Sex-Associated Differences in Left Ventricular Function in Aortic Stenosis of the Elderly

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The role of sex is being increasingly and importantly acknowledged in the expression of a broad spectrum of cardiac diseases. The study by Carroll et al. in this issue of Circulation describes intriguing sex-related cardiac responses to aortic stenosis that have potential clinical importance. In this retrospective study, the authors report that elderly women with the same degree of aortic stenosis as men have on average distinctly different contractile performance. Women tend to have smaller ventricles with well-preserved systolic function, whereas men tend to have exaggerated ventricular hypertrophy and reduced indexes of systolic performance. In fact, in a subgroup of 41% of women, ventricular performance was supernormal, reminiscent of the elderly patients (largely female) with hypertension and hypertrophic myopathy reported by Topol et al. The authors postulate that basic biological differences related to sex are responsible.

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Before accepting this hypothesis, the data should be considered in the context of the known geometric and physiological differences between male and female hearts. Foremost among these is the fact that hearts from male subjects in general tend to be larger. In human studies, this is true both in absolute terms and also if the data are indexed to body surface area, although Devereux has shown that if heart mass is normalized to lean body mass the sex difference is eliminated. This suggests that the difference in heart size is to some extent secondary to body size rather than a genetically determined characteristic and also that men have a relative degree of hypertrophy in the absence of any pathological load. Relevant to the present report are data from the Framingham Study that suggest that with aging, female hearts continue to enlarge, whereas male hearts, although still larger than females, show a slight decline in size. In addition (and probably related), women tend to have higher resting heart rates than men, probably reflecting both decreased blood hemoglobin content and increased adrenergic tone that would translate into a relatively smaller stroke volume and reduced end-diastolic dimension. In fact, to increase cardiac output during submaximal acute dynamic exercise, healthy women tend to increase cardiac output by increasing end-diastolic volume, whereas men tend to increase ejection fraction.

Two alternate approaches to the present data are suggested by this physiology: The first is to view the hearts in this study as isolated organs pumping against fixed resistances. The similar valve areas should theoretically impose equivalent resistances in both the larger male and the smaller female hearts. However, despite the 41% increase in left ventricular mass in male hearts, the female hearts generated similar absolute stroke volumes but with a greater systolic pressure and dP/dt and a smaller end-systolic dimension. The ability to perform in this manner may conceivably have been related to the more favorable ventricular geometry, resulting in lower systolic wall stress in the women.

A second interpretation is to envision distinct chronic adaptations to gradually increasing systolic afterload in men and women, the most salient feature of which is exaggerated hypertrophy in the men. It is not known when aortic stenosis becomes hemodynamically significant either in men or in women, but it is likely that there are many years of increased systolic loading before the patients present. It is also conceivable (though unlikely) that the onset of degenerative aortic stenosis may be at a younger age in men than in women and that the hearts in this study were subjected to different durations of increased afterload. In general, however, healthy men have greater cardiac output and lower heart rates and therefore comparatively larger stroke volumes than women. Thus, as aortic stenosis develops in the two sexes, the systolic load would be greater in the male hearts, leading to an increase in systolic wall stress, exaggerated hypertrophy, ventricular dilation, and earlier ventricular dysfunction.

Having offered these alternate interpretations of the data, in fact there are ample clinical and experimental studies that support the conclusion that intrinsic sex-specific differences in cardiac muscle physiology and biochemistry do exist. For example, male mice have greater mitochondrial respiratory and lysosomal enzyme activities than female mice, and female rats have greater myosin ATPase activities and a higher percentage of the V1 myosin isozyme than male rats. The myosin isoenzymes and ATPase activities in female hearts are upregulated by estrogen and, to a greater extent, by testosterone. In addition, testosterone causes cardiac muscle hypertrophy and increases inotropy in the absence of an effect on preload or systemic vascular resistance in rats. Intriguing data (not yet demonstrated in cardiac muscle) suggest that testosterone can...
also upregulate α-adrenergic receptors in myometrium\textsuperscript{9,10} and increase collagen and elastin deposition by fibroblasts in vascular smooth muscle.\textsuperscript{11} The hypertrophic response to hypertension is greater in female than in male rat hearts.\textsuperscript{12}

Clinical data assessing the role of sex in the development of cardiac hypertrophy and ventricular dysfunction are relatively sparse, and what data do exist are colored by the referral patterns of physicians and by intercurrent illnesses. However, the literature suggests that whereas women develop symptoms of congestive heart failure as commonly as men, the patterns of ventricular contraction that develop are more consistent with diastolic than with systolic abnormalities. In an early small study of 50 patients with clinical congestive heart failure, Echeverria et al\textsuperscript{13} demonstrated impaired systolic performance in 72% of the men and only 40% of the women. Similar data demonstrating a female preponderance among patients with congestive heart failure and normal left ventricular function have been reported by others.\textsuperscript{14,15} Strikingly, and in modest contrast to the data presented in the present study, the female subjects in these studies all had significant and disproportionate degrees of left ventricular hypertrophy. In fact, DeVereux et al.\textsuperscript{16} have noted that women with essential hypertension have an increased prevalence of left ventricular hypertrophy when normalized to body mass versus men when these data are adjusted to sex-specific standards.

Cardiac hypertrophy transits through different stages. There is evidence in experimental animals that early in the response to pressure overload, there may be a period of enhanced function associated with upregulation of biochemical factors that relate to the velocity of contraction and relaxation.\textsuperscript{17} Only after longer periods of overload are the decreases in contraction and relaxation characteristic of pathological hypertrophy observed. This early augmentation is similar to that seen in experimental animals with exercise-induced cardiac hypertrophy.\textsuperscript{12} In humans with congenital aortic stenosis, there appears to be an overcompensation of myocardial contraction early on\textsuperscript{18} that is similar to that described in the subgroup of women with hyperfunction in the present study. The mechanisms underlying this enhancement of systolic function in the hypertrophied myocardium of experimental animals have been related to upregulation of both contractile protein enzymatic activity, either through shifts in the myosin isoenzymes or other sarcomeric regulatory proteins, and to enhanced calcium uptake by the sarco-/plasmatic reticulum. There is not yet compelling evidence that these mechanisms are important in humans, and certainly no information is available as to why these ill-defined phenomena might be more prevalent in female than in male hearts. It is clear that in end-stage failing myocardium, myofibrillar ATPase activity is depressed,\textsuperscript{19} and sarco-/plasmatic reticular function may be impaired.\textsuperscript{20}

The possible clinical significance of the present study relates to natural history, to determining the correct time for surgery, and to the risks and results of surgery. Several studies have demonstrated that asymptomatic patients with aortic stenosis have a good prognosis until the time that they develop symptoms\textsuperscript{21,22} and that once symptoms develop, they are at risk for rapid deterioration and early death. One might postulate that patients in the hyperkinetic group, despite the fact that they were symptomatic, would have different natural histories than those with myocardial dysfunction. Although that is a reasonable hypothesis, its validation would require a prospective study. It is likely that those patients with systolic dysfunction will develop symptoms earlier and therefore require earlier surgical intervention. It is also possible that one group or other might be more subject to serious ventricular arrhythmias. Finally, it is well understood that although patients with ventricular dysfunction benefit from aortic valve replacement, the more severe the dysfunction, the higher the surgical mortality and less favorable will be the long-term effect of surgery.\textsuperscript{23} Therefore, discovery of early dysfunction in asymptomatic patients would dictate more frequent noninvasive evaluations. Data do not exist at present indicating that women with aortic stenosis have either more favorable natural histories than men or are less likely to require surgery. The study by Carroll et al.\textsuperscript{14} therefore stimulates provocative scientific questions related to the possible role of sex in heart functions and responses not only to aortic stenosis but to other disease processes. It also raises practical clinical questions related to the care of patients with valvular aortic stenosis.

References


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