Bicuspid aortic valve syndrome: heterogeneous but predictable?

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This editorial refers to ‘Aortic elasticity and size in bicuspid aortic valve syndrome’ by S. Nistri et al., on page 472

Bicuspid aortic valve (BAV) has long been associated with a spectrum of vascular complications such as ascending aortic dilatation, aortic aneurysms, and catastrophic aortic root dissection. The mechanism responsible for the associated vascular complications in this seemingly benign and common congenital lesion of aortic valve morphology remains controversial. Some argue that flow dynamics from the mis-shapen outflow valve result in aberrant post-valvular haemodynamics that trigger progressive aortic dilatation. In many patients with advanced valvar dysfunction this mechanism probably contributes to the progression of aortic pathology. However, is this the key initiating and co-ordinating event? More recent evidence suggests that patients with BAV have an intrinsic defect in the aortic wall that results in an aortopathy independent of aortic valve function.

The heterogeneity of the bicuspid aortic valve syndrome (BAVS) has made progress difficult with respect to defining key mechanisms underlying this disease. Some patients with BAV have rapidly progressive valve and aortic dysfunction while some remain without complications for a lifetime. The clinical phenotype is heterogeneous with respect to valve morphology (location of raphe), valve dysfunction (aortic stenosis vs. regurgitation), as well as the rate and magnitude of aortic dilatation. Interestingly, new data suggest that BAVS is also heterogeneous with respect to molecular and cellular events in disease progression. We observed extracellular matrix dysregulation in the aortic wall of patients with BAVS. Matrix proteins and their proteolytic enzymes were markedly altered in selected patients with BAV while they were preserved in others. Due to a small sample size we were unable to determine if specific factors were independently associated with these alterations. However, our data and others suggest that BAVS is heterogeneous on a clinical, cellular, and molecular basis.

The implications of this heterogeneity are numerous. The candidate genes and molecular markers that mediate the valve and aortic complications remain elusive. It is tempting to speculate that BAVS is a final common pathway for a wide variety of altered molecular events and genetic defects. Perhaps similar to left ventricular dilatation in the failing heart, BAV and associated aortic dilatation result from different aetiologies but manifest similarly on a clinical basis. Because the lesion may have diverse molecular triggers, it may be difficult to characterize the inciting events that result in a BAV and its associated aortopathy. Currently, extracellular matrix dysregulation and cell death pathways show promise as important molecular mechanisms of the aortopathy, while candidate genes such as NOTCH may reflect important genetic triggers.

An improved understanding of the cellular and molecular mechanisms underlying BAVS may lead to improved management strategies. Using these data, targeted improvements could be made in the timing of surgical intervention vis-à-vis aortic dimensions, the frequency and need for follow-up studies and screening, and the development of novel pharmacological treatments to limit aortic complications and perhaps the progression of valvar disease.

Nistri and colleagues report on their use of non-invasive ultrasound imaging to assess the elasticity of the aorta in BAV patients without overt BAVS. The findings of this study have important and broad implications for the ongoing investigation of this disorder. First, measures of aortic elasticity were altered in BAV patients without significant valvar dysfunction and aortic dilatation. Importantly, these data support the opinion that a pathological process underlies the BAV aorta that is not a result of altered haemodynamics secondary to chronic valve dysfunction. Secondly, despite similar valve function and aortic dimensions, there was a significant variation in the degree of aortic elasticity parameters among BAV patients. This indicates a wide spectrum of aortic tissue characteristics. Therefore, BAV patients are heterogeneous at the level of aortic function. The implication of this observation is that some patients may be at higher risk of aortic complications despite a seemingly similar and benign clinical phenotype. This
point is further supported in that BAV was independently predicted by abnormal parameters of aortic elasticity.

Nistri and colleagues have introduced a novel strategy to assess aortic tissue characteristics non-invasively using widely accessible technology. Although not formally evaluated in their study, their assessment of aortic elasticity may become an important predictive tool to determine the future risk of aortic complications for individual patients with BAV. Clinicians, particularly surgeons, are often forced to make difficult judgements as to the timing and extent of aortic repair in patients with aortic dilatation and BAV disease. At the time of aortic valve replacement, when aortic dilatation is mild (4.0–5.0 cm), the gross appearance, thickness, and feel of the aorta during surgery will sometimes dictate the fate of the aorta in a surgeon’s hands. A non-invasive means to identify aortic wall dysfunction would guide these interventions and possibly improve outcomes. It is possible that selected patients with BAV and extensive aortic dysfunction, even with mild degrees of aortic dilatation, would benefit from more aggressive primary aortic resection strategies. Given the heterogeneity of this common disease, earlier intervention would only be warranted if the risk of future events (i.e. rate of aortic growth or incidence of dissection) can be predicted with some degree of reliability. Perhaps the most exciting aspect of the work of Nistri and co-workers has yet to come. Further study of this patient population over time will determine the predictive value of this innovative and potentially useful imaging strategy. In turn, the predictive value of this strategy will determine its ability to improve mechanistic insights and guide future therapeutic approaches.

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References