Bicuspid aortic valve in children: importance of aortic shape, role of follow up and risk of aortic dilatation

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Patients with bicuspid aortic valve (BAV) have a higher risk of developing aortic disfunction and progressive proximal aorta dilatation. Some of these complications already appear in paediatric age, even if most children are symptomless. Partly, vascular involvement may be due to typical molecular alterations in association with valvular dysfunction. In paediatric patients, the correlation between dysfunction grade, aortic dilatation and aortic shape is not well documented but nowadays it is a matter of growing interest. We consider aortic shape as a possible predictor of the aortic dilatation's progression. Identifying the risk factor of aortic dilatation during childhood is useful to optimize a follow-up. This should be considered in prophylactic therapy.

Bicuspid aortic valve (BAV) is the most common congenital heart disease, affecting about 1% of population. BAV is commonly known not only as a disorder of valvulogenesis, but it also represents coexistent aspects of a genetic disorder of aorta and/or cardiac development. Even if many children are completely symptomless, they are predisposed to different complications regarding the valve itself (regurgitation, stenosis, endocarditis) and vessels (dilatation, aneurysm, dissection) (1). Studies have reported that approximately 50% of subjects with BAV show aortic root dilatation (2).

Some authors have suggested correlation between BAV and aorthopathies due to haemodynamic perturbations: the turbulent flow jet passing through the BAV into the aortic root increases sheer stress on the aortic wall, producing vessel enlargement (3). Another proposed mechanism considers inherited weakness of aortic wall that leads to progressive dilatation (4), with a fundamental role of genetic factors (5, 6). BAV seems to be inherited in an autosomal dominant pattern with increasing prevalence among first-degree relatives. The most common gene identified is NOTCH1 (5).

Pathogenesis

The typical histologic alteration is known as Erdheim medial necro-cystic degeneration. This alteration includes increased vascular smooth muscle cells apoptosis with a reduced production of extracellular matrix proteins, elastic

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fragmentation and deficiency of fibrillin-1, which leads to matrix disruption. In addition, molecular analyses have detected an increased production of metalloproteinases (most of all MMP-2 and MMP-9) with altered equilibrium between these and their tissue inhibitors (TIMPs) (4). This characteristic plays an important role in generating aortic aneurysms. Another probably involved factor is TGF-β (7). Its hyperexpression increases elastic fibres fragmentation and reduces vascular smooth muscle cells connections.

Many currently published studies focus on the identification of risk factors of unfavourable outcomes of BAV during adulthood; but just few of them focus on paediatric population. The incidence of severe primary cardiac events in children with BAV in relatively low (8), however aortic dilatation already appears in paediatric age.

Different valvular morphologies seem correlated to different complications: bicuspid aortic valve with left-right coronary cusps fusion is associated with higher risk of aortic dilatation, otherwise non-coronary and left/right cusps fusion most frequently present valvular defects (9). In addition, valvular function plays an important role in determining progression rate of enlargement. Patients with severe aortic stenosis and moderate-severe insufficiency seem to have a faster progression rate than others (10). In our previous retrospective study, we purposed to correlate aortic shape with age, valvular dysfunction and general grade of dilatation.

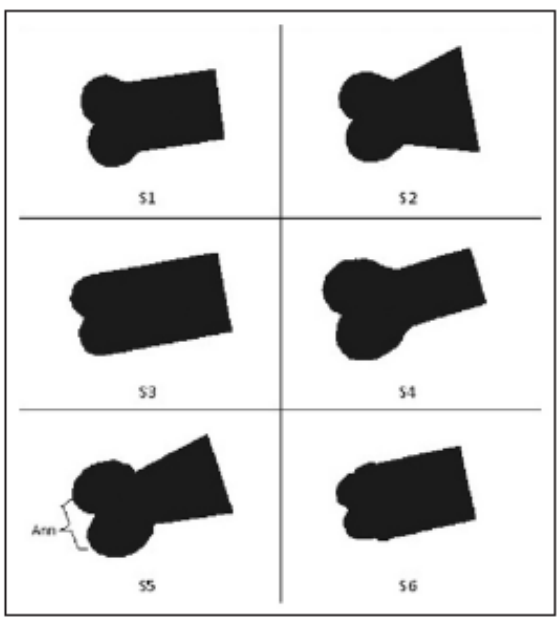

Fig. 1. ***S1*** *- normally shape aorta with single dilatation of annulus;* ***S2*** *- enlarged ascending aorta;* ***S3*** *- effacement of the sinotubular ridge;* ***S4*** *- Marfan-like with enlarged sinus;* ***S5*** *-enlarged sinus of Valsalva and ascending aorta;* ***S6*** *- normal annulus and enlarged sinus of Valsalva, sinotubular ridge and ascending aorta.*

Indeed, considering paediatric population, six patterns of dilated aorta were found (Fig. 1) (11). Studies on adults identified four aortic shapes (12-15), corresponding to the first four group in children, likely S5 and S6 shape progressively turn in another shape during years (11).

Patients with bicuspid aortic valve (BAV) should be considered as a risk population for developing aortic dysfunction and progressive proximal aorta dilatation during growth. Paediatric cardiologists are aware about risk of valvular complications in children, especially when a rapid progression is highlighted in the first years of life. Aortic enlargement in children with bicuspid aortic valve is not well described in literature. This situation does not occur in a homogenous manner (16) and today the focus on vessels' shape patterns appears interesting to understand the mechanisms of vascular dilation. Aortic valve dysfunction seems to be an independent factor from aortic shape, but it could contribute to aggravate aortic enlargement, probably because of a hemodynamic effect (17).

Similarly, the role of therapy is not well standardized. Even if heart failure therapy in severe valvular involvement is fundamental, the role for prophylactic strategy to avoid future complication is not clear. Focusing on therapy, Losartan was the most frequently used drug. This is because of its double role: it has an antihypertensive effect, but it also acts as TGF-β antagonist (18). Considering that it was noticed as a hyperexpression of this marker in patients with BAV and aortic aneurysm, Losartan could have an "etiopathogenetical" role, as already tapped in Marfan syndrome (18). Further studies will be necessary to validate aorticshape role in thefollow-up of patients with BAV and aortic dilatation to improve the accuracy of prophylactic therapy and timing of echocardiographic controls.

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