JACC: CARDIOVASCULAR IMAGING
VOL. 2, NO. 4, 2009

ISSN 1936-878X/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2009.01.004

EDITORIAL COMMENT

Aortic Stenosis: Look Globally, Think Globally*

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In the past, calcific aortic valve stenosis (AS) was thought to be a degenerative process. However, there is a now a strong body of evidence suggesting that calcific AS is in fact an active disease akin to atherosclerosis, and in this context, it is not surprising that many patients with AS also have manifestations of atherosclerosis in other target organs. Hence, calcific AS should not be viewed as an isolated disease strictly limited to the aortic valve but rather as a systemic disease that often includes increased rigidity of the aorta caused by atherosclerosis or aging and alterations of left ventricular (LV) function secondary to coronary artery disease, systemic hypertension, or diabetes. This new face of the disease underlines the need for a more comprehensive assessment of AS severity going beyond the classical measurement of transvalvular pressure gradient and aortic valve area. Given its noninvasive, radiation-free, low-cost, and highly versatile nature, Doppler echocardiography is the method of choice for taking a global look at this complex and multifaceted disease. In the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study, Doppler echocardiograms of 1,873 patients with asymptomatic AS were prospectively obtained in 173 sites and analyzed in a core laboratory. This database provides a unique opportunity to depict the current pattern of calcific AS and to elucidate the determinants of its progression and outcome. The main findings of the SEAS substudy published in this issue of *iJACC* (1) are: 1) one-third of AS patients with no symptoms and preserved left ventricular ejection fraction (LVEF) have an impairment of systolic myocardial function as reflected by reduced LV mid-wall shortening; 2) the global, that is, valvular plus arterial, hemodynamic load as estimated by the valvulo-arterial impedance is the main determinant of myocardial dysfunction; and 3) one-third of asymptomatic AS patients have reduced stroke volume despite preserved LVEF. This pattern, referred to as paradoxical low flow AS by Hachicha et al. (2), is associated with more pronounced LV concentric remodeling, smaller LV cavity, increased global LV load, and reduced mid-wall shortening (Fig. 1). Moreover, these patients often present with a low transvalvular gradient even though they have a severe stenosis on the basis of valve area, and this situation may lead to an underestimation of stenosis severity and an underutilization of valve replacement (2).

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Valvulo-Arterial Impedance: An Index of Global Hemodynamic Load

As highlighted by recent studies (2,3) including the one by Cramariuc et al. (1), a large proportion (51% in the SEAS study) of patients with calcific AS also have concomitant arterial hypertension. Hence, the LV of AS patients often faces a double load: valvular plus arterial and, in these patients, the occurrence of symptoms and adverse events should logically be related to the global hemodynamic burden faced by the ventricle. This global load not only includes the valvular load but also the pulsatile and steady components of the arterial load, which are associated with reduced arterial compliance and increased vascular resistance, respectively. To assess the global LV hemodynamic load in AS patients, we recently proposed a new index easily measured

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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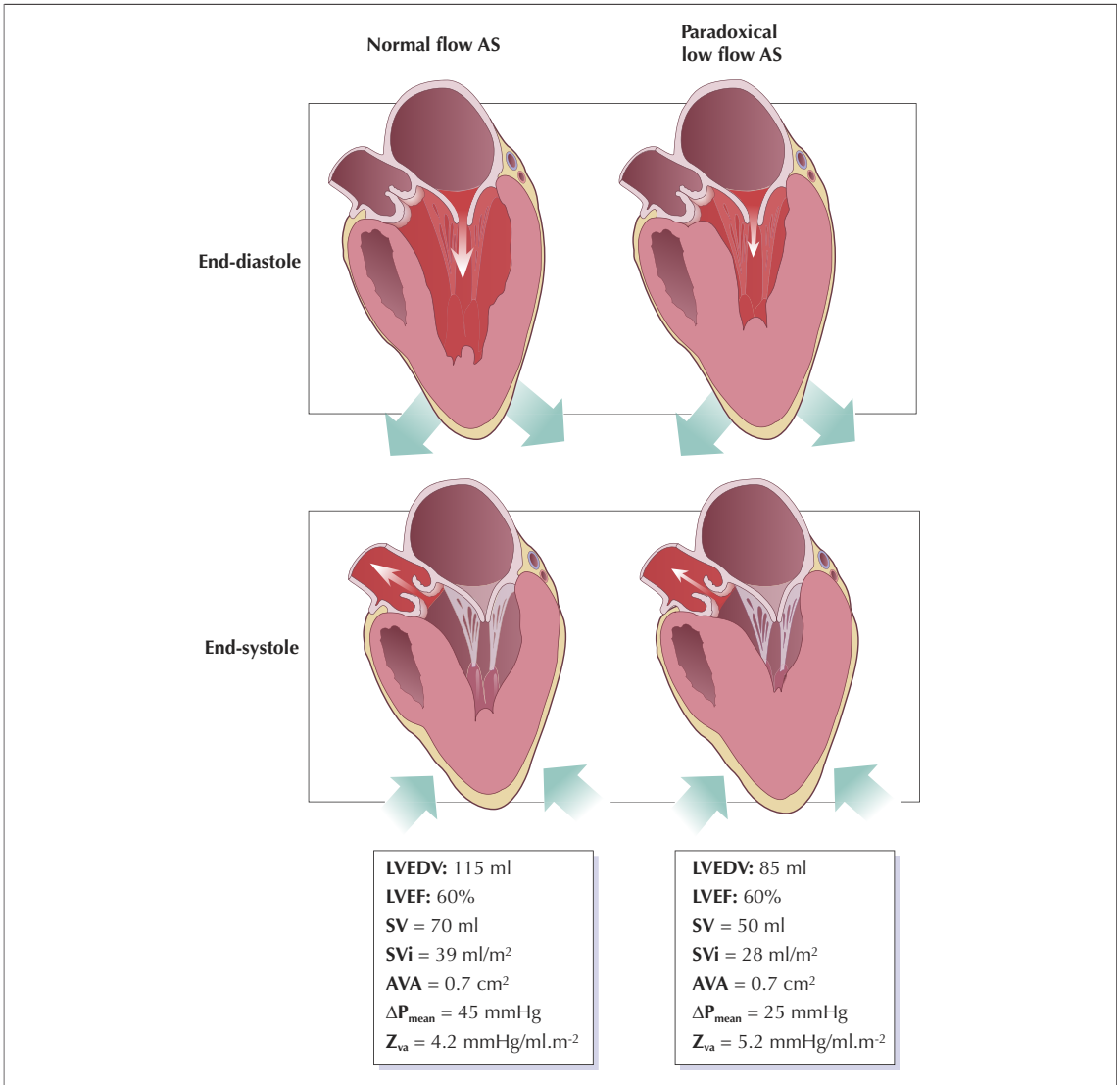

Figure 1. Comparison of Typical LV Geometry and Doppler Echocardiographic Findings in Normal Versus Paradoxical Low Flow Aortic Stenosis

AS = aortic valve stenosis; AVA = aortic valve area; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; SV = stroke volume; SVi = stroke volume index; Z_{va} = valvulo-arterial impedance; ΔP_{mean} = mean transvalvular gradient.

by Doppler echocardiography: the valvulo-arterial impedance (Z_{va}), which is the ratio of the estimated LV systolic pressure to the stroke volume indexed for body size (3). This index in fact represents the valvular and arterial factors that oppose ventricular ejection by absorbing the mechanical energy developed by the LV. As confirmed in this article (see Fig. 1 of Cramariuc et al. [1]), myocardial dysfunction is essentially determined by global LV load and hence, the LV of a patient with moderate AS and concomitant hypertension may face a global hemodynamic load that is equivalent or superior to that of a patient with severe AS and no hypertension. Hence, in such a patient myocardial dysfunction may develop and/or the patient may become symptomatic because of the contribution of concomitant hypertension to an increased hemodynamic load and the calculation of Z_{va} may help to reconcile the apparent discordance between the moderate stenosis severity and the symptomatic status. If the Z_{va} is low, the symptoms may be related to a concomitant disease such as coronary artery disease. On the other hand, if the Z_{va} is high, the symptoms could be caused by the additive effects of a moderate AS and reduced arterial compliance and/or increased vascular resistance.

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 4, 2009
APRIL 2009:400–3

Normal LVEF Does Not Mean Normal Myocardial Function

The most important and novel finding of the study by Cramariuc et al. (1) is that 1 of 3 patients with asymptomatic AS and preserved LVEF has a significant impairment of myocardial systolic function as reflected by reduced stress-corrected mid-wall shortening. This important finding reminds us that LVEF is influenced by both intrinsic myocardial function and LV cavity geometry. Hence, for a similar extent of intrinsic myocardial shortening, the LVEF or any parameter based solely on endocardial displacement (e.g., fractional shortening) will tend to increase in relation to the extent of LV concentric remodeling (4). The LVEF may therefore markedly underestimate the extent of myocardial impairment in the presence of LV concentric remodeling such as is generally the case in AS patients. Hence, what is normal for an LV with normal geometry may be abnormal for an LV with concentric remodeling. As highlighted by the results the SEAS substudy (1), an LVEF >50% as well as the absence of symptoms cannot exclude the presence of intrinsic myocardial dysfunction. These findings provide further impetus for the systematic measurement of LV mid-wall and/or longitudinal shortening to unmask subclinical myocardial dysfunction that is often not detected by LVEF (2,4). These findings also raise the following provocative question: should we consider early valve replacement in asymptomatic patients with severe AS and preserved LVEF who present with reduced mid-wall shortening? Pending further studies on this issue, exercise stress testing could be contemplated in these patients to confirm the patient's symptomatic status.

Another important finding of the SEAS substudy (1) is that the global hemodynamic load estimated by the Z_{va} is by far the most powerful determinant of intrinsic myocardial dysfunction in asymptomatic AS patients. This subclinical and insidious alteration of myocardial function may eventually become irreversible, which could, in turn, translate into increased mortality and morbidity. In light of the findings of the SEAS study (1) as well as of our previous study (3), a value of $Z_{va} \geq 4.5$ mm Hg/ml·m$^{-2.0}$ (when using stroke volume indexed for body surface area in the formula of Z_{va}) or ≥ 7.0 mm Hg/ml·m$^{-2.04}$ (when using stroke volume indexed for height$^{2.04}$) may be useful to identify patients who are at high risk for deterioration of myocardial function. In the present study, Cramariuc et al. (1) also proposed a multiparameter score to predict the presence of myocardial systolic dysfunction. However, this score brings little additional predictive value over that provided by Z_{va} (area under the receiver-operator characteristic curve: 0.87 vs. 0.80) and would certainly be more complicated to implement for routine clinical use. These findings (1–3) underline the point that the main determinant of intrinsic myocardial dysfunction is the global hemodynamic load faced by the LV, regardless of the origin (valvular and/or arterial) of the load. The next important step in this regard would now be to determine the usefulness of the Z_{va} to predict adverse outcomes in asymptomatic AS patients.

Normal LVEF Does Not Mean Normal Stroke Volume

The data of the SEAS substudy (1) further confirm the findings of Hachicha et al. (2) showing that about one-third of patients with calcific AS have reduced stroke volume (stroke volume/body surface area <35 ml/m^2 or stroke volume/height$^{2.04}$ <22 ml/m$^{2.04}$) despite preserved LVEF. The reduction in LV output may, in turn, result in lower than expected transvalvular gradients (Fig. 1) and pseudonormalization of peripheral blood pressure in a large proportion of these patients (1–3). In the SEAS substudy (1), 56% of the low flow AS patients with severe stenosis defined by an energy loss index <0.55 cm^2/m^2 had a mean gradient <30 mm Hg. Clinically, this situation is highly insidious because both AS and hypertension may appear less severe on the basis of the transvalvular gradients and blood pressure, when in fact these patients have a higher global hemodynamic load and a more pronounced impairment of intrinsic myocardial function, consistent with a more advanced stage of the disease.

Because clinicians generally give more weight to the gradient than to other parameters, this paradoxical low flow pattern often leads to an underestimation of stenosis severity and/or symptoms and thereby to inappropriate delay of aortic valve replacement (2). Moreover, such patients have a much better outcome with aortic valve replacement than with medical treatment.

It thus follows that the proper identification of patients with paradoxical low flow is crucial and an important caveat is that measurement errors such as underestimation of LV stroke volume could lead the clinician to erroneously conclude that the patient has low flow severe AS when, in fact, the AS

is only moderate. Fortunately, however, these patients have a cluster of findings and a more comprehensive and integrated evaluation that includes the calculation of relative wall thickness ratio, LV dimension, stroke volume index, mid-wall radius shortening, and Z_{va} may help the clinician to identify the patients with paradoxical low flow severe AS (Fig. 1). In case of discordance among the echocardiographic parameters (e.g., low stroke volume measured by pulsed wave Doppler in the LV outflow tract in conjunction with a normal/high LV end-diastolic volume and ejection fraction), measurements should be meticulously verified, and if the discordance persists, further investigations using other diagnostic modalities should be contemplated. Proper identification of this entity is all the more important because although LVEF is within normal range (>50%) and gradient is relatively low (<30 to 35 mm Hg), such patients are at higher risk for development of myocardial dysfunction or symptoms and should thus be monitored very closely.

Conclusions

Cramariuc et al. (1) should be commended for an important study and we certainly concur with them that further prospective studies are urgently needed to determine prognosis and most appropriate treatment in asymptomatic patients presenting with evidence of high global LV load and intrinsic myocardial dysfunction.

Acknowledgment

The authors thank Nicolas Girerd, MD, MS, for his contribution in the preparation of the figure.

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Key Words: aortic valve ■ stenosis ■ hypertension ■ hemodynamics ■ Doppler echocardiography.