

Can We Modify the Course Towards Aortic Stenosis?

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Aortic stenosis has acquired greater importance with the continuous increase in life expectancy. It is estimated to occur in 1-2% of individuals above 65 years of age, reaching 5.5% in people over 85 years; it has thus become the third most common cardiovascular disorder after hypertension and coronary artery disease.¹

These data exclude congenital aortic stenosis, which comprises 6-8% of congenital abnormalities, and rheumatic aortic stenosis, which has become rare with the extinction of rheumatic fever in developed countries. Another entity that eventually results in severe calcific stenosis is the congenitally bicuspid valve, which is found in 1-2% of the total population.² It is estimated that about one half of these individuals will progress to severe stenosis around their 6th decade.

Both types were considered until a few years ago to be a “wear and tear” phenomenon. However, with newer data accumulating, it is currently appreciated that they are influenced by the same factors that produce atherosclerosis. These include age, male gender, hypertension, hyperlipidemia, diabetes mellitus, the metabolic syndrome, and smoking.³

Moreover, disorders of calcium homeostasis, notably chronic renal failure and primary hyperparathyroidism, are as-

sociated with decreased bone density, osteoporosis and aortic sclerosis.

The common realization is that calcium deposition is not a passive process. The activity of osteoblasts is upregulated; at least 20 bone morphogenetic proteins are increased. They are multifunctional cytokines, most notably osteopontin and osteocalcin. Thus an osteoblastic phenotype is considered to develop.⁴

We have recently determined a great number of predisposing factors, such as calcifying (sclerostin) collagen synthesis (tenascin C) and degradation (MMP-2), and inflammatory agents (IL-2, TNF α , TLRs), in the serum of patients undergoing aortic valve replacement for severe calcific aortic stenosis.⁵

Finally, micro-RNAs are emerging markers that are being recognized as having a distinct signature in both tricuspid and bicuspid aortic valve stenosis. A down-regulation of the anti-calcifying miRNAs 26a, 195, 30b, and 141 has been found.^{6,7} Lipid deposition is not a passive process either, being associated with increased oxidative stress, cytokines, growth angiogenic factor secretion, and inflammation.

Hemorrhage in the cusp is another factor. Hemodynamic factors are clearly operative: an initial restriction to flow begets vortex formation, which further activates the abovementioned factors, espe-

cially in the bicuspid aortic valve, with the aortic side of the cusp being more severely affected.⁸ Antoniou et al recently studied novel indices of severity.⁹

Another recent realization is that the aortic cusps are not simple “curtains” of collagen. They are populated by valvular interstitial cells. Five distinct valvular interstitial cells have been recognized, which can secrete osteoblastic and inflammatory factors.^{10,11}

Computed tomography can very well quantify valvular calcium.^{12,13} As regards diagnostic considerations, a new modality that can image both ongoing inflammatory and calcifying processes is positron emission tomography, employing FDG-18 for the former and NaF for the latter.^{14,15}

Thus if we can evaluate the great multitude and diversity of factors which predispose to stenosis, a “vulnerable aortic valve” can be defined. Apart from the native valve, the same term also holds true for bioprosthetic valves implanted surgically or inserted invasively.

It is true that surgery and transcatheter procedures (TAVI) for aortic valve replacement have attained very low levels of mortality. However, for such a common disorder, it is clear that satisfactory preventive measures should be developed. In fact, efforts directed towards atherosclerotic and hypertensive heart disease have been much more intense.

Unfortunately, statins have disappointed and they are currently not recommended,¹⁶ although additional studies are ongoing. The same holds true for angiotensin-converting enzyme inhibitors.¹⁷ Moreover, bisphosphonates, used in osteoporosis, do not retard the process towards stenosis.¹⁸

The association between decreased bone density and increased vascular and valvular calcification has already been mentioned. Anti-sclerostin antibodies and anti-NFκB antibodies such as denosumab are being considered. The latter has been found to retard vascular calcification in mice.^{19,20}

Pioglitazone has been found to attenuate the progression of aortic valve calcification in rabbits.²¹ This is a widely used drug and could thus have a noticeable impact on the valve cusps.

Finally, the senior author’s group has shown that local application of paclitaxel may hold promise.²² As in mitral valvotomy, one might envisage balloon opening of a non-critically stenotic valve and application of paclitaxel.

Thus, there is clearly a need for better preventive measures that will help towards “passivation” of the “vulnerable” aortic valve and retardation of the

course of calcifying aortic stenosis. This would entail the necessity of identifying patients who present with factors associated with features predisposing to early calcium accumulation, in either the bicuspid or the tricuspid valve. The same would hold true when the necessity for valve replacement arises. A surplus of factors indicating a risk for early calcification and consequently dysfunction of the bioprosthetic valve would tilt the preference towards a mechanical prosthesis.

Thus, the increasing prevalence of aortic sclerosis clearly necessitates more integrated and intensive approaches.

References

1. Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993; 21: 1220-1225.
2. Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol.* 1997; 30: 1809-1812.
3. Helske S, Miettinen T, Gylling H, et al. Accumulation of cholesterol precursors and plant sterols in human stenotic aortic valves. *J Lipid Res.* 2008; 49: 1511-1518.
4. Rajamannan NM, Subramaniam M, Rickard D, et al. Human aortic valve calcification is associated with an osteoblast phenotype. *Circulation.* 2003; 107: 2181-2184.
5. Kapelouzou A, Tsourelis L, Kaklamanis L, Kostakis A, Cokkinos DV. Serum biomarkers in calcific aortic stenosis. A cause or effect phenomenon? 5th Biennial Conference on Heart Valve Biology and Tissue Engineering. May 2012.
6. Nigam V, Sievers HH, Jensen BC, et al. Altered microRNAs in bicuspid aortic valve: a comparison between stenotic and insufficient valves. *J Heart Valve Dis.* 2010; 19: 459-465.
7. Yanagawa B, Lovren F, Pan Y, et al. miRNA-141 is a novel regulator of BMP-2-mediated calcification in aortic stenosis. *J Thorac Cardiovasc Surg.* 2012; 144: 256-262.
8. Rajamannan NM. Mechanisms of aortic valve calcification: the LDL-density-radius theory: a translation from cell signaling to physiology. *Am J Physiol Heart Circ Physiol.* 2010; 298: H5-15.
9. Antoniou CK, Chrysohoou C, Brili S, Pitsavos C, Stefanadis C. Novel indices in calcific aortic valve stenosis. *Hellenic J Cardiol.* 2012; 53: 310-317.
10. Alexopoulos A, Kaoukis A, Papadaki H, Pyrgakis V. Pathophysiologic mechanisms of calcific aortic stenosis. *Ther Adv Cardiovasc Dis.* 2012; 6: 71-80.
11. Chester AH, Taylor PM. Molecular and functional characteristics of heart-valve interstitial cells. *Philos Trans R Soc Lond B Biol Sci.* 2007; 362: 1437-1443.
12. Kizer JR, Geftter WB, deLemos AS, Scoll BJ, Wolfe ML, Mohler ER 3rd. Electron beam computed tomography for the quantification of aortic valvular calcification. *J Heart Valve Dis.* 2001; 10: 361-366.
13. Budoff MJ, Takasu J, Katz R, et al. Reproducibility of CT measurements of aortic valve calcification, mitral annulus

- calcification, and aortic wall calcification in the multi-ethnic study of atherosclerosis. *Acad Radiol.* 2006; 13: 166-172.
14. Dweck MR, Jones C, Joshi NV, et al. Assessment of valvular calcification and inflammation by positron emission tomography in patients with aortic stenosis. *Circulation.* 2012; 125: 76-86.
 15. Marincheva-Savcheva G, Subramanian S, Qadir S, et al. Imaging of the aortic valve using fluorodeoxyglucose positron emission tomography increased valvular fluorodeoxyglucose uptake in aortic stenosis. *J Am Coll Cardiol.* 2011; 57: 2507-2515.
 16. Parolari A, Tremoli E, Cavallotti L, et al. Do statins improve outcomes and delay the progression of non-rheumatic calcific aortic stenosis? *Heart.* 2011; 97: 523-529.
 17. O'Brien KD, Probstfield JL, Caulfield MT, et al. Angiotensin-converting enzyme inhibitors and change in aortic valve calcium. *Arch Intern Med.* 2005; 165: 858-862.
 18. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? *J Am Coll Cardiol.* 2012; 59: 1452-1459.
 19. Quemerais-Durieu MA, Kerlan V, Chabre O. Therapeutic innovation in osteoporosis (antisclerostin antibody and denosumab). *Ann Endocrinol (Paris).* 2011; 72 Suppl 1: S15-22.
 20. Fiter Aresté J. Present and future of the treatment of osteoporosis with monoclonal antibodies. *Rheumatol Clin.* 2011; 7 Suppl 2: S8-12.
 21. Li F, Cai Z, Chen F, et al. Pioglitazone attenuates progression of aortic valve calcification via down-regulating receptor for advanced glycation end products. *Basic Res Cardiol.* 2012; 107: 306.
 22. Spargias K, Milewski K, Debinski M, et al. Drug delivery at the aortic valve tissues of healthy domestic pigs with a paclitaxel-eluting valvuloplasty balloon. *J Interv Cardiol.* 2009; 22: 291-298.