

# Aortopathy associated with congenital heart disease: A current literature review

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## ABSTRACT

**In patients born with congenital heart disease, dilatation of the aorta is a frequent feature at presentation and during follow-up after surgical intervention. This review provides an overview of the pathologies associated with aortopathy, and discusses the current knowledge on pathophysiology, evolution, and treatment guidelines of the aortic disease associated with congenital heart defects.**

**Keywords:** Aortic root, aortopathy, congenital heart disease

## INTRODUCTION

Dilatation of the aortic root and the ascending aorta is frequently encountered in patients with congenital heart disease (CHD) at initial presentation and during follow-up.

Primary aortic dilatation is mainly associated with coarctation of the aorta (CoA), bicuspid aortic valve (BAV), and conotruncal abnormalities such as tetralogy of Fallot (TOF), pulmonary atresia with ventricular septal defect (PA/VSD), or truncus arteriosus. It can be a key feature in genetic syndromes with connective tissue disorders, such as Marfan, Loeys-Dietz, vascular Ehlers-Danlos, aneurysm-osteoarthritis, and Turner syndrome.

Secondary dilatation of the aortic root and to a lesser extent of the ascending aorta is seen after congenital cardiac surgery, when the original aortic root is replaced by a pulmonary autograft, as in the Ross operation, or modified as in the arterial switch operation (ASO) or systemic outflow tract reconstruction in single ventricle (SV) patients. In these situations the neo-aortic root consists mainly of pulmonary arterial root tissue introduced in the high-pressure left-sided system, often leading to dilatation in a time-dependent fashion.

The dilatation of the aorta or the neo-aortic root cannot be considered as a stand-alone characteristic, but needs to be regarded as part of the aorto-ventricular complex, comprising the systemic ventricle, the aortic valve, the aortic root, and the aortic vascular wall. Each component of this complex may by itself influence the other components, thus introducing a dysfunction at multiple levels, often defined as “aortopathy”.<sup>[1]</sup>

The magnitude of this problem continues to grow; as large cohorts of surgically treated patients survive into adulthood. Over the last decade, cumulative documentation of progressive aortic pathology in patients with CHD has been published.

The objective of this review is to summarize the current knowledge on aortic pathophysiology, diagnostic tools, and options and guidelines for prevention and treatment of the dilated aortic root and ascending aorta, associated with CHD. The aortic dilatation in genetic syndromes will not be discussed, as it presents a very large topic with specific features, not always applicable to patients with CHD.

## MORPHOGENESIS OF THE AORTIC AND PULMONARY ROOT

The aortic and pulmonary trunks originate from the remodeling of the pharyngeal arch arteries during the early embryonic development. The original six symmetrical arteries, attached to the dorsal aorta, give rise to the ascending aorta (partly derived from the left fourth artery), and pulmonary trunk (derived from the left sixth artery), with two branch pulmonary arteries attached.<sup>[2]</sup> Neural crest cells migrate to the

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caudal pharyngeal arches and into the common outflow truncus of the primitive heart tube, participating in distal septation of the common outflow tract into two independent separate extra-pericardial vessels. The formation of the semilunar valves of the aorta and pulmonary trunk evolves from the differentiation of the mesenchymal wedges of the proximal truncus into valvular tissue, thus contributing to the intra-pericardial portions.<sup>[3]</sup> [Figure 1]

A lot of controversy exists about the origin of the smooth muscle cells in the tunica media of the arterial trunks. From the onset of its development, the truncus wall is encircled by myocardial cells from the second heart field.<sup>[4]</sup> Some suggest that these cells may change from a myocardial phenotype to an arterial one;<sup>[5]</sup> others considered that the initial population of cells surrounding the outflow tract originate from neural crest cells,<sup>[6]</sup> that differentiate into tunica media and tunica adventitia, with the exception of the intra-pericardial wall of the aortic and pulmonary trunk, whose components are myocardial cells and vascular smooth muscle cells (VSMC) derived from the second heart field.<sup>[7]</sup>

In utero, the developing pulmonary artery is exposed to pressures identical to these of the fetal systemic circulation in the absence of flow through the lungs, as both outflow tracts are connected through the ductus arteriosus.<sup>[8]</sup> Studies in sheep have demonstrated that each of the major components of the arterial walls (elastin, collagen, and VSMC) undergo important changes in the perinatal period, induced by changes in local hemodynamic conditions, thus influencing the structural composition of the main arteries.<sup>[9,10]</sup>

At birth, systemic arterial pressure and aortic flow increase as a result of the decrease in pulmonary vascular resistance, the closure of shunts, and the disappearance

of the placental vascular bed. In the week surrounding birth, very rapid accumulation of elastin and collagen in the aorta has been noted, more pronounced in the thoracic than in the abdominal aorta.<sup>[10]</sup> At the same time the pressure in the pulmonary artery drops, and after closure of the ductus arteriosus, it receives all of the right ventricular output in a high flow/low pressure circulation. As a result, the wall thickness, the elastin and collagen content become significantly higher in the proximal ascending aorta than in the pulmonary artery a few weeks after birth, while the percentage of VSMCs in both trunks is comparable.<sup>[8]</sup>

There is evidence that new changes in differential flow or pressure through both great vessels after neonatal life may induce continuous changes in the smooth muscle and collagen content through regulatory signals from the vascular extracellular matrix.<sup>[11]</sup> The elastin content in the vascular wall, however, does not change much after birth because of its very low turnover and long half-life of about 40 years. Following post-natal development, expression of elastin drops to low levels, and remains low throughout life.<sup>[12]</sup>

All these mechanisms may help to understand some of the findings noted in the dilated aorta of children with CHD.

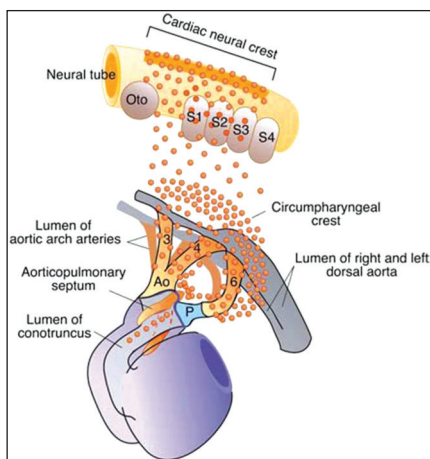
## PRIMARY AORTIC DILATATION ASSOCIATED WITH CHD

The prevalence of a primary dilated aorta is high in association with CoA, BAV, and conotruncal abnormalities. Often the large aorta is already noted at the fetal echocardiography, and may be used as a distinct diagnostic feature. The evolution of the aortic size after birth will result from a combination of intrinsic pathology, associated malformations, surgical or catheter interventions, and control of risk factors later in life; they may all influence the natural course of the aortic dilatation.

### Coarctation of the aorta

CoA accounts for 5-8% of CHD.<sup>[13]</sup> Isolated forms occur in less than half of the patients, CoA is often found in combination with BAV and mitral valve anomalies. It is usually sporadic, but genetic influences can play a role: There is a male predominance of 1,5-1,7/1, and 10-15% of Turner syndrome patients have aortic CoA.<sup>[14]</sup>

Patients that are symptomatic in the neonatal period often present with a variable degree of aortic arch hypoplasia, and when a VSD is associated, the ascending aorta is usually not enlarged due to the preferential flow through the pulmonary artery. A dilated ascending aorta and aortic arch can be found in patients with a previously undetected significant CoA, that present in



**Figure 1: Schematic representation of migration of the neural crest cells to the caudal pharyngeal arches and the common outflow tract prior to remodeling of the aortic arch arteries. Adapted from Snider *et al.* (ref. 2)**

adolescence or adulthood with upper limb hypertension, an incidental murmur, or exertional leg fatigue.<sup>[14]</sup> In a long-term follow-up study of patients after CoA surgery, Stewart *et al.*, found a dilated aortic root and arch in 16%. There was a trend to a more abnormally widened aorta in patients that had surgery later in life, and 5 of the 6 patients out of their series that died from aortic aneurysm rupture, had original surgery at a mean age of 19 years, and were known with associated hypertension.<sup>[15]</sup>

It is unsure if early repair of CoA will always be able to prevent late aortic dilatation. We know that even neonatal intervention does not prevent the occurrence of late hypertension, which by itself may trigger aortic dilatation.<sup>[16]</sup> Biopsy studies comparing the aortic wall structure above and below the CoA, have shown increased amounts of collagen and a decreased smooth muscle cell content in the pre-stenotic region, with near normal findings distally, even in young children.<sup>[17]</sup> A functional study in patients with repaired CoA demonstrated an impaired flow-mediated dilatation and increased vascular stiffness in the brachial artery. However, in this study, CoA repair before 4 months of age was associated with preserved elastic properties of the upper limb arteries, but reduced reactivity remained.<sup>[18]</sup>

### Bicuspid aortic valve

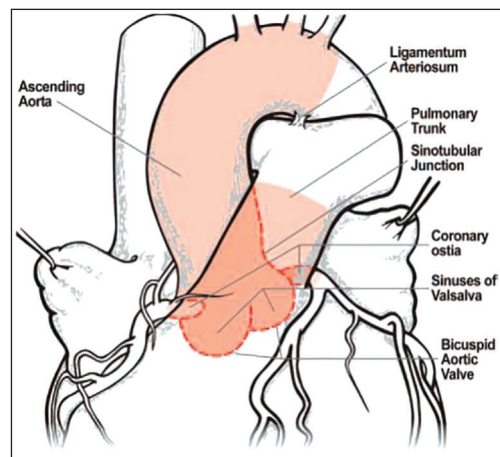
The BAV is the most frequent congenital cardiac malformation, with a prevalence of 1-2% in the general population. Concomitant aortic dilatation is seen in 80% of patients.<sup>[19]</sup> Three valve morphologies have been identified: Type I (the most prevalent, 69-85%) has a fusion of right and left coronary cusps, type II is fusion of right and non-coronary cusps, and type III (the least prevalent) shows fusion of the left and non-coronary cusp. The concomitant aortic dilatation can be confined to the ascending aorta, the aortic root, or extend from the aortic annulus up to the proximal aortic arch. The descending aorta is usually not dilated.<sup>[20]</sup> The lifetime risk of aortic dissection in patients with BAV has been reported to be 9 times higher than that of the general population.<sup>[21]</sup>

It has long been thought that the dilated aorta was a sole consequence of the altered blood flow through the eccentrically opening bicuspid valve and the resulting asymmetrical wall stress (the hemodynamic theory), but our understanding of this disease entity has evolved ever since. Many studies have pointed out that the dilatation results from a combination of intrinsic aortic wall modifications (the genetic theory) and hemodynamic changes induced by the bicuspid valve.<sup>[22,23]</sup> The marked heterogeneity of BAV disease leads to different phenotypes, resulting in a large clinical variation of BAV patients.

The BAV inheritance pattern is autosomal dominant with incomplete penetrance of 9 to 30%.<sup>[24]</sup> The male predominance of 3/1 and the association with Turner syndrome suggest an X-linked etiology. Mutations in the ACTA2 and NOTCH1 genes have been found in some BAV patients, but not the FBN1 gene associated with Marfan syndrome.

The strong association of BAV with CoA may indicate that BAV disease involves the ascending aorta and aortic arch extending to the ligamentum arteriosum [Figure 2]. The fact that the pulmonary trunk in BAV patients shows histological changes similar to those seen in the ascending aorta, points to a development spectrum involving that part of the great vessels that is derived from neural crest cells.<sup>[25]</sup>

Recent evidence has indicated that dilatation of the ascending aorta occurs as a consequence of aortic medial degeneration, similar to the one seen in connective tissue disorders resulting from apoptosis of neural crest derivatives.<sup>[21,26]</sup> Immunohistochemistry studies in the ascending aorta of BAV patients show non-inflammatory loss of VSMCs with multifocal apoptosis, in contrast with the significant inflammation and cystic medial necrosis that is usually found in the dilated aortas of patients with tricuspid aortic (TAV) valves.<sup>[27]</sup> BAV patients have been found to show a genetic profile characterized by over-expression of polymorphisms of matrix metalloproteinase-9 (MMP-9) and MMP-2, and reduced expression of MMP-14, compared to patients with TAV and dilated aorta.<sup>[27-29]</sup> The extracellular matrix plays an important role in maintaining the structural integrity of the vascular wall, and is under the balanced control of MMPs and its specific tissue inhibitors. A disturbed balance with increased MMP activity, as found in BAV aortas, can lead to apoptosis and degeneration of the aortic wall, and predispose to aneurysm formation.



**Figure 2: Schematic diagram of the anatomic boundaries of BAV disease. The structures involved in BAV disease (in pink) include the aortic valve, aortic annulus, sinuses of Valsalva, sinotubular junction, ascending aorta, pulmonary trunk and coronary ostia. Adapted from Tadros *et al.* (ref. 21)**

Dilatation in BAV patients occurs earlier in life than in TAV, where aortic distension seems more related to age and hypertension.<sup>[27]</sup> In asymptomatic BAV patients with normally functioning valves, the mean aortic diameter is usually larger than in their TAV peers of the same age.<sup>[22,25]</sup> Long-term follow-up studies have shown that ascending BAV aortas continue to expand at a higher rate than TAV aortas, ultimately leading to a higher rate of late aortic events and reoperation, despite aortic valve replacement.<sup>[30,31]</sup>

Notwithstanding this growing evidence for the genetic theory, it must be acknowledged that hemodynamics play an important role in the development of aortic dilatation. The histological and biomolecular changes described above often show an asymmetric spatial distribution, pointing towards a flow-related change.<sup>[32]</sup>

Four-dimensional flow MRI studies have demonstrated turbulent flow and changes in regional wall shear stress distribution related to the orientation of the BAV: Type I cusp orientation induces increased shear stress on the right-anterior wall, type II on the right-posterior wall of the aorta. Dilatation of the aortic root or involving the entire ascending aorta and arch was found in the majority of patients with type II orientation, but not in type I.<sup>[33,34]</sup> However, Jackson *et al.*, could not identify a pattern of aortic dilatation in relation to valve orientation in a large number of surgical BAV patients.<sup>[35]</sup> Della Corte *et al.*, rather found a relationship between the aortic valve pathology and the location of the aortic dilatation: Mid-aortic dilatation was more associated with aortic valve stenosis, suggesting a post-stenotic dilatation, where root dilatation was more prevalent in young men and aortic incompetence, and unrelated to the presence or severity of stenosis.<sup>[22]</sup>

The discovery of true detrimental flow patterns and pathological genes in association with aortic dilatation in BAV patients may help to identify high-risk genotypes, improving risk stratification and treatment choice.

### **Conotruncal anomalies: Tetralogy of Fallot and pulmonary atresia/ventricular septal defect**

TOF is the most common form of cyanotic CHD and accounts for 10% of all congenital heart defects. Dilatation of the proximal aorta is a common feature in patients with unrepaired TOF and PA/VSD, which can already be observed at fetal echocardiography. The aorta in TOF is dilated mainly at the root, tapering down towards the ascending aorta; the aortic arch is usually of normal size.

Corrective surgery has dramatically improved long-term prognosis, with nearly 90% of patients now surviving well into adulthood.<sup>[36]</sup> However, persistent aortic root dilatation is increasingly reported in adult patients, years after corrective surgery. Single case

reports of progressive aortic dilatation long after repair of TOF began appearing in the early 1970s. In 1982 Capelli and Somerville mentioned persistence of a large aortic root, but considered it an acquired feature due to long-standing volume overload by years of aortopulmonary shunts before complete repair, and suggested that earlier repair in the first decade of life might prevent this complication.<sup>[37]</sup> In 1997 the first series on progressive aortic root dilatation many years after TOF repair was published by the Mayo Clinic group.<sup>[38]</sup> Despite excellent clinical results, a substantial cohort of patients developed progressive aortic dilatation and subsequent aortic valve incompetence, necessitating reoperation on the aortic root.

The underlying mechanism of the aortic dilatation in conotruncal abnormalities is unclear; both hemodynamic<sup>[37]</sup> and intrinsic wall abnormalities<sup>[38-40]</sup> have been suggested. It has been attributed to left-sided volume overload in the context of right outflow obstruction and right-to-left shunt, and seems to be more pronounced in the pulmonary atresia variant. A right-sided aortic arch, male gender, history of an aortopulmonary shunt, and complete repair at older age have been associated with late aortic dilatation.<sup>[41]</sup> Some have suggested a genetic factor to be implicated, as 22q11 deletion and FBN1 mutations have been associated with TOF.<sup>[42,43]</sup> Intrinsic aortic pathology can be coexistent, as histological studies in children of all ages with TOF have shown fibrosis, fragmentation of elastin, and cystic medionecrosis both on biopsies and post-mortem specimen, wall changes similar to those seen in Marfan patients with aortic dilatation, however often in patients operated late.<sup>[39,40]</sup> The age at repair may play a role in the severity of the histological disturbance: In a homogeneous patient cohort that we repaired at the age of 6 months, we found less pronounced histological changes in the aortic wall, mainly fibrosis and accumulation of ground substance. No VSMC necrosis or apoptosis was demonstrated, and in only 1 patient with a very large aorta some degree of elastin fiber fragmentation was found.<sup>[44]</sup> We speculate that increased fibrosis may be the first feature of aortic degradation, and that, once medionecrosis, smooth muscle cell disarray, and severe elastin fragmentation have occurred, repair mechanisms may not be able to completely restore the aortic wall integrity after TOF repair. This may explain why increased stiffness and higher pulse wave velocity in the aorta of repaired TOF patients have been described, several years after correction.<sup>[45-47]</sup>

We and others have demonstrated a significant regression of indexed aortic root diameters over time after early repair in infancy, with a chance of normalizing the initially dilated root within 7 to 8 years.<sup>[48,49]</sup> In a homogenous cohort of TOF patients repaired early in infancy, we found that the ascending aortic size really

decreases with growth of the patient during the first years after surgery, irrespective of the total histology score at operation<sup>[44]</sup> [Figure 3]. These findings support the presumption that mitigation of the transaortic flow by early surgical repair of TOF triggers a remodeling process that may interrupt the progression of the limited histological alterations of the aortic root related to increased aortic stiffness, thus preventing late aortic dilatation.

The real prevalence and severity of dilated aortic root and its associated complications in the adult TOF population remain to be defined, as more evidence emerges that not all patients develop important aortic dilatation. In a recent review Mongeon *et al.* found, in adult patients, 35 years after repair of TOF at a mean of 7 years of age, an aortic dimension of  $\geq 40$  mm in 29%, but only an observed-to-expected aortic root dimension ratio of  $>1.5$  in 7%, and moderate to severe aortic regurgitation in 3.5% of patients.<sup>[50]</sup> Only 3 cases of aortic dissection late after TOF repair have been described in the literature so far, all in severely dilated aortas of  $>70$  mm.<sup>[51-53]</sup> In the section on guidelines for treatment, these findings will be taken into account.

### Secondary aortic dilatation after repair of CHD

In this section we will consider the occurrence of dilatation of the aortic root, and to a lesser extent of the ascending aorta, after congenital cardiac surgery, by which the original aortic root is replaced by a pulmonary autograft, as in the Ross operation, or modified as in the ASO or systemic outflow tract reconstruction in SV patients. In these situations the neo-aortic root consists mainly of pulmonary arterial root tissue introduced in the high-pressure left-sided system, often leading to dilatation in a time-dependent fashion. In contrast with

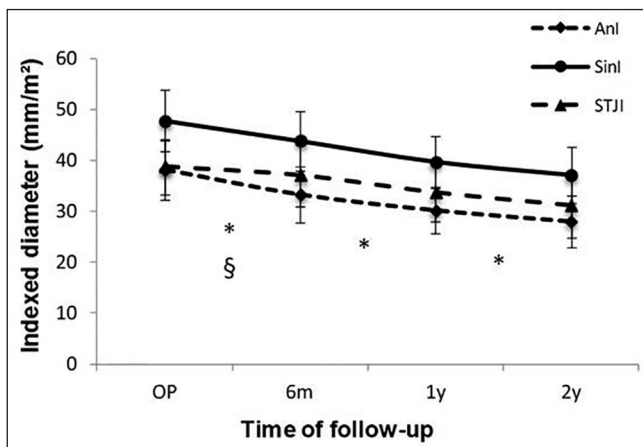
the primary aortic dilatation, the literature on secondary aortic dilatation is less extensive, probably because this feature only started to emerge as a clinical problem during the last decade.

### After Ross procedure

Since the introduction by Sir Donald Ross in 1967 of the Ross procedure, comprising aortic replacement by the pulmonary autograft, this operation has gained widespread applicability both in children and adults with congenital aortic valve disease.<sup>[54]</sup> Technically, the pulmonary autograft can be implanted as a full root replacement, or as a subcoronary replacement, inserting the pulmonary autograft as an inclusion cylinder in the existing aortic root. The right ventricular outflow tract reconstruction is mostly performed with a pulmonary homograft or biological xenograft root.

In growing children, where only the full root replacement can be used, the procedure has remained the first choice for aortic replacement, because of its potential for growth of the neo-aortic root along with the patient's somatic growth, thus preventing the need for repetitive aortic reoperations. In adults, after a first wave of enthusiasm, the popularity of the technique has dropped during the last decade, after several reports of disproportionate neo-aortic root dilatation and secondary aortic incompetence occurring a few years after the original operation. In the German-Dutch Ross Registry, the rate of autograft re-interventions was significantly higher in adults than in children.<sup>[55]</sup> Freedom from autograft reoperation has been reported between 74% and 93% at 10 years,<sup>[56-59]</sup> and between 65% to 82% at 15 years.<sup>[60,61]</sup> The freedom from more than moderate autograft regurgitation is reported between 56% and 85% at 10 years, but aortic incompetence by itself does not always necessarily trigger reoperation.<sup>[58,59]</sup> A relationship exists between increasing valve regurgitation and progressive dilatation of sinotubular junction and ascending aorta.<sup>[62]</sup>

The neo-aortic root after the Ross procedure dilates mainly at the sinus portion and the sinotubular junction, and less at the neo-aortic annulus itself, that usually grows in proportion to the somatic growth in children.<sup>[62]</sup> Dilatation occurs rapidly within the first days after surgery, with a further increase during the first year of follow-up, without causing significant aortic regurgitation in the medium-term phase.<sup>[63]</sup> In a study in children, Solymar *et al.*, demonstrated that during the first year after the operation, the mean z-value of the proximal autograft increased from 0.2 to 2.2, indicating a more rapid increase than predicted, and significantly higher than in controls, suggestive of passive dilatation in the early postoperative period.<sup>[64]</sup> After the first year, z-value changes in patients and control subjects were very similar. The postoperative distension of the pulmonary autograft leads to remodeling of the wall and the valve



**Figure 3: Evolution of indexed aortic root diameters after correction for tetralogy of Fallot. Anl: Indexed aortic annulus diameter; Sinl: Indexed sinus diameter; STJI: Indexed sinotubular junction diameter. \* $P < 0.05$  for change at each aortic root component; §  $P < 0.05$  for change at level of annulus and sinus. Adapted from François *et al.* (ref. 44)**

leaflets, as was demonstrated by the finding of intimal thickening, medial elastin fragmentation, hypertrophic smooth muscle cells, increased medial and adventitial fibrosis, and thickening of valve leaflets in pulmonary autografts explanted for various reasons.<sup>[65]</sup> As the Ross operation is applied for BAV disease in 65% to 81% of cases,<sup>[55,66]</sup> the intrinsic pulmonary wall abnormalities as described in BAV may enhance the neo-aortic dilatation on top of the distension due to the introduction of the pulmonary valve in the systemic circulation.<sup>[21]</sup>

Risk factors for neo-aortic root dilatation have been searched for, in order to improve the long-term results and diminish the risk for late neo-aortic valve failure.

Patient factors related to neo-aortic root dilatation and a shorter time to autograft reoperation are the presence of preoperative pure aortic incompetence,<sup>[55-57,61]</sup> and older age.<sup>[62]</sup>

Technical factors implicated in increasing neo-aortic root diameters are somehow controversial, but mostly relate to freestanding root replacement as compared to subcoronary implantation,<sup>[55,66]</sup> and the absence of annulus reinforcement strips in an aortic root of >28 mm,<sup>[57]</sup> a surgical modification that may prevent late annular dilatation.<sup>[55]</sup> In adults, equivalent and durable results were obtained with subcoronary implantation compared to root reinforcement with a tissue or synthetic strip.<sup>[57]</sup> In the more recent years the application of a Dacron tube for external support of the pulmonary autograft, to prevent sinus and sinotubular junction dilatation in freestanding roots, has gained renewed interest.<sup>[67]</sup> A combined ascending aortic replacement for aneurysm had no influence on late autograft function in a 5-year follow-up study, but the long-term fate of the neo-aortic valve in this setting is not known.<sup>[59]</sup>

#### **After arterial switch operation**

Over the past two decades, the ASO has become the procedure of choice for repair of transposition of the great arteries in neonates and young infants.<sup>[68,69]</sup> The ASO leads to anatomic correction, in contrast to atrial switch operation, and thus avoids the long-term complications of systemic atrioventricular valve regurgitation and ventricular failure. However, several factors are of potential concern for the evolution of the neo-aortic root later in life. After ASO, the native pulmonary valve and root assume the role of systemic arterial valve and root. As was described previously, the pulmonary and aortic valves are macroscopically indistinguishable at birth, but the aortic valve develops more collagen and elastin fibers in the perinatal period.<sup>[10]</sup> It has been demonstrated, however, that the structural changes in the medial connective tissue of the pulmonary trunk, that normally accompany decreasing pulmonary arterial pressure in infants, do not occur if pressure in the native pulmonary

trunk remains high.<sup>[70]</sup> This finding may further stimulate to perform the ASO in transposition with intact septum during the first days of life, in order to improve the tissue characteristics of the neo-aortic valve. However, even after early ASO, distensibility of the aortic root is reduced, leading to increased left ventricular mass and diastolic dysfunction.<sup>[71,72]</sup> This finding was strongly associated with age, suggesting the usefulness of long-term follow-up studies for early onset of degenerative cardiovascular disease.

In medium- and long-term follow-up studies after ASO, several risk factors for late neo-aortic root dilatation and aortic regurgitation have emerged. The presence of a VSD, previous pulmonary artery banding, older age at repair, and the association with CoA are patient factors associated with increased neo-aortic dilatation.<sup>[73-76]</sup> Technical factors such as acute angulation of the aortic arch after ASO<sup>[77]</sup> and closure of the VSD through the pulmonary artery,<sup>[74]</sup> have been associated with late aortic regurgitation and aortic dilatation in some reports.

Freedom from moderate neo-aortic valve regurgitation was found to be between 70% and 81% at 15 years postoperatively.<sup>[73,74,78]</sup> The progression of regurgitation is slow and little progressive, is probably more related to the technique, and is correlated with the size of the neo-aortic annulus, not of the sinotubular junction.<sup>[75,78]</sup>

A dilated neo-aortic root (defined as larger than the 95<sup>th</sup> percentile) is seen in at least 50% of all patients after ASO.<sup>[74]</sup> Dilatation is more pronounced at the sinus level than at the sinotubular junction.<sup>[78]</sup> Hutter *et al.*, noted rapid dilatation of the root during the first postoperative year, as seen after the Ross procedure, followed by growth towards normalization of the annulus and sinus over the next 10 years.<sup>[79]</sup> In contrast, Marino *et al.*, described a gradual and continuous dilatation of the neo-aortic root in ASO that does not seem to level off during the follow-up period. Aortic dilatation by itself is rarely associated with aortic valve regurgitation.<sup>[73]</sup> However, severe root dilatation appears to be closely related to significant neo-aortic valve regurgitation, mainly as a result of a time-dependent and reciprocal process.<sup>[76]</sup>

Freedom from aortic root reoperation was between 83% and 97% at 15 years, during reoperation preservation of the neo-aortic valve was rarely possible due to the asymmetry of the valve leaflets.<sup>[75,80]</sup>

Because the factor “time” is the principal determinant of late neo-aortic valve dysfunction and root dilatation, strict serial surveillance after ASO is mandatory.

#### **Single ventricle situations**

Since the introduction of staged procedures for patients with SV physiology two decades ago, an increasing

number of survivors with a Fontan circulation grow into adolescence and adulthood.

When the native aortic valve functions as the only outlet valve, and no surgery to the original aortic root has been performed during staging, the chances of this valve deteriorating over time are small, as the architecture and wall characteristics are apt to sustain systemic pressures. However, when volume loading persists during a considerable period of time, and the Fontan completion is postponed at an older age, or when the aortic valve is bicuspid, the aortic root and ascending aorta may dilate over time and become aneurismal.<sup>[81]</sup>

After staged Fontan for hypoplastic left heart syndrome (HLHS) and its variants, the pulmonary valve functions as the systemic neo-aortic valve. In these situations, there is probably more reason for concern towards future valve function and neo-aortic dimensions. The physiological environment is comparable to the situation after a Ross procedure or an ASO, but with the additional risk of volume overload during the first and second Fontan stages, the presence of an asymmetrical patch in the ascending aorta and arch, and the possibility of recurrent distal arch stenosis during follow-up. Kojima *et al.*, demonstrated increased pulse wave velocity in the ascending aorta in SV patients during routine catheterization at all Fontan stages.<sup>[82]</sup> Aortic stiffness was significantly higher in the group with dilated aorta, independent of aortic volume load. Histological analysis of a resected neo-aortic root, in a patient with a root aneurysm 10 years after Fontan, demonstrated no evidence of inflammation but rather fragmentation of elastic fibers, deposition of myxoid material, and loss of medial VSMC. These findings, commonly seen in other forms of aortopathy associated with bicuspid valves and connective tissue disorders, have been related to increased vascular stiffness in humans.<sup>[83]</sup>

Serial follow-up studies on the neo-aortic function after Fontan completion for SV are scarce. Neo-aortic regurgitation seems to be progressive over time: Mild systemic valve incompetence was noted in 25% during the first year after Norwood procedure,<sup>[84]</sup> and in 61% several years after total cavopulmonary anastomosis, but was rarely more than mild.<sup>[85]</sup>

In a study with a median follow-up of 9 years after Fontan completion, neo-aortic root progressively dilated out of proportion to body size over time, with 98% of patients having a root z-value of  $>2$  at most recent follow-up. The authors concluded that early volume unloading had no beneficial impact on the size of the neo-aortic root.<sup>[85]</sup> Only a few case reports of quickly progressive neo-aortic root dilatation necessitating surgical intervention, have been published.<sup>[86-88]</sup> In the majority of cases, a valve-sparing operation was attempted, with variable results.

For now, neo-aortic root dilatation and neo-aortic regurgitation in the setting of HLHS have not a major impact on outcome, however, close observation is warranted, as cases of quickly progressive diameter increase have been described.<sup>[88]</sup>

## DIAGNOSTIC MODALITIES

The cornerstone investigation in all pathologies described above, remains transthoracic echocardiography (TTE). It is the first line tool to delineate the exact valve anatomy, valve function, severity of regurgitation, and ventricular function. Measurement of the aortic root needs to be performed at four levels during end-diastole: Aortic annulus, sinus, sinotubular junction, and proximal ascending aorta. It may be difficult to appreciate the distal ascending aortic diameter on TTE. Sometimes better image quality can be obtained with transesophageal echocardiography, but usually some form of sedation is needed, and the mid-segment of the aorta cannot be completely viewed.

To obtain a complete view of the aorta and its branches using a multi-plane modality, a magnetic resonance imaging study (MRI) is preferable to a CT scan, because of the absence of ionizing radiation, and because patients with dilated aortas will need multiple studies during their lifetime. MRI may be the preferred investigation when TTE is suboptimal, to exactly measure regurgitant valve fraction, and appreciate left ventricular function. Diameter measurements on CT and MRI are 1-2 mm larger than obtained on TTE, as the aortic wall segments are included.<sup>[89]</sup>

When following patients with aortic dilatation, not only the absolute diameter of the aortic segments is important, but also the diameter indexed to body surface area. This allows serial comparison of diameters in growing children, and may be also very useful in short statured adults. The upper limit of normal is defined as an indexed diameter of  $>21 \text{ mm/m}^2$ , significant dilatation of the aortic root as  $>25 \text{ mm/m}^2$ ,<sup>[90]</sup> and significant risk for rupture from  $>27.5 \text{ mm/m}^2$ .<sup>[91]</sup>

The use of z-values to follow the aortic size is also validated. The z-value represents the number of standard deviations from the mean diameter, normalized for the patient's body surface area, gender and age.<sup>[92]</sup> A mild aortic dilatation is defined as a z-value  $>1.9-3$ , moderate from 3-4.<sup>[93]</sup>

Some studies define significant aortic dilatation as observed versus predicted diameter  $>1.5$ .<sup>[50]</sup>

When performing serial follow-up, it is important to always compare the measurement obtained by the same diagnostic technique.

### Guidelines for follow-up and treatment

Guidelines for the follow-up and surgical treatment of adult patients with valvular heart and thoracic aortic

disease are well established, and regularly updated.<sup>[94-96]</sup> In these guidelines, only BAV with thoracic aorta dilatation receives special attention. All guidelines are based on diameters; aortic size index is never used up to now.

Regarding follow-up, all patients with an aortic diameter of >40 mm should be follow-up regularly. When the diameter is >45 mm, and patients have a family history of dissection or show rapid progression, yearly imaging is mandated.

Surgery to the ascending aorta in BAV patients is mandated (Class IIa, level C):<sup>[95]</sup>

- for an ascending aorta of >50 mm, when the patient has a family history of dissection, or the size progression is >5 mm/year
- for an ascending aorta of >55 mm, when there are no risk factors
- for an ascending aorta of >45 mm, when surgery for the valve is obligatory; replacement of the aortic sinuses needs to be individualized

In contrast, nearly no guidelines exist for aortopathy in CHD.<sup>[97,98]</sup> In the ESC guidelines for grown-up CHD, only the following are mentioned:<sup>[97]</sup>

- surgical treatment for ascending aortic dilatation in CoA may be considered when the diameter is >55 mm (>27.5 mm/m<sup>2</sup>) or if rapid progression
- aortic surgery should be considered after ASO when the neo-aortic root is >55 mm providing adult stature (Class IIa/level C)

In the absence of guidelines for the other pathologies previously discussed, a pragmatic attitude is probably appropriate: As no case reports have appeared about ruptured aortas <55 mm in adult sized patients, this diameter should be used as a cut-off. A diameter of >60 mm is considered the hinge point for the ascending aorta, above which the chance for rupture increases exponentially.<sup>[99]</sup> In small children, rapid progression in size may urge faster intervention.

#### Medical therapy

Co-existent arterial hypertension in patients with CHD must be effectively treated, as hypertension has been shown to accelerate the aortic dilatation.<sup>[100]</sup>

The usefulness of medical treatment to prevent aortic expansion in normotensive patients with primary or secondary aortic dilatation related to CHD, is controversial. Despite a larger cohort of patients survives into adulthood, a paucity of data remains on the applicability of any medical therapy in the CHD patient group. The only existing guidelines are restricted to patients with Marfan disease with dilated aorta. As some histological and functional similarities have been shown between the aortas in CHD patients and those with Marfan syndrome, similar medical therapies have been recommended, however without strong clinical evidence.

The most recent guidelines for the management of aortic aneurysm in non-Marfan patients recommend the use of  $\beta$ -blockers to decrease the blood pressure and the load on the aortic wall.<sup>[96]</sup> Another option may be to influence the angiotensin pathway, as the angiotensin-receptor blocker losartan was found to specifically inhibit the TGF $\beta$ -mediated activation pathway, inducing a decrease in MMP-2, MMP-9 and apoptosis in Marfan syndrome.<sup>[101]</sup>

It is clear that multicenter trials are needed to study medical therapy in patients with CHD-related aortopathy.

#### Surgical therapy

Valve-sparing procedures are usually preferred in growing children and young adults, whenever possible.<sup>[87]</sup> Surgery should be performed in centers with experience in thoracic aortic surgery.<sup>[102]</sup> Extensive discussion on this topic can be found in the literature.

## CONCLUSION

Dilatation of the aortic root and the ascending aorta is frequently encountered in patients with CHD at initial presentation and during follow-up. As large cohorts of surgically treated patients survive into adulthood, more retrospective studies emerge discussing progressive aortopathy in patients with CHD. Specific guidelines about indication for medical and surgical treatment are largely lacking. Future recommendations should include indexed size measurements, adapted to growing children.

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