique is quite similar: ring implantation begins at the postero-septal commissure, advancing along the antero-posterior annulus to the anteroseptal
commissure, avoiding the conduction tissue along the septal annulus. The tricuspid ring is asymmetric, with two curves in the ring to allow it to follow the shape of the native anteroposterior annulus. The shorter curved segment should be placed at the antero-septal commissure, and the longer curved segment at the postero-septal commissure.

The biodegradable ring was first tested in a juvenile pig model (7). Histological analysis showed that the ring material was gradually degraded within 6 months after implantation, with gradual increase in thickness of annular fibrous tissue filling the space left by the degraded implant material, reaching the diameter of implant at 12 months after implantation.

**Clinical Results**

The biodegradable ring has been reported in clinical use in several subsets of patients, which will be reviewed.

*Endocarditis.* One third of patients with infective endocarditis will require operative intervention. Given the superiority of valve repair over valve replacement in many indications other than endocarditis, there has been increasing interest and an increasing number of reports of excellent results of valve repair in acute infective endocarditis. Operative principles for infective endocarditis include complete debridement of infected tissues, drainage of abscess cavities followed by restoration of anatomic relationships.

It is tempting to avoid an annuloplasty ring when fixing limited leaflet destruction from mitral or tricuspid valve infective endocarditis, under the assumption that the underlying mechanism is acute regurgitation and usually doesn’t involve annular dilatation. Annuloplasty plays an important role in valve reconstruction, particularly if a significant infected leaflet segment must be resected, to relieve tension on the repaired leaflets and ensure long-term stability of the repair. Traditional annuloplasty rings and bands, predominantly made of polyester mesh, are susceptible to seeding and infection. Ciprofloxacin-coated polyester annuloplasty ring mesh was shown to confer infection resistance in a subcutaneous animal implantation model (8),
however these devices haven’t been reported in clinical use to date. The theoretically ideal material for valve repair in this setting is non-permanent, “vanishing” material, not at risk of seeding or colonization, such as the biodegradable ring.

Infection resistance of the biodegradable was tested in a rat subcutaneous implantation model, looking at “clean” implantations and implantations associated with inoculation of Staphylococcus Aureus (M. Cikirikcioglu, personal communication, to be presented at AATS mitral conclave 2013, May 2nd 2013; http://aats.org/mitral/abstracts/2013/E57.cgi). Compared to traditional Carpentier-Edwards rings, the biodegradable rings showed fewer positive cultures (2/16 vs. 11/16, P = 0.003) and lower colony counts (181±130 CFU/ml vs. 7175 ± 5936 in conventional rings, P < 0.0005).

Clinical use of the biodegradable ring has been reported in infective endocarditis by Kazaz et al. (9) and by our group (10–12). We previously reported our initial experience of using this ring from 2004 to 2009 in 17 patients with acute infective endocarditis, 13 in the mitral, 3 in the tricuspid and 1 in both valves (10). There were 3 early deaths, and no late evidence of endocarditis recurrence, valve dysfunction, reoperations or deaths at a mean follow-up of 30 months. We updated this report with our experience in 8 children with infective endocarditis (11). There were no early or late deaths, reoperations or evidence of endocarditis recurrence at a mean follow-up of 56 months.

Valve repair for endocarditis often entails large debridement of infected tissue, followed by reconstruction. This is often done using pericardium, although mitral and tricuspid valve patch augmentation is associated with poor outcomes, due to retraction of autologous pericardium or early calcification of glutaraldehyde-fixed autologous or xenogenic pericardium (13). Biodegradable scaffolds used as patches, such as intestinal submucosa marketed as CorMatrix© (14), promise to extend the theoretical advantages advanced for biodegradable annuloplasty to leaflet reconstruction, and offer the potential for valve repair with entirely degradable materials. Their use in atrioventricular valve repair has been reported in a limited study by Boston
Children’s Hospital, which didn’t include any patients with endocarditis (15), and further research is needed in this subject area.

**Congenital mitral regurgitation.** Preservation of the growth potential of the native atrioventricular annulus is critical to avoid acquired stenosis after valve repair in small children. In our experimental study in a model of fast-growing juvenile pigs, who increased their weight from a mean of 48 kg to 195 kg (+406%) during post-implantation follow-up, the growth potential of the tricuspid annulus was preserved (7).

Clinical experience with the biodegradable ring in this indication is still sparse. We reported our experience using the biodegradable annuloplasty ring in 22 patients with congenital mitral regurgitation, compared to 18 controls who had posterior biodegradable suture annuloplasty using 4-0 or 5-0 PDS, and 17 controls with posterior pericardial band fixed onto the native annulus by interrupted mattress polypropylene stitches. Unlike the two control groups, patients with a biodegradable ring showed homogeneous growth of the mitral anteroposterior and lateral annular diameters, similar to physiologic growth over a follow-up of 57±12 months, with two patients developing moderate mitral regurgitation. The Boston Children’s Hospital reported their experience with the biodegradable ring in 6 young patients (median age: 5.4 years) with complex congenital heart defects (16). The atrioventricular valve anteroposterior and lateral diameters, areas, and related z-scores were significantly reduced in all 6 patients. This reduction was more pronounced on the anteroposterior diameter, thus creating the more typical oval-shaped AV valve annulus. During a mean follow-up of 42 months, there were 2 atrioventricular valve reoperations, not linked to the biodegradable ring.

There have been limited case reports or series in other indications for mitral valve repair in children. Myers et al. reported the successful management of congenital ischemic mitral regurgitation associated with an ALCAPA (17). The biodegradable ring has also been used for left or right atrioventricular valve repair at or after atrioventricular canal repair defect repair (16,18).
**Rheumatic mitral disease in children.** We recently reported our 13 year experience with mitral valve repair for rheumatic disease in children, comparing results with the biodegradable ring to traditional rigid Carpentier-Edwards annuloplasty rings (19). The aortic cross-clamp and cardiopulmonary bypass times were shorter by 10-12 minutes in the biodegradable ring group. The systolic left ventricular function, as assessed by shortening fraction, was also better preserved at 1 week after repair with the biodegradable ring, perhaps because this flexible ring better preserves the three-dimensional geometry of the mitral annulus. Mitral inflow gradients during the first post-operative year were lower with the biodegradable ring, with no significant difference in terms of recurrent regurgitation or reoperations.

**Degenerative mitral regurgitation.** We recently reviewed our experience with the biodegradable ring in mitral valve repair for degenerative mitral regurgitation. Between 2005 and 2007, we included 102 consecutive patients who underwent mitral valve repair with the biodegradable ring, and matched them to contemporaneous patients who underwent mitral valve repair a traditional Carpentier-Edwards ring. During a follow-up of 3 years, the biodegradable ring group showed lower mitral inflow gradients (3.0±1.2 mmHg, vs. 5.2±1.8 mmHg in controls) at 1 year. The inflow gradients continued to increase in the control group at 3 years post-operatively (5.2±2.2 mmHg), while it gradually decreased for 2 years before reaching a plateau on the third year after repair (2.3±0.4 mmHg). There was no significantly different rate of recurrent mitral regurgitation between groups. As in our study in children with rheumatic mitral regurgitation, we also found a significantly smaller decrease in shortening fraction early after surgery (3 weeks). Finally, we measured the dynamic annular diameters during follow-up, which showed that the anteroposterior diameter maintained a 15±3% variation during the cardiac cycle after biodegradable ring annuloplasty, which wasn’t the case in controls, and we didn’t see any late re-dilatation of the annulus.

**Minimally invasive and Robotic annuloplasty.** One last area that hasn’t been investigated quite as much, is the applicability of the implantation technique of the biodegradable
ring in minimally invasive cardiac surgery. Minimally invasive and robotic surgery is an emerging field in cardiac surgery. Although initially more complicated for the surgeon, these surgeries have been shown to be less traumatic for the patient and to provide a faster recovery, without compromising the quality of the repair (20,21). Dedicated surgical instruments have been developed to fit these approaches, although traditional annuloplasty devices have not been adapted to minimally invasive surgery, and still require multiple suture placement and knot tying, which are somewhat difficult, tedious and time-consuming in minimally invasive surgery. The biodegradable ring, as outlined previously, can be inserted directly into the native annulus, using the suture extensions at each extremity. No further sutures are required, thereby simplifying the implantation in minimally invasive cardiac surgery (22). We recently reported our experience in 10 consecutive patients who underwent successful tricuspid annuloplasty with the biodegradable ring (23).

**Conclusions**

Annuloplasty using a biodegradable ring has shown excellent early- and mid-term results, with particular advantages compared to traditional annuloplasty rings in specific subsets of patients, namely children, endocarditis and minimally invasive cardiac surgery. Longer-term follow-up is currently being assessed and we look forward to expanding on our current knowledge of these biodegradable devices.

**References**


Atrioventricular Valve Annular Remodeling With a Bioabsorbable Ring in Young Children

A portion of this chapter has been published in J Am Coll Cardiol 2012;60(21):2256-8, by Victor Bautista-Hernandez, Patrick O. Myers, Hugo Loyola, Gerald R. Marx, Emile A. Bacha, Christopher W. Baird and Pedro J. del Nido.

This paper reviewed the initial experience at Boston Children’s Hospital in using the biodegradable annuloplasty ring for repair of congenital mitral regurgitation. This contribution was significant, in that it represented the first report of using this device in North America under a humanitarian exemption compassionate use, and because it reported it’s use in a group of small children, previously not studied.
Atrioventricular (AV) valve repair for regurgitation has been shown to be preferable to valve replacement in young children (1). Besides valvuloplasty technique, annulus reduction and stabilization with a ring have been demonstrated to be necessary to maintain effective leaflet coaptation. In young children, however, placement of a permanent annuloplasty ring is rarely performed because it carries the risk that a re-operation will likely be required as the child grows.

The concept of annuloplasty with biodegradable material, as an adjunct to AV valve repair, is not new. More recently, a flexible intra-annular AV valve ring that is constructed of absorbable biopolymer has been introduced for mitral valve (MV) and tricuspid valve repair (2,3). Unlike rigid or semirigid rings, this new device is a partial ring made of flexible material, which loses tensile strength as the ring material absorbs, thus potentially permitting normal growth of the valve annulus. There are limited data available on outcomes of absorbable ring implantation in young children with complex congenital heart disease (CHD).

Six children (4 months to 8 years, median age: 5.4 years) with CHD and severe AV valve regurgitation underwent AV valve plasty and insertion of a biodegradable annuloplasty ring (Bioring SA, Lonay, Switzerland). Four children had previously had AV canal defect repair (2 had associated heterotaxy syndrome and 1 Shone’s complex), 1 a dysplastic MV, and another had hypoplastic left heart syndrome. Food and Drug Administration approval for device implantation was obtained for all patients under compassionate use exemption. Institutional review board approval and informed consent were obtained on all patients.

There were no perioperative deaths or complications such as AV block or coronary compromise. By early post-operative echocardiography, the AV valve anteroposterior (AP) and lateral diameters, areas, and related z-scores were significantly reduced in all 6 patients ($p \leq 0.05$ for all variables) and increased—while remaining in the normal range—during the follow-up period (Fig. 1). This reduction was more pronounced on the AP diameter, thus creating the more typical oval-shaped AV valve annulus.
During a mean follow-up of 42 months (range: 26 to 48 months), there were no deaths, late-onset arrhythmias, or ventricular dysfunction. Four patients required reoperation, 2 nonrelated to the AV valve (aortic valve replacement and Fontan completion). One patient with a dysplastic MV required reoperation for mitral stenosis due to recurrent endocardial fibroelastosis. None of the other 5 patients had evidence of significant stenosis, with a mean post-operative, and at latest follow-up, inflow gradient of $2.0 \pm 2.5$ mm Hg and $2.7 \pm 4.3$ mm Hg, respectively. One patient with an AV canal defect was reoperated on late for dehiscence of the superior bridging leaflet of the left AV valve. This leaflet had been detached and repositioned to eliminate subaortic obstruction. In both redo patients, the bioring was fully reabsorbed and subsituted by fibrotic tissue located in the intra-annular position. One patient with AV canal redeveloped significant AV valve regurgitation 2 years after repair, but remains asymptomatic with stable left ventricular dimensions and function.

Valve repair in children is challenging due to the complexity of the underlying anatomic abnormalities and growth of the valvular structures over time. Unlike adults, implanting an annuloplasty ring is usually not performed in young children due to the risk of acquired stenosis.
with growth. We have evaluated our results with the bioring in 6 pediatric patients with complex CHD and severe AV valve regurgitation. In our series, all patients had a significant reduction and normalization of the annular measurements after ring implantation. We did, however, observe annular growth over time, which was proportional to somatic growth because the z-scores remained normal, and with a more oval-shaped annulus than before valvuloplasty (Fig. 1).

The pediatric experience with absorbable annuloplasty ring implantation has been primarily in Europe, where this device is available for clinical use. Kalangos et al. (4) recently updated their experience with this device in children with rheumatic MV disease. The use of a biodegradable MV ring resulted in a significantly lower mean gradient during the first year of implantation compared with the Carpentier-Edwards ring. However, the mean age of the patients in this study was 11.8 years at repair, which is significantly older than our study population. A more recent report on 11 children (median age: 4.5 years) undergoing tricuspid valve repair with the bioring demonstrated tricuspid annular growth over time (3).

In summary, we have used an absorbable annuloplasty partial ring in 6 children with complex CHD and achieved a competent AV valve with normalization of the AP and lateral diameters, area, and z-scores. During a median follow-up of 42 months, reduction of those parameters remains significant, and the annulus area has increased appropriate to somatic growth. This time period is important because the prosthesis is predicted to be absorbed after 6 months of implantation. Our initial experience and the published experience in Europe indicate that a larger clinical trial with this ring is warranted.

References


Techniques to Relieve Leaflet Tethering or Restriction

Leaflet Suspension To The Contralateral Annulus To Address Restriction Or Tethering-Induced Mitral And Tricuspid Regurgitation In Children

A portion of this chapter has been published in J Thorac Cardiovasc Surg 2010;140:1110-6, by Patrick O. Myers, Jan T. Christenson, Mustafa Cikirikcioglu, Cécile Tissot, Yacine Aggoun and Afksendiyos Kalangos.

This paper reported the mid-term results of a novel technique, first described by Kalangos et al., to relieve leaflet restriction or tethering of mitral and tricuspid valve leaflets. This technique was used as a last resort during valve repair, after all usual techniques had been used to try to make a valve competent (such as secondary or primary chordae resection, leaflet thinning or patch augmentation) and residual leaflet restriction or tethering persisted. This study showed that the technique was safe, in that the prevalence of significant stenosis wasn’t higher in patients who required this technique, and because the suspension stitch didn’t fail (or break) in any patient.
Abstract

BACKGROUND: Acceptable coaptation can’t always be obtained using standard repair techniques. We assessed the safety and mid-term results using a novel technique to address leaflet retraction or tethering in children with type III mitral or tricuspid regurgitation as an addition to standard valve repair techniques.

METHODS: 40 children were included, 36 for the mitral valve and 4 for the tricuspid valve, with a mean age of 11.3±3.9 years. A polypropylene suture was placed on the free edge of the retracted or tethered leaflet segment, and anchored to the atrial side of the opposite annulus. This avoided valve replacement in all patients. 40 children matched for age, etiology, leaflet retraction or tethering and operation in which the suspension stitch was not used constituted the control group.

RESULTS: Mean aortic cross-clamp and CPB times were 36±9 and 57±9 minutes. There were no early or late deaths. At discharge, no patient had more than mild regurgitation with gradients of 4.4±2.4 mmHg in the mitral position and 2±1.75 in the tricuspid position. Results weren’t significantly different compared to the controls. During a follow-up of 37.7±18.4 months, three patients required reoperation for mitral valve replacement in the suspension stitch group, and 2 within the control group. At echocardiography of the remaining patients, the repair remained stable, with no suspension suture breakage.

CONCLUSIONS: This suspension technique improves coaptation and can avoid or delay valve replacement in patients with type III regurgitation, with acceptable transvalvular gradients in most patients, which did not significantly increase with growth.
Introduction

Mitral and tricuspid valve repair, if technically feasible, remains the procedure of choice for most etiologies of mitral and tricuspid regurgitation. However, when the leaflets are retracted or tethered as in type III regurgitation, acceptable coaptation can’t always be obtained using standard repair techniques as described by Carpentier (1), such as ring annuloplasty, leaflet shaving, resection of retracted secondary or primary chordae tendineae and pericardial patch leaflet augmentation. Several alternate techniques have been proposed to specifically address retraction or tethering, such as papillary muscle relocation (2-4), edge-to-edge (Alfieri) repair (5), or ventricular remodeling (6, 7).

We previously reported our initial experience with suspension of the retracted posterior leaflet free edge to the ipsilateral annuloplasty ring in 10 rheumatic patients (8). This suspension stitch was conceived by the senior author (A.K.) and refined by suspending the leaflet free edge to the contralateral annulus, to allow for better coaptation. The aim of this study is to assess the safety and mid-term results using this novel technique used to address leaflet restricted motion or tethering of any etiology in children.

Methods

The study was reviewed and approved by the local Ethics Committee, and patient consent was waived.

Demographics. From March 2003 through May 2009, 40 consecutive children who underwent mitral or tricuspid repair for regurgitation were found to have unacceptable residual regurgitation after the use of standard repair techniques as described by Carpentier (1), and required leaflet suspension to the contralateral annulus, as described below, as a salvage procedure in order to avoid a potential valve replacement. A portion of these patients has been reported previously in other studies (9-12).

Thirty-six of these patients who underwent surgery had this technique applied on the mitral valve (rheumatic mitral regurgitation in 22, congenital 11, functional 1, degenerative 1 and...
endocarditis 1) and 4 on the tricuspid valve (dysplastic tricuspid valve 2, Ebstein’s anomaly 2), with a mean age of 11.4±3.9 years. For the purpose of evaluating this novel technique, 40 patients having undergone similar operations, matched for age, etiology and mechanism of valve regurgitation, but not requiring techniques beyond the traditional mitral or tricuspid repair techniques (1), were identified within the same timeframe and used as a control group. Regardless of the group they were in, all patients presented type I mitral or tricuspid regurgitation from annulus dilatation with the exception of one patient (see below), and type III regurgitation due to tethering or retraction, confirmed by preoperative echocardiogram and intraoperative valve analysis. Patient demographics of the entire study population are summarized in Table 1.
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<td>15 (37.5%)</td>
<td>20 (50%)</td>
<td>.27</td>
</tr>
<tr>
<td>Previous cardiac operation‡</td>
<td>12 (15%)</td>
<td>7 (17.5%)</td>
<td>5 (12.5%)</td>
<td>.76†</td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>7 (8.8%)</td>
<td>3 (7.5%)</td>
<td>4 (10%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Aortic valve repair</td>
<td>1 (1.3%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>AVC defect repair</td>
<td>2 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Coarctation repair</td>
<td>2 (2.5%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>.49</td>
</tr>
<tr>
<td>Subaortic stenosis repair</td>
<td>1 (1.3%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Congenital coronary anomaly repair§</td>
<td>2 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>72 (90%)</td>
<td>36 (90%)</td>
<td>36 (90%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>44 (55%)</td>
<td>22 (55%)</td>
<td>22 (55%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Congenital</td>
<td>22 (27.5%)</td>
<td>11 (27.5%)</td>
<td>11 (27.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Functional</td>
<td>2 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Degenerative</td>
<td>2 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>8 (10%)</td>
<td>4 (90%)</td>
<td>4 (90%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Dysplastic</td>
<td>4 (5%)</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>4 (5%)</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Concomitant procedure</td>
<td>29 (36%)</td>
<td>16 (40%)</td>
<td>13 (32.5%)</td>
<td>.64†</td>
</tr>
<tr>
<td>Aortic valve repair</td>
<td>6 (7.5%)</td>
<td>2 (5%)</td>
<td>4 (10%)</td>
<td>.68†</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>3 (3.8%)</td>
<td>1 (2.5%)</td>
<td>2 (5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Tricuspid valve repair</td>
<td>11 (13.8%)</td>
<td>6 (15%)</td>
<td>5 (12.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Bidirectional Glenn shunt</td>
<td>2 (2.5%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>.49</td>
</tr>
<tr>
<td>VSD repair</td>
<td>1 (1.3%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>ASD repair</td>
<td>3 (3.8%)</td>
<td>2 (5%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>PFO repair</td>
<td>1 (1.3%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Partial AVC defect repair</td>
<td>1 (1.3%)</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Cox-Maze procedure</td>
<td>4 (5%)</td>
<td>1 (2.5%)</td>
<td>3 (7.5%)</td>
<td>.62†</td>
</tr>
<tr>
<td>ALCAPA repair</td>
<td>1 (1.3%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Subaortic stenosis repair</td>
<td>1 (1.3%)</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
</tbody>
</table>

*Independent samples Student t test between suspension stitch and control groups.
†Fisher’s exact test. ‡Performed at another institution. §Congenital coronary anomalies included an ALCAPA repair and unroofing of congenital ostial left main coronary artery stenosis. AVC, atrioventricular canal; VSD, ventricular septal defect; ASD, atrial septal defect; PFO, patent foramen ovale; ALCAPA, anomalous left coronary artery originating from the pulmonary artery.

Table 1 – Patient characteristics.
**Operative Technique:** Cardiopulmonary bypass was established by ascending aortic and bicaval cannulation. All patients were operated by the same surgeon (A.K.) at normothermia and myocardial protection consisted of cold antegrade hyperkalemic crystalloid cardioplegia repeated every 20 minutes. The mitral valve was explored through a left atriotomy performed in the interatrial groove. Each structure of the mitral valve was analyzed systematically. In all patients with the exception of 2, annuloplasty was performed using a Bioring Kalangos biodegradable ring (Bioring SA, Lonay, Switzerland), as described previously (9, 13). The mean annuloplasty ring size was 26.6±3.6 (range 16-34) in the mitral position (suspension group 26.2±3.9, control group 26.9±3.3, p = 0.42) with a mean age of 11.3±4 years, and 27±3.6 (range 24-34) in the tricuspid position (suspension group 24.5±1.0, control group 29.5±3.4, p = 0.03) with a mean age of 11.6±3.2 years. Two patients did not have annuloplasty during the studied operation: one patient underwent mitral valve repair in heart failure during the acute phase of rheumatic heart disease. The repair included annuloplasty with a biodegradable ring. Although significant posterior leaflet retraction was noted at the time, suspension was not considered due to the extreme fragility of the inflamed tissues. The patient developed progressively moderate-to-severe regurgitation, and underwent reoperation 3 months after the primary operation. The suspension stitch was successfully used on the healed, retracted posterior leaflet segments, avoiding valve replacement. This second operation was included in the suspension stitch group. The other patient presented with a hammock mitral valve, with significant mitral stenosis (mean transvalvular gradient 20 mmHg); commissurotomy, leaflet mobilization by papillary muscle splitting and suspension of P2-P3 was performed, and annuloplasty was not considered due to concerns with stenosis.

The surgical procedures included leaflet-level chordal shortening at the free-edge of prolapsing segments, chordal transfer, secondary or primary posterior chordal resection, commissurotomy, commissuroplasty, triangular resection, sliding plasty and vegetation resection (see Table 2). Secondary chordal transfer to the primary position was mainly used either in cases
of anterior leaflet prolapse due to chordal rupture or in case of anterior leaflet pseudoprolapse due
to restricted posterior leaflet motion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire study population</th>
<th>Suspension stitch group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic crossclamp (min)</td>
<td>36.0 ± 9.3</td>
<td>35.4 ± 10.3</td>
<td>36.6 ± 8.3</td>
<td>.57*</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (min)</td>
<td>56.9 ± 9.4</td>
<td>57.9 ± 8.3</td>
<td>55.8 ± 10.4</td>
<td>.31*</td>
</tr>
<tr>
<td>Valve repair technique</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ring annuloplasty</td>
<td>78 (97.5%)</td>
<td>38 (95%)</td>
<td>40 (100%)</td>
<td>.49†</td>
</tr>
<tr>
<td>Leaflet-level chordal shortening</td>
<td>18 (22.5%)</td>
<td>5 (12.5%)</td>
<td>13 (32.5%)</td>
<td>.06†</td>
</tr>
<tr>
<td>Leaflet indentation closure</td>
<td>46 (57.5%)</td>
<td>20 (43.5%)</td>
<td>26 (65%)</td>
<td>.26†</td>
</tr>
<tr>
<td>Leaflet cleft closure</td>
<td>14 (17.5%)</td>
<td>7 (17.5%)</td>
<td>7 (17.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Commissuroplasty</td>
<td>22 (27.5%)</td>
<td>6 (15%)</td>
<td>16 (40%)</td>
<td>.02†</td>
</tr>
<tr>
<td>Primary chordae resection</td>
<td>11 (13.8%)</td>
<td>5 (12.5%)</td>
<td>6 (15%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Secondary chordae resection</td>
<td>10 (12.5%)</td>
<td>3 (7.5%)</td>
<td>7 (17.5%)</td>
<td>.31†</td>
</tr>
<tr>
<td>Chordal transfer</td>
<td>11 (13.8%)</td>
<td>5 (12.5%)</td>
<td>6 (15%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Artificial chordae</td>
<td>1 (1.3%)</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Triangular leaflet resection</td>
<td>3 (3.8%)</td>
<td>3 (7.5%)</td>
<td>0 (0%)</td>
<td>.24†</td>
</tr>
<tr>
<td>Sliding fundoplasty</td>
<td>6 (7.5%)</td>
<td>0 (0%)</td>
<td>6 (15%)</td>
<td>.03†</td>
</tr>
<tr>
<td>Leaflet pericardial patch augmentation</td>
<td>1 (1.3%)</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Papillary muscle fenestration</td>
<td>11 (13.8%)</td>
<td>7 (17.5%)</td>
<td>4 (10%)</td>
<td>.52†</td>
</tr>
<tr>
<td>Commissurotomy</td>
<td>8 (10%)</td>
<td>4 (10%)</td>
<td>4 (10%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Vegetation resection</td>
<td>1 (1.3%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Ebstein’s anomaly repair</td>
<td>4 (5%)</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>1.00†</td>
</tr>
</tbody>
</table>

*Independent sample t test between suspension stitch and control groups. †Fisher’s exact test.

Table 2 – Operative data.

After completing these procedures, water testing revealed significant residual
regurgitation due to persistent restricted motion or tethering of a leaflet in the 40 patients included
in the suspension stitch group. These patients were considered candidates for valve replacement,
and our additional technique was applied first as a salvage procedure to potentially avoid
replacement. A 5-0 polypropylene suture was placed on the free edge of the retracted leaflet
segment responsible for residual regurgitation, and then anchored to the atrial side of the
contralateral annulus, on an autologous pericardial pledget if the annular tissue appeared fragile (Figure 1). The length of this horizontal mattress suture was regulated while tying its two strands together on the contralateral annulus. This allowed the retracted or tethered leaflet to be brought up and rest closer to the natural coaptation plane. The primary aim was to achieve coaptation rather than an anatomical function of the retracted or tethered leaflet. The risk for leaflet abrasion or suture tearing over time was regarded as low, because the suspended leaflet is not part of the leaflet movement and the suture is placed to resist the relatively low diastolic pressures. Two patients required posterior mitral commissure suspension, while the remaining 34 required posterior mitral leaflet suspension (see Table 3). Among the 4 patients who underwent tricuspid repair, 3 required septal leaflet suspension and 1 required posterior leaflet suspension.

Figure 1 – Schematic illustration of the suspension stitch in the mitral position. The P2-P3 junction is suspended using a Polypropylene suture to the anterior annulus over a pledget, bringing the restricted or tethered leaflet segment up to the coaptation plane.
At the completion of repair, valve competence was tested using a bulb syringe to inject saline solution into the left or right ventricle. Concomitant procedures were performed in 29 patients (see Table 1). Intraoperative transesophageal echocardiography was performed in all patients before skin incision and after termination of cardiopulmonary bypass to evaluate the valvular repair.

**Follow-up:** Transthoracic echocardiography was carried out in all patients before surgery, before discharge from the hospital, and at 3 and 6 weeks postoperatively in the outpatient clinic of our institution before returning to their referring cardiologist or countries of origin. Doppler echocardiographic grade of mitral regurgitation was measured with color Doppler flow and graded according to the width and length of the regurgitant jet in the left atrium (grade I to IV). The mean gradient across the mitral valve was estimated by measuring the peak diastolic velocity from Doppler studies in a four-chamber view. All 80 patients (100%) were thereafter followed in outpatient clinics by cardiologists in their countries of origin, who periodically informed us of the patients’ evolution by filling out a questionnaire including clinical, echocardiographic, and medication information. Follow-up in this study was achieved until December 2009. We followed standard published guidelines in reporting freedom from valve-related events (14).

Table 3 – Leaflet suspension.

<table>
<thead>
<tr>
<th>Leaflet segment suspended</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve</td>
<td>n (%)</td>
</tr>
<tr>
<td>P1</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>P1-P2</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>P2</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>P2-P3</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>P3</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>P1 and P3</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Posterior commissure</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>n (%)</td>
</tr>
<tr>
<td>Posterior leaflet</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Septal leaflet</td>
<td>3 (7.5%)</td>
</tr>
</tbody>
</table>
**Statistical Analysis:** Statistical analyses were performed with SPSS software (SPSS Inc, Chicago, IL). Data are presented as mean±SD. Continuous variables were analyzed with independent samples Student t test and categorical variables using Fisher’s exact test. Actuarial estimates were calculated using the Kaplan-Meier method and differences between curves assessed by the log-rank test. Univariable and stepwise Cox multivariable regression analyses were used to identify the independent predictors of late reoperation and transvalvular gradients above or equal to 7 mmHg, as well as to assess if being in the suspension stitch group was a predictor of these two outcome measures. Preoperative and operative variables with a univariable p < 0.1 or those judged to be clinically important (age, sex, valve treated, prior cardiac, surgery concomitant cardiac surgery, suspension stitch group versus controls) were entered into the Cox models. Hazards ratios for risk factors for reoperation were calculated using univariable and multivariable Cox proportional hazards estimates. All statistical tests were two-tailed and p values < 0.05 were taken as significant.

**Results**

**Early Outcomes:** mean aortic cross-clamp and cardiopulmonary bypass (CPB) times were 36±9.3 and 56.9±9.4 minutes, respectively, with no significant difference between the suspension stitch group and the control group (cross-clamp 35.4±10.3 min and 36.6±8.3, p = 0.57; CPB 57.9±8.3 and 55.8±10.4 respectively, p = 0.31). After applying the suspension stitch, valve replacement was avoided in all 40 patients. There were no hospital deaths or major postoperative morbidity. No patients required reoperation within 30 days.

**Late outcomes:** follow-up was complete in all patients. Mean and median follow-up was 37.7±18.4 and 37 months respectively, ranging from 3 months to 7 years. The median follow-up in the suspension stitch group was 26 months and 41 months for the control group. This difference in median follow-up stems from the fact that, although both groups were operated on within the studied timeframe, we started using the suspension technique gradually since 2003, with an exponential increase in it’s use over time, while the controls were more uniformly
operated on during the study. There were no deaths during follow-up. No thromboembolic or hemorrhagic events were observed up to the most recent follow-up examinations.

A total of 5 patients (6.3%) with rheumatic mitral regurgitation underwent reoperation for severe mitral valve dysfunction after a mean period of 19.4±16.7 months (range, 3 to 43) from the initial mitral valve repair, 3 within the suspension stitch group (7.5%), and 2 within the control group (5%). The mean period to reoperation was shorter in the suspension stitch group, with a mean and median of 8±5.6 and 7 months respectively (range 3-14) compared to 36.5±9.2 and 36.5 months respectively in the control group (range 30-43, p = 0.02).

Actuarial freedom from reoperation due to significant valve dysfunction was 96±2.2% at 1 year, 94.2±2.9% at 3 years, and 91.2±4.1% at 5 years (see Figure 2). For the suspension stitch group, freedom from reoperation was 97.5±2.5% at 6 months, 92.4±4.2% at 1 year and then remained unchanged to 7 years. For the control group, the freedom from reoperation was 96.6±3.4% at 6 months, 1 and 3 years, and 91.2±6.1% at 5 years. The difference between groups was not statistically significant (log rank test, p = 0.52). On Cox proportional hazards modeling, the suspension stitch was not a predictor of reoperation (univariable hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.09-3.38, p = 0.53; multivariable-adjusted HR 1.89, 95% CI 0.29-12.06, p = 0.51).
Figure 2 – Survival curves after mitral or tricuspid valve repair regurgitation in 80 children. The difference between the curves didn’t reach statistical significance (log-rank test, $p = 0.52$).

**Valve function & transvalvular gradients**: among patients who required the suspension stitch, 1 patient in the mitral group had mild regurgitation at discharge while the remainder presented trivial or no regurgitation, with a mean transvalvular gradient of 4.4±2.4 mmHg (range 1.3-11, $>7$ in 3), and all patients had no or trivial tricuspid regurgitation, with a transvalvular gradient of 2±1.75 mmHg. In the control group, 2 patients in the mitral group had mild...
regurgitation, with a transvalvular gradient of 3.3±2.6 (range 2-10, >7 in 2, p = 0.09 compared to suspension group) and all patients had no tricuspid regurgitation with a transvalvular gradient of 3.7±1.7 mmHg (p = 0.14). At echocardiography of the 75 patients who didn’t require reoperation, the repair remained stable. In the suspension group, the mean transvalvular gradient slightly decreased to 4.2±1.6 mmHg (range 2-11, >7 in 1) for the mitral valve and was unchanged at 2±1.75 mmHg for the tricuspid valve, with no suspension suture breakage. In the control group, the mean transvalvular gradient decreased to 2.8±2.3 mmHg (range 1-10, >7 in 2, p = 0.005 compared to suspension group) for the mitral valve and 3.6±1.5 mmHg for the tricuspid valve (p = 1.00). Left ventricular systolic (4.6±0.4 cm in the suspension stitch group vs. 4.7±0.4 cm in the control group, p = 0.9) and diastolic dimensions (2.8±0.5 cm vs. 2.9±0.4 cm respectively, p = 0.74) were not significantly different between groups at latest follow-up. On Cox proportional hazards modeling, the suspension stitch was not a predictor of transvalvular gradient equal or higher to 7 mmHg at latest follow-up (univariable HR 0.98, 95% CI 0.22-4.37, p = 0.97; multivariable-adjusted HR 1.68, 95% CI 0.3-9.3, p = 0.56). Greater age at operation (multivariable-adjusted HR 0.52, 95% CI 0.31-0.89, p = 0.02) and prior cardiac operation (multivariable-adjusted HR 0.004, 95% CI 0-0.71, p = 0.04) were independent predictors of this outcome measure.

**Discussion**

Surgical management of mitral and tricuspid regurgitation in the young is problematic, because of the lack of an ideal valve substitute within this age group. Prosthetic valves carry significant drawbacks, such as suboptimal preservation of ventricular function, reduced survival, problems related to growth and future pregnancy, difficult lifelong anticoagulation and panus formation for mechanical valves, and rapid deterioration and calcification for biological valves (15). Long-term results in surgery for mitral regurgitation have shown that repair is preferable over replacement in terms of survival and thrombo-embolic and bleeding complications (16). A restricted posterior leaflet is characteristic in rheumatic mitral regurgitation (8, 17); tethering is
often one of the mechanisms responsible for regurgitation in functional and dysplastic mitral and tricuspid regurgitation (18, 19). Both of these mechanisms of type III regurgitation aren’t addressed with ring annuloplasty, although newer three-dimensional rigid rings have been developed for this reason and are currently being evaluated in adults (20). One of the tenets of Carpentier’s strategy toward valve repair is to provide a functional repair, rather than an anatomical repair (1), often transforming the mitral valve into a functionally unicupid valve with adequate leaflet coaptation from full motion of the anterior leaflet. We postulated that by bringing the restricted posterior leaflet up to the coaptation plane, regurgitation could be improved sufficiently to avoid valve replacement in patients with rheumatic mitral posterior leaflet retraction. This was first done by anchoring sutures on the free edge of the posterior leaflet, which were brought up to the posterior annuloplasty ring and tied down (8). We refined this technique, postulating that by bringing this suture across the valve to the opposing annulus, better coaptation could be obtained. This technique has subsequently been used in instances of leaflet restriction or tethering other than rheumatic regurgitation, as reported herein.

One issue always in mind during valve repair in children is the durability of the repair, on the one hand due to the very long life expectancy of the patient, on the other hand with somatic growth of the child, and particularly the concern of the possibility of iatrogenic-induced stenosis with ring annuloplasty and this suspension stitch. During a mean follow-up of just over 3 years, no patient developed symptomatic mitral or tricuspid stenosis, and the transvalvular gradients decreased from a mean of 4.4±2.4 mmHg to 4.2±1.6 mmHg in the mitral position, and remained stable at 2±1.75 mmHg in the tricuspid position. In the control group, the mean gradients decreased from 3.3±2.6 mmHg to 2.8±2.3 mmHg in the mitral position, and 3.7±1.7 to 3.6±1.5 mmHg in the tricuspid position. Although the relative change in gradient was not significant within each group and position, the gradients were statistically significantly lower in the control than in the suspension stitch group in the mitral position at latest follow-up. This stability in transvalvular gradients in both groups is consistent with our experience using the Bioring.
Kalangos biodegradable annuloplasty ring in children in the mitral position (9). It is important to note that all the patients in this study, with the exception of 1, had annuloplasty with a Bioring Kalangos biodegradable ring. This could explain this decrease in gradients during follow-up. We previously showed that, among 220 children with rheumatic mitral regurgitation, those who had annuloplasty with a Carpentier-Edwards ring had a mean increase of 1.8 mmHg during the first year, compared to 0.5 mmHg in children who received a biodegradable annuloplasty ring (9). In an experimental juvenile pig model, in which the animals’ mean weight increased by 500% during the year of follow-up after Bioring implantation, transvalvular gradients remained stable and the measured valve area showed regular somatic growth (13). Mrowczynski et al. showed that the tricuspid annulus continues to grow after Bioring implantation, along the curve of normal somatic tricuspid annular growth in children with congenital tricuspid regurgitation (unpublished data, presented at Society of Thoracic Surgeons 2010 annual meeting, poster P48). It is thus possible that the relatively low rates of reoperation and of elevated transvalvular gradient are favorably biased by the use of this biodegradable ring, and caution is advised if applying the results of this study in conjunction with other annuloplasty devices or techniques.

This study is limited by the relatively small sample size, retrospective, non-randomized design and mid-term follow-up. Although both groups were matched for presence of leaflet restricted motion or tethering, age, valve operated on and etiology of valve disease, and although no significant differences between preoperative patient characteristics were found, the control group does not represent an exactly similar patient group, as standard repair techniques were sufficient to relieve leaflet restriction or tethering without resorting to our additional suspension stitch in the control group; furthermore, the sample size did not allow for propensity score analysis. The use of the suspension stitch was based on subjective criteria at the time of water testing of the mitral or tricuspid valve when standard techniques were not sufficient to decrease the degree of residual insufficiency. Selection bias can thus not be ruled out. The multivariable models used in Cox proportional hazards modeling are limited by the number of events:
depending on the outcome measure, there were 5 events for 8 degrees of freedom in the models using reoperation as an outcome, and 7 events in the models using high transvalvular gradient as an outcome, although 5-10 times more events than degrees of freedom are usually recommended. Finally, follow-up echocardiographic data was interpreted and analyzed, for the most part, by the referring cardiologist in the patients’ country of origin. This introduces the risk of estimator bias, as the echocardiographic images couldn’t be interpreted by an independent echocardiography lab blinded to the surgery and clinical outcome. Furthermore, more detailed data, such as right ventricular dimensions or quantitative methods of grading regurgitation such as the actual width of the vena contracta or PISA, could not be obtained in a large proportion of patients.

**Conclusion**

The suspension technique described is simple and safe. It moves the retracted or tethered leaflet up to the coaptation plane, thus creating a larger coaptation area that can eliminate regurgitation. In our experience of 40 children, adequate leaflet coaptation was achieved and allowed to avoid valve replacement. This result was maintained in all but 3 children during a median follow-up of 37 months, extending up to 7 years. There were no technical failures of the stitch and no leaflet abrasion during follow-up, without the development of stenosis. These results were comparable to controls.

**References**


**Right Ventricular Papillary Muscle Approximation (RV-PMA)**

**Rationale**

Regurgitation due to leaflet tethering is most often functional, due to ventricular dilatation, or due to dysplasia of the subvalvular apparatus of the mitral or tricuspid valve, such as failure of the papillary muscles to delaminate from the right ventricular free wall, as seen in Ebstein’s anomaly of the tricuspid valve or the dysplastic tricuspid valve in pulmonary atresia with intact ventricular septum. Leaflet or annular techniques of valve repair can improve coaptation and relieve tethering, but a subvalvular approach would theoretically be closer to the origin of tethering and perhaps afford better results.

In a parallel to adult cardiac surgery, the repair of ischemic mitral regurgitation, due to apical displacement of the papillary muscles and leaflet tethering, has poor results. Several groups have proposed to address tethering at the level of the papillary muscles, in the RING+STRING approach, by tacking the displaced papillary muscles more basally along with remodeling annuloplasty. This approach hasn’t been reported yet in children.

We developed a technique of Right Ventricular Papillary Muscle Approximation (RV-PMA) to the ventricular septum, to address tricuspid valve leaflet tethering. This technique was shown, as outlined below, in ex vivo and in vivo animal models, to relieve tethering, improve coaptation and remodel the dilated right ventricle. This section reviews the initial clinical experience, looking at the safety from iatrogenic stenosis or technical failures of the technique, efficacy, and preliminary data on right ventricular remodeling in a subset of patients with Ebstein’s anomaly of the tricuspid valve using 3 dimensional echocardiography.
Safety

A portion of this data was presented at the American College of Cardiologists 2012 Scientific Sessions by Patrick O. Myers, Haruo Yamauchi, Francis Fynn-Thompson, Sitaram Emani, Christopher W. Baird and Pedro J. del Nido.

Introduction

Acceptable coaptation and valve function can’t always be obtained using standard repair techniques in tricuspid valve repair for congenitally tethered leaflets. Papillary muscle repositioning has been proposed to relieve tethering in adult functional mitral regurgitation (1) A novel technique of right ventricular papillary muscle approximation (RV-PMA) has been shown in ex vivo (2) and in vivo (3) pig models to successfully correct tricuspid regurgitation (TR), reducing tethering, remodelling the RV and avoiding stenosis. The aim of this study was to review our initial clinical experience using technique in tricuspid valve repair. We assessed the safety and mid-term results using this technique of RV-PMA to address tricuspid leaflet tethering in children.

Methods

Study design. This is a retrospective single-center review. All tricuspid valve procedures from 2009 and 2012 were included. Controls were paired 2:1 wit the study patients, matched by diagnosis, age and mechanism of tricuspid regurgitation. The study was IRB approved and patient consent was waived. Primary outcome measures were tricuspid valve reoperation and moderate or more regurgitation.

Surgical technique. RV-PMA consisted of suturing the anterior papillary muscle to the ventricular septum, so as to bring the papillary muscle and anterior leaflet closer to the posterior and septal leaflets.
Figure 1 – RV-PMA technique and tricuspid valve anatomy.

Statistical analysis. Survival estimates were calculated using the Kaplan-Meier method and differences between curves assessed by the log-rank test.

Results

Among 175 tricuspid valve repairs during the study period, 37 patients required RV-PMA. The anatomy in the RV-PMA group was Ebstein’s anomaly in 15 patients (as an adjunct to cone repair), pulmonary atresia with intact ventricular septum in 9 patients, tetralogy of Fallot in 5 patients, hypoplastic left heart syndrome in 2, atrioventricular canal defects in 1, endocarditis in 1 and other tricuspid dysplasia in 4 patients. 74 patients (2:1 matched) were included in the control group. The mean age was 14.5±14.1 years in the study group, compared to 15.4±20.4 in the control group (P = 0.68).

Figure 2 – Patient baseline fundamental diagnosis.
Surgical technique. Techniques used to repair the tricuspid valve, concomitant to RV-PMA, are listed in Table 1, and compared between the RV-PMA group and controls.

<table>
<thead>
<tr>
<th>Sub-Procedures</th>
<th>RV-PMA (n = 37)</th>
<th>Controls (n = 74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annuloplasty</td>
<td>18 (49%)</td>
<td>30 (41%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Ring annuloplasty</td>
<td>15 (41%)</td>
<td>24 (32%)</td>
<td>1</td>
</tr>
<tr>
<td>Suture annuloplasty (“de Vega”)</td>
<td>3 (9%)</td>
<td>5 (7%)</td>
<td>1</td>
</tr>
<tr>
<td>Commissuroplasty</td>
<td>3 (8%)</td>
<td>11 (15%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Leaflet repair (including cone repair)</td>
<td>31 (84%)</td>
<td>57 (77%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Chordal repair</td>
<td>7 (19%)</td>
<td>13 (18%)</td>
<td>1</td>
</tr>
<tr>
<td>Papillary muscle</td>
<td>37 (100%)</td>
<td>36 (49%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RV reduction</td>
<td>2 (5%)</td>
<td>7 (9%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Table 1 – Surgical techniques of tricuspid valve repair.

Outcomes. There were no early deaths, and one reoperation in the RV-PMA group for tricuspid valve re-repair due to dehiscence of the septal leaflet in a cone repair of Ebstein’s anomaly and bidirectional Glenn shunt for severe RV dysfunction.

At discharge, all but one patients in the RV-PMA group (97%) had less than mild regurgitation and with a mean inflow gradient of 0.65±1.33 mmHg, while 2 patients in the control group (3%) had moderate regurgitation with a mean inflow gradient of 0.41±1.08 mmHg.

During a follow-up of 16.6±13 months, there were 2 late deaths (1.8%) in the study group and none in the control group. 5 patients required reoperation, 1 (2.8%) in the RV-PMA group and 4 (5.4%) in the control group. All patients had tricuspid valve re-repair, with the exception of one control who had tricuspid valve replacement. The mode of failure was RV-PMA suture breakage in the one patient from the study group.
At latest follow-up, all but 4 patients with RV-PMA (89%) had ≤ mild regurgitation, and the mean inflow gradient was 1.1±1.8 mmHg (range 0-7). All but 4 controls (94%, P = 0.16) had ≤ mild regurgitation with a mean inflow gradient of 1.1±2.5 mmHg (P=0.98, range 0-14).

Figure 4 - Kaplan-Meier survival estimates of freedom from tricuspid valve reoperation (left) and tricuspid valve reoperation and/or moderate or severe tricuspid regurgitation.
Conclusions

RV-PMA is simple, safe and can improve coaptation with acceptable inflow gradients.

Further studies are required to assess RV remodeling from this repair.

References


Right Ventricular Papillary Muscle Approximation as a Concomitant Procedure for Ebstein’s Anomaly: Analyses of the Tricuspid Annular and Right Ventricular Dimension by Three-Dimensional Echocardiography

A portion of this data was presented at the Asian Society for Cardiovascular Surgery (ASCVTS) by Haruo Yamauchi, Patrick O. Myers, Christopher W. Baird, Gerald R. Marx, Sitaram Emani and Pedro J. del Nido.

This study assessed the tricuspid annulus and right ventricular remodeling added by RV-PMA, in a case-control study of 20 patients who underwent cone repair of Ebstein’s anomaly of the tricuspid valve with or without RV-PMA.

OBJECTIVE

The Cone procedure for Ebstein’s anomaly leads to fairly good outcomes, but it could be better by actively remodeling annulus and ventricle. We performed right ventricular-papillary muscle to septum approximation (RV-PMA) concomitant with Cone procedure for these patients and assessed its effects on annular and right ventricular (RV) dimension.

METHODS

From September 2009 to January 2012, 10 patients (9 Ebstein’s anomaly and 1 Ebsteinoid dysplasia of tricuspid valve) who underwent RV-PMA concomitant with Cone-type repair, and 10 controls matched with the study patients by diagnoses, were retrospectively enrolled for this study by pre-op and post-op (at discharge) 3-dimensional echocardiographic (3DE) data availability.
The grade of tricuspid regurgitation (TR, none 0 to severe 4), tricuspid valve annular dimension, and RV sphericity index (RVSI) were measured by 3DE and the % change of each parameter from pre-op to post-op was compared between the RV-PMA and control groups by Student’s t test.

Figure 2 – Assessment of tricuspid valve and right ventricular dimensions by 3D echocardiography.
RESULTS

There were no deaths. TR grade improved in the both groups (RV-PMA, 3.9±0.3 to 1.7±0.8, -56±22%; Control, 3.6±0.7 to 1.8±0.6, -47±25%; p=0.39). As compared to the controls, the RV-PMA group patients further reduced the septal-lateral dimension of tricuspid annulus (RV-PMA, 35.3±11.3 to 22.7±4.3, -33±13%; Control, 27.7±15.3 to 19.7±4.1, -21±17%; p=0.11), the antero-posterior dimension of tricuspid annulus (RV-PMA, 40.8±17.3 to 21.4±4.6, -42±20%; Control, 26.8±13.4 to 18.8±7.3, -25±21%; p=0.09), the tricuspid annular area (RV-PMA, 13.5±8.2 to 4.7±1.6, -60±12%; Control, 8.0±9.9 to 3.7±2.1, -38±26%; p=0.02).
In addition, RV-PMA also improved the systolic RVSI (RV-PMA, 0.65±0.05 to 0.53±0.13, -18±15%; Control, 0.63±0.17 to 0.59±0.19, 0±45%; p=0.27), and the diastolic RVSI (RV-PMA, 0.69±0.04 to 0.53±0.13, -24±12%; Control, 0.63±0.02 to 0.64±0.18, 1±27%; p=0.02).

Figure 5 – Right ventricular remodeling.
CONCLUSIONS

RV-PMA adjunct to the Cone procedure improves the remodeling effects on tricuspid annulus and RV compared to Cone-type repair alone for Ebstein’s anomaly. Longer follow-up period is required to assess continued improvement.
Chapter 3 - Triple Valve Repair in Children with Rheumatic Heart Disease: Long-term experience

A portion of this data was published in J Heart Valve Dis 2012;21(5):650-4 by Patrick O. Myers, Mustafa Cikirikcioglu, Cécile Tissot, Jan T. Christenson, Maurice Beghetti and Afksendiyos Kalangos.

This study reviewed the Geneva experience in combined triple valve repair in children with rheumatic heart disease. There is relatively little data on triple valve surgery in children, limited to 2 series of 12 and 21 patients each, respectively, and a few case reports. This report showed, despite being limited by the small sample size, that in this particularly challenging group, triple valve repair was safe and provided satisfactory mid-term results, but with a rate of reoperation at the long term. This strategy can thus be seen as a valid palliative approach.
Abstract

OBJECTIVE: Triple valve replacement has poor early and long-term results, particularly in children. Little data is available on triple valve repair. We report our single-center long-term results on combined aortic, mitral and tricuspid valve repair in rheumatic children.

PATIENTS AND METHODS: Ten children with severe rheumatic aortic, mitral and tricuspid regurgitation (mean age 12±3 years) underwent triple valve repair over a 17 year period, using tailored cusp extension to repair the aortic valve, and ring annuloplasty and Carpentier’s techniques to repair the mitral and the tricuspid valves.

RESULTS: There were no early deaths. During a median follow-up of 58 months (range 3 months – 16 years), no late death occurred and 4 patients (40%) required reoperation at a median of 3 years (range 2.7 – 12 years), 1 for mitral valve replacement, 1 for aortic valve replacement and 2 for aortic and mitral valve replacement. Freedom from reoperation was 100% at 1 year, 63±17% at 3, 5 and 10 years, and 47±19% at 15 years.

CONCLUSIONS: Triple valve repair, in this particularly challenging patient group, provided satisfactory initial and mid-term results, with a high burden of reoperation at the long-term, allowing a median of 3 years of growth and subsequent placement of a larger valve at the time of actual valve replacement. This strategy could be considered a good palliative surgical approach.
Introduction

Surgical management of multiple valve lesions in the young is problematic, because of the lack of an ideal valve substitute within this age group. Long-term results of triple valve replacement in adults are unimpressive (1), with high mortality and reoperation rates, and no data is available on triple valve replacement in children. Rheumatic mitral valve repair has been shown to be feasible and have good midterm results (2), and aortic cusp extension has shown reasonable results (3-5), even at long term (6). With triple valve repair, previous reports have shown up to 90% freedom from valve reoperation at 5 years, with follow-up extending to 7 years at most (7, 8). The aim of this brief report was to review a single-center experience and long-term results of triple valve repair of rheumatic aortic, mitral and tricuspid regurgitation in children with rheumatic heart disease.

Patients and Methods

Demographics

The study was reviewed and approved by the local Ethics Committee, and patient consent was waived. From March 1993 through May 2010, 92 consecutive children underwent cusp extension aortic valve repair for rheumatic aortic regurgitation grade III or more due to cusp retraction, and 342 underwent mitral valve repair for rheumatic mitral regurgitation grade III or more. Sixty nine of these patients required combined aortic and mitral valve repair, 10 of whom also required tricuspid valve repair for rheumatic involvement of the tricuspid valve with grade III or more regurgitation, making a total of 10 patients (mean age 12±3 years, 5 boys, mean weight 33±8 kg) requiring combined triple valve repair. The patient characteristics are summarized in Table 1. One patient was in acute rheumatic carditis at the time of repair. All of
the patients were from African and Asian countries and had a well-documented history of rheumatic fever determined by the revised Jones’ criteria (9).

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>AVP</th>
<th>MVP</th>
<th>TVP</th>
<th>Follow up (months)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>Male</td>
<td>Cusp extension (autologous fresh pericardium)</td>
<td>CE 30</td>
<td>De Vega</td>
<td>187</td>
<td>NYHA I</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Male</td>
<td>Cusp extension (autologous fresh pericardium)</td>
<td>CE 28</td>
<td>De Vega</td>
<td>187</td>
<td>NYHA I</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>Male</td>
<td>Cusp extension (autologous fresh pericardium)</td>
<td>CE 30</td>
<td>De Vega</td>
<td>175</td>
<td>NYHA I</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>Female</td>
<td>Cusp extension (autologous fresh pericardium)</td>
<td>CE 30</td>
<td>De Vega</td>
<td>142</td>
<td>Reoperation (MVR)</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>Female</td>
<td>Cusp extension (autologous fresh pericardium)</td>
<td>CE 30</td>
<td>De Vega</td>
<td>32</td>
<td>Reoperation (AVR)</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>Male</td>
<td>Commissurotomy, cusp extension (PhotoFix)</td>
<td>CE 28, commissurotomies</td>
<td>De Vega</td>
<td>34</td>
<td>Reoperation (AVR, MVR, CE, TVP)</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>Male</td>
<td>Cusp extension (PhotoFix)</td>
<td>CE 30, commissurotomies, leaflet shaving, primary and secondary chordae resection</td>
<td>CE 28</td>
<td>82</td>
<td>NYHA I</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>Female</td>
<td>Cusp extension (PhotoFix)</td>
<td>CE 30, commissurotomies, P2 secondary chordae resection</td>
<td>CE 28</td>
<td>33</td>
<td>Reoperation (AVR, MVR)</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>Female</td>
<td>Cusp extension (glutaraldehyde-fixed bovine pericardium)</td>
<td>Bioring 24, P1 and P2 primary chordae resection, anterior commissurotomy and commissuroplasty</td>
<td>Bioring 26</td>
<td>3</td>
<td>NYHA II</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>Female</td>
<td>Cusp extension (glutaraldehyde-fixed bovine pericardium)</td>
<td>CE Physio II 26, anterior and posterior commissuroplasty, posterior leaflet secondary chordae resection</td>
<td>Bioring 26</td>
<td>4</td>
<td>NYHA I</td>
</tr>
</tbody>
</table>


Table 1 – Patient characteristics and outcomes.

**Operative procedure**

All operations were performed by the senior author (A.K.). One patient had previously undergone mitral valve repair using a Puig-Massana-Shiley annuloplasty ring. In all patients, the
mitral valve was repaired first, using annuloplasty and various techniques as reported previously (2). Nine patients received a Carpentier Edwards ring (mean size $29\pm1.4$ mm) and 1 received a Bioring Kalangos ring (24 mm). Five patients required additional repair techniques, such as pericardial patch repair of the posterior leaflet, commissurotomy, commissuroplasty and primary or secondary chordae resection. The aortic valve was repaired using our tailored cusp extension technique as described previously (3). One patient underwent aortic commissurotomy before proceeding to aortic cusp extension. In 5 patients, fresh autologous pericardium was used to extend the aortic cusps, while Photofix© bovine pericardium (Sorin CarboMedics, Milano, Italy) and glutaraldehyde-fixed bovine pericardium (St Jude Medical Inc. St. Paul, Minnesota) was used in 3 and 2 patients respectively, who had pericardial adhesions generated by repeated episodes of rheumatic fever and pancarditis. Tricuspid annuloplasty was performed on a beating heart after the other repairs were finished, using De Vega annuloplasty in 6 patients, Carpentier Edwards tricuspid ring annuloplasty in 2 patients (both 28 mm) or Bioring Kalangos biodegradable annuloplasty ring in 2 patients (both 26 mm). Intraoperative transesophageal echocardiography examinations were performed in all patients before skin incision and after termination of cardiopulmonary bypass.

**Follow-up**

Transthoracic echocardiography was carried out in all patients before surgery, before discharge from the hospital, and at 3 and 6 weeks postoperatively before returning to their countries of origin. Patients were thereafter followed by cardiologists in their country of origin, who periodically informed us of the patients’ evolution by filling out a questionnaire including clinical, echocardiographic, and medication information. Follow-up in this study was achieved until July 2010.
Results

The mean aortic cross-clamp time was 106±28 minutes (range 75-161 minutes), and the mean cardiopulmonary bypass time was 129±27 (range 98-180). There were no operative deaths and major postoperative complications.

Follow-up was complete in all patients. Mean and median follow-up was 88±77 months and 58 months, respectively, ranging from 3 months to 16 years overall. No thromboembolic or hemorrhagic events were observed up to the most recent follow-up examinations. Four patients (40%) underwent reoperation of one or more of the operated valves during follow-up: one for mitral valve replacement with a 27 mm CarboMedics mechanical valve 11 years and 10 months from the repair, one for aortic valve replacement with a homograft at 2 years and 8 months from the repair and two for combined aortic and mitral valve replacement, one at 2 years and 8 months from the repair with a 20 mm Aspire aortic bioprosthesis and a 29 mm Carpentier-Edwards Perimount mitral bioprosthesis, and the other at 2 years and 10 months from the repair with Carbomedics mechanical prostheses, 21 mm in the aortic position and 31 mm in the mitral position. This last patient also required concomitant tricuspid annuloplasty with Carpentier-Edwards 28 mm tricuspid annuloplasty ring, after failed previous De Vega annuloplasty. Three of the patients undergoing aortic valve replacement had had fresh autologous pericardium as substrate for cusp extension, while one had PhotoFix pericardium.

Among the 7 patients followed-up who did not require aortic valve reoperation, the repair remained stable with no or trivial aortic valve regurgitation and a mean peak gradient of 21±9 mmHg at their last follow-up. Among the 7 patients who did not require mitral valve reoperation, the repair also remained stable, with no or trivial regurgitation at the latest follow-up, and the tricuspid repair remained stable in all 9 patients who did not require reoperation.

Actuarial freedom from reoperation was 100% at 1 year, 75±12% at 2 years, 63±17% at 3, 5 and 10 years and 47±19% at 15 years.
Discussion

Long-term results in surgery for mitral regurgitation have demonstrated that repair is advantageous over replacement in terms of survival and incidence of thromboembolic and bleeding complications. Mitral valve repair has become the treatment of choice, and its feasibility has led to the recommendation of earlier surgery to preserve ventricular geometry and function. Aortic valve repair in rheumatic patients has also shown acceptable results up to the long term, with freedom from reoperation of 88±4% at 5 years, 81±5% at 10 years and 75±6% at 15 years (6). Combined triple valve replacement has unimpressive results, with an early mortality as high as 17% and survival of 80±7%, 75±8%, and 41±15% respectively at 1, 5, and 10 years after primary triple valve surgery (1).

Prabhakar et al. reported their experience in 12 patients (mean age 16.7 years) who underwent triple valve repair (8), with a hospital mortality of 16.7% and 45% rate of reoperation and 15% late mortality. Grinda et al. reported their experience in 21 children (mean age 11±4 years) who underwent triple valve repair for rheumatic disease, with much better results using Carpentier’s techniques (10). Operative mortality was 4.7% and freedom from reoperation was 90% at 5 years. Little other data exists on triple valve repair, with the exception of rare case reports (11, 12). Our data confirms these results, with no perioperative deaths and acceptable mid-term results, although the long-term freedom from reoperation were significantly worse due to progression and relapse of the underlying rheumatic disease. A large proportion of our patients had mixed disease (requiring aortic commissurotomy in 1 patient and mitral commissurotomy in 4 patients), a known risk factor for reoperation in aortic (13) and mitral valve repair (2, 14), and one required operation during the active phase of acute rheumatic carditis. Our policy is to begin steroids and anti-inflammatory medication in acute rheumatic carditis and wait until the inflammatory markers (such as c-reactive protein and erythrocyte sedimentation rate) decrease close to normal values. Early surgery is therefore avoided unless the child develops hemodynamic
instability or pulmonary edema due to the sudden deleterious impact of new mitral and/or aortic valvular lesions and its hemodynamic consequences.

There were 4 types of mechanisms of failure, requiring reoperation: (1) early failure due to active valvular tissue inflammation either as a cause of technical failure or as a rapid conversion of inflammatory reaction under anti-inflammatory medication to fibrosis and retraction; (2) early failure of repair techniques or use of repair techniques not appropriate for the underlying type of lesion; (3) the severity of tissue retraction and thickening (decreasing the leaflet mobility) as well as the degree of involvement of the subvalvular apparatus, with the presence of multiple retracted, shortened chordae, at the time of initial repair; (4) recurrence of postoperative rheumatic fever episodes, which accelerate the degradation of valve tissue. To lower the reoperation rate, we suggest to avoid surgery during the acute phase of carditis unless there is a clear indication for urgent surgery, insure an optimal repair with a residual leak equal to or less than mild and a mean transmitral gradient below 5 mmHg, and be very vigilant with the postoperative antibiotic prophylaxis to avoid repeated rheumatic fever episodes.

This study suffers from several limitations. It is a retrospective and nonrandomized review and represents a 17 year period of evolving experience with aortic, mitral and tricuspid valve repair. As such, any inferences drawn from this data are limited by confounding variables such as extent of disease and severity of preoperative aortic or mitral stenosis. We do not have a comparable group of patients having undergone triple valve replacement or triple valve surgery combining repair and replacement. Our sample size also limits our ability to perform statistical adjustments for these differences. Finally, follow-up echocardiographic data was interpreted and analyzed, for the most part, by the referring cardiologist in the patients’ country of origin. This introduces the risk of estimator bias, as the echocardiographic images couldn’t be interpreted by an independent echocardiography lab blinded to the surgery and clinical outcome.
Conclusion

Triple valve repair, in this particular challenging patient group, provided satisfactory initial and mid-term results, with a high burden of reoperation at the long-term, allowing a median of 3 years of growth and subsequent placement of a larger valve at the time of actual valve replacement. This strategy could be considered a good palliative surgical approach.

References


Chapter 4 - Valve Repair in Borderline Heart Hypoplasia

Staged Left Ventricular Recruitment Following Single Ventricle Palliation

in Patients with Borderline Left Heart Hypoplasia


This study showed how, by combining aortic and mitral valve repair with procedures aimed to relieve diastolic left ventricular dysfunction and increase blood through the left heart, hypoplastic left heart structures can be grown through staged recruitment in patients with hypoplastic left heart syndrome and be brought to a biventricular conversion after initial single ventricle palliation. This paper’s significant contribution is that it blurs the traditionally-viewed dichotomous pathways for management of this patient group, either through Norwood single ventricle palliation or biventricular repair.

Abstract

Objectives: To review results of a novel management strategy intended to rehabilitate the left heart (LH) in patients with LH hypoplasia who have undergone single ventricle palliation (SVP).

Background: Management of patients with hypoplastic LH syndrome and borderline left ventricle (LV) is dichotomous: SVP or biventricular (BiV) repair. We hypothesize that staged LV recruitment and BiV conversion may be achieved following SVP by a strategy consisting of relief of inflow and outflow tract obstructions, resection of endocardial fibroelastosis, and promotion of flow through the LV.
**Methods:** Patients with hypoplastic LH and borderline LV who underwent traditional SVP (n=34) or staged LV recruitment (n=34) between 1995 and 2010 were retrospectively analyzed and compared to a control SVP group.

**Results:** Mean initial Z-scores for LH structures prior to Stage 1 were not significantly different between groups. Mortality was 4/34 following LV recruitment and 7/34 following traditional SVP. LH dimension Z-scores increased significantly over time following LV recruitment, whereas they declined following traditional SVP, with significant interaction between stage of palliation and treatment group. Restriction of the atrial septum (done in 19/34) was the only predictor of increase in LVEDV (P<0.001). Native BiV circulation has been achieved in 12 patients following staged LV recruitment with all of these having had restriction at the atrial septum.

**Conclusion:** In patients with borderline LH disease who undergo SVP, it is possible to increase LH dimensions by LV recruitment strategy. In a subset of patients, this strategy has allowed establishment of biventricular circulation.
Introduction

Neonates with hypoplastic left heart (LH) disease can present a unique challenge. At the extremes of mild LH hypoplasia associated with aortic stenosis (AS) or coarctation on one end, and hypoplastic left heart syndrome (HLHS) with aortic and mitral atresia on the other, the appropriate management is typically obvious. Patients with mild LH hypoplasia may require relief of valvular or aortic arch obstruction, in order to maintain biventricular physiology, whereas single ventricle palliation (SVP) with staged procedures starting with the Norwood operation is applied to patients with severe hypoplasia (1).

At the center of the spectrum, accounting for about 65% of patients, are many variants of borderline LH hypoplasia for which management is not so clear but usually single ventricle palliation is the most commonly applied approach (2,3). In this group, all levels of the LH complex are often affected, with valvular stenosis, ventricular hypoplasia, and endocardial fibroelastosis (EFE) that prevent independent function of the left ventricle (LV) as the systemic ventricle. Some patients with a borderline LH may be amenable to eventual biventricular management, but are at higher risk if such a strategy is pursued definitively, particularly in the newborn period (4-7). In order to pursue the possibility of eventual biventricular circulation in patients who are at high risk for initial biventricular repair, we have applied a strategy in which the circulation is initially supported with SVP while staged procedures are employed to relieve inflow and outflow tract obstructions, resect EFE, and promote blood flow through the LV. We have termed this approach “staged LV recruitment”.

We hypothesized that staged LV recruitment results in growth of LH structures, and eventual biventricular conversion, in patients with borderline LH who are at high risk, or are deemed not candidates for definitive early biventricular repair. The primary goal of this study was to examine the effects of this strategy upon LH dimensions, and compare these results to the natural history of LH dimensions in a similar group of patients following traditional SVP. In
addition, we sought to determine the effects of staged LV recruitment upon the clinical outcomes at mid-term follow-up, and determine the predictors of increase in LH dimensions among patients undergoing staged LV recruitment.

**Methods**

**Study design**

This study is a retrospective review of all patients who presented to Children’s Hospital Boston between 2001 and 2010 with a postnatal echocardiographic diagnosis of hypoplastic LH disease and borderline LV who underwent staged LV recruitment. Borderline LH was defined by a combination of clinical and anatomic criteria. LH hypoplasia, with aortic, mitral, and LV end-diastolic volume (LVEDV) Z-scores between -5 and -0.5, and presence of LV EFE were pertinent anatomic features. Candidates were deemed to be dependent upon prostaglandin infusion or have failed initial attempts at biventricular repair (e.g. balloon dilation of aortic valve, coarctation repair). Patients were excluded if they had aortic or mitral atresia, ventricular septal defect, heterotaxy syndrome, or atrio-ventricular or ventriculo-arterial discordance. Patients undergoing staged LV recruitment were compared to a control group of patients meeting anatomic criteria for borderline LH disease, i.e. LH structure Z-scores between -5 and -0.5, who underwent traditional SVP between 1995 and 2010. This atypical case control group included historical as well as contemporary controls. The study was approved by the Children’s Hospital Boston Institutional Review Board.

The primary outcome measures included change in size of LH structures, indexed to body surface area, over time as measured by echocardiography and MRI, and clinical outcomes (mortality, biventricular conversion). In addition, clinical or treatment variables affecting the size of LH structures were recorded to determine predictors of increased LH size over time. Interventions performed prior to stage 1 SVP (fetal or postnatal balloon dilation of the aortic
valve, attempted biventricular repair), details of staged operative procedures, postoperative course, and reinterventions following biventricular conversion were documented.

**Staged LV Recruitment Strategy**

The staged LV recruitment strategy employed a combination of procedures applied as adjuncts to the initial Norwood procedure, Bidirectional Glenn or Fontan or as separate procedures when necessary. The following techniques were applied:

**Resection of endocardial fibroelastosis**

EFE resection involved removal of the non-compliant fibroelastic endocardial material by sharp dissection. At stage 1 palliation, this was performed through the mitral valve orifice, and at subsequent stages visualization was attained either through the mitral valve or the LV outflow tract. EFE resection was initiated on the posterior LV wall, inferior to the mitral apparatus, and continued down to the apical and septal surface of the LV.

**Mitral valvuloplasty**

The mitral valve was approached transeptally, and commonly employed techniques to reduce inflow obstruction included division of tethering secondary or accessory chordae, separation of fused papillary muscles, chordal elongation, commissurotomy, augmentation of deficient leaflets, and removal of fibroelastic tissue that thickened the leaflet.

**Aortic valvuloplasty**

Techniques employed for left ventricular outflow tract obstruction included commissurotomy, primary repair for leaflet tear when present, débridement of thickened aortic valve leaflets, augmentation of deficient leaflets with pericardium, and subvalvular resection of membrane, muscle, or accessory mitral chordal attachments.
Atrial septal defect restriction

Restriction of the interatrial communication was performed in some patients either by partial primary reapproximation of the rim of the atrial septal defect (ASD) or by fenestrated pericardial patch closure (4 mm fenestration) as a means of promoting blood flow through the LV. Early in the experience (2001-2004), all patients undergoing rehabilitation procedures underwent restriction of the ASD, whereas subsequently the decision to restrict was based upon the subjective impression of adequacy of LH structures, successful EFE resection, and growth potential. In patients undergoing restriction of the ASD, the duration of restriction and transeptal gradient were recorded. Significant restriction was defined as: 1. Restriction of the atrial septum at any surgical stage; 2. Presence of a trans-septal gradient of greater than 5 mmHg by echocardiographic measurement; and 3. Maintenance of this gradient for duration greater than 30 days following surgical restriction.

Transcatheter interventions

Transcatheter balloon dilation of the aortic and mitral valves was performed for recurrent stenosis following surgical valvotomy in selected patients. Balloon atrial septostomy or stent placement was applied in patients who developed significant left atrial hypertension following surgical ASD restriction.

Addition of accessory pulmonary blood flow

In the subset of patients who underwent a stage 2 - bidirectional Glenn procedure (BDG), a right ventricle- or systemic- to pulmonary artery shunt was provided to increase pulmonary venous return in an attempt to augment LV preload, either at the time of the BDG or as a separate procedure. The decision to augment pulmonary blood flow was based upon the surgeon’s subjective impression of the potential for LV recruitment.
Biventricular conversion

Candidates were considered favorable for conversion once near normalization of LH structures size and function was demonstrated by noninvasive and invasive imaging. The biventricular conversion procedure included takedown of the aortopulmonary anastomosis, re-establishment of separate left and right ventricle outflow tract continuity either by direct reanastomosis or by translocation of the pulmonary artery root into the LV outflow tract with conduit reconstruction of the right ventricular outflow tract. In patients who had undergone a BDG, the superior vena cava was disconnected from the pulmonary artery and reconnected to the right atrium, usually at the appendage. In patients with a completed Fontan circulation, the inferior cavopulmonary baffle was also taken down. Following biventricular conversion, the need for re-intervention was documented, and the most recent echocardiogram was reviewed to determine the LV outflow gradient, dimensions of the left-sided structures, and tricuspid valve regurgitation jet velocity to estimate RV pressures.

Echocardiographic measurements

All initial postnatal echocardiograms were reviewed to determine the initial LV, mitral valve, and aortic valve dimensions prior to stage 1 SVP. All measurements were indexed to body surface area and expressed as Z-scores. The presence of mitral or aortic regurgitation was recorded, and the atrial septum was examined to determine the size of the defect. The gradient across the atrial septum was determined by color wave Doppler analysis.

To determine the progression of LH dimensions over time, serial echocardiographic measurements of LH size were obtained from patients who survived beyond the BDG. In these patients, the echocardiograms prior to each subsequent stage of palliation as well as most recent follow up were examined. For the patients in staged LV recruitment group who underwent biventricular conversion, the echocardiogram prior to biventricular repair was used to measure “most recent” LH dimensions. Likewise, for patients in the traditional SVP group who
underwent cardiac transplantation, the echocardiogram prior to transplantation was evaluated as the “most recent” study.

**Valvular Regurgitation Score**

The cumulative duration of significant valvular regurgitation (moderate or greater) for both aortic and mitral valves was calculated by reviewing each subject’s echocardiogram and summing the durations of the intermittent periods of significant valvular regurgitation.

**Statistical analysis**

Gender, percentage of patients undergoing fetal or postnatal balloon aortic valvuloplasty in the traditional SVP and the staged LV recruitment groups were compared by Fisher’s exact test. LH dimensions (LVEDV, long-axis dimension, and aortic and mitral valve diameters) were compared over time between patients undergoing staged LV recruitment and traditional SVP. A two-way mixed model repeated-measures analysis of variance (ANOVA) approach was used to compare differences in Z-scores for LH dimensions at different stages of repair (baseline = prior to Stage I, prior to BDG, prior to Fontan) between patients in each group. A compound symmetry correlation structure was used to handle the longitudinal data from the same patients over time with the Akaike information criterion to assess model fit to the longitudinal data (8). All Z-scores are reported in terms of the mean and standard error and two-tailed P values are Bonferroni adjusted to correct for multiple comparisons (9). A subgroup analysis was conducted to evaluate the effect of significant restriction of atrial septum on each of the four Z-scores in the staged LV recruitment group using the same ANOVA strategy. Longitudinal analysis of ejection fraction (EF) for LV rehab group was performed using repeated-measures ANOVA. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc./IBM, Chicago, IL).
Results

Patient characteristics

From January 1995 to December 2010, there were 34 patients with borderline LH disease who underwent staged LV recruitment and 34 patients who underwent traditional SVP. Attempts at staged LV recruitment were initiated in 2001. The traditional SVP group consisted of 11 patients who underwent stage 1 palliation prior to 2001, and 23 patients who were contemporary with the staged LV recruitment patients. LH dimensions on the initial postnatal echocardiogram as well as other demographic and patient characteristics are shown in Table 1. There were no significant differences in LH dimensions between the two groups at the time of initial postnatal evaluation. In the traditional SVP group, 5 of 34 patients underwent attempts at biventricular management by postnatal balloon aortic valvuloplasty prior to undergoing stage 1 palliation. Significantly more patients in the staged LV recruitment group underwent fetal and postnatal aortic balloon valvuloplasty, and two patients had surgical procedures for biventricular repair prior to the stage 1 procedure.
Table 1 – Preoperative patient characteristics and size of LH structures.

Clinical Outcomes

A flowchart depicting the clinical progression of patients in each group at most recent follow up is shown in Figure 1. At a median post-stage 1 follow-up of 9.0 years (1 to 16 years), 7 of 34 patients in the traditional SVP group died, 25 patients had Fontan physiology, and one underwent cardiac transplantation. At a median follow up of 5.2 years (1 to 9 years) 4 of 34 patients in the staged LV recruitment group died, 2 following a stage 1 procedure, and 2 after stage 2 palliation. Of these patients, one was diagnosed with centrotubular myopathy following the stage 1 procedure, and medical care was redirected. The other 3 patients died likely of cardiac causes, one approximately 1 month following stage 1 palliation, one following BDG due to severe biventricular dysfunction, and another following BDG due to tricuspid regurgitation and RV dysfunction. Thirteen patients underwent biventricular conversion, but one subsequently underwent cardiac transplantation due to ventricular dysfunction. Thus, at most recent follow-up, of the 30 survivors, 3 patients (10%) had BDG physiology, 15 patients (50%) had Fontan physiology, and 12 patients (40%) had native biventricular circulation.
Figure 1 - Flowchart depicting clinical course of patients with borderline left heart hypoplasia who underwent traditional SVP or staged LV recruitment.

Operative details

Technical details of each staged procedure, including specific LH rehabilitation techniques employed, are outlined in Table 2. Accessory pulmonary blood flow was provided only in patients with BDG physiology and was achieved via PTFE conduit to the pulmonary artery from the innominate artery in 5, right ventricle in 8, and ascending aorta in 2 patients. In addition to LH rehabilitation performed at the time of stage 1, BDG, or Fontan, 11 additional procedures solely for LH rehabilitation were performed in 9 patients. Thus the median total number of surgical procedures required between stage 1 palliation and most recent follow-up was 3 for traditional SVP and 4 for staged LV recruitment patients (p<0.05).
Table 2 - Operative Details of Staged Palliative Procedures.

<table>
<thead>
<tr>
<th>Stage</th>
<th>LH Rehabilitation</th>
<th>Traditional SVP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (days)</td>
<td>18.2 (0–190)</td>
<td>9.1 (0–146)</td>
</tr>
<tr>
<td>BTS (%)</td>
<td>18 (53%)</td>
<td>24 (71%)</td>
</tr>
<tr>
<td>EFE resection</td>
<td>21 (62%)</td>
<td>—</td>
</tr>
<tr>
<td>Mitral valvuloplasty</td>
<td>19 (56%)</td>
<td>—</td>
</tr>
<tr>
<td>Aortic valvuloplasty</td>
<td>13 (38%)</td>
<td>—</td>
</tr>
<tr>
<td>ASD restriction</td>
<td>13 (38%)</td>
<td>—</td>
</tr>
<tr>
<td>Post-operative ECMO</td>
<td>6 (18%)</td>
<td>4 (12%)</td>
</tr>
</tbody>
</table>

| Stage 2             |                   |                 |
| Median age (months) | 6.4 (3–14)        | 5.9 (2–12)      |
| EFE resection       | 18 (58%)          | —               |
| Mitral valvuloplasty| 15 (48%)          | —               |
| Aortic valvuloplasty| 12 (39%)          | —               |
| ASD restriction     | 10 (32%)          | —               |
| Accessory pulmonary blood flow | 15 (48%) | — |
| Post-operative ECMO | 2 (6%)            | 1 (3%)          |

| Stage 3             |                   |                 |
| Median age (yrs)    | 2.6 (1.6–5.1)     | 2.7 (1.6–4.8)   |
| EFE resection       | 7 (41%)           | —               |
| Mitral valvuloplasty| 6 (35%)           | —               |
| Aortic valvuloplasty| 7 (41%)           | —               |
| ASD restriction     | 3 (18%)           | —               |

Values are median (range) or n (%).
ASD = atrial septal defect; BTS = Blalock-Taussig shunt; ECMO = extracorporeal membrane oxygenation; EFE = endocardial fibroelastosis; LH = left heart; SVP = single-ventricle palliation.

Left atrial hypertension following restriction of ASD

Twelve of the 19 patients with significant ASD restriction underwent catheter-based septal balloon dilation and/or stenting due to development of left atrial (LA) hypertension. The indications for ASD balloon dilatation/stenting were respiratory insufficiency requiring
reintubation in 3 patients, persistent inotropic support in 2, and asymptomatic LA hypertension demonstrated at elective catheterization in 7. Among these 19 patients with ASD restriction, 6 required an unplanned catheterization and catheter-based intervention. The mean LA pressure in these patients at the time of ASD enlargement was $19 \pm 2.6$ mmHg. Four patients underwent repeat restriction of the communication at a subsequent staged operation. The 19 patients with ASD restriction had a mean ventilatory time after ASD restriction of $9.4\pm8.0$ days (median 6.0, range 1–28) and a mean ICU stay of $17.5\pm22.5$ (median 7.0, range 1-96).

**Left heart dimensions as a function of time**

Longitudinal echocardiographic measurements of LH dimensions were obtained from the 30 patients in the staged LV recruitment group and the 28 patients in the traditional SVP group who survived beyond the BDG (Figure 2). With respect to LVEDV and LV long-axis Z-scores, ANOVA showed a significant interaction between stage of palliation and group ($F = 13.76$, $P<0.001$) and $F = 34.04$, $P<0.001$, respectively), which indicated no differences in Z-scores prior to stage 1 but significant differences between groups prior to BDG ($P<0.005$) and prior to Fontan or biventricular repair ($P<0.001$), with more positive Z-scores among patients who underwent staged LV recruitment. With respect to mitral and aortic valve Z-scores, ANOVA showed a significant interaction between stage of palliation and group ($F = 5.30$, $P=0.007$ and $F = 28.98$, $P<0.0001$, respectively), indicating no differences in Z-scores prior to stage 1 or prior to BDG, but highly significant differences between the two groups prior to the Fontan or biventricular repair ($P<0.001$).
Figure 2 – Left heart dimensions at various palliative stages in patients undergoing staged LV recruitment or traditional SVP. Significant interaction between stage and treatment group was identified for each LH dimension (P<0.01 by ANOVA). ○ Staged LV recruitment; ● Traditional SVP. Error bars are standard errors.

Impact of valvular regurgitation upon biventricular conversion

In patients undergoing staged LV recruitment, significant mitral valvular regurgitation was seen in 17 of 34 patients. The median cumulative duration of mitral regurgitation in these
patients was 115 days (range 2 to 564 days). Significant aortic regurgitation was seen in 14 of 34 patients, with a median duration of 232 days (range 5 to 1790 days). There was no correlation between duration or presence of valvular regurgitation and successful biventricular conversion by univariate analysis.

**Relationship between ASD restriction and LH dimensions**

Patients undergoing staged LV recruitment were analyzed separately to determine the predictors of increase in LH dimensions. By univariate analysis, the only variable found to be predictive of increase in LVEDV over time was significant restriction of the ASD at any stage. Repeated-measures ANOVA revealed significant differences in LVEDV, LV long-axis, and aortic valve Z-scores between patients with and without ASD restriction prior to the Fontan (P<0.05 for each dimension) with no significant differences detected prior to stage 1 or BDG (Figure 3). Mitral valve Z-scores were not significantly different at baseline between patients who had an ASD restriction and those who did not (P=0.45) although Z-scores were significantly more positive in the ASD restricted subgroup prior to BDG (P=0.04) and prior to the Fontan (P=0.004). All patients who eventually underwent biventricular conversion had significant restriction of the ASD during staged LV recruitment.
Figure 3 – Comparison of left heart dimensions between ASD and no ASD restricted subgroups. Patients with restriction of the ASD had significantly higher Z-scores for each LH dimension prior to Fontan or biventricular repair (all P<0.01). Error bars are standard errors.

**Ejection Fraction**

Longitudinal analysis of echocardiograms from patients who underwent staged LV recruitment indicated significant increase in ejection fraction from initial postnatal echocardiogram to that obtained just before BDG or Fontan / Biventricular conversion (overall change across the whole
period, \( P = .004 \), suggesting a benefit of the surgical approach with respect to function. (Figure 4)

Figure 4 – Mean ejection fraction (EF) at each stage in patients undergoing LV recruitment.

Mean EF at BDG and Fontan or biventricular repair is compared to value prior to Stage 1 procedure. Ejection fraction increased over time in this cohort.

**Length of Hospitalization**

The cumulative duration of hospitalization for surgery, catheterization, or medical treatment from Stage 1 to most recent follow-up was a median of 94 days in the LV recruitment group (range 37-518), compared to 54.5 days in the traditional SVP group (range 8-348, \( P = 0.006 \)). However, the
length of hospitalization was shorter in the second half of the BiV group, with a median of 87 days (range 39-224), and not significantly different from the SVP group (P = 0.08).

**Biventricular conversion**

Thirteen of 34 patients in staged LV recruitment group underwent biventricular conversion procedure. Ten of the 13 patients underwent conversion from BDG circulation, one following Stage 1 procedure, and two patients underwent takedown of the Fontan. A median of 4 surgical procedures (3 to 6) had been performed in these patients prior to conversion. Echocardiographic measurements obtained prior to biventricular conversion revealed mean LVEDV Z-score of 0.21 + 0.78, aortic valve Z-score of -0.57 +0.60, and mitral valve annular diameter Z-score of -0.77 + 0.37. Figure 5 presents echocardiograms from a patient who underwent LV rehabilitation, and demonstrates increased LV size over time. On the MRI obtained prior to biventricular conversion, the average indexed LVEDV was 67 + 5.5 ml/m2, and the average mitral / tricuspid valve inflow ratio was 1.3 + 0.2. At catheterization prior to biventricular conversion, the mean LA pressure measured during balloon occlusion of the ASD was 14 + 4.7 mmHg.
Figure 5 – Echocardiogram of a representative patient who underwent staged LV recruitment. The LV is EFE bound and non-apex forming prior to stage 1 (A) but apex forming and normal in size prior to biventricular conversion (B).

At median follow-up of 2.9 years (1 to 6 years) following biventricular conversion, there has been no mortality. Re-operation after biventricular conversion was performed in four patients: mitral valve repair in 1, mitral replacement in 1, an aortic valve repair in 1, and ventricular assist device followed by cardiac transplantation due to progressive LV dysfunction due to coronary insufficiency in 1. The mean aortic valve gradient at most recent follow-up in the 7 patients with native biventricular circulation is $12 \pm 4$ mmHg. The estimated RV pressure (by TR jet velocity) was less than or equal to $\frac{1}{2}$ systemic pressure in 4 patients and greater than $\frac{1}{2}$ systemic in 2 (RV pressure could not be estimated due to the lack of TR in one patient).

Discussion

This study documents the natural history of LH dimensions in patients with borderline LH hypoplasia who undergo SVP, and demonstrates how a surgical strategy of staged LV recruitment may alter the natural history of LH diminution. In the cohort of patients that underwent LH
rehabilitation, cumulative restriction of the ASD for at least 30 days was associated with higher likelihood of increased LH dimensions over time. Patients undergoing staged LV recruitment demonstrated gradual improvement in LV ejection fraction. Finally, this study demonstrates that staged LV recruitment can result in LV salvage and eventual conversion to a biventricular circulation in a significant subset of patients. However, this approach is associated with increased duration of hospitalization and need for additional surgical procedures compared to traditional SVP.

**Rationale for LV recruitment**

The staged LV recruitment strategy is designed to facilitate flow through and loading of the LH in an effort to stimulate flow- and load-mediated growth. The growth potential of the LV has been demonstrated in patients with borderline LH structures who undergo initial biventricular repair by balloon dilation of the aortic valve with adjunctive surgical repair of coarctation, aortic stenosis, and mitral stenosis when necessary (10,11). However, the potential to achieve ongoing enlargement of LH structures in patients following SVP has not been previously demonstrated. This study extends the findings of previous studies by demonstrating the potential to increase LH dimensions following SVP if adjunctive LH rehabilitation procedures are employed.

**ASD restriction as a predictor of LH growth**

This study found that restriction of the ASD had the greatest impact upon increase in LH dimensions over time, and our current practice is to perform ASD restriction in all patients who have been judged to have adequate resection of EFE and relief of aortic and mitral stenosis. Although ASD restriction was found to be the single most important predictor of increased LH structures, a definitive causative relationship could not be established. ASD restriction may simply serve as a surrogate for adequacy of EFE resection and valvuloplasty, since it is employed at the discretion of the surgeon. Since all patients undergoing staged LV recruitment underwent
EFE resection, it is difficult to distinguish the impact of this component upon the overall outcome. Although ASD restriction was associated with LH growth, it cannot be inferred that ASD restriction alone without other LH rehabilitation maneuvers will be equally effective at increasing LH dimensions.

The effects of ASD restriction on LVEDV may be due to the increase in LA pressure, which contributes to both a rightward shift of the LV end-diastolic pressure-volume relation, and to true growth due to chronic increased loading of, and blood flow through, the LV. The stimulus for ventricular growth is LV blood flow, and all components of LH rehabilitation are designed to optimize LV blood flow (12).

**Optimal degree of ASD restriction**

Although patients who underwent ASD restriction demonstrated significant enlargement in LH dimensions, subsequent balloon dilation of the ASD was required in a significant number of patients due to elevated LA pressure. Further investigation is required to determine the degree of ASD restriction that promotes LH enlargement without deleterious elevation of LA pressures. Our current practice is to maintain a 4 mm fenestration within the ASD patch, which typically results in a transeptal gradient of 5-7 mmHg.

**Timing of LV recruitment**

Most patients undergoing LH rehabilitation demonstrated the greatest increase in LH dimensions following the BDG. Since preload- and flow-mediated increase in LH dimensions is a time-dependent process, the short duration (4 months) between the stage 1 and BDG may partly explain the relatively minor changes within that time period. Furthermore, LH rehabilitation maneuvers - particularly EFE resection, mitral and aortic valvuloplasty – are technically challenging to perform in neonates as part of the stage 1 SVP. The result is suboptimal EFE
resection and relief of valvular stenosis. The more extensive EFE resection and valvuloplasty that are possible at the time of the BDG may explain the subsequent increase in LH dimensions.

**LV growth versus dilation**

From this clinical experience it is not possible to state definitively whether the observed increase in ventricular dimension represents true LV “growth” or merely dilation. It is important to note however, that the changes in chamber volume occurred gradually over weeks and months even in the presence of a significant higher left atrial and LV end diastolic pressures, compared to right atrial and RV, respectively.

LV growth implies increase LV mass by cardiomyocyte hyperplasia and hypertrophy concomitant with LV dilation. On the other hand, LV dilation without increase in myocardial mass implies remodeling that may be detrimental long-term. Furthermore, intrinsic myocardial abnormalities have been described in patients with hypoplastic left heart disease, and the effects of staged LV recruitment upon these intrinsic abnormalities warrant further investigation.(13)

**Improvement in Ejection Fraction**

Although EFE is generally felt to impede diastolic myocardial performance by preventing relaxation, the study demonstrates that ventricular function can significantly improve with LV rehabilitation procedures, specifically EFE resection. Given the cartilaginous consistency and thickness of the EFE material, it is likely that this material can restrict both diastolic and systolic function.

**Limitations**

Attempts at biventricular conversion in this patient population are guided by the assumption that a biventricular circulation will result in improved maximal oxygen delivery relative to traditional SVP, and avoid the long-term complications of leaving the right ventricle as the systemic
ventricle, as well as the impact of chronic elevation of systemic venous pressures on end organ function. However, this hypothesis has not been proven previously, nor was it addressed by this study.

An attempt was made to compare serial LH dimensions in patients undergoing staged LV recruitment to those taken from a set of closely matched patients who underwent traditional SVP. However, since this is a retrospective study, and since a large proportion of traditional SVP patients were from an earlier era (prior to 2001), some degree of inherent selection bias is likely present. Similarly, although ASD restriction was associated with LH enlargement, it is possible that this therapy was applied in the most favorable candidates, since decision to perform restriction was based upon the surgeon’s judgment rather than objective criteria.

**Impact on current institutional approach**

Following the experience outlined in this manuscript, our institutional approach has been to attempt staged LV recruitment in all patients with borderline LH hypoplasia. LH rehabilitation procedures, particularly EFE resection and ASD restriction, are rarely performed at the stage 1 procedure, but are applied at the BDG stage and beyond. All patients undergo ASD restriction to 4 mm at the BDG. Asymptomatic LA hypertension is tolerated, and ASD enlargement is limited to patients who demonstrate clinical sequelae.

**Conclusion**

Staged LV recruitment results in growth of LH structures over time, and facilitates conversion to biventricular circulation in a subset of patients. ASD restriction is predictive of increase in LH dimensions, although a causative relationship cannot be definitively established. Excessive restriction can result in left atrial hypertension and require subsequent enlargement; further investigation is required to determine the optimal size of ASD restriction that balances LV
throughput with LA hypertension. Long term follow-up and hemodynamic comparison of patients following staged LV recruitment and traditional SVP are necessary to establish the long term benefits of this novel strategy.

References


Conclusions

Rationale for valve repair in children

Management of heart valve disease in the infants and children is problematic, because of the lack of an ideal valve substitute in this age group. Prosthetic valves carry significant drawbacks, such as difficult lifelong anticoagulation with a prohibitive cumulative risk of thrombo-embolic complications as well as valve dysfunction due to panus formation for mechanical heart valves, and rapid deterioration and calcification for biological valves (1). Prosthetic valve replacement thus can’t be considered a definitive and risk-free solution in children.

Alternate surgical approaches have been used, such homo- or autograft (Ross procedure) valvular replacement (2). However, they haven’t demonstrated their superiority over conventional prosthetic valve replacement (3). Cadaveric homografts calcify rapidly in young infants and children, requiring repeated valve replacement as the child grows. These procedures, although low risk in children and young adults with congenital heart disease for replacement of the pulmonary valve (4, 5), are technically demanding in patients with a homograft in the aortic position, requiring repeated reoperations for aortic root replacement with coronary reimplantation. This has prompted alternative options, such as valve-in-valve reoperation for reoperation after aortic homograft replacement (6, 7).

The Ross procedure, which places the pulmonary valve in the aortic position, was initially considered as a technically demanding option for aortic valve replacement, but which avoided anticoagulation and preserved the growth potential of the neo-aortic valve. However, more extensive experience and follow-up have shown that this autograft in the aortic position isn’t the perfect option, as the neoartic root and sino-tubular junction diameters increase out of proportion with somatic growth, ultimately resulting in neo-aortic regurgitation (8-10).
Furthermore, reoperations are frequent in this patient group, with a reported reoperation rate of 43% at 10 years, with a hospital mortality for the reoperation of 10% (11).

Given these limitations of valve replacement, alternative strategies have been developed, following in the pioneering footsteps of Alain Carpentier (12), to preserve and repair diseased valves in children. Furthermore, with improved results in the repair of congenital heart disease and increasing interest in complex valve reconstruction, the number of patients being referred for valve repair is increasing (13, 14). The current results of valve repair are excellent, as outlined in chapters 1 and 2, prompting a reappraisal of the management of the holy grail of congenital cardiac surgery, hypoplastic left heart syndrome and turning it into a biventricular heart. Nonetheless, heart valve disease in children remains a palliative approach in most patients, as outlined in chapter 3 in patients with triple valve involvement, to delay valve replacement as long as possible, allowing for growth and placement of a larger or adult-sized prosthetic valve.

**How can we improve the results of valve repair in children?**

The answer to this question is related to three inter-related factors: understanding the initial mechanism of valve failure requiring an intervention to allow for a mechanism-based and tailored repair, patient selection, and understanding the mechanism of valve repair failure. This thesis reviewed a standardized and tailored technique for aortic valve repair in children, cusp extension valvuloplasty, which has shown impressive freedom from valve repair failure or reoperation (see figure 1) up to 20 years. However, some authors question the durability of this repair, while also reporting extremely rare but significant potential coronary ischemic events, prompting them to recommend valve replacement (15, 16). Improvement in the durability of repair would further confirm the long-term superiority of aortic valve repair over replacement in children, and may come from new patch materials.
Figure 1 – Kaplan-Meier estimate of freedom from aortic valve reoperation after cusp extension valvuloplasty. Reproduced from (17).

Leaflet restriction or congenital hypoplasia, as seen in mitral and tricuspid regurgitation and stenosis, is also amenable to repair by leaflet augmentation with patches (18). However, the ideal patch material hasn’t been found yet: fresh autologous pericardium shows progressive retraction with gradual loss of pliability due to fibrous degenerative changes over time, while glutaraldehyde-fixed pericardium rapidly calcifies in children. Other patch materials used for valve repair have limited data available. Expanded polytetrafluoroethylene has been used for aortic valve repair by cusp extension in adults (19). It has the theoretical advantage of being
relatively stable and non-calcifying, but doesn’t preserve growth potential and its use hasn’t been reported in children.

**Patient selection and mechanism-based approach to valve repair**

As with any intervention, selecting patients amenable to valve repair is the most important factor in ensuring good long-term results. As more data is being made available on valve repair in children, mechanisms of valve disease and individual tailored techniques are being identified to improve results. Leaflet tethering or restriction is an important cause of mitral or tricuspid regurgitation. This thesis described two techniques, both at the leaflets (20) and sub-valvular apparatus (21), designed to relieve tethering or restriction, and shows results in patients used in patients who would likely would have required a valve replacement as a “bail-out” repair technique, which are safe and non-inferior to matched patients who could have a more simple repair. Further investigation into long-term follow-up and the effect on annular and ventricular remodeling are required and currently underway.

**Regenerative medicine applied to valve repair in children**

Valve repair in a growing child should, theoretically, use materials which allow for growth. Biodegradable materials, which vanish and are replaced by autologous tissue, would be ideal tools in this setting, and the principles of regenerative medicine are being applied in two avenues: biodegradable annuloplasty rings and biological scaffolds for patch materials.

This thesis reviewed in detail the data on the biodegradable annuloplasty ring for mitral and tricuspid valve repair, going from bench to bedside and long-term clinical results. This annuloplasty ring has been shown to provide excellent results for mitral and tricuspid valve repair in children requiring intervention for diverse reasons, from congenital, rheumatic, functional or infectious etiologies. It has also been shown to allow for growth, while durably remodeling the valve annulus.
Regarding patches, the ideal material for leaflet or cusp augmentation would remain pliable after implantation (without eliciting an important fibrotic reaction, at risk of late retraction of the material), be non-calcifying, and allow for growth. New patch materials are being developed to realize the dream of in vivo valvulogenesis, using scaffolds intended to be colonized and replaced by autologous tissue. Several synthetic scaffolds have been proposed in vitro and in animal models, such as polydioxanone (22), polyglycolic acid, poly-L-lactic acid (23) or polyurethane. Their clinical application as a biodegradable patch for valve repair remains to be reported.

Biological scaffolds have also been developed, predominantly using extracellular matrix (ECM). The structural and functional components of ECM are transient, due to the rapid rate of degradation of ECM scaffolds in vivo (24); they could be considered as temporary controlled release vehicles for naturally occurring growth factors. The characteristic of the intact ECM that distinguishes it from other scaffold materials is its diversity of structural proteins and associated bioactive molecules and their unique spatial distribution. ECM can be harvested for use as a therapeutic scaffold from the dermis, submucosa of the small intestine and urinary bladder, pericardium, basement membrane and stroma of the decellularized liver, and the decellularized Achilles tendon. As reviewed in detail by Badylak (24), ECM scaffolds that remain essentially unchanged from native ECM other than decellularlization and sterilization elicit a host response that promotes cell infiltration and rapid scaffold degradation, deposition of host derived neomatrix and constructive tissue remodeling with minimal scar tissue; this represents a fundamentally different scaffold material than ECM that has been chemically or otherwise modified.

CorMatrix© is a commercially available ECM scaffold made of non-modified small intestinal submucosa. Initially approved for pericardial replacement, its use has been expanded as a patch for intracardiac (25) and vascular reconstruction (26). Its application in heart valve repair is relatively new, and there is a paucity of data available. In a retrospective study of 25 children
with congenital mitral or tricuspid lesions who underwent leaflet patch augmentation with CorMatrix©, the reoperation rate was similar to matched controls who had leaflet patch augmentation with glutaraldehyde-treated pericardium at 12 months follow-up, although the mechanism of failure tended to differ, with more patch retractions in the pericardium group (27).

The investigation into using bioscaffolds in valve repair has just started. There is no significant experimental data to support the theoretical advantages, although CorMatrix© is approved for clinical use in valve repair, and experimental as well as clinical studies are necessary to ensure the safety and efficacy of these patch materials.

These evolving biodegradable devices, from annuloplasty rings to patch materials, offer the potential for valve repair with degradable materials replaced with autologous tissue. This is a perfect example of translational medicine, going from in vivo animal models investigating biodegradation and resistance to infection, to clinical application in the hopes that these properties could further improve the results of valve repair in children.

References


