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EDITORIAL COMMENT

The Symptoms of Aortic Stenosis

A Step Closer to Understanding Their Cause*

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The onset of the classic symptoms of aortic stenosis (AS), angina, syncope, and those of heart failure marks a dramatic worsening in the prognosis of the disease. Remarkably, there have been no specific hemodynamic markers predicting this critical change in clinical status. To be sure, the presence an aortic valve area of <1.0 cm^2 and/or a transaortic jet velocity exceeding 4.0 m/s makes it likely that symptoms will ensue in a relatively short period of time (1). However, no specific valve area or pressure gradient has been found to predict symptom status.

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This was confirmed in the current study by Park et al. (2) in this issue of *iJACC*, and left ventricular (LV) mass and wall thickness were also similar in symptomatic and asymptomatic AS patients. So what causes the crucial onset of the symptoms of AS, and how do the current data help explain the pathophysiology driving these symptoms?

Mechanisms Determining LVH in AS

Whereas the magnitude of left ventricular hypertrophy (LVH) did not by itself explain the symptoms of AS in the current study, it is hard to imagine that symptoms are not related to LVH or that LVH is a mere epiphenomenon of the disease. Indeed, severe LVH in AS clearly affects disease prognosis (3). Almost 4 decades ago, Grossman et al. (4) postulated that systolic wall stress (σ) was the mechanical factor in pressure overload that stimulated the myocardium to grow. Indeed, an increase in stress increases myocardial protein synthesis by 35% within 6 h of pressure overload (5). However, identical increases in load can cause vastly different individual hypertrophic responses (Fig. 1) (6). This variation is presumably caused by genetic differences in the many biologic signaling pathways that transduce the mechanical stimulus of increased systolic stress into muscle mass. Signal transduction is complicated further because the stenotic valve is not the only resistance to LV outflow. Vascular resistance, which is increased in the elderly patient with AS, also plays an important role (7). Thus, it is not surprising that neither pressure gradient nor aortic valve area by themselves are predictive of symptom onset because those factors do not by themselves control the myocardium's response to AS.

Dyspnea

Reassuringly, the severity of diastolic dysfunction correlated best with the symptom of dyspnea in the current study. Although, in 2012, we still are not exactly certain what causes dyspnea, left-sided filling pressures seem to have a good correlation with the symptom (8). Accordingly, diastolic dysfunction, which increases LV filling pressure, predicted dyspnea. The next question is what causes the diastolic dysfunction?

LVH and diastolic filling. Diastole is conventionally divided into 2 parts, early active relaxation followed by passive filling (9). Early relaxation is described by LV pressure decay time, whereas passive filling is characterized best by the diastolic pressure-volume relationship of the LV (10). It would seem intuitive

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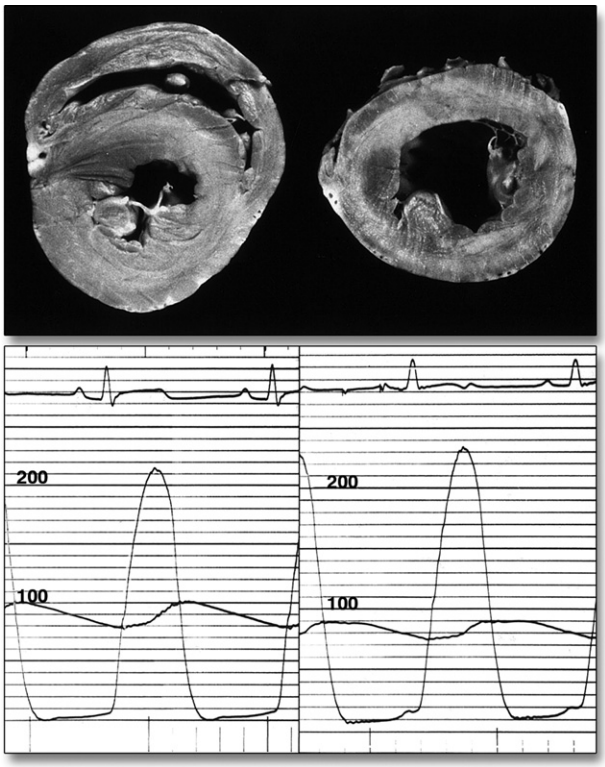

Figure 1. Similar Load Causes Wide Variation in Hypertrophy

Left ventricular cross sections from 2 dogs with aortic stenosis are shown. Despite virtually identical loading, dramatic differences in the amount of left ventricular hypertrophy are shown. Reprinted, with permission, from Koide et al. (6).

that increased LV wall thickness would mandate diastolic dysfunction during passive filling: that is, that more pressure would be required to fill a thicker ventricle. Although there must be some truth to this concept, the relationship between LVH and diastolic filling is complex. For example, elite athletes that perform primarily isometric exercise, such as weight lifters, demonstrate concentric LVH (albeit not as severe as that seen in AS) and usually have normal diastolic function (11). Thus, an increase in wall thickness alone does not necessarily mandate increased LV filling pressure. The observation of normal diastolic function despite LVH in athletes suggests differences between that kind of physiologic LVH versus the hypertrophy that occurs in pathologic conditions such as AS.

Early active relaxation is slowed in pathologic LVH, reflecting abnormalities in the calcium handling that pumps calcium back into the sarcoplasmic reticulum, reducing actin-myosin interaction (12). This slowing of active relaxation delays the diastolic fall in LV pressure during isovolumic relaxation, in turn delaying mitral valve opening and shortening the time for the LV to fill.

Passive filling in pathologic LVH is characterized by a shift in the diastolic pressure-volume relation of the LV upward and leftward, thus requiring increased filling pressure to fill the LV to any given volume because the LV is stiffer than normal. Increased LV stiffness in pathologic LVH accrues both from intrinsic and extrinsic factors. Intrinsically, myocytes are thicker and also imbued with a denser than normal cytoskeleton (13), in turn causing the myocyte to be stiffer than normal. Increased chamber stiffness is also due to increased extracellular components including the collagen network that holds the LV together and that connects the myocyte to the chamber (14). Thus at least 4 factors—LV thickness, active relaxation, myocyte structure, and extracellular matrix—can vary from patient to patient, in turn altering diastolic function. This complexity helps explain why, in the current study, the magnitude of LVH did correlate well with the symptom of dyspnea.

Syncope

Syncope occurs when there is inadequate systemic blood pressure to support cerebral blood flow. The current study sheds light on why this might occur. The group with syncope had the smallest LV mass and LV volumes, in turn producing the lowest stroke volume index and the lowest cardiac output at rest. Additionally E/e′, a guide to filling pressure, was also lowest in this group. These data suggest that patients with syncope have remodeled in such a way as to have smaller hearts that generate less cardiac output, possibly compounded by lower LV filling pressure further limiting cardiac output.

Angina

Angina occurs when myocardial oxygen demand exceeds oxygen supply and the milieu of the AS patient is rich in potential anginal causes. On the oxygen demand side, oxygen demand is determined in large part by the product of systolic wall stress and heart rate. In many AS patients, wall stress is elevated (15) so that the heart rate–stress product during exercise may be very high, helping to explain the onset of angina. These exercise parameters were not addressed in this study of resting patients.

On the oxygen supply side, it is well known that coronary flow reserve is reduced in AS patients (16). This reduction is in part related to increased filling

pressure reducing the coronary flow driving gradient and probably also due to decreased capillary density in the hypertrophied muscle (17,18). However, the best correlate of the symptom of angina in AS is reduced diastolic filling time, which is the time available for coronary blood flow to occur (19,20). Thus, it is reassuring that parameters other than diastolic filling time in the current study did not differ very much in the group of patients with angina when compared with angina-free patients.

AS creates an amazingly complex array of biologic events that affect the LV and the patient. Outflow obstruction acts with peripheral resistance to impede LV ejection, in turn summoning LVH as a compensatory mechanism, and understanding this interaction is important to understanding the origins of LVH. Unfortunately, LVH in this setting is attended by a series of pathologic consequences derived from the composition of the myocardium. This composition varies from patient to patient, probably based largely on variation in genetic makeup. Thus, 1 size hardly fits anyone, and there is wide variation in the magnitude of LVH and in myocardial composition from patient to patient. Despite this variability, the current study confirms that the effects of LVH in AS have measurable consequences. Diastolic dysfunction is a key driver of dyspnea in patients with normal ejection fraction, whereas smaller LV volumes reduce cardiac output, pre-disposing the patient to syncope.

Imaging today is focused on measuring cardiac motion and geometry. However, inroads are being made into imaging the components of the LV. It is highly likely that we will be able to image specific molecular changes in the future, and these advances are likely to give further insight into what causes the deadly symptoms of AS—knowledge that almost inevitably will affect disease management.

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