Bicuspid aortic valve and coarctation: two villains part of a diffuse problem

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Bicuspid aortic valve and coarctation of the aorta are congenital abnormalities often mistakenly considered as simple lesions that are discrete and localised. Evidence is mounting, however, that both their aetiology and pathophysiology are intimately related, and that they are part of a spectrum of a more generalised arteriopathy

important mechanism underlying the loss of smooth muscle cells in the ascending aorta of patients with bicuspid aortic valve and contribute to aortic dilatation.⁹ It is possible that an intrinsic or genetic signal precipitates the apoptosis or perhaps it sometimes results from the stimulus of hypertension. This may explain why there is a higher incidence of dissection and rupture with coexistent coarctation of the aorta.

Microfibrillar proteins within the aortic matrix may be deficient in patients with bicuspid aortic valve, and inadequate production of fibrillin-1 during valvulogenesis may alter the formation of both the aortic cusps and root, thereby reducing their structural integrity.¹⁰ A single genetic locus responsible for the extracellular matrix has not yet been associated with bicuspid aortic valve, but transcriptional regulation of protein production may be abnormal. Matrix metalloproteinases are endogenous enzymes that accelerate matrix disruption and are produced by a variety of cell types including smooth muscle cells. Some aortic aneurysms have been associated with increased activity of certain metalloproteinases¹¹ and they may be hyperactive in fibrillin deficient aortas of patients with bicuspid aortic valve, thereby enhancing the potential for dilatation and dissection.

Bicuspid aortic valve is the most common congenital cardiovascular anomaly, occurring in 1–2% of the population. It has a male predominance and often occurs in multiple members of the same family, suggesting that it may have an autosomal dominant inheritance, perhaps with variable penetrance.^{1,2} Much of the data relating to its complications derive from necropsy studies since reliable diagnosis has only been possible for the last 15 years or so by two dimensional echocardiography. The most common complication is aortic stenosis and it is the most frequent cause of patients under 60 years of age requiring aortic valve replacement. Aortic stenosis appears to result from an active disease process reminiscent of atherosclerosis.^{3,4} It has features similar to the degenerative calcification that occurs on tricuspid aortic valves, but tends to occur at an earlier age, perhaps because of different mechanical or shear stresses on the bicuspid valve. Other complications include aortic regurgitation and infective endocarditis.

PATHOLOGY OF THE AORTIC MEDIA

The association of bicuspid aortic valve with aortic medial abnormalities has been known for decades and has been confirmed in many reports. Histologic examination of the ascending aorta frequently shows loss of smooth muscle cells and severe degeneration of the medial elastic fibres—so called “cystic medial necrosis”. The presence of a bicuspid valve increases the risk of dissection at least ninefold,⁵ and dissection tends to occur in younger patients than in those with tricuspid aortic valves.⁶ While the jet above a stenotic aortic valve may cause haemodynamic perturbation and aortic dilatation, a functionally normal aortic valve is often associated with a dilated aorta.^{7,8} The progression of aortic root dilatation is variable and not just related to age or hypertension. Nonetheless, there is considerable heterogeneity in aortic dimensions and perhaps there is a subgroup of patients whose aortas dilate. Both dissection and rupture have been reported in these patients. Apoptosis may be an

COARCTATION: A DIFFUSE ARTERIOPATHY

Coarctation of the aorta is often regarded as a localised abnormality, commonly just distal to the left subclavian artery, but should be regarded as a diffuse arteriopathy and part of the spectrum of pathology associated with bicuspid aortic valve. In the presurgical era, dissection of the aorta caused death in 19% of cases of coarctation of the aorta but 50% when coarctation coexisted with a bicuspid aortic valve.¹² Whether the associated bicuspid aortic valve represents a more severe manifestation of a heterogeneous arteriopathy remains uncertain. Interestingly, about 10% of patients with coarctation also have intracranial aneurysms; this supports the hypothesis of a more diffuse arterial pathophysiology, perhaps related to a developmental abnormality of neural crest tissue which gives rise to the muscular arteries of the heart, aortic arch, and cervico-cephalic arteries. In some way these neuroectodermal immigrants may influence medial degeneration and cause both aortic dilatation and cerebral aneurysm.¹³

It is also noteworthy that both coarctation and bicuspid aortic valve occur more frequently in males with a prevalence of approximately 4:1. A high prevalence of these same cardiovascular

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lesions is also found in women with Turner's syndrome¹⁴—a sex aneuploidy syndrome caused by the complete absence of an X chromosome or the presence of a structurally abnormal one. Thus, since aortic disease is mainly a "male domain" and the absence of a normal second X chromosome is associated with aortopathy, one might speculate that a genetic factor that modulates the development of the aorta and valve might be located on the X chromosome.

Even after surgery to correct the coarctation, vascular reactivity and mechanical properties of large conduit arteries may be impaired despite successful repair in the first few months of life.¹⁵ Whether this represents early "programming" of vascular reactivity in utero or an inherent abnormality remains uncertain. The aetiology of hypertension after coarctation repair is not completely understood. It has been shown that early repair is associated with a lower prevalence of systemic hypertension; however, O'Sullivan and colleagues reported a 7–16 year follow up of children having coarctation repair at the age of 2–3 months and found a disappointingly high prevalence of hypertension.¹⁶ Of 119 children, 28% had hypertension at rest or during ambulation, including 21% who had no residual aortic obstruction. Whether this is part of a generalised arterial abnormality or an irreversible result of "stress" on the proximal vessels before repair remains speculative.

Animal studies have shown decreased nitric oxide bioavailability proximal to a coarctation whereas concentrations below are normal, suggesting that it is a problem confined to the proximal arterial system rather than a diffuse one.¹⁷ Nitric oxide is a biological modulator with diverse physiological activities including vasodilatation, and its deficiency causes hypertension. Endothelium derived nitric oxide is critical in the regulation of cell growth and apoptosis, and it has been implicated as a major mediator of vascular remodelling. Interestingly, mice with a deficiency of endothelial nitric oxide synthase (eNOS) also have a high incidence of bicuspid aortic valve,¹⁸ although how it might modulate valve morphogenesis remains to be determined.

As such, patients with repaired coarctation should never be considered "cured" and life expectancy remains reduced. Late complications include re-coarctation, stroke, and aortic aneurysm formation with dissection and rupture. Particularly troubling is the high incidence of premature coronary artery disease, which was the major cause of death in the largest series published,¹⁹ and the mean age at death for the whole group was only 38 years.

TWO LESIONS: A SINGLE DISEASE?

Thus bicuspid aortic valve and coarctation are two villainous cardiovascular lesions in cahoots with a similar pathophysiology that is part of a diffuse arteriopathy. Neither can be considered a benign lesion. Several questions regarding their treatment strategies, however, remain unanswered. Whether β blockade helps to prevent aortic dilatation, as has been demonstrated in Marfan's syndrome, is undetermined. The

timing of surgical repair of the dilated aortic root is also uncertain, although most centres use the same criteria as that used for Marfan's syndrome. When both coarctation and aortic valve disease coexist, novel surgical treatment strategies may be necessary.²⁰ Whether aggressive treatment of coronary risk factors will delay or avert the development of aortic stenosis in the setting of a bicuspid aortic valve is also unproven. Certainly patients with one or both of these abnormalities need meticulous lifetime follow up.

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