The Aortic Stenosis Complex

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Traditionally, calcification of the tricuspid aortic valve resulting in aortic stenosis was thought to be secondary to a wear-and-tear effect on the valve due to the aging process. Over the last several years, however, accumulated evidence suggested that inflammation and other risk factors related to the pathogenesis of atherosclerosis are responsible for valvular calcification and for the development of calcific aortic stenosis [1–7]. Dr. Pomerance [8] introduced almost 5 decades ago the possible role of inflammation in valve calcification. In her pioneering work, she described inflammatory changes in areas adjacent to calcification in the mitral annulus. In this study, the incidence of mitral annular calcifications in patients older than 50 years was 8.5%. Importantly, the incidence of aortic valve calcification in male and female patients with mitral annular calcification was 36% and 30%, respectively.

In a review paper published in *Cardiology*, Dr. Rajamannan discussed in detail the similarities and differences between atherosclerosis and aortic stenosis [9]. She nicely described that atherosclerosis over time may differentiate to form “bone” in the heart producing coronary artery and/or left heart valve calcification; this process has been defined as “osteocardiology.” In Dr. Rajamannan’s paper, several pathways leading to calcific aortic stenosis

were described along with traditional risk factors. Further, in an attempt to explain differences between coronary artery disease (CAD) and calcific aortic stenosis, fluid dynamics based on the Bernoulli equation were discussed [9].

Incidence of Coronary Atherosclerosis in Patients with Calcific Aortic Stenosis: The Role of Aortic Valve Anatomy

The frequency of coronary atherosclerosis and calcific aortic stenosis increases with age. In a study from our laboratory, it was found that 62.2% of patients with a tricuspid aortic valve and calcific aortic stenosis who had aortic valve replacement, and 26.3% of patients with a bicuspid aortic valve and calcific aortic stenosis who had aortic valve replacement, required concomitant coronary artery bypass graft (CABG) surgery [10]. Patients with bicuspid aortic valve stenosis were younger than those with tricuspid aortic stenosis (62 ± 13 vs. 71 ± 10 , respectively). The incidence of CAD requiring CABG in patients with a tricuspid aortic valve and calcific aortic stenosis was much higher than expected based on the preva-

lence of CAD in the USA (19.8%) among persons ≥ 65 years of age [11]. Likewise, the incidence of CAD requiring CABG in patients with a bicuspid aortic valve and calcific aortic stenosis was also higher than expected based on the prevalence of CAD in the USA (7.1% for those 45–64 years of age and 19.8% for those ≥ 65 years) [11]. This information suggests that risk factors related to the development of coronary atherosclerosis also play a role in the development of calcific aortic stenosis even in patients with a bicuspid aortic valve. Further, it implies that the anatomy of the aortic valve, regardless of risk factors, plays a crucial role in the development of calcific aortic stenosis since patients with a bicuspid aortic valve develop aortic stenosis at a much younger age than those with a tricuspid aortic valve.

Despite this close association between aortic stenosis and CAD, many patients with risk factors and coronary atherosclerosis do not develop aortic stenosis and vice versa (i.e., many patients with aortic stenosis do not have evidence of vascular atherosclerosis). Thus, there are likely other parameters that lead to calcific aortic stenosis in addition to traditional risk factors. Studies have suggested that even in a normal trileaflet aortic valve, the size of the 3 leaflets may vary slightly. This minor anatomic difference, in addition to other genetic factors, may be a key factor predisposing to aortic calcification and aortic stenosis [12, 13]. This hypothesis, however, remains to be proven. Further, it should not be forgotten that the aortic valve is a part of the aorta, and, thus, functional abnormalities of the aorta may also play a crucial role in the pathogenesis of calcific aortic stenosis.

The Role of Aortic Function in the Pathogenesis of Calcific Aortic Stenosis

It is well documented that a bicuspid aortic valve is associated with functional abnormalities of the aorta in both a normally sized and dilated aortas. Moreover, it should be emphasized that all patients with coronary atherosclerosis have abnormal aortic function related to the atherosclerotic process, decreased vasa vasorum flow to the aortic wall, and aging [14, 15]. Thus, abnormal aortic function for all practical purposes is present in all patients with aortic stenosis. These functional abnormalities of the aorta may precede the development of calcific aortic stenosis by years. In the elderly, significant changes in the aortic wall occur in addition to the accumulating effect of risk factors. In young individuals, the proximal aorta expands by approximately 10% with each ventricular con-

traction. Due to the repetitive stretch of the aortic wall over time, fatigue and fracture of the elastic lamellae occurs, which is associated with an increase in the collagen content and a subsequent decrease in the elastic properties of the aorta. These age-related changes are in addition and independent of those related to risk factors and the atherosclerotic process [16].

Abnormal aortic function may also play a role in the development of calcific aortic stenosis both in bicuspid and tricuspid aortic valves. Aortic pulse wave velocity and reflected wave velocity increase when the elastic properties of the aorta are abnormal. In this case, reflected wave velocities from the periphery return earlier to the root of the aorta and fuse with the systolic portion of the pulse wave resulting in systolic hypertension [15]. Further, different blood flow patterns have been described above the aortic valve using magnetic resonance imaging (MRI) [17]. Using these techniques, turbulent blood flow has been shown in the root of the aorta in certain conditions and diseases. In the elderly, increased turbulent blood flow and diminished forward velocities with accelerated retrograde velocities have been shown [18–20]. Of interest, using a glass model of the aorta that was connected to the left ventricle of an ox, Leonardo da Vinci described aortic flow patterns in the sinuses of Valsalva with remarkable accuracy in the 16th century (Fig. 1). Furthermore, Otto et al. [21] demonstrated that the first abnormalities in aortic stenosis were observed on the side of the aortic valve leaflets (i.e., in the area where turbulent blood flow occurs). Early lesions of aortic stenosis were characterized by subendothelial thickening, increased intracellular and extracellular lipid levels, and mineralization.

Trends in the Incidence of Coronary Atherosclerosis and Aortic Stenosis

Age-adjusted mortality rates for CAD have declined steadily in the USA since the 1960s. Even during a short period of time (2006–2010), the prevalence of CAD has declined from 6.7 to 6% (overall prevalence) [11]; 47% of the decline is attributed to improvement in treatment and 44% to a reduction in risk factors. Trends in the prevalence of aortic stenosis, however, are much less clear and not well defined. Several factors determine the prevalence of calcific aortic stenosis. As the population ages, the prevalence is expected to increase since aortic stenosis increases with age. Improvements in surgical techniques and transcatheter valve replacement are also expected to increase the prevalence of the disease since these patients

Fig. 1. Left: Leonardo da Vinci's drawings of the aorta illustrating vertical flow at the level of the sinuses of Valsalva [from the assistant Curator, photographic services, The Royal Library, Windsor Castle]. Right: Flow pattern above the aortic valve recorded using magnetic resonance imaging (MRI) techniques [from 17]. Note the similarities between Leonardo da Vinci's drawing and MRI.

Fig. 2. Factors contributing to the development of calcific aortic stenosis are shown schematically. In the bicuspid aortic valve, anatomic abnormality is the primary disorder for the development of aortic stenosis (thick arrow), but risk factors also play a role. For the tricuspid aortic valve, risk factors are the major contributors for the development of aortic stenosis (thick arrow); minor ana-

tomic abnormality of the valve and genetic predisposition also contribute to the development of the disease. Abnormal flow patterns related to a stiff aorta may also contribute to the development of calcific aortic stenosis. Finally, disorders related to calcium and phosphorus metabolism may also play a role [modified from 10].

live longer after the procedure. In contrast, controlling risk factors is expected to decrease the prevalence of calcific aortic stenosis.

In a nationwide study of the Swedish population, it has been shown that the crude mortality rates and age-adjusted mortality in aortic stenosis have declined substantially from 1989 to 2009. This decrease in mortality was similar to that observed in heart failure and acute myocardial infarction [22]. It is quite plausible that controlling risk factors in a large proportion of the population has contributed to a decrease in the overall prevalence of aortic stenosis, as has been the case with CAD. This decrease due to risk factor control could offset the increase in the prevalence of aortic stenosis expected from the aging population and to a better management of the disease. Thus, the age of the population, better risk factor control, and effective management of the disease at any particular time and in any specific population are the major determinants of the prevalence of calcific aortic stenosis.

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Make everything as simple as possible, but not simpler
Einstein

Risk factors related to atherosclerosis accelerate the disease process in patients with a bicuspid aortic valve and play an even more important role in patients with a tricuspid aortic valve (Fig. 2). In addition to the traditional risk factors, it appears that many other factors are involved in the development of calcific aortic stenosis. Anatomic abnormalities in the aortic valve, more prominent in bicuspid and less in tricuspid valves, certainly play an important role [23]. A stiff aorta related to aging, risk

factors, atherosclerosis, abnormal structure of the aortic wall in a bicuspid aortic valve, and turbulent blood flow in the root of the aorta may also play a role in the development of calcific aortic stenosis [14–16]. Cardiovascular calcification is inversely related to the mineral density of bone tissue, and diseases related to mineral metabolism, for example, osteoporosis, chronic kidney disease, and Paget disease, are associated with higher incidence rates of vascular calcification and calcific aortic stenosis [24–26]. Genetic predisposition certainly also plays an important role in the development of calcific aortic stenosis [3, 23]. Better understanding of anatomic, genetic, molecular, and pathophysiologic mechanisms responsible for the development of calcific aortic stenosis will help the clinicians to optimize current disease management and eventually prevent the development of the disease. The contributions by Dr. Rajamannan in this area are greatly appreciated.

It can be concluded that multiple factors contribute to the development and progression of calcific aortic stenosis. Several of these factors (e.g., arterial hypertension, age, cholesterol, and smoking) also affect aortic function. Aortic dysfunction, in turn, may precipitate and initiate the development of calcific aortic stenosis. Moreover, aortic stenosis results in left ventricular hypertrophy that may lead to ventricular dysfunction and heart failure. Thus, aortic stenosis is not an isolated aortic valve abnormality, but rather a complex entity with global implications for the cardiovascular system.

Disclosure Statement

The authors report no conflicts of interest.

References

- 1 Rajamannan NM, Evans FJ, Alikawa E, et al: Calcific aortic valve disease: not simply a degenerative process: a review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: calcific aortic valve disease – 2001 update. *Circulation* 2011; 124:1783–1793.
- 2 Lazaros G, Toutouzas K, Drakopoulou M, Boudoulas H, Stefanadis C, Rajamannan N: Aortic sclerosis and mitral annular calcification: a window to vascular atherosclerosis? *Expert Rev Cardiovasc Ther* 2013;11:863–877.
- 3 Thanassoulis G, Campbell CY, Owens DS, et al: Genetic association with valvular calcification and aortic stenosis. *N Engl J Med* 2013; 368:503–512.
- 4 Demer LL, Tintut Y: Inflammatory, metabolic, and genetic mechanisms of valvular calcification. *Arterioscler Thromb Vasc Biol* 2014; 34:715–723.
- 5 Kate GL, Bos S, Dedic A, et al: Increased aortic valve calcification in familial hypercholesterolemia: prevalence, extent, and associated risk factors. *J Am Coll Cardiol* 2015;66:2687–2695.
- 6 Clarke R, Peden JF, Hopewell JC, et al: Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518–2528.
- 7 Petlier M, Trojette F, Sarano ME, Gridioni F, Slama MA, Tribouilloy CM: Relation between cardiovascular risk factors and nonrheumatic severe calcific aortic stenosis among patients with a three-cuspid aortic valve. *Am J Cardiol* 2003;91:97–99.
- 8 Pomerance A: Pathological and clinical study of calcification of the mitral ring. *J Clin Pathol* 1970;23:354–361.
- 9 Rajamannan NM: Osteocardiology: defining the go/no-go time point for therapy. *Cardiology* 2018;139:175–183.

- 10 Boudoulas KD, Wolfe B, Ravi Y, Lilly S, Nagaraja HN, Sai-Sudhakar CB: The aortic stenosis complex: aortic valve, atherosclerosis, aortopathy. *J Cardiol* 2015;65:377–382.
- 11 Centers for Disease Control and Prevention: Prevalence of coronary heart disease – United States 2006–2010. *MMWR Morb Mortal Wkly Rep* 2011;60:1377–1381.
- 12 Boudoulas KD, Borer JS, Boudoulas H: Etiology of valvular heart disease in the 21st century. *Cardiology* 2013;126:139–152.
- 13 Boudoulas H: Valve disease; in American College of Cardiology Foundation, American College of Cardiology: ACCSAP Version 7: Adult Clinical Cardiology Self-Assessment Program. Washington, American College of Cardiology Foundation, 2009, chapt 19.
- 14 Boudoulas KD, Vlachopoulos C, Raman SV, et al: Aortic function: from the research laboratory to the clinic. *Cardiology* 2011;121:31–42.
- 15 Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H: Aortic distensibility abnormalities in coronary artery disease. *Am J Cardiol* 1987;59:1300–1304.
- 16 O'Rourke MF, Safar MF, Dzau V: The cardiovascular continuum extended: aging effects of the aorta and microvasculature. *Vasc Med* 2010;15:461–468.
- 17 Kilner PJ, Young GZ, Mohiaddin RH, et al: Helical and retrograde secondary flow patterns in the aortic arch studied by three-dimensional magnetic resonance velocity mapping. *Circulation* 1993;88:2235–2247.
- 18 Mohiaddin RH, Firmin DN, Longmore DB: Age-related changes of human aortic flow wave velocity measured noninvasively by magnetic resonance imaging. *J Appl Physiol* 1993;74:492–497.
- 19 Whitlock MC, Hundley GM: Noninvasive imaging of flow and vascular function in disease of the aorta. *JACC Cardiovasc Imaging* 2015;8:1094–1106.
- 20 Bissel MM, Azmellina ED, Choudhury PR: Flow vortices in the aortic root: in vivo 4D-MRI confirms predictions of Leonardo da Vinci. *Eur Heart J* 2014;35:1344.
- 21 Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD: Characterization of the early lesion of “degenerative” valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994;90:844–853.
- 22 Martinsson A, Li X, Anderson C, Nilsson J, Smith G, Sundquist K: Temporal trends in the incidence and prognosis of aortic stenosis. A nationwide study of the Swedish population. *Circulation* 2015;131:988–994.
- 23 Padang R, Bagnall RD, Semsarian C: Genetic basis of familial valvular heart disease. *Circ Cardiovasc Genet* 2012;5:569–580.
- 24 Ferguson JF, Matthews GJ, Townsend RR, et al: Candidate gene association study of coronary artery calcification in chronic kidney disease: findings from the CRIC study (Chronic Renal Insufficiency Cohort). *J Am Coll Cardiol* 2013;62:789–798.
- 25 Pawade TA, Newby DE, Dweck MR: Calcification in aortic stenosis. The skeleton key. *J Am Coll Cardiol* 2015;66:561–577.
- 26 Dweck MR, Khaw HJ, Sng GKZ, et al: Aortic stenosis, atherosclerosis, and skeletal bone: is there a common link with calcification and inflammation? *Eur Heart J* 2013;34:1567–1574.