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Congenital Aortic Stenosis in Childhood

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1. Introduction

Aortic valve stenosis is the obstruction to outflow from the left ventricle because of an abnormal aortic valve. The discharge restriction to the systemic ventricle may also be produced by an anomaly at a sub or supravalvar level. Nevertheless, the most common site of occurrence is by far the annulus (70%). Although congenital aortic stenosis is frequently associated with other significant cardiovascular lesions (20%) such as the hypoplastic left heart syndrome, mitral disease and coarctation of the aorta, we will mainly discuss the isolated congenital aortic valve stenosis in this chapter.

Congenital aortic valve stenosis accounts for approximately 5% of all cases of congenital heart disease, with reported incidences ranging from 0.04 to 0.38 per 1000 live births (Botto et al., 2001; Hoffman & Kaplan, 2002). A clear male predominance (Wagner et al., 1977) has been reported, with a gender ratio of 4:1. There is recent evidence of familial predisposition for aortic valve anomalies (recurrence risk ~3% and ~15% in offspring of an affected father or mother respectively). This valvar defect occurs sporadically in most cases however. There is a controversy whether consanguinity has an influence on the incidence of congenital heart disease; while some studies emphasized the increased risk in the rate of congenital cardiac malformations (Badaruddoza et al., 1994; Bassili et al., 2000; Gatrad et al., 1984), others failed to show such association (Robida et al., 1997; Subramanyan et al., 2000). Recent large case series demonstrated that parental consanguinity increases the risk of valvar aortic stenosis as well as atrial septal defect and tetralogy of Fallot, wich supports the involvement of autosomal recessive genes in its bearing (Nabulsi et al., 2003; Chehab et al., 2007). Lately, aortic valvar anomaly in families with autosomal dominant transmission was found to be secondary to a mutation in the *NOTCH1* gene (Garg et al., 2005). This apparent contradiction could be explained by the existence of many cases where a gene may be responsible for autosomal recessive and dominant inheritance, depending on the types of mutations.

Turner syndrome, a congenital disease caused by structural and/or functional aberrations of the X chromosome, is associated with an increased risk of cardiovascular malformations (Bondy & Turner Syndrome Study Group, 2007). It has been reported that 17 to 59% of the patients carrying this chromosomal alteration are affected with at least one structural cardiovascular anomaly, mainly coarctation of the aorta and bicuspid aortic valve, but also mitral valve disease and dilatation of the aortic root (Landin-Wihelmsen et al., 2001; Sybert, 1998). Although some authors have found no correlation between karyotype and heart

defects (Poprawski et al., 2009; Ruibal et al., 1997), others reported congenital cardiovascular malformations in 39% of patients with X chromosome monosomy, in 24% with mosaicism and in 12% with structural aberrations (Gravholt, 2001, 2004). The current guideline of the Turner syndrome Study Group (Bondy & Turner Syndrome Study Group, 2007) recommends cardiology assessment including echocardiography. They also recommend physical examination and echocardiography during adolescence and again every 3-5 years in adulthood even if cardiovascular abnormalities were not detected in childhood. Based on the increased risk of hypertension and aortic dissection of these patients, blood pressure should be measured at least twice a year. Girls with bicuspid aortic valve require periodical monitoring for future development of aortic stenosis, regurgitation, and aortic root dilatation.

Bicuspid aortic valve disease is the most common congenital heart defect, with an estimated prevalence of 0.5-2% and male predominance (3:1) (Basso et al., 2004; Roberts, 1970; Ward, 2000). A recent prospective echocardiographic study in newborns showed a high prevalence of 4.6 in 1000 live births (7.1 per 1000 male newborns versus 1.9 per 1000 female newborns) (Tutar et al., 2005). Nowadays, this condition is considered not only a valvar anomaly but a genetic disorder of the aorta and cardiac development (Siu & Silversides, 2010). It is often associated with coarctation of the aorta and dilatation of the thoracic aorta. About 50-75% of patients with coarctation have bicuspid aortic valve (Roos-Hesselink et al., 2003). Other congenital lesions such as ventricular septal defects, patent *ductus arteriosus* or atrial septal defects have been also associated with bicuspid aortic valve. There are few syndromes whose cardiac involvement includes bicuspid aortic valve and left-sided obstructive lesions: Shone syndrome (multiple left-sided anomalies), Williams syndrome (supravalvar stenosis) and Turner syndrome (coarctation of the aorta). The importance of this disease lies in the fact that valvar dysfunction may develop at any time during life span (stenosis or incompetence) as well as disturbances of the aortic wall. In children, 70-85% of stenotic aortic valves are found to be bicuspid (Mack & Silberbach, 2000). An autosomal dominant pattern of inheritance was suggested (Clementi, 1996; McDonald & Maurer, 1989) , and there are reports of 24% prevalence of bicuspid aortic valve in families with more than one affected member (Glick & Roberts, 1994). Recent research demonstrated that bicuspid aortic valve is likely due to mutations in different genes with dissimilar patterns of inheritance (Cripe et al., 2004). The 9% prevalence of bicuspid aortic valve in first-degree relatives of patients with this valvar disturbance supports the current guidelines of the American College of Cardiology/ American Heart Association suggesting echocardiographic screening for bicuspid aortic valve in first-degree relatives (Warnes & American College of Cardiology/ American Heart Association [ACC/AHA], 2008).

2. Anatomical pathology

The obstruction of the left ventricle outflow tract may occur at the subvalvar, valvar or supravalvar levels. Subvalvar stenosis can be produced by a fibrous membrane, a fibromuscular ridge or a diffuse fibromuscular tunnel. Supravalvar obstruction can be a result of an external hourglass deformity with a corresponding luminal narrowing, a fibrous diaphragm or a diffuse narrowing (Edwards, 1965; Iwata et al., 2008). Nevertheles, we will only discuss the most common type at the valvar level, the focus of this chapter. The normal aortic valve is tricuspid, also refered to as trileaflet or trifoliate (3 comissures). The 3 cusps are typically designated as: left coronarian, right coronarian and noncoronarian. Aortic

valvar stenosis may be caused by unicuspid, bicuspid or tricuspid valves. Quadricuspid aortic valve is very rare in the exception of the truncus arteriosus malformation.
Unicuspid valve is commonly found in neonates and infants but rare in children, adolescents or adults (Falcone et al., 1971; Mookadam et al., 2010; Roberts & Ko, 2007). All three cusps are fused, with a central opening (acomissural) or an eccentric orifice (unicomissural, with only one fully developed commissure, commonly in a posterior location). It has no attachement or a single lateral attachment to the aorta at the level of the orifice. It is usually observed as a primitive and myxomatous tissue with a pinhole opening, often associated with severe aortic arch obstruction, underdeveloped aortic valve ring, and hypoplastic left heart syndrome. In infants critical stenosis causes a low output syndrome.
Bicuspid (or bileaflet) valve constitutes the most common aortic valve anomaly (Siu & Silversides, 2010). It is clasically formed by 2 unequal-sized leaflets. The larger leaflet has a central raphe resulting from commissural fusion (called "functional" or "fused" bicuspid valve). According to which commissures are fused, there are different morphologic patterns, the most frequent involve fusion of the right and left cusps (60%). Less often, there is no raphe ("pure" or "truly" bicuspid valve). Dilatation of the thoracic aorta is commonly associated with aortic bicuspid valve. It was thought to be secondary to abnormal flow dynamics, but recent evidence indicates structural abnormalities at the cellular level (Niwa et al., 2001; Pachulski et al., 1991). These aberrations are independent of the hemodynamic alteration. They include decreased fibrillin-1, elastin fragmentation and apoptosis. They are thought to play a decisive role in thoracic aorta dilatation and subsequent dissection. These structural anomalies are also found in the main pulmonary artery of patients with bicuspid aortic valves, with unclear clinical significance (De Sa et al., 1999). Obstruction or incompetence of bicuspid aortic valves may develop at any age, mainly in relation to increasing adhesion of remaining commissure margins as well as leaflet thickening or calcification.
Tricuspid valve is the least common cause of congenital aortic stenosis in the youth compared to the various forms of bicuspid valves which represent 70-85% in this age group. The obstruction may be produced by an incomplete leaflet opening and/or cusp thickening, and the stenosis may develop and/or progress over time.

3. Physiopathology

A compensatory left ventricular concentric hypertrophy results proportionally to the degree of the outflow obstruction. A mild stenosis usually produces minimal or no myocardial hypertrophy. The degree of obstruction tends to increase in relation to periods of rapid somatic growth (Wagner et al., 1977). Severe hypertrophy and valvar obstruction may cause myocardial ischemia from the combination of limited cardiac output, reduced coronary perfusion and increased myocardial oxygen consumption. Fibrosis may occur in areas of the myocardium damaged by ischemia (Alsoufi et al., 2007). Post-stenotic aortic root dilatation, defined as dilatation of the vessel wall distal to the area of a partial stenosis, may be caused by the hemodynamic abnormality, but also by intrinsic aortic parietal structural anomalies, especially in bicuspid aortic valve disease. A stenosed aortic valve may also develop valvar incompetence, with secondary left ventricular dilatation in case of significant regurgitation.
During prenatal development, severe aortic stenosis causes increased left cardiac chambers pressures. The blood in the left atrium flows preferencially to the low-pressure right atrium (Alsoufi et al., 2007; Turner et al., 2009). The subsequent reduced antegrade flow through the left heart structures induces detention of left ventricular growth, with the potential development of a hypoplastic left heart syndrome. Occasionally the left ventricle is normal

in size, with depressed function of the damaged fibrotic myocardium. The increased afterload contributes to left ventricular hypertrophy and dysfunction. Ventricular hypertrophy and increased intracavitary pressure may lead to subendocardial ischemia with the development of endocardial fibroelastosis which further impairs the ventricular function. In fetuses with aortic stenosis and an intact or restrictive atrial septum, there is no low-pressure outlet for blood entering the left heart, so the left atrium and ventricle may become severely dilated. This may lead to severe mitral regurgitation due to mitral annular dilation, with the resultant elevated pressure and compression of the right heart causing right heart failure, fetal hydrops, and severe pulmonary vascular changes leading to pulmonary hypertension in the neonatal period (Rychik et al., 1999).

4. Clinical manifestations

Although severe stenosis may manifest as exercise induced thoracic pain, fainting, exercise intolerance or even sudden death during childhood, most of the children with valvar aortic stenosis are asymptomatic. The diagnosis is often made during the evaluation of an asymptomatic heart murmur. The typical auscultatory features (Fyler, 1992) consist on an early systolic ejection click followed by a crescendo-decrescendo systolic murmur that reaches peak intensity in mid-systole. In advanced aortic stenosis, the murmur is best heard at the second intercostal space in the right upper sternal border, it radiates to the neck and it is often associated with a systolic thrill in the suprasternal notch. The second sound aortic component is delayed secondary to the left ventricular systole extension, proportionate to the severity of the obstruction. This may result in a narrowly split second heart sound or even with the aortic closure appearing after pulmonary closure (reverse, or paradoxical splitting). The length but not the intensity of the murmur correlates with the degree of the stenosis. The murmur intensity of valvar aortic stenosis increases upon squatting and, in opposition to what happens in cases of hypertrophic obstructive cardiomyopathy, decreases with Valsalva maneuvers. An early diastolic regurgitant murmur may be heard when valvar insufficiency is also present.
Bicuspid aortic valve disease is commonly assymptomatic in childhood; it is estimated that only 1 in 50 children present a clinically significant valve disease by adolescence (Bonow & ACC/AHA, 2008). Globally, only 10-15% of patients present clinical manifestations within the first 12 months of life (Brown et al., 2003; McCrindle et al., 2001). Newborns with critical aortic stenosis usually have a dramatic presentation soon after birth. As the *ductus arteriosus* starts closing, a decreased systemic and coronary perfusion is established. This situation carries a high morbidity and mortality, fatal within hours if left untreated. Neonates and infants with milder stenosis may present with failure to thrive, tachypnea and respiratory distress secondary to pulmonary vascular congestion. Prenatally, only critical stenosis may have clinical repercussion. As previously explained, when an intact or restrictive atrial septum is present, left chambers may become severely dilated leading to heart failure, fetal hydrops and demise. On the other hand, when a non-restrictive *foramen ovale* coexists with critical stenosis, left chambers may be underdeveloped. The myocardium may be damaged, but the systemic output is usually secured at least untill birth through the *ductus arteriosus*.

5. Diagnostic tests

5.1 Electrocardiography

In mild cases there are no electrocardiographic changes. When the stenosis is at least moderate, abnormalities reflecting left ventricular hypertrophy may be observed with or

without strain pattern. These findings include increased left ventricular voltages, left bundle-branch block, decreased right anterior forces, T-wave inversion and ST-segment depression. Although electric changes are much more likely with severe stenosis, electrocardiography is not a reliable indicator of the degree of obstruction (Botto et al., 2001; Fowler et al., 1982). In neonates with critical obstruction, the electrocardiogram usually shows right ventricular dominance with evidence of diffuse T-wave and ST-changes secondary to left ventricular strain (Lofland et al., 2001). ACC/AHA guidelines include: "An Electrocardiogram is recommended yearly in the asymptomatic adolescent or young adult with aortic stenosis who has a Doppler mean gradient greater than 30 mmHg or a peak velocity greater than 3.5 m/sec (peak gradient greater than 50 mmHg) and every 2 years if the echocardiographic Doppler mean gradient is less than or equal to 30 mmHg or the peak velocity is less than or equal to 3.5 m/sec (peak gradient less than or equal to 50 mmHg) *(Class I; Level of Evidence C)*" (Bonow & ACC/AHA, 2008).

5.2 Chest X-ray

The heart size is usually normal in children. A prominent ascending aorta is occasionally identifiable because of the dilatation of the ascending aorta, and it is observed as a bulge on the right upper mediastinum or a prominence of the aortic knob on the left upper mediastinum. Those newborns or infants in congestive heart failure due to a critical stenosis show cardiomegaly and pulmonary vascular congestion.

5.3 Echocardiography

Transthoracic echocardiography confirms the diagnosis. The degree of obstruction refers to pressure loss across the valve in systole. This gradient was historically measured by cardiac catheterization. Peak-to-peak gradients determined by cardiac catheterization have constituted the basis of natural history studies and clinical-decision making. Although early investigations suggested that peak Doppler gradient reliably estimated the peak-to-peak catheter gradient (Currie et al., 1985), it was later demonstrated that it consistently overerestimates it by 20-30%, with an exacerbation in presence of significant valvar regurgitation (Baumgartner et al., 1999; Levine et al., 1989; Villavicencio et al., 2003). This is explained by the fact that Doppler technique reflects the maximal instantaneous velocity while peak-to-peak catheter gradient refers to the maximal difference between pressures measured in the left ventricle and the aorta, and also due to the phenomenon of pressure recovery (Clark, 1976). Pressure recovery occurs when the pressure drop across a stenotic orifice is partially recovered distal to the obstruction from conversion of kinetic energy into potential energy. Continuous-wave Doppler measures the point of highest velocity and lowest pressure or vena contracta, so the measured gradients will overestimate the catheter gradient if significant pressure recovery occurs. As higher flow rates secondary to greater resting heart frequencies and small aortas have been shown to exacerbate the phenomenon of pressure recovery (Baumgartner et al., 1999) and both features are often present in children with aortic stenosis. This phenomenon is considered to play an important role while interpreting data derived from ultrasonography studies in this clinical context. To note, pressure recovery has been found to be more significant in mild to moderate aortic valve stenosis (Levine et al., 1989). Moreover, the mean Doppler gradient is a better estimate of the catheter-derived gradients (Fyler, 1992; Levine et al., 1989), although not consistent with the known fluid mechanics principles of left ventricular ejection.

The echocardiogram usually allows to determine with great accuracy the anatomical features of the valve, as well as to identify other cardiovascular lesions which may be associated with this valvulopathy, a subaortic membrane or supravalvar stenosis, if present. A normal aortic valve is formed by three thin cusps which open fully in systole and close completely in diastole. In opposition, a stenotic aortic valve usually has one or two leaflets, usually thick in appearance, with incomplete opening in systole. The parasternal short-axis plane is the best view to identify the number, mobility and thickening of the aortic cusps. A normal aortic valve has a "Y" pattern in diastole and a complete leaflet excursion in systole. It is crucial to explore in detail the hole cardiac cycle, because a bicuspid valve may appear normal in diastole but its typical "fish-mouth" opening can be observed in systole. In addition, the model of systolic opening serves to distinguish a raphe from a commissure. On parasternal long-axis plane (bidimensional and M-mode), a bicuspid valve usually has an eccentric diastolic line of coaptation, whereas a centered line is observed in normal aortic valves. A dome-shaped image secondary to limited excursion of the leaflets is often identified in stenosed aortic valves. The M-mode allows precise measurement of left ventricular function, enlargement and hypertrophy.

The valve area estimate is underused in the typical clinical practice in general. Jet velocity, defined as the antegrade systolic highest velocity across the narrowed aortic valve, is measured using continuous-wave Doppler ultrasound. Accurate data recording mandates multiple acoustic windows in order to determine the peak velocity. Apical and suprasternal or right parasternal most frequently yield the highest velocity. Subcostal or supraclavicular windows are rarely required. Careful patient positioning and adjustment of transducer position and angle are crucial as velocity measurement assumes a parallel intercept angle between the ultrasound beam and direction of blood flow (Baumgartner et al., 2009). Peak Doppler gradient (in mmHg) can be calculated by the modified Bernoulli´s equation: 4 x (jet velocity in m/s)^2. Mean transaortic Doppler pressure gradient is defined as the average difference in pressure between the left ventricle and the aorta during the entire systole. The mean transaortic gradient is easily measured with current echocardiography systems and provides useful information for clinical decision-making. It is calculated by averaging the instantaneous gradients over the ejection period, a function included in most clinical instrument measurement packages using the traced velocity curve. The acoustic windows used to measure the mean Doppler gradient are the same as those used in determining the jet velocity (Baumgartner et al., 2009). Table 1 shows the current classification of the various degrees of aortic stenosis based on the echocardiography.

	Mild stenosis	Moderate stenosis	Severe stenosis
Mean gradient	< 25 mmHg	25-40 mmHg	> 40 mmHg
Jet velocity	< 3 m/s	3-4 m/s	> 4 m/s

Table 1. Aortic stenosis degrees based on echocardiographic parameters in patients without left ventricular dysfunction. Current guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) (Bonow & ACC/AHA, 2008).

A special remark has to be done in reference to ultrasonographic findings of critical aortic stenosis. A small, poorly contracting left ventricle is often observed with varying degrees of endocardial fibroelastosis (seen as areas of increased echogenicity). Hypoplasia of the aortic annulus and the ascending aorta are other commonly associated features. Pulmonary

hypertension may develop secondary to left ventricular failure, causing right ventricular dilatation and tricuspid regurgitation. Finally, the severity of aortic stenosis stratification is not reliable when cardiac function is significantly altered in cases with critical stenosis.
Occasionally associated with aortic stenosis, valvar regurgitation plays a decisive role on clinical decision-making. Although echocardiographic criteria for aortic regurgitation have not been completely established for the pediatric population, some parameters (summarized in Table 2) have been proposed (Snider, 1997; Tribouilloy et al., 1991).

	Mild regurgitation	Moderate regurgitation	Severe regurgitation
Color jet ending	Proximal to the tip of the anterior mitral valve leaflet	Distal to the mitral valve	Distal to the mitral valve
Jet width	< 30%	> 30%	> 30%
Pressure half time	> 600 ms	< 600 ms	< 600 ms
End-diastolic retrograde flow in the descending aorta	< 20 cm/s	20-40 cm/s	> 40 cm/s
Other		Pandiastolic retrograde flow in the abdominal aorta, and dilated left ventricle.	Moderately to severely dilated left ventricle.

Table 2. Aortic regurgitation degrees according to echocardiographic parameters. Jet width refers to the regurgitant flow compared with the left ventricular outflow tract diameter.

ACC/AHA guidelines include: "Doppler echocardiography is recommended yearly in the asymptomatic adolescent or young adult with aortic stenosis who has a Doppler mean gradient greater than 30 mmHg or a peak velocity greater than 3.5 m/sec (peak gradient greater than 50 mmHg) and every 2 years if the Doppler gradient is less than or equal to 30 mmHg or the peak jet velocity is less than or equal to 3.5 m/sec (peak gradient less than or equal to 50 mmHg) *(Class I; Level of Evidence C)*" (Bonow & ACC/AHA, 2008).
Recently, three-dimensional echocardiography became more readily available, permitting "en face" views of intracardiac structures and volumetric measurements (Acar, 2006). In selected patients with valvar aortic stenosis, this emerging imaging technique can be helpful in assessing the morphology and number of leaflets, as well as the degree of fusion between the raphes. It may be useful in the differential diagnosis of valvar and subvalvar obstructions, especially in cases where an infravalvar membrane is very close to the valve and that had not been clearly defined by bidimensional echocardiography (Rubio et al., 2008).
Fetal echocardiography makes a detailed prenatal diagnosis of suspected or known congenital heart disease feasible allowing thus an improved counseling of families; guidance for timing and optimal location of delivery, identification of fetuses requiring specific early postnatal therapy (especially those with ductal dependent lesions such as critical left heart obstructive lesions), and prompt evaluation of genetic syndromes and analysis of the fetal karyotype. It can also serve to identify potential candidates for *in utero* cardiac interventions (Jone & Schowengerdt, 2009). Mild cases of aortic stenosis can be detected prenatally. It is suggested

that prenatal diagnosis of aortic valvar stenosis, and other congenital heart disease alike, is associated with improved postnatal outcome (Chang et al., 1991).

5.4 Cardiac catheterization

The indications of cardiac catheterization for pure diagnostic purposes are very limited nowadays. The catheterization performed at the hemodynamics laboratory with the patient sedated. Peak-to-peak transaortic gradient has been considered for several decades the gold-standard for grading the severity of aortic stenosis. As the aortic systolic pressure is higher and delayed compared to the ventricular pressure (the so-called "standing wave effect") (Lock, 1987), it is not recommended to compare pressures between left ventricle and a distal artery (such as a femoral artery) in order to avoid a gradient underestimation. Other parameters including degree of aortic regurgitation, cardiac output, left ventricular systolic function and aortic annulus diameter can be also determined during catheterization.

Diagnostic cardiac catheterization is currently recommended for adolescents and young adults, equally valid for children, in the following situations (Bonow & ACC/AHA, 2008):

Cardiac catheterization for the evaluation of aortic stenosis is an effective diagnostic tool in the asymptomatic adolescent or young adult when results of Doppler echocardiography are equivocal regarding severity of aortic stenosis or when there is a discrepancy between clinical and noninvasive findings regarding severity of aortic stenosis *(Class I; Level of Evidence C)*.

Cardiac catheterization is indicated in the adolescent or young adult with aortic stenosis who has symptoms of angina, syncope, or dyspnea on exertion if the Doppler mean gradient is greater than 30 mmHg or the peak velocity is greater than 3.5 m/sec (peak gradient greater than 50 mmHg) *(Class I; Level of Evidence C)*.

Cardiac catheterization is indicated in the asymptomatic adolescent or young adult with aortic stenosis who develops T-wave inversion at rest over the left precordium if the Doppler mean gradient is greater than 30 mmHg or the peak velocity is greater than 3,5 m/sec (peak gradient greater than 50 mmHg) *(Class I; Level of Evidence C)*.

Cardiac catheterization for the evaluation of aortic stenosis is a reasonable diagnostic tool in the asymptomatic adolescent or young adult who has a Doppler mean gradient greater than 40 mmHg or a peak velocity greater than 4 m/sec (peak gradient greater than 64 mmHg) *(Class IIa; Level of Evidence C)*.

Cardiac catheterization for the evaluation of aortic stenosis is reasonable in the adolescent or young adult who has a Doppler mean gradient greater than 30 mmHg or a peak velocity greater than 3.5 m/sec (peak gradient greater than 50 mmHg) if the patient is interested in athletic participation or becoming pregnant, or if the clinical findings and the Doppler echocardiographic findings are disparate *(Class IIa; Level of Evidence C)*.

5.5 Exercise testing

Exercise testing can be useful in borderline cases (e.g., in patients interested in engaging in vigorous physical activities), but should be avoided in symptomatic patients owing to a high risk of complications. Stress testing can identify a limited exercise capacity, abnormal blood pressure responses, exercise-induced symptoms or electrocardiographic changes (ST-segment depression or T-wave inversion). A significant obstruction may be present when

any of these abnormalities is identified. ACC/AHA guidelines refer to exercise testing as follows: "Graded exercise testing is a reasonable diagnostic evaluation in the adolescent or young adult with aortic stenosis who has a Doppler mean gradient greater than 30 mmHg or a peak velocity greater than 3.5 m/sec (peak gradient greater than 50 mmHg) if the patient is interested in athletic participation, or if the clinical findings and Doppler findings are disparate *(Class IIa; Level of Evidence C)"* (Bonow & ACC/AHA, 2008).

5.6 Holter monitor

The prevalence of serious ventricular arrhythmias (multiform premature ventricular contractions, ventricular couplets and ventricular tachycardia) is increased in patients with aortic stenosis. When the invasive peak-to-peak gradient is over 50 mmHg there is a higher incidence of sudden death (Keane et al., 1993; Wolfe et al., 1993). Considering that a clear consensus is well stated for the clinical decision-making of mild and severe cases (medical follow-up and intervention, respectively), Holter monitoring may be a useful tool in those patients with a moderate degree of aortic stenosis, but evidence based data is unavailable.

5.7 Magnetic resonance

Cardiovascular magnetic resonance has emerged as an alternative noninvasive imaging without ionizing radiation, particularly useful in patients with poor acoustic windows. It provides precise images of valve anatomy and allows quantitative evaluation of stenosis and regurgitation (Cawley at al., 2009). Delayed myocardial enhancement magnetic resonance can serve to delineate the location and transmural extent of endocardial fibroelastosis in infants, thus providing an accurate roadmap for the surgical planning of fibroelastosis resection and for monitoring the results (Tworetzky et al., 2005). Magnetic resonance is also proposed to aid fetal ultrasonography in the prenatal assessment of congenital cardiac malformations (Manganaro et al., 2008).

6. Natural course

Critical aortic stenosis produces severe congestive heart failure and shock in fetuses, neonates and infants. It usually leads to death within hours or days if left untreated. Before the era of surgery, it was estimated that aortic valvar stenosis presenting within the first year of life carried a mortality rate of 23% (Campbell, 1968). In a necropsy series of 26 children with aortic stenosis under 15 years old, 43% died within the first month of life and 77% within the first year (Samánek et al., 1988). Beyond these ages, children with untreated severe aortic stenosis seldom live more than 5 years from the time of diagnosis, similar to life expectancy reported in adults (Kitchiner et al., 1993; Wagner et al., 1977). The survival of patients with mild obstruction is slightly lower than that of the general population, probably related to sporadic deceases secondary to infective endocarditis or to unexpected quick incremental severity (Keane et al., 1993; Kitchiner et al., 1993). In patients with moderate obstruction who receive no treatment, the reported survival rate is 72.2% at 5 years and 45.6% at 20 years (Kitchiner et al., 1993).

The report from the Natural History Study of Congenital Heart Defects which included 462 patients with aortic stenosis (60% between 2-11 years and 24% between 11-21 years at initial evaluation), observed that the obstruction tends to increase over time, especially in cases with higher gradients on enrolment. Whereas only 20% of those patients with initial peak-

to-peak transaortic gradient lower than 25 mmHg at initial catheterization required a cardiac intervention during 25 years of follow-up, children with baseline peak-to-peak transaortic gradient over 50 mmHg were at risk for serious cardiovascular events, including arrhythmias, endocarditis and sudden death, at a rate of 1.2% per year (Keane et al., 1993; Kitchiner et al., 1993). The rate of aortic stenosis progression is highly variable and appears to be age related. It is fast in infants, moderate in children and slow in adolescents; probably related to the inability of the valve orifice to increase in proportion to somatic growth (el-Said et al., 1972). In line with this assumption, a study in which 129 children with aortic stenosis were followed periodically with serial echocardiograms, showed that 89% of children under 2 years old and 61% of children over 2 years old experimented progression of the obstruction (Kiraly et al., 2003). Although significant and progressive aortic regurgitation is commonly acquired after surgery or percutaneous balloon valvuloplasty, it can also occur in patients with untreated aortic stenosis (Keane et al., 1993).

Sudden death, with an average incidence of 0.3% per year (Keane et al., 1993), occurs almost exclusively in patients with a peak Doppler gradient higher than 50 mmHg even in the absence of symptoms (Keane et al., 1993; Otto et al., 1997). About half of these fatal events occur during or immediately after exercise (Lambert et al., 1974). Bacterial endocarditis occurs in 1-4% of patients with untreated aortic stenosis (18-31 per 10000 patient-years) (Campbell, 1968; Gersony et al., 1993; Hossack et al., 1980). The risk is present in mild cases, with higher incidence in patients with more severe stenosis. Aortic regurgitation does not seem to increase the risk of developing bacterial endocarditis however (Gersony et al., 1993).

Clinical presentation of patients with bicuspid aortic valve varies from severe valve disease in infancy to asymptomatic valve or thoracic aorta disease in the older child, but symptoms usually develop in adulthood (Siu & Silversides, 2010). Although aortic stenosis can be present in children secondarily to a small valve orifice, the valve usually has none or mild degree of obstruction in childhood and experience a progressive worsening over time because of sclerosis and calcification (Chui et al., 2001). High levels of serum cholesterol have been associated with an acceleration of the sclerosing process of the bicuspid valve (Chui et al., 2001). A study performed on adult patients with bicuspid aortic valves showed a median increase of 0.7 mmHg per year in peak Doppler gradient (Tzemos et al., 2008). Pure aortic incompetence due to a prolapsed leaflet may occur in childhood but is more likely to develop and progress later in time; nevertheless, this remains an infrequent cause of intervention requirement even in adults. Aortic root dilatation has been documented in childhood, suggesting that this process begins early in life (Beroukhim et al., 2006; Gurvitz et al., 2004). Its progression is more likely in children with a larger aorta at baseline, but it is extremely rare to necessitate intervention before adulthood (Holmes et al., 2007).

7. Management

Balloon aortic valvoplasty constitutes the therapeutic procedure of choice in most centers for the treatment of congenital aortic stenosis (Khalid et al., 2006). Other interventional options, including both surgical and hybrid techniques and also fetal intervention are also discussed.

7.1 Balloon aortic valvoplasty

Balloon aortic valvoplasty, first described in the early 1980s, is a widely used technique in the treatment of valvar aortic stenosis in children (Lababidi, 1983; Lababidi et al., 1984). The

technique is performed under deep sedation, with the exception of the neonates and the critically ill patients. Vascular access is usually obtained with a retrograde approach using the femoral artery. In neonates and small infants, other sites of access have been used in order to avoid the risk of femoral arterial compromise (Weber, 2006). These include:

The umbilical artery route was initially advocated as a way to avoid femoral artery injury in view of the large diameter balloon dilatation catheters that were available at the time (Beekman et al., 1991). Although technically feasible, it may be difficult to traverse the tortuous umbilical-iliac artery system, may introduce bacteria from the umbilicus and may cause excessive loss of blood during wire and catheter exchanges.

The right scapular artery was reported to be safe and effective in infants with critical aortic valve stenosis (Alekyan et al., 1995). It typically requires surgical exposure of the artery and is contraindicated in the presence of an aberrant right subclavian artery.

The anterograde transvenous approach may be performed via the *foramen ovale* or by a transeptal puncture when the atrial septum is intact (Hausdorf et al., 1993). This procedure spares the femoral arteries for potential future use but may be technically challenging and may cause mitral valve damage.

The right carotid artery was firstly used based on the extensive experience with carotid artery cannulation for extracorporeal membrane oxigenation in newborns (Fischer et al., 1990). it is reported to be effective and safe, and it allows performing the entire procedure at the bedside with the aid of continuous transesophageal echocardiographic guidance, thus avoiding the use of fluoroscopy (Weber et al., 2000). Its disadvantages include the risk of carotid artery injury with potential neurologic complications and the need of surgical exposure.

Above all, the retrograde femoral arterial approach remains the most commonly used. The potential associated complications have been significantly reduced with the availability of low profile diameter balloons. Once the vascular access is assured, the aortic annulus diameter and the degree of aortic regurgitation are determined, a complete right and left cardiac catheterization is performed and the peak-to-peak transaortic gradient is determined from simultaneous or sequential measurements of left ventricular and ascending aorta pressures.

Balloon aortic valvoplasty is contraindicated when an aortic regurgitation of moderate or higher degree is present, and it is not recommended if the valve is significantly calcified. It is performed in cases of critical aortic stenosis with variable institutional preferences. Recommendations for aortic balloon valvoplasty in adolescents and young adults, which may be applied to children, are the following (Bonow & ACC/AHA, 2008):

Aortic balloon valvotomy is indicated in the adolescent or young adult patient with aortic stenosis who has symptoms of angina, syncope, or dyspnea on exertion and a catheterization peak LV–to–peak aortic gradient greater than or equal to 50 mmHg without a heavily calcified valve *(Class I; Level of Evidence C)*.

Aortic balloon valvotomy is indicated for the asymptomatic adolescent or young adult patient with aortic stenosis who has a catheterization peak LV–to–peak aortic gradient greater than 60 mmHg *(Class I; Level of Evidence C)*.

Aortic balloon valvotomy is indicated in the asymptomatic adolescent or young adult patient with aortic stenosis who develops ST or T-wave changes over the left precordium on ECG at rest or with exercise and who has a catheterization peak LV–to–aortic gradient greater than 50 mmHg *(Class I; Level of Evidence C)*.

Aortic balloon valvotomy is reasonable in the asymptomatic adolescent or young adult patient with aortic stenosis when catheterization peak LV–to–peak aortic gradient is greater

than 50 mmHg and the patient wants to play competitive sports or desires to become pregnant *(Class IIa; Level of Evidence C)*.

In the adolescent or young adult patient with aortic stenosis, aortic balloon valvotomy is probably recommended over valve surgery when balloon valvotomy is possible. Patients should be referred to a center with expertise in balloon valvotomy *(Class IIa; Level of Evidence C)*.

Aortic balloon valvotomy should not be performed when the asymptomatic adolescent or young adult patient with aortic stenosis has a catheterization peak LV–to–peak aortic gradient less than 40 mmHg without symptoms or ECG changes *(Class III; Level of Evidence C)*.

The recommended size of the balloon for the valvoplasty is 80-90% of the measured aortic annulus; smaller ones may not be able to accurately relief the obstruction. If the reduction in gradient is below 50% or the residual gradient is higher than 50 mmHg and the degree of insufficiency remains less than moderate, sequential progressive dilatations using larger balloons may be performed, but the size of the balloon may not exceed 120% of the diameter of the valvar ring in order to avoid iatrogenic regurgitation (McCrindle et al., 1996; Phillips et al., 1987; Sholler et al., 1988). The balloon is carefully positioned across the aortic valve and then inflated until the waist produced by the valve on the balloon disappears. This technique can be performed by using one balloon, or two for large diameter valves. In the double-balloon valvoplasty, two separate arterial catheters are used to cross the aortic valve. The typical flattening of the balloons against each other during inflation mandates a higher ratio of the sum of the balloons nominal diameters to valve annulus to around 130% (both with similar diameter and length); the two balloons are positioned across the valve and inflated simultaneously. The results in terms of gradient relief and degree of iatrogenic aortic regurgitation are similar when compared to the single-balloon procedure, with the additional advantages to reduce vessel trauma and to avoid the complete obstruction of the left ventricular outflow tract as would occur during inflation of a single large balloon (Beekman et al., 1988; Mullins et al., 1987). The rapid movements of the inflated balloon up and down at the left ventricular outflow tract during valvoplasty, is thought to favor aortic insufficiency (Daehnert et al., 2004). Hence, different maneuvers such as the use of more rigid wires, induced asystole with adenosine or ventricular fibrillation have been employed aiming to improve balloon stability (Kahn et al., 1998, 2000). Rapid ventricular pacing, is an alternative effective and safe way to stabilize the balloon. It consists on electrically stimulating the right ventricle rapidly to accelerate the ventricular frequency until a 50% systolic aortic pressure drop is achieved, and inflating the balloon at this point (David et al., 2007). An effective relief of the obstruction is usually achieved by the valvoplasty, with a 50-70% reduction of the pressure gradient in children with isolated aortic stenosis and in those with associated cardiovascular lesions (Crespo et al., 2009; Gatzoulis et al., 1995; Kusa et al., 2004; McCrindle et al., 1996; Rao et al., 1989). Independent risk factors for suboptimal gradient reduction are high pre-valvoplasty transaortic gradient, children aged less than a month or more than 14 years, high pre-procedural left ventricle end diastolic pressure, the use of a balloon to annulus ratio less than 0.9, and fused bicuspid valve as opposed to pure bicuspid valve (Crespo et al., 2009; Kusa et al., 2004; McCrindle et al., 1996). Repeated balloon dilatation, and valvoplasty for residual stenosis after surgical valvotomy seem to be efficient (Crespo et al., 2009; Meliones et al., 1989; Phillips et al., 1987; Shim et al., 1997; Sholler et al., 1988). Valvoplasty may cause aortic regurgitation as the result of commissural avulsion, cusp dehiscence and or tear perforation. This iatrogenic regurgitation, which was described to be associated with fused bicuspid valves (Reich et al., 2004), has been proven to be related to oversized balloons which

lead to improve practice and guidelines, therefore high degrees of immediate post procedural insufficiency became uncommon (McCrindle et al., 1996; Phillips et al., 1987; Sholler et al., 1988). The rate of at least moderate aortic regurgitation shortly after the procedure is between 7.3-22.6% and may progress afterwards (Crespo et al., 2009; Fratz et al., 2008; McCrindle et al., 1996; McElhinney et al., 2005; Reich et al., 2004). Iatrogenic aortic insufficiency, severe hypotension, ventricular arrhythmias, vessel damage, complete atrioventricular block, cardiac tamponade and mitral valve injury are the main serious procedural related complications. In a large multi-institutional series of 630 balloon dilatations which did not exclude children with associated cardiovascular anomalies major complications occured in 7.1%, significantly more frequent in newborns (McCrindle et al., 1996). Mortality attributable to the valvoplasty varies between 0 and 2.1%, again with a clearly higher incidence during the neonatal period (Kusa et al., 2004; McCrindle et al., 1996; Crespo et al., 2009; Moore et al., 1996). Both progressive worsening of aortic regurgitation and an increase in residual transvalvar gradient seem to be inevitable. Aortic inssuficiency of at least moderate grade varies between 22.3% and 35% after 5 to 5.3 years (McElhinney et al., 2005; Reich et al., 2004) and is about 50% at 7.5 years follow-up interval (Pedra et al., 2003). The increase in residual transvalvar gradient, or restenosis, varies between 0% and 32.1% according to different definitions of residual gradients used by different investigators (Balmer et al., 2004; Rao et al., 1989; Reich et al., 2004). In a very recent series, including both neonates and older children, 10% of the patients needed reintervention in the long term due to restenosis (Fratz et al., 2008). The survival rate after valvoplasty at 6 and 14.4 years varies between 93% and 100% in older children (Fratz et al., 2008; Galal et al., 1997; Moore et al., 1996; Reich et al., 2004), whereas it varies between 71–74.6% (Fratz et al., 2008; McElhinney et al., 2005) and 71% (Reich et al., 2004) at 10 and 14.4 years respectively when performed in the neonatal period. The freedom from reintervention at mid and long-term follow up varies between 46 and 76% (Fratz et al., 2008; Galal et al., 1997; Moore et al., 1996; Rao, 1999; Reich et al., 2004) after 8–14.4 years in older children, whereas it varies between 47–57.6% (Fratz et al., 2008; McElhinney et al., 2005; Villalba et al., 2002) and 26% (Reich et al., 2004) at 5–10 years and 14.4 years respectively when performed in the neonatal period. A significant decrease in dispersion of the ventricular repolarisation is reported following valvoplasty in patients with severe congenital aortic stenosis, which would theoretically diminish the electrical instability, preventing ventricular arrhythmias later on in life (Sarubbi et al., 2004). In conclusion, balloon valvoplasty is a safe an effective method for the treatment of congenital aortic valve stenosis, constituting the therapeutic procedure of choice in most centers.

7.2 Fetal intervention

Congenital heart disease constitutes the most frequent congenital anomaly and the main cause of death among infants in the United States, thus it is an attractive target for prenatal diagnosis and therapy (Turner et al., 2009). In the case of critical aortic stenosis, early *in utero* relief of the obstruction is thought to reverse the progression toward left ventricular hypoplasia (De Oliveira et al., 2004; Tweddell et al., 2002). As hypoplastic left heart syndrome is one of the most severe congenital heart defects that requires multi-staged palliative surgery or even heart transplantation, severe aortic valve stenosis is the defect for which fetal intervention is most likely to be considered (Brown et al., 2003; McCrindle et al., 2001; McElhinney et al., 2005). The aim of fetal aortic valvuloplasty is to relief the left obstruction of the ventricle outlet to prevent progression to endocardial

fibroelastosis and ventricle hypoplasia. Some echocardiographic features found in midgestation fetuses with aortic stenosis and normal left ventricle length including retrograde flow in the transverse arch, left-to-right flow across the *foramen ovale*, monophasic mitral inflow and left ventricular dysfunction have been reported to predict progression to hypoplastic left heart syndrome (Makikallio et al., 2006). Fetal aortic valvuloplasty must be performed in the early second trimester. The procedure can be performed by laparotomy to expose the uterus or by uterine incision and fetal exposure. These invasive techniques offer better ultrasound imaging quality and shorter distance to the fetal heart, but they carry the risk of increased maternal morbidity and premature delivery. For these reasons less invasive techniques are preferred. Under bidimensional ultrasound guidance, a 19G cannula and stylet needle are advanced through the maternal abdomen, uterine wall and fetal chest wall, accessing the fetal heart by the left ventricle. The valvoplasty is performed with a small coronary artery balloon over a thin, floppy guide wire. The balloon is inflated and the procedure is considered successful if there is clear evidence of increased anterograde flow across the valve and/or new aortic regurgitation by color-Doppler (Marshall et al., 2005; McElhinney et al., 2009; Wilkins-Haug et al., 2006). Complications of valvoplasty in the fetus include bradycardia (50% upon needle access to the ventricle), pericardial effusion, significant iatrogenic aortic regurgitation and fetal demise. Boston Children´s Hospital has the largest experience with the technique (McElhinney et al., 2009): 70 interventions were attempted in fetuses expected to progress to hypoplastic left heart syndrome without intervention; 52 procedures were considered successful (74%); hemodynamic changes (bradycardia and ventricular dysfunction) treated with intramuscular and/or intracardiac medications and/or hemopericardium for which drainage was attempted occurred in 28 fetuses (40%) (Mizrahi-Arnaud et al., 2007); moderate or severe aortic regurgitation was noted in 20 fetuses (38%), resolved or improved to mild regurgitation in all but 1 case. In the Boston series, 1 pregnancy was terminated and 8 others (13% total) ended in fetal death or preterm stillbirth. The rate of growth of the left cardiac structures was greater among fetuses that underwent successful intervention. Finally, 20 of the 70 patients (29%) achieved the ultimate goal of biventricular circulation.

In conclusion, fetal aortic valvoplasty may be useful in fetuses with aortic stenosis. The potential benefits of the procedure must be weighted against the inherent serious risks. Based on the current knowledge, fetal aortic valvoplasty should not be performed in fetuses with aortic stenosis that will not otherwise progress to hypoplastic left heart syndrome.

7.3 Surgery

Two opposed clinical situations have to be considered when referring to surgical procedures in aortic stenosis. The single-ventricle end of the spectrum is characterized by a severe degree of underdevelopment of the left heart-aorta complex, resulting in obstruction to the systemic cardiac output and the inability of the left heart to support the systemic circulation. The two-ventricle end of the spectrum is characterized by a normal or moderately underdeveloped left heart-aorta complex, able to fully support the systemic circulation.

7.3.1 Two-ventricle repair

Surgical valvotomy is of historic interest and is rarely used as first attempt in children. When balloon aortic valvoplasty is ineffective or significant aortic regurgitation is present, valve repair or replacement may be necessary (Bonow & ACC/AHA, 2008).

7.3.1.1 Valvotomy

Open valvotomy with cardiopulmonary bypass, firstly described in 1958 (Spencer et al., 1958), has remained the main therapeutic option for congenital aortic stenosis in neonates and infants until the advent of balloon valvoplasty in the early 1980s. It offers the advantage of a detailed examination of the valve and accurate valvotomy, in opposition to the blind dilatation of the balloon procedure. Its main disadvantages are the morbidity and mortality related to the surgery and the cardiopulmonary bypass, and an increase in the complexity of a future surgery due to redo sternotomy. The operation is performed on cardiopulmonary bypass with mild hypotermia, through median sternotomy (Hraska et al., 2007). The anterior part of the aortic root is dissected to identify the origin of the right coronary artery, and the aorta is incised 5-10 mm above the origin of the coronary artery. Holding sutures are placed on the edges of the aortotomy and the aortic valve is carefully examined. Finally, the fused commissures are carefully divided, ensuring that the leaflets are well supported and not liable to prolapse. Other techniques such as closed transventricular valvotomy have been also used for the initial management of critical neonatal aortic stenosis in some centers (Brown et al., 2006). Both the reduction of the transaortic gradient (53-67%) and the creation of significant aortic regurgitation (8-21%) after the surgical valvotomy are similar to those described for the valvoplasty technique (Alexiou et al., 2001; Brown et al., 2003; Miyamoto et al., 2006; Zafra et al., 1993). Early mortality after neonatal surgical aortic valvotomy was very high in the early experience but was significantly reduced in subsequent publications, with rates varying between 2.1% and 18% (Alexiou et al., 2001; Bhabra et al., 2003; Brown et al., 2003; Gildein et al., 1996; Hawkins et al., 1998; Miyamoto et al., 2006; Zain et al., 2006). Several risk factors for increased operative mortality include endocardial fibroelastosis, hypoplastic left ventricle, hypoplastic aortic annulus, associated cardiovascular anomalies, extremely small neonates, earlier era surgery, monocuspid aortic valve and impaired left ventricular function (Bhabra et al., 2003; Brown et al., 2006; Hawkins et al., 1998; Miyamoto et al., 2006). Similarly to what happens after balloon dilatation, progressive worsening of aortic insufficiency and re-stenosis occurs at long-term follow up after surgical valvotomy. The freedom from reintervention is 80-85% after 5-7 years (Brown et al., 2006; Cobanoglu & Dobbs, 1996; Miyamoto et al., 2006), 55-78% after 10 years (Alexiou et al., 2001; Brown et al., 2006; Hawkins et al., 1998; Miyamoto et al., 2006) and 53-65% after 15-20 years (Brown et al., 2006; Miyamoto et al., 2006). Long-term survival rate is 74-100% at 5-10 years (Alexiou et al., 2001; Bhabra et al., 2003; Brown et al., 2003; Cowley et al., 2001; Gaynor et al., 1995; Hawkins et al., 1998) and 84-88% at 15-20 years (Brown et al., 2003; Gaynor et al., 1995). A retrospective review of infants undergoing primary surgical aortic valvotomy showed better long-term outcomes (in terms of survival and freedom from reintervention) when surgery resulted in trileaflet rather than bileaflet anatomy (Bhabra et al., 2003).

7.3.1.2 Repair procedures

When the aortic stenosis coexists with a severe degree of valvar incompetence both primarily or after a first approach by either balloon dilatation or surgical valvotomy, some authors have proposed reconstructive techniques such as reattachment of an avulsed cusp to the aortic annulus, relief of commissural fusion and debridement of thickened cusps instead of valvar replacement (Alsoufi et al. 2006; Bacha et al., 2001; Hawkins et al., 1996; Odim et al., 2005; Polimenakos et al., 2010; Schäfers et al.; 2008). Bicuspidisation procedure, whose principles are elevation of the comissure and augmentation of the cusps, has been advocated for unicuspid aortic valves (Schäfers et al.; 2008). This conversion into bicuspid anatomy has

been reported to have no mortality, good functional results and appropriate freedom from reintervention (67%) and from valve replacement (100%) at 4 years. Other non replacement strategy is aortic cusp extension valvuloplasty with selective use of tricuspidization (Polimenakos et al., 2010). Pericardial cusp extension counteracts the valve's inherent sinuses of Valsalva shallowness, reestablishes normal depth of the sinuses, secures adequate and longer coaptation surface and restores the normal "crownlike" appearance of the valve; while tricuspidization ensures a larger central opening and minimizes turbulence. This technique has been proven to effectively reduce aortic insufficiency and regurgitation, and to improve left ventricular wall thickness and dimensions in infants and children. Its long-term outcomes at 1, 5 and 10 years are 97, 71 and 51% free from moderate or greater aortic regurgitation; 97, 67 and 54% free from moderate or greater aortic stenosis; and 97, 71 and 56% free from aortic valve replacement.

7.3.1.3 Aortic valve replacement

7.3.1.3.1 Ross operation

The Ross operation was firstly described in 1967 (Ross, 1967). It was initially considered too complex by the surgical community and was relegated to single curiosity until 1988, when its long-term results were reported (Ross, 1988). The Ross procedure consists on aortic valve replacement with a pulmonary autograft. During the operation, the pulmonary native valve was substituted by a homograft in the first series, or alternatively by a valved conduit in subsequent practice constituted by a gluterhaldeheyde preserved bovine jugular vein. When the left ventricular outflow tract is enlarged during the procedure, then the surgery is denominated Ross-Konno (Reddy et al., 1996). The Ross operation appeared to be the panacea of aortic valve replacements for growing infants and children due to the excellent hemodynamic performance and growing capacity of the autograft, the long-term expected durability of the homograft and a very low thrombogenecity which makes anticoagulant therapy unnecessary (Elkins, 1999; Oury, 1996), but some patients did require reoperations because of autograft or homograft failure and progressive dilatation of the neo-aortic root. New improvements were applied to prevent neoaortic root dilatation and autograft regurgitation using graft inclusion techniques. A Ross operation may be considered whenever replacement of the aortic valve is indicated, especially in the youngest patients. Moreover, it is contraindicated in case of primary or iatrogenic lesions of the pulmonary valve for obvious reasons, in Marfan syndrome and in autoimmune tissue diseases (Corno et al., 2001). Early mortality is 1-2.5% (Brown et al., 2009; Kouchoukos et al., 2004; Oury et al., 1998) with a 10-15-year survival rate of 96-98% (Brown et al., 2009; Kouchoukos et al., 2004), observing significantly better outcomes for children older than 1 year of age compared to children under 1 year (Brown et al., 2009). In a large series with infants, children and adults, overall freedom from reoperation was 91% at 15 years (Brown et al., 2009). In a study on older children and young adults, event-free survival (freedom from death, reoperation, thromboembolism and endocarditis) was 93% at 5 years, 78% at 7 years, and 73% at 10 years postoperatively (Kouchoukos et al., 2004). A recent series of 27 infants less than 18 months of age who underwent the Ross procedure showed 3 early and no late deaths, and freedom for reintervention of 87% at 8 years (Williams et al., 2005).

7.3.1.3.2 Mechanical valve replacement

The selection of the most appropriate substitute in children with irreparable aortic valve lesion remains controversial. The first mechanical model was the caged-ball mechanical prosthesis,

used in the 1960s and early 1970s. The xenograft valve was introduced in the early to mid-1970s and was initially considered better suited for children, but unfortunately these valves demonstrated early failure (Robbins et al., 1988). The new generation mechanical valves exhibit minimal structural degeneration, but continue to be prone to valve-related complications. Mechanical prosthetic valves carry the risks of thromboembolism, requiring anticoagulation. The use of these valves also faces the need of iterative replacement because of the valve outgrowth in the growing young patient. Nevertheless, its safety and reproducible implantation technique, good hemodynamic performance, low incidence of valve-related events, acceptable short and long-term outcomes and prolonged durability, convert it into a good alternative in cases where aortic valve replacement is mandatory (Alexiou et al., 2000). The longevity of mechanical prostheses is superior compared to bioprosthetic valves, but its implantation has been associated with very high early re-intervention rate and poor survival in neonates and small infants, limiting its use in these ages (Karamlou et al., 2005). Aortic valve replacement using mechanical prosthetic valves in children often requires annular enlargement to insert commercially available prostheses. This enlargement can be performed by different techniques: the Konno procedure involves incision of the ventricular septum, which might cause ventricular dysfunction, atrioventricular conduction block or arrhythmias; the Manouguian procedure with extension of the incision to the anterior mitral leaflet might cause mitral inssufficiency; and Yamaguchi procedure with an anterior incision in the aortic annulus is directed into the commissure between the right and left coronary cusps continued downward across the aortic ring to near full thickness of the right ventricular wall, is nowadays the technique of choice because it does not damage the ventricular septum or the mitral valve (Masuda et al., 2008). Operative death rate varies between 0-5% in several series (Alexiou et al., 2000; Karamlou et al., 2005; Masuda et al., 2008; Mazzitelli et al., 1998; Popov et al., 2009; Turrentine et al., 2001), mostly involving children with severe preoperative pulmonary hypertension or myocardial dysfunction. Although previous series showed worse outcomes, more recent studies report actuarial survival of 89-95% at 10 years (Alexiou et al., 2000; Turrentine et al., 2001), 87-92% at 15 years (Masuda et al., 2008) and 85% at 20 years (Alexiou et al., 2000). Freedom from surgical re-intervention ranges between 80-92% at 10 years (Alexiou et al., 2000; Champsaur et al., 1997; Mazzitelli et al., 1998; Turrentine et al., 2001), 85-86% at 15 years (Alexiou et al., 2000; Turrentine et al., 2001) and 54-86% at 20 years (Alexiou et al., 2000; Mazzitelli et al., 1998). A very recent series from Japan of 45 children with a median follow-up of 9.2 years showed excellent outcomes, with an actuarial freedom from reoperation of 94% at 15 years (Masuda et al., 2008). This publication also noted that 40 of the 42 (95%) survivors had a peak Doppler gradient less than 3 m/s at the latest evaluation. This finding endorses the previous report of 44 of the 50 (88%) survivors being in NYHA class I with a mean Doppler gradient across the aortic prosthesis of 17.9 mmHg at last follow-up (mean follow-up of 7.7 years) (Alexiou et al., 2000), thus highlighting the importance of the functional status and the hemodynamic performance. Some authors have observed a correlation among transprosthetic flow velocity and manufactured valve area, suggesting that implantation of mechanical valves of 19 mm or larger may not require further re-replacement (Masuda et al., 2008; Shanmugan et al., 2005). This is obviously a clear limitation for the low spectrum of the pediatric age group.

7.3.2 Single-ventricle repair

The single ventricle end of the spectrum is characterized by a severe degree of underdevelopment of the left heart-aorta complex, with a resulting inability of the left heart

to support the systemic circulation. The hypoplasia of the left cardiac structures makes a biventricular approach unfeasible, which lead to the complex medical surgical management with a single ventricle multistage palliation and heart transplantation in specific situations.

7.3.2.1 Staged surgical palliation

The goal of staged reconstruction is creating separate pulmonary and systemic circulations supported by a single (right) ventricle. The Norwood procedure is usually the initial palliative procedure in the newborn, followed by a hemi-Fontan or bidirectional Glenn anastomosis (bidirectional cavopulmonary shunt) at 4-6 months and by a modified Fontan procedure (total cavopulmonary connection) at 2-4 years of age (Ashburn et al., 2003; Barron et al., 2009; Bove et al., 2004).

The Norwood procedure (Norwood et al., 1983) consists on atrial septectomy, reconstruction of the aortic arch to remove associated hypoplasia or coarctation, connection of the main pulmonary artery into this reconstructed arch and placement of a small shunt between the systemic and the pulmonary circulations achieved either by a Blalock-Taussig or by a Gore-tex shunt (the classical Norwood operation) or by a right ventricular to pulmonary artery conduit (the Norwood procedure with the Sano modification) (Sano et al., 2004). The Sano modification typically eliminates the diastolic runoff into the pulmonary circulation with subsequent coronary steal and potential risk of sudden death, with the limiting factor of limited pulmonary artery growth requiring performing the bidirectional cavopulmonary shunt earlier than what is required following the classical Norwood procedure. Early mortality of the first stage of palliation was very high (30-35%) in the first series but has dramatically improved, with current early survival of 80-90% (McGuirk et al., 2006; Stasik et al., 2006; Tweddell et al., 2002). Several operative risk factors have been identified including late initial presentation, prematurity, low birthweight (less than 3 kg), associated genetic anomalies, an ascending aorta smaller than 2 mm, intact or restrictive atrial septum, moderate or severe tricuspid regurgitation and pre-existing ventricular dysfunction (Ashburn et al., 2003; Azakie et al., 2001; Stasik et al., 2006; Tweddell et al., 2002). Although the Norwood operation remains one of the highest risk procedures in pediatric cardiac surgery, the second and third stages are much less hazardous, with 1-6% of early mortality (Gentles et al., 1997; Hirsch et al., 2008). Considering both peri-procedural and interstage mortality, actuarial survival after a Norwood procedure is 58-66% at 1 year (Ashburn et al., 2003; McGuirk et al., 2006; Tweddell et al., 2002), 40-61% at 5 years (Ashburn et al., 2003; Azakie et al., 2001; McGuirk et al., 2006; Tweddell et al., 2002) and 50% at 10 years (McGuirk et al., 2006). Long-term and functional outcome data following the staged univentricular palliation is being evaluated, with the expectation that these ventricles are likely to fail, on the basis of observations of other situations in which the right ventricle supports the systemic circulation, such as congenitally corrected transposition (Barron et al., 2009).

7.3.2.2 Cardiac transplantation

The concept of transplantation as a treatment for hypoplastic left heart syndrome developed together with the palliative approach of the Norwood procedure. Data from several centers show an 11-14% early mortality following the procedure (Chrisant et al., 2005; Razzouk et al., 1996), with a post-transplant actuarial survival of 84% (Razzouk et al., 1996), 72-76% (Chrisant et al., 2005; Razzouk et al., 1996) and 70% (Razzouk et al., 1996) at 1, 5 and 7 years, respectively. Innovations in peri-transplant management such as the development of new immunosuppressive strategies and the realization that ABO incompatibility is possible in

neonatal transplantation because the immune response is not mature, have contributed to significantly improve its outcomes. Unfortunately, 20-25% of the patients die while awaiting for suitable donors (Jenkins et al., 2000; Razzouk et al., 1996), decreasing the rate of actuarial survival to 54-55% at 5 years when also accounting for these deaths (Chrisant et al., 2005; Jenkins et al., 2000). Although the benefit of a biventricular physiology produces better quality of life in children who receive a successful transplant compared with age-matched palliative-staged patients, major disadvantages of cardiac transplantation include high mortality on the waiting list as well as the immunosuppressant side-effects and morbidities. Some authors have suggested that cardiac transplantation may be offered to those patients at higher risk in staged surgery (Jenkins et al., 2000).

7.3.2.3 The hybrid procedure

The hybrid procedure has recently emerged as an innovative alternative to the Norwood operation (Akintuerk et al., 2002). This technique offers the advantage of avoiding cardiopulmonary bypass, cardioplegic arrest and circulatory arrest in the neonatal period. As infants are thought to be less vulnerable to postoperative myocardial and neurologic injury than neonates, this strategy may be associated with improved neurodevelopmental and functional outcomes (Akintuerk et al., 2002; Bacha & Hijazi, 2005; Galantowicz & Cheatham, 2005). The hybrid procedure, which involves both surgeons and interventional cardiologists, consists on placing bilateral pulmonary bands to limit flow to the lungs, implanting a stent in the *ductus arteriosus* and performing a balloon atrial septostomy (occasionally placing a stent). It is performed through a standard sternotomy but does not require cardiopulmonary bypass. The second step of the staged palliation is carried out as usual at 4-6 months. It will include both cavopulmonary shunt and aortic arch reconstruction, typically without full circulatory arrest to the brain. It has been advocated that it may have an overall survival advantage due to the fact that an in-series circulation (hybrid procedure) is more stable than a balanced circulation (Norwood procedure), and it might also have a role in stabilizing patients awaiting suitable cardiac donors (Bacha et al., 2006). On the other hand, complications such as stent migration and stent occlusion may occur, and the second stage of the palliation may be more extensive and complex thus carrying increased operative mortality. Finally, no consensus exists on the future of the hybrid approach. The potential benefits it offers may be weighted against the risks it carries.

7.4 Percutaneous aortic valve replacement

Percutaneous valve replacement is being developed. Although semilunar valve replacement has been successfully performed in adults for the aortic position and also in children for the pulmonary valve position, an aortic replacement during childhood seems to be more challenging technically due to sheath size, coronary artery blockage and potential mitral valve injury (Schneider et al., 2004). Anyway, percutaneous valve implantation is currently in development and may have a role on selected pediatric patients in the future.

7.5 Physical activity

Physical activity is not restricted in asymptomatic patients with mild aortic stenosis; these patients can participate in competitive sports. Patients with severe aortic stenosis should be restricted from all competitive athletic sports, while those with moderate aortic stenosis should avoid competitive sports that involve high dynamic and static muscular demands.

Other forms of exercise can be performed safely, but it is advisable to evaluate such patients with an exercise test before they begin an exercise or athletic program. Patients with treated aortic stenosis are restricted from competitive sports on the basis of subsequent residual gradients after intervention by the same criteria (Bonow et al., 2005).

7.6 Endocarditis prophylaxis

Endocarditis prophylaxis for the prevention of infective endocarditis was recommended in the past for any degree of valvar aortic stenosis and even in patients with normal functioning bicuspid aortic valve. Antibiotic prophylaxis is no longer indicated in these patients. This new guideline emphasizes that maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure. ACC/AHA recommendations are outlined in table 3 (Nishimura & ACC/AHA, 2008).

Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa:
1. Patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair *(*Class *IIa; Level of Evidence B).*
2. Patients with previous infective endocarditis *(Class IIa; Level of Evidence B).*
3. Patients with CHD (Class IIa; Level of Evidence B): • Unrepaired cyanotic CHD, including palliative shunts and conduits. • Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization).
4. Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve *(Class IIa; Level of Evidence C).*
Prophylaxis against infective endocarditis is not recommended for nondental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection *(Class III; Level of Evidence B).*

Table 3. Current infective endocarditis prophylaxis recommendations of the ACC/AHA related to aortic valvar stenosis and bicuspid aortic valve (Nishimura & ACC/AHA, 2008).

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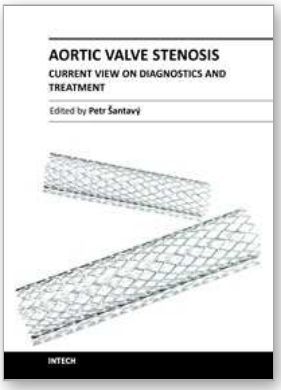

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Currently, aortic stenosis is the most frequent heart valve disease in developed countries and its prevalence increases with the aging of the population. Affecting 3-5 percent of persons older than 65 years of age, it makes a large personal and economical impact. The increasing number of elderly patients with aortic stenosis brings advances in all medical specialties dealing with this clinical entity. Patients previously considered too old or ill are now indicated for aortic valve replacement procedures. This book tries to cover current issues of aortic valve stenosis management with stress on new trends in diagnostics and treatment.

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