

Aortic Valve Sclerosis is Associated with an Echocardiographically Determined Thinner Aortic Wall

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Background and aim of the study: The aortic valve leaflets plus the aorta and sinuses of Valsalva are a functional unit that optimizes distribution of the diastolic pressure load on the aortic valve leaflets. The study aim was to examine the hypothesis that echocardiographically measured parameters of aortic wall stress at the level of the sinuses of Valsalva, namely aortic wall thickness and luminal diameter, are associated with the presence of aortic valve sclerosis (AVS).

Methods: Among 103 patients (age range 60-70 years) referred for echocardiography at a university hospital, 59 with AVS were compared to an age-matched control group (n = 44) with no echocardiographic abnormalities. Subjects with congenital bicuspid aortic valves were excluded from the study. Transthoracic echocardiographically obtained digital loop recordings were reviewed and two-dimensionally guided measurements were made at the level of the aortic annulus and sinus of Valsalva using electronic calipers, from the parasternal long-axis view.

Results: There was a significant linear relationship and direct correlation between aortic root diameter at

the sinus of Valsalva and body surface area (BSA) ($r = 0.488$, $F = 31.6$, $p < 0.001$) in both the AVS ($r = 0.491$, $F = 18.1$, $p < 0.001$) and control ($r = 0.571$; $F = 20.3$; $p < 0.001$) groups. After adjusting for BSA, aortic wall thickness was significantly ($p < 0.05$) smaller in AVS patients compared to controls. Luminal diameter was not significantly different between the two groups. The specificity of the relationship with sinus of Valsalva wall thickness was confirmed by an absence of any difference in aortic root thickness at the level of the aortic annulus in AVS compared to controls.

Conclusion: AVS is associated with a thinner aortic wall at the level of the sinus of Valsalva. This novel finding suggests that a thinner aortic wall, a reflection of its constituents, likely acting through its contribution to reduced aortic compliance and increased aortic stress, leads to the thickening of aortic valve leaflets characteristic of AVS. Further understanding of this relationship may unravel the pathophysiology of this type of aortic valve disease.

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Recent attention has focused on aortic valve sclerosis (AVS), a condition of thickening and calcification of the normal trileaflet aortic valve without obstruction to left ventricular outflow. This condition is a likely precursor of aortic stenosis and, importantly, is associated with an increased incidence of coronary events (1,2). Indeed, compared to individuals without this condition, AVS is associated with a 50% increase in death from all cardiovascular causes, and significantly increases the risk of myocardial infarction, heart failure and stroke (1,2). As the prevalence of rheumatic valvular

heart disease decreases, degenerative aortic valve disease is becoming an increasingly greater proportion of valvular heart disease cases (3). The development of AVS is, in part, a function of aging, as its prevalence increases from 20-28% in patients aged 55 to 74 years, and to 48-75% in those aged >85 years (4,5). AVS is not an invariable accompaniment of aging, however, and the condition may develop at a younger age, perhaps due to specific risk factors that accelerate its development (5,6).

Hypotheses to explain the development of AVS include: (i) degenerative processes (7); (ii) processes leading to atherosclerosis such as dyslipidemia and hypertension (5,6,8); (iii) polymorphism of apolipoprotein A1, B or E resulting in lipid deposition in the valve leaflets (9); (iv) polymorphism of the vitamin D receptor, leading to tissue calcification (10); (v) endothelial

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dysfunction (11); and (vi) inflammatory processes as reflected by increased C-reactive protein (CRP) levels (12). There is of course, no requirement for exclusivity of each of these mechanisms; rather, it is more likely that multiple mechanisms lead to the manifestation of thickening of the aortic valve leaflets. One factor that has not been previously addressed in detail with respect to AVS pathophysiology is the complex interaction between the aortic valve and the adjacent aorta.

Investigations of the aortic valve, especially with respect to its surgical replacement, have highlighted the need to consider the aortic valve as a functional unit of three cusps along with their corresponding sinuses plus the sinotubular junction (STJ) (13). Together, this unit creates an environment that is optimal for the distribution of diastolic pressure load on the aortic valve (13). The sinuses of Valsalva not only provide a larger functional space so as to prevent the aortic leaflets from hitting the aortic wall, but also permit the generation of eddy currents (14). These eddy currents, the discovery of which is attributed to Leonardo da Vinci, permit the leaflets to close more gently in late diastole, producing a smooth and coordinated aortic valve closure (14). Aortic valve leaflet stress, especially near their attachment edge, is transferred to the aortic root tissue in a 'stress-sharing' process (13). Thus, the sinuses of Valsalva play a very important role in minimizing stress in the aortic leaflets (15).

Wall stress in a thin-walled tube or cylinder (in which form the aorta is often modeled) is directly proportional to the internal diameter and pressure, and inversely related to wall thickness (16). Wall thickness and internal diameter are also critical determinants of the aortic wall compliance (17), and each is readily measurable using echocardiography. Thus, the study aim was to examine the hypothesis that echocardiographically measurable parameters of aortic wall stress at the level of the sinuses of Valsalva - namely aortic wall thickness and luminal size - were each associated with the presence of AVS.

Clinical material and methods

Patient selection

Patients referred to the echocardiography laboratory of a university teaching hospital were examined. A consecutive series of patients with an echocardiographic diagnosis of AVS was selected. AVS was defined as thickening of the aortic leaflets in the absence of bicuspid aortic valve, or significant outflow tract obstruction defined as a transaortic peak velocity <2.0 m/s (equivalent to a peak gradient of <16 mmHg if the short form of the Bernoulli equation were appropriate in this situation). The specified age range of 60 to 70 years was selected in order to obtain a uniform

age, and to minimize the impact of older age, which can be associated with dilatation of the aortic root and thickening of the aortic valves (18,19). Control subjects were individuals seen during the same time period as the AVS patients, but who had no abnormalities identified on echocardiography (i.e., the echocardiographic examination was considered normal). The body weight and height were recorded for each patient, and the body surface area (BSA) calculated.

Echocardiography

Transthoracic echocardiography was performed in standard manner using commercially available instruments. Gain was adjusted to avoid blooming artifact in all patients. None of these patients had heavy or dense aortic valve calcification (as occurs in aortic stenosis) that might have affected the measurement of aortic wall thickness. Studies were recorded, the digital loop

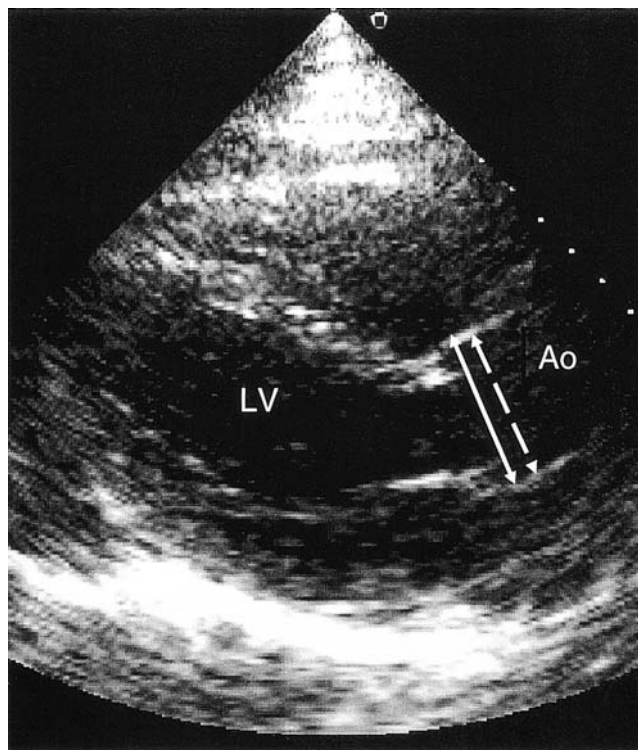


Figure 1: Measurement of aortic wall thickness at the level of the aortic sinus. The left ventricle (LV) and aorta (Ao) are identified in the echocardiographic image.

Measurements were made from leading edge to leading edge (outside of the aortic wall to inside edge of aortic lumen of the posterior aortic wall (solid arrow) and from inside edge of aortic lumen to the inside edge of aortic lumen of the posterior aortic wall (dotted arrow)). The difference is the thickness of the anterior portion of the aortic wall. A systolic frame is shown to illustrate the site of the sinus of Valsalva; this image is not intended to identify other sites of measurement such as the aortic annulus.

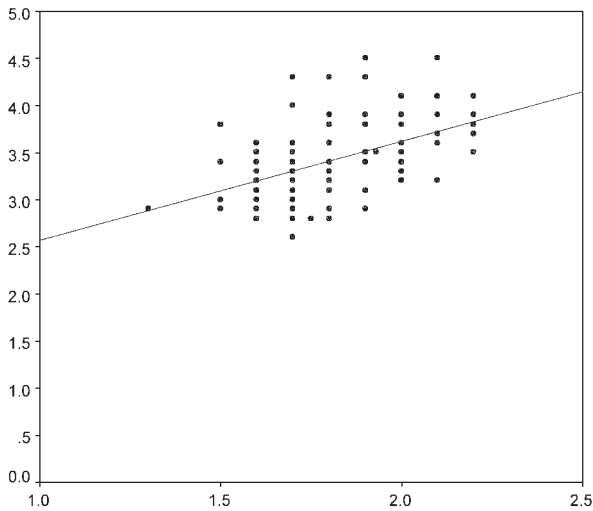


Figure 2: Relationship between the diameter of the aorta at the level of the sinus of Valsalva and body surface area (BSA). Aortic diameter was calculated using the leading edge method.

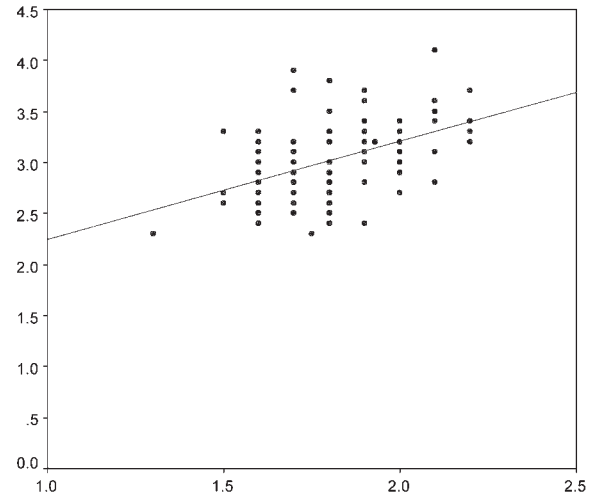


Figure 3: Relationship between the internal diameter of the aorta at the level of the sinus of Valsalva and body surface area (BSA).

recordings reviewed, and measurements performed offline. The real-time echocardiographic imaging was stopped at diastole and systole, defining the level of the aortic annulus and sinus of Valsalva (20). Measurements were taken directly from the two-dimensional images, using electronic calipers, from the parasternal long-axis view for each subject. In order to eliminate intra-observer variability, all measurements were made by one observer who was unaware of the specific hypothesis being tested. The aortic root was measured at the level of the aortic sinuses of Valsalva and aortic annulus following American Society of Echocardiography recommendations that also specified a leading edge to leading edge parameter (20). Because these recommendations overestimate true aortic root lumen, the internal diameter was also measured (Fig. 1). Anterior aortic wall thickness was measured in the parasternal long-axis view; these measurements were not biased as the observer, again, was blinded to the hypothesis under test.

Data analysis

Data analyses were conducted using SPSS version 10.0. A linear least squares regression analysis was used, while between-group comparisons were made using an independent sample *t*-test. The null hypothesis was rejected if the *p*-value was <0.05.

Results

Subjects

During the study time frame, 59 patients were identified with AVS, and 44 controls with no echocardiographic abnormalities.

The mean age of both groups was almost identical (Table I).

Aortic root and BSA

To determine whether the aortic measurements were related to body size, the relationship between aortic root diameter at the level of the sinus of Valsalva and BSA was examined by linear least squares regression analysis (Fig. 2). There was a significant linear relationship and direct correlation between aortic root diameter and BSA ($r = 0.488$, $F = 31.6$, $p < 0.001$). This was present both for those with AVS ($r = 0.491$, $F = 18.1$, $p < 0.001$) and in controls ($r = 0.571$; $F = 20.3$; $p < 0.001$). The internal aortic diameter at the level of the sinus of Valsalva was also significantly and directly correlated with BSA ($r = 0.498$, $F = 33.3$, $p < 0.001$) (Fig. 3); this was apparent both for those with AVS ($r = 0.483$, $F = 17.3$, $p < 0.001$) and in controls ($r = 0.520$; $F = 15.6$; $p = 0.001$). As anticipated, the aortic root diameter correlated closely with the internal diameter of the aorta measured at the level of the sinus of Valsalva ($r = 0.897$; $F = 414$; $p < 0.001$) (Fig. 4).

Table I: Clinical characteristics of the study groups.

Parameter	Control	AVS
Age (years)*	64.9 ± 2.7	65.3 ± 2.9
Gender ratio (M:F)	18:26	37:22
Body surface area (m ²)*	1.78 ± 0.19	1.86 ± 0.19
Aortic peak velocity (m/s)*	1.10 ± 0.22	1.18 ± 0.38

*Values are mean ± SEM.

AVS: Aortic valve sclerosis.

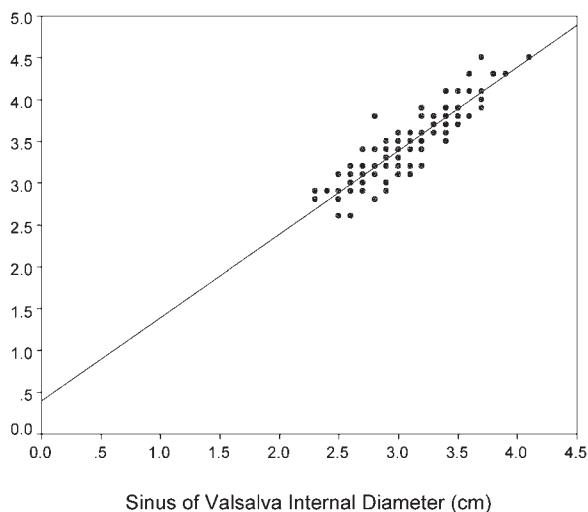


Figure 4: Relationship between the diameter of the aorta at the level of the sinus of Valsalva, calculated using the leading edge and the internal diameter of the aorta at the level of the sinus of Valsalva.

Aortic root dimension and aortic wall thickness in AVS

In view of the correlation between aortic root diameter and BSA, comparison of the aortic root dimension at the level of the sinus of Valsalva requires adjustment for BSA. Aortic wall thickness at the level of the sinus of Valsalva was significantly ($p = 0.023$) less in subjects with AVS than in controls (Fig. 5). The aortic wall thickness in AVS was 24.7% smaller than in control subjects, but there was no inter-group difference in aortic root internal diameter. As might be anticipated, aortic root size, after adjusting for BSA (measured by the leading edge method) was significantly ($p = 0.013$) smaller in subjects with AVS compared to controls.

In order to determine whether the relationship of aortic dimensions was specific for the aortic root at the level of the sinus of Valsalva, measurements of aortic root at the level of the aortic annulus were examined. The aortic root dimension at the level of the aortic annulus was also significantly related to BSA ($r = 0.556$; $p < 0.001$); this was apparent both for those with AVS ($r = 0.491$; $F = 18.12$; $p < 0.001$) and for controls ($r = 0.571$; $F = 20.299$; $p < 0.001$). After adjusting for BSA, there were no significant difference between subjects with AVS or controls for aortic root internal diameter or wall thickness at the level of the aortic annulus (Fig. 6).

Because of the greater proportion of men in the AVS group, the data were examined in relation to gender. There were no gender-related differences with respect to the presence of a smaller aortic root thickness in AVS compared to controls.

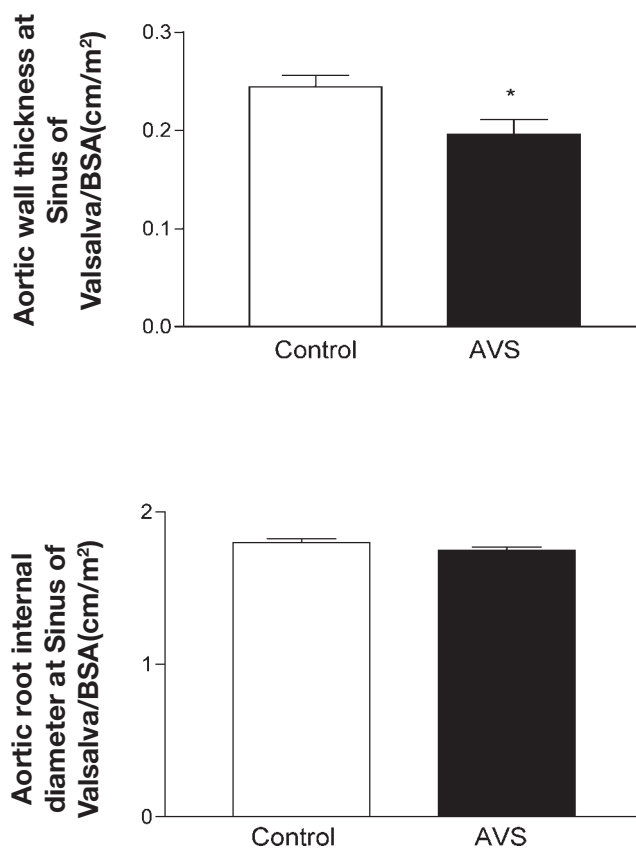


Figure 5: Aortic dimensions (mean \pm SEM) at the level of the sinus of Valsalva for AVS and control groups. Upper panel: Anterior aortic wall thickness. Lower panel: Aortic root internal diameter. * $p < 0.05$.

Discussion

The novel finding of a thinner aortic wall at the level of the sinus of Valsalva in persons with AVS might have considerable implications for the pathophysiology of this condition. Aortic root measurements were standardized for BSA because they were found to correlate significantly with that parameter. This finding was consistent with the results of other studies (21-23). Case studies and population-based studies, such as the Framingham study, have shown that BSA and age are the principal determinants of echocardiographically measured aortic root dimensions, while the additional influence of blood pressure is small (21-23). The present study adjusted for age by examining a defined age group, and in so doing included two groups that were very closely matched for age. Whilst the proportions of men and women differed between the two groups, gender did not impact upon the findings of the study.

Echocardiographic measurement of the aortic root is a relatively precise procedure, as it has been validated and correlates closely with direct measurement of the

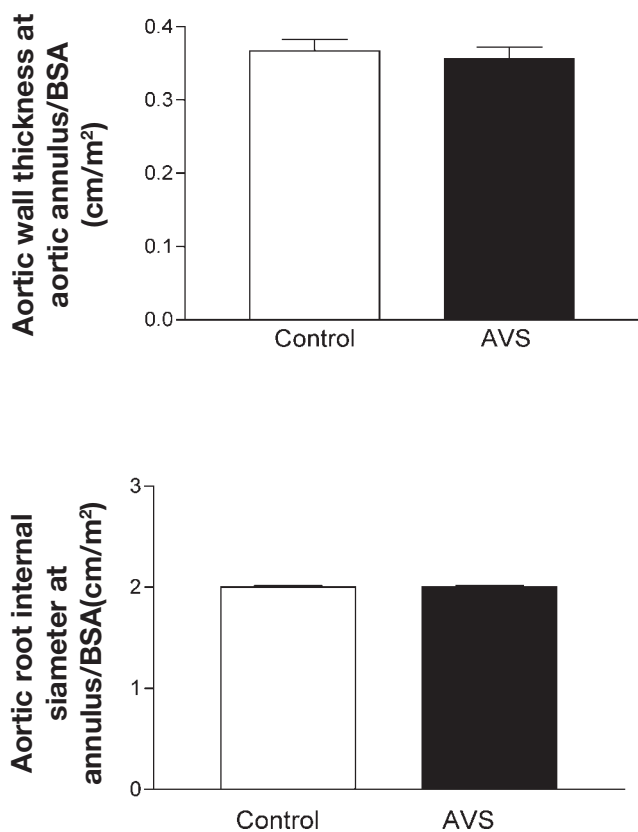


Figure 6: Aortic dimensions (mean \pm SEM) at the level of the aortic annulus for AVS and control groups. Upper panel: Anterior aortic wall thickness. Lower panel: Aortic root internal diameter.

aortic root at the time of surgery (24). The specificity of finding a smaller aortic root thickness at the level of the sinus of Valsalva in AVS is supported by the absence of a similar difference in the aortic root at the level of the aortic annulus. The aortic root at the level of the sinuses of Valsalva was not enlarged in AVS patients; rather, the changes were in the degree of aortic wall thickness.

Pathophysiology

The present finding that aortic wall thickness at the level of the sinus of Valsalva is associated with AVS provides the basis for examination of the pathophysiologic mechanism(s) responsible for the condition. The finding of a thinner aortic wall at one part of the aorta might be considered evidence that a model of aortic valve sclerosis as part of the atherosclerotic process, that would be anticipated to increase the thickness of the aortic wall, is too simplistic. In recognizing that associations do not prove causality, it is likely that the smaller aortic root produced AVS, rather than the reverse Aortic wall thickness was selected for investi-

gation because of its central role as one of the determinants of both compliance of the aorta (17) and stress of the aortic wall (16). With the caveat that blood pressure is an essential element in the consideration of aortic wall stress, but contributes little to aortic root dimensions (21-23), it could be speculated that stress in the sinuses of Valsalva is a likely pathophysiologic mechanism linking aortic root thickness and AVS. A thinner aortic wall during systole, when the aortic valve is opened, represents a less compliant aorta so that at end-systole/early diastole at the level of the sinuses of Valsalva there is increased pressure or stress on the aortic leaflets, which in turn may lead to the structural change of valve sclerosis (25). The sinuses of Valsalva were selected for investigation because they play a very important role in minimizing stress in the aortic leaflets (15). The circumferential curvature of the sinus decreases from systole to diastole to produce stress-sharing in the leaflet-sinus of Valsalva unit so that the sinuses of Valsalva are essential to keep stress in the aortic valve leaflets at its lowest value (15). Aortic wall stress is a function of the ratio of internal radius divided by wall thickness (16). Similarly, the tangential elastic modulus of the aortic wall is a function of wall thickness (16). Consequently, a thinner-walled aorta should produce a greater stress at the level of the aortic sinus of Valsalva, leading to aortic valve thickening. Increased wall stress predisposes to the development of atherosclerosis (26) in the aorta, and a similar process might be operative in the pathophysiology of aortic valve sclerosis.

A common defect of aortic wall and aortic valve structure at either the collagen, elastin, cellular or extracellular matrix elements in the aorta and aortic valve is an intriguing possibility, but requires an explanation as to how a similar defect would produce discordant changes - that is, a thinner aortic wall but thicker valve leaflets. Aging, which is associated with the development of AVS, is linked with changes in the cellular composition of the aortic wall, including an accumulation of ground substance, disruption of the elastic lamellar units and increases in the collagen fragmentation of elastic fibers (27). The constituents of the arterial media account for its viscoelastic properties, including its stiffness (17,28). The concept has been advanced that the aortic root stiffens progressively with aging (29) as the loss of elastic recoil shifts the role of load-bearing from the elastic fibers to the collagen fibers (28,29). Stiffening of the aortic root at the level of the sinus of Valsalva may change aortic leaflet function from smooth and coordinated to irregular leaflet function which would place more strain on the aortic leaflets that might eventually produce aortic valve sclerosis (30).

Study limitations

Several important limitations may be considered relevant to the study methodology and its extrapolation. A defined age group was selected to adjust for the effect of age for two major reasons. First, the cross-sectional area of the aorta at the STJ, as well as the volumes of the sinuses of Valsalva, measured at autopsy, are significantly and directly related to age (31). Second, the age group was selected to increase homogeneity and to ensure a high prevalence of aortic sclerosis and yet have a control group with a sufficient number of individuals without the condition. Younger subjects have a lower prevalence of AVS, while older subjects have a lower prevalence of normal aortic valve (3,4). Third, aortic wall thickness is sometimes difficult to measure because of its small size. Fourth, although blood pressure was not measured in this study and the underlying association of hypertension with AVS needs to be recognized (5,6,8), the aortic root diameter at the level of the sinus of Valsalva, measured echocardiographically, is not significantly different in hypertensive subjects compared to controls in clinical epidemiologic or pathologic studies when the confounding influence of aging is considered (21-23,27,32). In the absence of blood pressure, wall stress was not calculated, though magnetic resonance imaging of the descending thoracic aorta with adjacent blood velocity measurements have shown that a thinner aorta correlates with greater shear stress (33). Fifth, other pathophysiologic mechanisms of AVS such as risk factors for atherosclerosis (smoking, lipid levels, or the presence of diabetes mellitus), polymorphism of the vitamin D receptor (10), CRP levels (12) or endothelial dysfunction (11) were not examined, though no data exist linking these factors to aortic wall thickness. Interestingly, intensive lipid-lowering therapy that reduces both low-density cholesterol and CRP did not halt the progression of calcific aortic stenosis, or induce its regression (34). Sixth, the control population was selected as having no echocardiographic abnormalities, yet their referral for evaluation implies a suspicion of cardiovascular disease. Seventh, the study was based on transthoracic measurements, while a transesophageal approach is more precise in some circumstances; however, TTE and TEE measurements do not differ in their measurement of aortic root diameter (35).

In conclusion, the identification of an association between aortic wall thickness and AVS does not prove causality. However, this novel association, taken together with the mathematical and biological basis for its relevance, suggests a potential pathophysiologic relationship and the need for prospective studies to determine whether aortic wall dimensions at the sinus

of Valsalva are associated with increased development of AVS. A thinner aortic wall may be a predictor of the development of AVS, a precursor of aortic stenosis.

References

1. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;341:142-147
2. Aronow WS, Ahn C, Shirani J, Kronzon I. Comparison of frequency of new coronary events in older subjects with and without valvular aortic sclerosis. *Am J Cardiol* 1999; 83:599-600
3. Rabkin SW, Chu-Chu-Lin SF. Epidemiology of valvular heart disease in Canada. *Can J Cardiol* 1988;4:412-416
4. Lindroos M, Kupari M, Heikkila 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
5. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29:630-634
6. Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. *Am J Cardiol* 1987;59:998-999
7. Edwards JE. On the etiology of calcific aortic stenosis. *Circulation* 1962;26:817-818
8. Roberts WC. The hypertensive diseases. Evidence that systemic hypertension is a greater risk factor to the development of other cardiovascular diseases than previously suspected. *Am J Med* 1975;59:523-532
9. Avakian SD, Annicchino-Bizzacchi JM, Grinberg M, Ramires JA, Mansura AP. Apolipoproteins AI, B, and E polymorphisms in severe aortic valve stenosis. *Clin Genet* 2001;60:381-384
10. Ortlepp JR, Hoffmann R, Ohme F, Lauscher J, Bleckmann F, Hanrath P. The vitamin D receptor genotype predisposes to the development of calcific aortic valve stenosis. *Heart* 2001;85:635-638
11. Poggianti E, Venneri L, Chubuchny V, Jambrik Z, Baroncini LA, Picano E. Aortic valve sclerosis is associated with systemic endothelial dysfunction. *J Am Coll Cardiol* 2003;41:136-141
12. Chandra HR, Goldstein JA, Choudhary N, et al. Adverse outcome in aortic sclerosis is associated with coronary artery disease and inflammation. *J Am Coll Cardiol* 2004;43:169-175
13. Thubrikar MJ, Nolan SP, Aouad J, Deck JD. Stress

- sharing between the sinus and leaflets of canine aortic valve. *Ann Thorac Surg* 1986;42:434-440
14. Robicsek F, Thubrikar MJ. Role of sinus wall compliance in aortic leaflet function. *Am J Cardiol* 1999;84:944-946
 15. Beck A, Thubrikar MJ, Robicsek F. Stress analysis of the aortic valve with and without the sinuses of Valsalva. *J Heart Valve Dis* 2001;10:1-11
 16. Bader H. Dependence of the wall stress in the human thoracic aorta on age and pressure. *Circ Res* 1967;20:354-361
 17. O'Rourke MF. Arterial function in health and disease. Churchill Livingstone Press, 1982
 18. Gerstenblith G, Frederiksen J, Yin FC, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56:273-278
 19. Kitzman DW, Edwards WD. Age-related changes in the anatomy of the normal human heart. *J Gerontol* 1990;45:33-39
 20. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-1083
 21. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol* 1989;64:507-512
 22. Kim M, Roman MJ, Cavallini C, Schwartz JE, Pickering TG, Devereux RB. Effect of hypertension on aortic root size and prevalence of aortic regurgitation. *Hypertension* 1996;28:47-52
 23. Vasan RS, Larson MG, Levy D. Determinants of echocardiographic aortic root size. *Circulation* 1995;91:734-740
 24. Francis GS, Hagan AD, Oury J, O'Rourke RA. Accuracy of echocardiography for assessing aortic root diameter. *Br Heart J* 1975;37:376-378
 25. Moore J, Jr., Xu C, Glagov S, Zarins CK, Ku DN. Fluid wall shear stress measurements in a model of the human abdominal aorta: Oscillatory behavior and relationship to atherosclerosis. *Atherosclerosis* 1994;110:225-240
 26. Schlatmann TJ, Becker AE. Histologic changes in the normal aging aorta: Implications for dissecting aortic aneurysm. *Am J Cardiol* 1977;39:21-26
 27. Dobrin PB. *Handbook of Physiology, Volume III*, 1983:65-102
 28. Roach MR, Burton AC. The reason for the shape of the distensibility curve of arteries. *Can J Biochem Physiol* 1957;35:681-690
 29. O'Rourke MF, Blazek JV, Morreels CL, Jr., Krovetz LJ. Pressure wave transmission along the human aorta: changes with age and in arterial degenerative disease. *Circ Res* 1968;23:567-579
 30. Robicsek F, Thubrikar MJ, Fokin AA. Cause of degenerative disease of the trileaflet aortic valve: Review of subject and presentation of a new theory. *Ann Thorac Surg* 2002;73:1346-1354
 31. Silver MA, Roberts WC. Detailed anatomy of the normally functioning aortic valve in hearts of normal and increased weight. *Am J Cardiol* 1985;55:454-461
 32. Pearson AC, Gudipati C, Nagelhout D, Sear J, Cone JD, Labovitz AJ. Echocardiographic evaluation of cardiac structure and function in elderly subjects with isolated systolic hypertension. *J Am Coll Cardiol* 1991;17:422-430
 33. Wentzel JJ, Corti R, Fayad ZA, et al. Does shear stress modulate both plaque progression and regression in the thoracic aorta? *J Am Coll Cardiol* 2005;45:846-854
 34. Cowell SJ, Newby DE, Prescott RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;352:2389-2397
 35. Stoddard MF, Liddell NE, Vogel RL, Longaker RA, Dawkins PR. Comparison of cardiac dimensions by transesophageal and transthoracic echocardiography. *Am Heart J* 1992;124:675-678