Sex Differences in Aortic Valve Calcification

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“There is still need to think and plan, but on a different scale, and along different lines.”

— C.S. Forester

Although sex differences in the pathophysiology and clinical expression of coronary artery disease are well appreciated, the impact of gender on valvular heart disease has not been extensively studied. Furthermore, the emphasis to date has been on understanding sex differences in the ventricular response to the pressure and volume overload posed by valvular disease rather than evaluating differences in the valves themselves. It is now known that women tend to respond differently than men to the increased afterload of worsening aortic stenosis (AS), with more concentric left ventricular (LV) hypertrophy, smaller LV cavities, and greater relative wall thicknesses. Recently, it has also been reported that although more women than men with severe AS have LV hypertrophy preoperatively, women more frequently experience reversal of hypertrophy shortly after aortic valve replacement. Lower collagen I and III, as well as matrix metalloproteinase 2 gene expression, in women versus men in the myocardial biopsy specimens performed at the time of surgery suggest that women have less fibrosis before surgery, leading to faster regression of LV hypertrophy postoperatively. On a molecular level, decreased extracellular fibrosis has been linked to the protective effect of estrogen in the setting of higher levels of estrogen receptors in women.

In this issue of Circulation: Cardiovascular Imaging, Aggarwal et al have directed their attention to the aortic valve itself, comparing the extent of aortic valve calcification (A VC) in men and women with comparable and at least mild degrees of AS. They prospectively examined A VC, measured in Agatston units (AU) by multidetector computed tomography (CT), and compared aortic valvular calcium load in 665 patients, 36% women, from 2 centers (Mayo Clinic, 502 patients, and Bichat Hospital, 162 patients). Each center included the same overall proportion of men and women, and this proportionality was maintained in the use of 16- or 64-slice CT scanners. AS severity was assessed on the basis of peak aortic velocity, mean gradient, and aortic valve area (AVA) indexed to body surface area with the mean interval between the studies being 4±11 days (range, 0–68 days). Although statistically different in women and men, the mean LV ejection fraction was well preserved in both groups (62% versus 59%, respectively).

The key finding was that although there was no overall difference in AS severity between the groups, A VC load was lower in women than in men. That this was not exclusively the result of the smaller body and annular sizes of women was supported by the fact that the difference in calcium load persisted after A VC load was indexed to body surface area (indexed A VC in women=996±781 versus 1345±823 AU/m² in men; P<0.0001). In addition, the authors coined the term AVC density, defined as A VC indexed to either cross-sectional area of the aortic annulus or LV outflow tract, and noted sex differences in this parameter as well (A VC density in women=502±384 versus 633±399 AU/cm² in men; P<0.0001). Even after adjustment for characteristics associated with high A VC load such as age, LV outflow tract diameter, peak velocity, and indexed AVA, men had 5-fold greater odds of having severe A VC. AVC, indexed A VC, and A VC density showed a good correlation with echocardiographic indexes of AS severity expressed as peak velocity, mean gradient, and indexed AVA, with women having more hemodynamically severe AS than men for the same A VC load. The authors conclude both that there are fundamental sex differences in the pathophysiology of AS and that A VC thresholds for the diagnosis of severe AS should be different in men and women.

Methodological Concerns

In any cross-sectional study, confounding variables not accounted for in the analysis are a concern. In this study, although patients with endocarditis, rheumatic valve disease, and prior aortic valve surgery were excluded, there is no mention of how many patients, if any, had bicuspid aortic valve. Bicuspid aortic valve is more prevalent in men with a male:female ratio of 3:1, with A VC typically observed by the fourth decade, and it is almost certain that the study group included a mixture of patients with bicuspid and tricuspid valves. It would have been helpful to have a secondary analysis in which patients with bicuspid aortic valve were excluded or, if numbers permitted, a subgroup analysis in which patients with tricuspid and bicuspid valves were considered separately. Second, although the mean values for AS severity were comparable in men and women, it would have been helpful to have another measure of central tendency for the data set or possibly an analysis with men and women paired on the basis of echo cardiographic indexes of severity. Such information would allay the concern that although mean AS severity was comparable in men and women, the analysis might be confounded by the fact that more women than men were outliers with extremely severe stenosis and thus disproportionately more women in the overall study.
group might have had milder stenosis as well, that is, a study group of relative extremes. The density of the data points in Figure 1 makes it impossible to address this concern by simple visual inspection. An additional concern is raised by reporting AS severity on the basis of body surface area-corrected values, a process that is controversial, particularly when applied to obese individuals. Although it is reassuring that the study findings using indexed AVA are consistent with those using unadjusted velocities and mean gradients, it would have been interesting to have the data analyzed on the basis of unadjusted valve area as well.

**Sex Differences in the Pathophysiology of AVC**

Until the early 1990s and the pivotal article of Otto et al, AVC was regarded as a passive process of degenerative age-related valve mineralization. It is now recognized that AVC is complex and active, with shared molecular mechanisms causing both arterial and valvular calcification. As outlined in the recent review by New et al, part of the thematic series in *Circulation Research* on the pathobiology of vascular calcification, calcification is the result of a sequence of events initiated by inflammation with important roles played by proinflammatory monocytes and activated endothelial cells that express adhesion molecules. Subsequent macrophage accumulation and the release of proteolytic enzymes, including matrix metalloproteases and cathepsins, stimulate the differentiation of myofibroblasts and smooth muscle cells into osteoblasts with resultant osteogenic activity. Lipoprotein retention and signaling, oxidative stress, and renin-angiotensin system activation may also play roles. The impact of sex at the cellular and molecular levels in the pathogenesis of AS promises to be an interesting avenue of investigation. Thus, although the authors do not offer hypotheses as to the basis for the reported sex differences in AVC, their study is, indeed, hypothesis generating.

**CT for the Diagnosis of AS?**

The authors also suggest that, when CT-assessed AVC load is used to judge the severity of AS, different cutoff values be used in men and women, implying a significant role for CT in the diagnosis of AS. This conclusion should be interpreted with caution because the role of AVC needs to be confirmed in future studies and there is overlap in AVC values for various degrees of AS severity.

**Prior CT Studies**

Kaden et al demonstrated a good correlation between AS severity and AVC load in 40 patients with varying AS severity using electron-beam CT, an older CT modality that has been largely replaced by multidetector CT. AVC load was measured using calcium area, a different scoring technique from the Agatston score used in other studies. Subsequently, a coauthor of the present article, Messika-Zeitoun, and his colleagues confirmed a good correlation between AVC load and AS severity in 100 patients using electron-beam CT and Agatston score. This study also reported the prognostic value of AVC independent of AVA, with higher values predicting lower event-free survival. A more recent study by Cuffe et al again showed good correlation between AS severity and AVC using 16-detector multidetector CT in 179 patients with LV ejection fraction >40% and derived the best sensitivity/specificity with a threshold of 1651 AU. This was also validated in 49 patients with LV ejection fraction <40%. Although these studies and the present report by Aggarwal et al show good correlation between AVC and AS severity, none provides convincing evidence that a given AVC score can rule in or exclude severe AS. Rather, each demonstrates scattering of AVA values for a given AVC score, and the present study also reports significant overlap in the AVC–AS severity relationship between men and women, particularly with milder forms of AS. In aggregate, these data suggest that AVC is related to but not a direct index of hemodynamic AS severity, undermining the argument that AVC score could be used to diagnose AS in an individual patient.

**Radiation Exposure**

The role of CT in diagnosing AS severity should be considered carefully because of the radiation exposure with which it is associated—in this study, 2 to 3 mSv. Because patients with cardiovascular diagnoses are likely to undergo repeated imaging over a lifetime, all studies involving ionizing radiation should be considered carefully for their incremental value. The gold standard for assessment of AS severity remains Doppler echocardiography, which has recently also provided means of identifying patients with severe AS despite low gradients. These arguably might be those for whom an ancillary imaging modality such as CT might be most useful. In the transcatheter aortic valve era, in which CT has assumed a larger role, this role is currently largely one of annular sizing, not assessment of severity, although these clinical studies may allow us to further study the use of CT in evaluating valvular anatomy.

**Conclusion**

The principal contribution of this study is the suggestion that there are sex differences in the pathophysiology of AS at the valvular and ventricular levels. It is therefore hoped that sex will be considered in ongoing and future research into the cellular and molecular bases of AS.

**Disclosures**

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**References**


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