

## Calcific Aortic Valve Disease Insights Into the Genetics of Vascular Ageing

Richmond W. Jeremy, MB, BS, PhD

The shifting global demographic profile toward an older population is well recognized and carries with it the increased burden of degenerative cardiovascular disease, with associated morbidity, mortality, and healthcare costs. Vascular ageing is characterized by increased arterial stiffness, systolic arterial hypertension, myocardial thickening and fibrosis, and associated atherosclerosis.<sup>1</sup>

### See Article by Martinsson et al

Calcific aortic valve stenosis (CAVS) is another manifestation and affects  $\approx 1$  in 30 people aged 75 years. Furthermore, CAVS is associated with several adverse vascular risk factors, including hypertension, hypercholesterolemia, and diabetes mellitus, as well as with underlying structural abnormalities, for example, bicuspid aortic valve.

Considerable resources are already devoted to health care consequent on vascular ageing and the load is increasing—as evidenced by the burgeoning need for operative and percutaneous aortic valve replacements.<sup>2</sup> If society is to better manage health costs for the older population, we need to better understand the mechanisms of vascular ageing and thereby develop and implement novel preventive strategies.

There is significant familial risk for atherosclerotic vascular disease, beyond familial hypercholesterolemia and hypertension, although the actual genetic factors responsible remain elusive. In this issue of *Circulation: Cardiovascular Genetics*, Martinsson et al<sup>3</sup> present evidence for a significant familial risk for CAVS in the general population. At the same time, there is also a lesser, but nonetheless significant, environmental risk.

The fascinating question is how we might explain these observations and whether we can now begin to formulate a hypothesis about why some individuals develop CAVS.

### Heritable Factors and CAVS

A systolic ejection murmur is a common finding in older patients and echocardiography has shown us that most individuals develop some thickening and restriction of leaflet motion of the aortic valve with increasing age. Despite this,

most such patients do not subsequently develop CAVS. For those who do develop CAVS, there are several potential mechanisms of heritable risk.

Differences in tissue maintenance and repair with age are likely contributors to risk of CAVS. Longer telomeres are thought to protect against age-related disease in humans. The increased incidence of degenerative aortic valve disease with age has been associated with reduced telomere length in elderly patients.<sup>4</sup> Experimental studies show that longer telomeres protect against age-related aortic valve degeneration in mice with *NOTCH1* haploinsufficiency.<sup>5</sup> Telomere shortening has been associated with dysregulation of gene expression of G-protein coupled receptors, and consequent likely impairment of endothelial shear stress mechanosensing. Reduced shear-related NOTCH signaling is in turn associated with reduced anticalcific gene expression.<sup>6</sup> As telomere length is heritable, apparent influence of paternal inheritance<sup>7</sup> this is one possible mechanism contributing to the observed heritability risk for CAVS.

There are also multiple candidate genes, for which either pathogenic mutations or functional polymorphisms, which may contribute to heritability of CAVS risk. In hypertensive siblings, the risk of aortic valve calcification is increased, with a sibling risk recurrence ratio=2.31 (1.72–3.11).<sup>8</sup> Linkage analysis identified a locus at C16q22.1–q22.3, candidate genes including *CDH13*, which encodes a member of the cadherin superfamily. This protein is thought to protect vascular endothelial cells from apoptosis because of oxidative stress, and is associated with resistance to atherosclerosis.<sup>9</sup>

One genome-wide association study has identified association of the single nucleotide polymorphism rs10455872 in intron 25 of *LPA* on chromosome 6 with aortic valve calcification (odds ratio=2.05), although there is no clear link between plasma lipid levels and CAVS.<sup>10</sup>

Families with *NOTCH1* mutations develop calcific degeneration of both bicuspid aortic valves and tricuspid aortic valves. NOTCH1 seems to participate in suppression of calcification in aortic valve interstitial cells via repression of the *BMP2* gene, thereby inhibiting osteoblast-like calcification pathways.<sup>11</sup> The transcription factor RUNX2 seems to integrate competing signaling via NOTCH, bone morphogenic protein, and WNT on osteoblast differentiation.<sup>12</sup> Dysregulation or induction of osteoblast activity, consequent on impaired Notch signaling, may therefore contribute to CAVS.

In experimental studies, multiple other gene variants affecting the TGF- $\beta$  (transforming growth factor- $\beta$ ) and bone morphogenic protein signaling pathways have been associated with bicuspid aortic valve disease, including *Adamts5* and *Alk2*.<sup>13</sup> A recent genome-wide association study has identified regulatory variants near *GATA4* as being associated with bicuspid aortic valve in humans.<sup>14</sup> The impact of these

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Sydney Medical School, University of Sydney, Newtown, NSW, Australia.

Correspondence to Richmond W. Jeremy, Department of Medicine, Sydney Medical School, University of Sydney, Suite 407, 100 Carillon Ave, Newtown, NSW 2042, Australia. E-mail richmond.jeremy@sydney.edu.au (*Circ Cardiovasc Genet.* 2017;10:e002012).

DOI: 10.1161/CIRCGENETICS.117.002012.)

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*Circ Cardiovasc Genet* is available at  
<http://circgenetics.ahajournals.org>

DOI: 10.1161/CIRCGENETICS.117.002012

different gene variants on development of CAVS is yet to be defined, but there is clearly a rich field of potential genetic contributors, probably acting synergistically, which may underlie the familial risks described by Martinsson et al.<sup>3</sup>

### Environmental Factors and CAVS

The key secondary finding from the present study is of increased risk of CAVS in spouses of patients presenting with CAVS.<sup>3</sup> This tells us that shared environmental factors are likely to be contributors, including cigarette smoking, diet and salt intake, physical activity levels, and air quality.

Cigarette smoking is associated with oxidative stress and impaired endothelial function, with abnormal nitric oxide mediation vasodilatation<sup>15</sup> and the relationship between smoking and calcific aortic stenosis has been known for many years.<sup>16</sup> Endothelial dysfunction, promotes calcification in underlying aortic valve interstitial cells—leading to calcific aortic valve disease. Gain or loss of endothelial nitric oxide availability can prevent or promote calcification of aortic valve interstitial cells.<sup>17</sup>

The adverse impact of multiple environmental factors on endothelial nitric oxide metabolism is likely to be a key contributor toward valve calcification. Although the hazard ratios (1.16 males, 1.18 females) may seem modest, even a 10% to 20% reduction in burden of CAVS may yield significant health and cost benefits. With current technology, these environmental factors may well prove easier to manage than genetic factors and vascular preventive strategies are warranted for individuals at risk.

It is likely therefore, that CAVS represents the culmination of effects of age and adverse environmental factors on the endothelial cells and aortic valve interstitial cells in those patients with an inherited vulnerability. Individuals with greater susceptibility to ageing, reduced endothelial protection, impaired cellular Ca<sup>++</sup> handling, or lower resistance to oxidative stress, will be more likely to progress to CAVS, whereas others with cellular mechanisms capable of compensation for environmental stress may only manifest valve sclerosis.

### Clinical Implications

The relative risk of sibling CAVS documented in the present study may well be the lower limit, as detection was based on diagnostic coding of CAVS. It is quite likely that other siblings had undetected early CAVS. Thus, follow-on studies, using imaging for detection of degenerative aortic valve changes, are desirable.

Although the authors note that echocardiography screening of relatives of patients with CAVS is not likely to be cost-effective, the advent of simple pocket echocardiography units could facilitate CAVS detection in the ambulatory care setting.<sup>18</sup> Investigation of first-degree relatives may also be prioritized toward those at higher risk, such as hypertensive or diabetic siblings.<sup>8</sup> Clinical studies of screening of such higher-risk groups, with comparative costs and outcomes analysis, would seem worthwhile.

### Road Ahead

Improved understanding of the pathogenesis of CAVS and vascular ageing will require carefully articulated clinical,

genetic, and molecular studies. The findings of Martinsson et al<sup>3</sup> point to new avenues of research into these changes in the cardiovascular system. An obvious next step is investigation of degenerative valve changes in twins. Congenital aortic stenosis and bicuspid valves are recognized in twins, and findings of concordant CAVS in twins (identical versus nonidentical) may be informative. Another step is intergenerational study of CAVS. Apparent heritability of CAVS has been described in large French kindreds<sup>19</sup> and further definition of heritability patterns could illustrate likely underlying genetic mechanisms (paternal suggesting telomere shortening effects; maternal suggesting epigenetic effects; and gender neutral suggesting autosomal gene variants).

Is CAVS a marker of overall biological age and of longevity? How well is CAVS correlated with other clinical or molecular markers of ageing? What factors might determine the rate of progress of CAVS in potentially predisposed individuals? These and many other questions can be addressed by study of younger and middle-aged individuals at risk of CAVS, according to their family history.

Longitudinal study of individuals with degenerative aortic valve disease, including those who do and do not progress to CAVS, with measurement of linked clinical, hemodynamic, genetic, and molecular markers is warranted, to identify the factors determining development and progression of CAVS and to focus on potential targets for intervention.

It is time to move beyond the common concept of CAVS as part of the inevitability of ageing and simply a target for future valve replacement. Instead, we should view CAVS as a long-term disease, with genetic and environmental contributions, which should be amenable to prevention and early therapeutic intervention.

### Disclosures

None.

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KEY WORDS: Editorials ■ aortic valve stenosis ■ apoptosis ■ atherosclerosis ■ bicuspid aortic valve ■ telomere

**Calcific Aortic Valve Disease: Insights Into the Genetics of Vascular Ageing**  
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*Circ Cardiovasc Genet.* 2017;10:

doi: 10.1161/CIRCGENETICS.117.002012

*Circulation: Cardiovascular Genetics* is published by the American Heart Association, 7272 Greenville Avenue,  
Dallas, TX 75231

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Print ISSN: 1942-325X. Online ISSN: 1942-3268

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