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Reduced Systemic Arterial Compliance Impacts Significantly on Left Ventricular Afterload and Function in Aortic Stenosis

Implications for Diagnosis and Treatment

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OBJECTIVES We sought to determine to what extent systemic arterial compliance (SAC) might impact on afterload and left ventricular (LV) function in patients with aortic stenosis (AS).

BACKGROUND Although AS and reduced SAC may often coexist in the same patient, their relative impact on LV function is not well understood.

METHODS Systemic arterial compliance was calculated as the ratio of stroke volume index to arterial pulse pressure in 208 patients with at least moderate AS. As a measure of global afterload, we calculated the valvulo-arterial impedance (Z_{va}), which theoretically accounts for the effects of both AS and SAC.

RESULTS Patients were divided into four groups: group 1, moderate AS and normal SAC (n = 77; 37%); group 2, moderate AS and low SAC (n = 50; 24%); group 3, severe AS and normal SAC (n = 45; 22%); and group 4, severe AS and low SAC (n = 36; 17%). The prevalences of LV diastolic and systolic dysfunction were 60% and 6% in group 1, 86% and 12% in group 2, 82% and 16% in group 3, and 94% and 31% in group 4. In multivariate analysis excluding Z_{va}, energy loss index and SAC were both independent predictors of LV dysfunction, but when Z_{va} was entered into the analyses, it became the only hemodynamic variable to be independently associated with LV dysfunction.

CONCLUSIONS Reduced SAC is a frequent occurrence in elderly patients with AS, where it independently contributes to increased afterload and decreased LV function. Systemic arterial compliance should be taken into consideration when evaluating these patients with regard to diagnosis and treatment. (J Am Coll Cardiol 2005;46:291–8) © 2005 by the American College of Cardiology Foundation

In patients with aortic stenosis (AS), the occurrence of left ventricular (LV) dysfunction, symptoms, and adverse outcomes does not always correlate with the classical markers of hemodynamic severity (i.e., valve effective orifice area [EOA] and transvalvular pressure gradients). Recently, we proposed a new index on the basis of valve EOA and cross-sectional area of the ascending aorta that takes into account the pressure recovery phenomenon (Fig. 1) (1,2). Hence, the energy loss coefficient provides an accurate estimation of the net energy loss due to the stenosis and is more representative of the increased burden imposed on the LV than the EOA calculated by the continuity equation. The energy loss coefficient indexed for body surface area (i.e., the energy loss index [ELI]) was also found to be superior to either EOA or indexed EOA in predicting adverse outcomes in patients with AS (1). Although the utilization of this index resulted in improved sensitivity and specificity for the prediction of outcomes, these values remained below 70%, therefore underlining the need for further improvement of risk stratification.

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Accelerated arterial stiffening has been linked to hypertension, dyslipidemia, diabetes, and atherosclerosis (3–7). Arterial stiffening reduces the compliance and thus the buffering function of the systemic arterial system. Reduced compliance in the large arterial circulation is regarded as a major factor in the development of systolic hypertension, contributing to increased LV afterload and myocardial oxygen demand and to diminished coronary flow during diastole (4), and it has been shown to be a strong and independent predictor of LV dysfunction and adverse outcomes (5–8). Patients with AS already have an increased

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Abbreviations and Acronyms

AS = aortic stenosis
BP = blood pressure
EOA = effective orifice area
ELI = energy loss index
LV = left ventricle/ventricular
PP = pulse pressure
SAC = systemic arterial compliance
SAP = systolic arterial pressure
SV = stroke volume
SVi = stroke volume index
Z_{va} = valvulo-arterial impedance

afterload due to their valve disease, and it remains to be determined whether reduced systemic arterial compliance (SAC) in these patients might not have an additive effect and further contribute to deteriorate LV function and increase adverse outcomes. In an acute animal model of severe AS, we recently observed that a decrease in SAC was indeed associated with a marked increase in peak systolic LV wall stress (9). We thus hypothesized that SAC might have a significant impact on LV function in AS patients, given that the LV faces a double load: valvular + arterial. The primary objective of this study was, therefore, to determine to what extent SAC might impact on afterload and LV function in these patients.

METHODS

Patients. The study included 208 consecutive patients (120 men, 88 women, mean age 69 ± 12 years) who underwent an echocardiographic evaluation and were found to have moderate or severe AS on the basis of the standards of the American Heart Association/American College of Cardiology (10). On this basis, 97 (47%) had moderate AS (aortic valve area ≤1.5 cm^2) and 111 (53%) had severe AS (valve area ≤1.0 cm^2). Data collected in these patients at the time of their echocardiographic evaluation included demographic characteristics, risks factors for heart disease, and presence or absence of symptoms (resting dyspnea, exercise dyspnea, angina, and/or syncope). Patients with moderate or severe coexisting aortic regurgitation or moderate or severe mitral valve disease were excluded. Patients with known hypertension or coronary artery disease were included because these conditions are frequent associations in degenerative AS and are precisely the conditions where SAC might be more susceptible to decrease. Hypertension was considered to be present when there was a history of hypertension requiring medical therapy. Patients were considered to have significant coronary artery disease if they had one of the following criteria: 1) history of myocardial infarction, coronary angioplasty, or coronary artery bypass graft surgery; 2) a > 50% stenosis on at least one epicardial artery on coronary angiography; and 3) a regional wall motion abnormality on echocardiogram.

Assessment of aortic valve function. Doppler-echocardiographic measurements included the LV stroke volume (SV), the peak and mean transvalvular gradients using the modified Bernoulli equation, the valve EOA using the standard continuity equation, and the ELI using this formula (Fig. 1):

$$ELI = \left[\frac{EOA \times A_A}{A_A - EOA}\right] \Big/ BSA \qquad [1]$$

where A_A is the aortic cross-sectional area calculated from the diameter of the aorta measured at the sino-tubular junction, and BSA is the body surface area. The LV stroke work loss was expressed as percentage and obtained as: 100 × (MG/MG + SAP), where MG is the mean transvalvular pressure gradient and SAP is the systolic brachial artery pressure (11).

Assessment of LV remodeling. Left ventricular mass was calculated with the corrected formula of the American Society of Echocardiography and was indexed for body surface area (12). By taking into account both values of LV mass index and relative wall thickness, patients were classified into four different LV patterns, as previously described by Ganau et al. (13).

Assessment of LV systolic function. The LV cardiac output was calculated as the product of heart rate and SV and was indexed for body surface area. The LV ejection fraction was assessed with the Quinones method (14), the Dumesnil method (15), and by visual estimate. In the case of a disagreement between these methods, the reviewing cardiologist selected the value that he estimated as being the most representative.

Assessment of LV diastolic function. Early (E) transmitral filling peak velocity and transmitral atrial (A) wave velocity were measured at rest and during phase II of the Valsalva maneuver (16). Diastolic function was classified

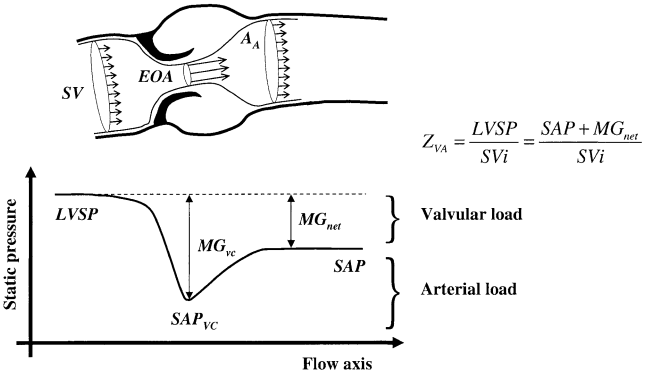

Figure 1. Schematic representation of the flow and static pressure across the left ventricular (LV) outflow tract, aortic valve, and ascending aorta during systole. A_A = aortic cross-sectional area; EOA = effective orifice area (i.e., the cross-sectional area of the vena contracta); LVSP = left ventricular systolic pressure; MG_{net} = transvalvular pressure gradient after pressure recovery (i.e., net MG); MG_{vc} = transvalvular pressure gradient at the vena contracta; SAP = systolic aortic pressure; SAP_{vc} = systolic aortic pressure at the vena contracta; SV = stroke volume; SVi = stroke volume index; Z_{VA} = valvulo-arterial impedance.

following the recommendations of the Canadian Consensus on Diastolic Dysfunction as follows: normal, impaired relaxation, pseudonormal, and restrictive pattern (17). A pseudonormal pattern was defined as present if these two criteria were met: 1) E/A ratio <1 with the Valsalva maneuver, and 2) decrease in E/A ratio >25% with the Valsalva maneuver (16).

Systemic arterial hemodynamics. Systemic arterial pressure was measured with the use of an arm-cuff sphygmomanometer at the same time as SV, measured in the LV outflow tract by Doppler. Brachial pulse pressure (PP) was calculated as the difference between systolic and diastolic arterial pressures. The ratio of SV to PP (SV/PP) was used as an indirect measure of total SAC (18). Given that it has been shown that SV/PP is related to body size in normal adults (7), we also calculated the ratio of SV index to PP (SVi/PP) (8). The systemic vascular resistance was estimated by the formula: (80 × MAP)/CO, where MAP is the mean arterial pressure and CO is the cardiac output.

Assessment of global LV afterload. A precise and complete description of the LV afterload imposed by the systemic arterial system is provided by the input impedance spectra of the systemic circulation (19), but this complex approach is not feasible in practice. Alternatively, the arterial impedance can be approximated by the systolic arterial pressure (SAP) to SVi ratio (20,21). In patients with AS, it is necessary to also take into account the load imposed by the stenotic valve on the LV. In these patients, the increase in LV systolic pressure may result from the increase in transvalvular pressure gradient, the increase in SAP (due to reduced SAC and/or increased systemic vascular resistance), or both abnormalities (Fig. 1). We therefore propose to estimate global LV afterload in AS patients by the "valvulo-arterial impedance" (Z_{va}) formulated as follows (2):

$$Z_{va} = \frac{SAP + MG_{net}}{SVi} \quad [2]$$

where MG_{net} is the mean net pressure gradient (i.e., the mean gradient taking into account pressure recovery), which was calculated with the equation proposed by Baumgartner et al. (22). To obtain a more accurate estimate of LV systolic pressure, it is indeed preferable to add the net pressure gradient rather than the pressure gradient at the vena contracta, to the SAP (Fig. 1). As with the stroke work loss, it was chosen to add the mean rather than the maximal gradient to SAP, because it is closer to the peak-to-peak gradient and will thus provide a better estimate of peak LV pressure (23,24). Hence, Z_{va} represents the valvular and arterial factors that oppose ventricular ejection by absorbing the mechanical energy developed by the LV.

Data analysis and statistics. To better assess the respective contributions of the valvular load and the arterial load to the variation of LV pattern and function, the patients were classified into four different subgroups: group 1, moderate AS and normal SAC defined as ELI >0.55 cm^2/m^2 and SVi/PP >0.6 $ml/m^2/mm$ Hg; group 2, moderate AS and low SAC defined as ELI >0.55 cm^2/m^2 and SVi/PP ≤0.6 $ml/m^2/mm$ Hg; group 3, severe AS and normal SAC defined as ELI ≤0.55 cm^2/m^2 and SVi/PP >0.6 $ml/m^2/mm$ Hg; and group 4, severe AS and low SAC defined as ELI ≤0.55 cm^2/m^2 and SVi/PP ≤0.60 $ml/m^2/mm$ Hg. The threshold values used to separate the groups were selected on the basis of the results reported in previous studies (1,2,7). Continuous data were expressed as mean ± SD and compared with one-way analysis of variance (SigmaStat 3.0, SPSS Inc., Chicago, Illinois). A Holm-Sidak test was used for pair-wise comparisons (25). Categorical data were given as a percentage and compared with a chi-square test. A forward stepwise logistic regression analysis was performed to identify the variables that are independently associated with the presence of LV diastolic and systolic dysfunction. Variables with a p value <0.1 in univariate analysis were entered in multivariate analysis.

RESULTS

Table 1 provides a comparison of the clinical, systemic arterial pressure, and AS severity data in the 208 patients. The mean age and proportion of women were significantly higher in group 4 as compared with group 1. Not surprisingly, patients in groups 2 and 4 had a significantly higher prevalence of systemic hypertension than patients in groups 1 and 3. Patients in group 4 also had a significantly higher prevalence of obesity (body mass index >30 kg/m^2) compared with group 1. Overall, the prevalence of symptoms was highest in group 4 and lowest in group 1, with intermediate values being observed in groups 2 and 3.

Aortic valve function. Not unexpectedly, the EOA, indexed EOA, energy loss coefficient, and ELI were significantly lower, and peak and mean gradients as well as LV stroke work loss were significantly higher in groups 3 and 4 as compared with groups 1 and 2 (Table 1). It should be noted, however, that despite similar AS severity in terms of EOA and ELI, patients in group 4 had a significantly lower LV stroke work loss as well as lower peak and mean gradients than the patients in group 3. These findings can be related to the fact that patients in group 4 had significantly lower SVs than patients in group 3 (Table 2).

Systemic arterial hemodynamics. By definition, groups 2 and 4 had reduced SAC, as illustrated by the lower SV/PP and SVi/PP, compared with the two other groups (Table 1). The lower SAC was associated with a higher systolic blood pressure (BP) and PP in these groups. It should also be noted that patients in group 4 had significantly lower systolic BP and PP compared with the patients in group 2, although SAC was similar in both groups. These findings can also be related to the fact that the patients in group 4 had lower SVs than the patients in group 2. Groups 2 and 4 also had significantly higher systemic vascular resistance compared with the two other groups.

Table 1. Comparison of Demographic, Clinical, Systemic Arterial Pressure, and Valve Stenosis Severity Data

	Group 1 ELI >0.55 and SVi/PP >0.60 (n = 77; 37%)	Group 2 ELI >0.55 and SVi/PP ≤0.60 (n = 50; 24%)	Group 3 ELI ≤0.55 and SVi/PP >0.60 (n = 45; 22%)	Group 4 ELI ≤0.55 and SVi/PP ≤0.60 (n = 36; 17%)	p Value
Gender, n (%)				*	0.04
Males	53 (69)	29 (58)	23 (51)	15 (42)	
Females	24 (31)	21 (42)	22 (49)	21 (58)	
Age, yrs	67 ± 13	72 ± 10	70 ± 12	73 ± 7*	0.01
Body surface area, m^2	1.81 ± 0.21	1.80 ± 0.03	1.79 ± 0.20	1.81 ± 0.21	NS
Co-existing diseases and risk factors					
Coronary artery disease	41 (53)	36 (72)	22 (49)	24 (67)	NS
Previous myocardial infarction	20 (26)	13 (26)	11 (24)	14 (39)	NS
Hypertension	43 (56)	41 (82)*	28 (62)	29 (81)*	0.005
Dyslipidemia	38 (49)	26 (52)	21 (47)	21 (58)	NS
Diabetes	15 (19)	11 (22)	11 (24)	10 (28)	NS
Smoking	38 (49)	21 (42)	17 (38)	20 (56)	NS
Obesity	18 (23)	16 (32)	14 (31)	19 (53)*	0.02
Presence of symptoms	50 (65)	35 (70)	36 (80)	33 (92)*†	0.02
Systemic arterial pressure data					
Systolic arterial pressure, mm Hg	129 ± 17	161 ± 17*	122 ± 15†	145 ± 20*†‡	<0.001
Diastolic arterial pressure, mm Hg	74 ± 11	78 ± 11	71 ± 12	73 ± 14	NS
Systolic arterial pressure >140 mm Hg	27 (35)	46 (92)	7 (16)	21 (58)	<0.001
Pulse pressure, mm Hg	55 ± 13	83 ± 16*	51 ± 13†	72 ± 16*†‡	<0.001
SV/PP, ml/mm Hg	1.58 ± 0.43	0.90 ± 0.17*	1.49 ± 0.48†	0.89 ± 0.21*‡	<0.001
SVi/PP, $ml/m^2/mm$ Hg	0.87 ± 0.21	0.50 ± 0.08*	0.83 ± 0.21†	0.49 ± 0.09*‡	<0.001
Systemic vascular resistance, $dyne \cdot s \cdot cm^{-5}$	1,467 ± 433	1,774 ± 419*	1,487 ± 363†	1,810 ± 384*‡	<0.001
Valve stenosis severity					
Aortic valve area, cm^2	1.15 ± 0.17	1.14 ± 0.18	0.70 ± 0.15*†	0.70 ± 0.17*†	<0.001
Indexed aortic valve area, cm^2/m^2	0.64 ± 0.12	0.64 ± 0.11	0.39 ± 0.06*†	0.39 ± 0.07*†	<0.001
Energy loss coefficient, cm^2	1.32 ± 0.21	1.32 ± 0.24	0.77 ± 0.17*†	0.77 ± 0.19*†	<0.001
Energy loss index, cm^2/m^2	0.74 ± 0.16	0.74 ± 0.15	0.43 ± 0.07*†	0.42 ± 0.08*†	<0.001
Peak gradient, mm Hg	43 ± 17	35 ± 14	79 ± 23*†	64 ± 26*†‡	<0.001
Mean gradient, mm Hg	25 ± 11	21 ± 8	48 ± 16*†	39 ± 18*†‡	<0.001
Percent of stroke work loss	16 ± 6	11 ± 4*	28 ± 7*†	21 ± 6*†‡	<0.001
Valvulo-arterial load					
Z_{va}, mm Hg/ml/m^2	3.3 ± 0.5	4.4 ± 0.9*	4.2 ± 0.7*	5.4 ± 1.1*†‡	<0.001

Data are mean ± SD or number of patients (%). *Significant difference versus group 1; †significant difference versus group 2; ‡significant difference versus group 3. SV/PP = ratio of stroke volume to pulse pressure; SVi/PP = ratio of stroke volume index to pulse pressure; Z_{va} = valvulo-arterial impedance.

LV geometry. There was no significant difference between groups in regard to LV mass index (Table 2). Patients in groups 3 and 4, however, had higher relative wall thickness and prevalence of LV concentric hypertrophy than patients in groups 1 and 2.

LV diastolic function. Among the 208 patients included in the study, 160 (77%) were found to have diastolic dysfunction. The prevalence of diastolic dysfunction was lowest in group 1 and highest in group 4, with intermediate values being observed in groups 2 and 3 (Table 2, Fig. 2). The variables that were independently associated with LV diastolic dysfunction in multivariate analysis were: an ELI ≤0.60 cm^2/m^2 and a SVi/PP ≤0.60 $ml/m^2/mm$ Hg (Table 3).

LV systolic function. Overall, 29 patients (14%) had a LV ejection fraction <50%. There was no significant difference among groups in regard to the average LV ejection fraction, but the proportion of patients with a LV ejection fraction <50% was significantly higher in group 4 than in group 1 (Table 2, Fig. 2). Patients in group 4 had a significantly lower SV, mean transvalvular flow rate, and cardiac index, compared with the patients in the three other groups; the proportion of patients with a cardiac index <2.5 $l/min/m^2$ was also higher in group 4 than in groups 1 and 2 (Fig. 2). It should be pointed out that the differences in LV systolic function between groups 3 and 4 were present, although the degree of AS severity was similar in both groups and, as evidenced by the results for EOA and ELI, they are likely due to the fact that the reduction in SAC significantly contributed to increased afterload in group 4.

In multivariate analysis, the factors independently associated with LV systolic dysfunction defined as an LV ejection fraction <50% were: the presence of coronary artery disease, an ELI ≤0.50 cm^2/m^2, and a SVi/PP ≤0.50 $ml/m^2/mm$ Hg (Table 4). It should be noted that the threshold values of ELI and SVi/PP that were the most discriminative to predict LV systolic dysfunction were lower than those used to predict LV diastolic dysfunction. This is consistent with the fact that LV diastolic dysfunction generally occurs at an earlier stage of the disease when LV afterload is only moderately increased, whereas LV systolic dysfunction occurs when there is a more pronounced and long-standing afterload excess.

Table 2. Comparison of LV Geometry and Function

	Group 1 ELI >0.55 and SVi/PP >0.60 (n = 77; 37%)	Group 2 ELI >0.55 and SVi/PP ≤0.60 (n = 50; 24%)	Group 3 ELI ≤0.55 and SVi/PP >0.60 (n = 45; 22%)	Group 4 ELI ≤0.55 and SVi/PP ≤0.60 (n = 36; 17%)	p Value
LV geometry					
LV mass, g	219 ± 77	207 ± 64	228 ± 64	219 ± 70	NS
LV mass index, g/m^2	119 ± 35	114 ± 30	126 ± 29	120 ± 32	NS
Relative wall thickness	0.47 ± 0.09	0.48 ± 0.09	0.52 ± 0.12*	0.53 ± 0.11*	0.01
LV remodeling					
Normal	28 (41)	17 (39)	6 (17)*	9 (30)	0.04
LV concentric remodeling	37 (54)	21 (48)	20 (56)	13 (43)	NS
LV hypertrophy—concentric	2 (3)	5 (11)	9 (25)*	8 (27)*	<0.001
LV hypertrophy—eccentric	1 (2)	1 (2)	1 (2)	—	NS
LV diastolic function					
Diastolic dysfunction	46 (60)	43 (86)*	37 (82)*	34 (94)*	<0.001
Abnormal relaxation	31 (40)	33 (66)*	25 (56)	28 (78)*	<0.001
Pseudo-normal	14 (18)	9 (18)	10 (22)	5 (14)	NS
Restrictive	1 (1)	1 (2)	2 (4)	1 (3)	NS
LV systolic function					
LV ejection fraction, %	66 ± 10	65 ± 13	68 ± 11	61 ± 15	NS
LV ejection fraction <50%	5 (6)	6 (12)	7 (16)	11 (31)*	0.007
LV stroke volume, ml	84 ± 18	74 ± 14*	72 ± 16*	62 ± 14*†‡	<0.001
LV ejection time (ms)	317 ± 45	309 ± 31	319 ± 44	308 ± 32	NS
Mean transvalvular flow rate, ml/s	267 ± 58	236 ± 40*	229 ± 50*	202 ± 44*†‡	<0.001
Cardiac index, l/min/m^2	2.96 ± 0.70	2.75 ± 0.56	2.78 ± 0.62	2.44 ± 0.37*†‡	<0.001
Cardiac index <2.5 l/min/m^2	20 (26)	15 (30)	16 (36)	20 (56)*†	<0.001

Data are mean ± SD or number of patients (%). *Significant difference versus group 1; †significant difference versus group 2; ‡significant difference versus group 3. Abbreviations as in Table 1.

Z_{va}. The Z_{va} purports to reflect increases in global LV afterload irrespective of the underlying cause. Hence, it was highest in the patients of group 4, who had a combination of both severe AS and low SAC (Table 1, Fig. 3), and lowest in the patients of group 1, who had normal SAC and only moderate AS. Interestingly, the patients in group 2 who had only moderate AS but low SAC had increases of Z_{va} similar to those found in the patients of group 3 who had severe AS but normal SAC. When Z_{va} was entered in the multivariate analysis, this variable became the only hemodynamic factor to be independently associated with LV diastolic and systolic dysfunction (Tables 3 and 4). The fact that the latter analyses no longer yielded SVi/PP and ELI as independent predictors indeed suggests that Z_{va} adequately represents the respective contribution of these two variables to the prediction of LV dysfunction.

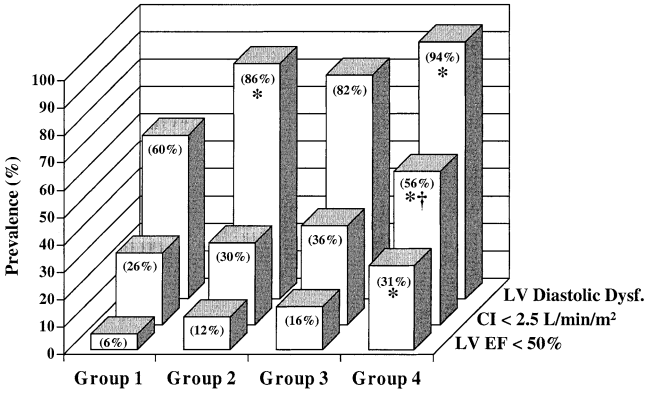

Figure 2. Comparison of the prevalence of left ventricular (LV) diastolic and systolic dysfunction in patients with moderate aortic stenosis (AS) and normal systemic arterial compliance (SAC) (group 1), patients with moderate AS and reduced SAC (group 2), patients with severe AS and normal SAC (group 3), and patients with severe AS and reduced SAC (group 4). *Significant difference versus group 1; †significant difference versus group 2. CI = cardiac index; Dysf. = dysfunction; LV EF = left ventricular ejection fraction.

DISCUSSION

The major finding of this study is that reduced SAC is a frequent occurrence in patients with AS and that it has a major influence on the occurrence of LV diastolic or systolic dysfunction. Indeed, the results in our four groups of patients clearly show that reduced SAC and AS seem to have additive effects in increasing afterload and deteriorating LV function.

The high prevalence of reduced SAC in association with AS should not be surprising given that the most frequent cause of AS nowadays is degenerative disease of the valve as it might occur in the elderly as opposed to other previously more prevalent causes such as congenital bicuspid valve or rheumatic fever. Moreover, the most frequently mentioned hypothesis to explain degeneration of the valve in the elderly is that it is probably due to an atherosclerotic process (26). Atherosclerosis is a pathologic process that may involve various components of the vascular system including the aorta. In this context, it should be emphasized that the average age of our patients was 69 ± 12 years; the patients in group 4 were significantly older (73 ± 7 years) than the patients in other groups, which is also consistent with the

Table 3. Independent Predictors of LV Diastolic Dysfunction

Variable	Model Without Z_{va}		Model With Z_{va}	
	Odd Ratio (95% CI)	p Value	Odd Ratio (95% CI)	p Value
ELI ≤0.60 cm^2/m^2	2.9 (1.5–5.8)	0.003	—	—
SVi/PP ≤0.60 $ml/m^2/mm$ Hg	3.1 (1.5–6.7)	0.003	—	—
Z_{va} ≥4.5 mm Hg/ml/m^2	N/A	N/A	5.4 (2.0–14.3)	<0.001

The output of the model was 0 for normal diastolic function and 1 for diastolic dysfunction.
CI = confidence interval; other abbreviations as in Table 2.

markedly increased prevalence and severity of atherosclerosis in elderly patients. These considerations also provide justification for not excluding from the present study patients with risk factors such as hypertension and coronary artery disease, because such exclusions would have introduced a bias that would have masked the clinical spectrum of the disease. Indeed, as for other manifestations of atherosclerosis, "degenerative" AS should be more appropriately considered as but one potential manifestation of a systemic process rather than a disease solely limited to the aortic valve. The present findings also suggest that the pathophysiology of AS becomes much more complex when it is associated with concomitant disease of the aorta and/or the LV, and that in such instances, a much more sophisticated diagnostic evaluation is required.

Clinical implications. These results have important clinical implications with regard to both the evaluation and treatment of these patients. Indeed, the aforementioned considerations suggest that degenerative AS is in fact a much more complex disease than previously thought and that limiting its evaluation to the hemodynamics of the aortic valve is probably a gross oversimplification that may lead to erroneous conclusions.

Relation between reduced SAC and hypertension. Systolic hypertension and increased PP are the hallmarks of reduced SAC, and the presence of these findings should alert the clinician that the degenerative process is not limited to the aortic valve, but also involves the vascular system distal to the valve. It should be emphasized, however, that there may actually be a pseudo-normalization of BPs in patients with concomitant LV dysfunction and reduced SV. Hence, it is interesting to note that almost all (92%) patients in group 2 had systolic hypertension, compared with only 58% of patients in group 4 (Table 1). This finding is, in all likelihood, owing to the fact that the latter patients have a much higher prevalence of LV dysfunction and that the resulting decreases in SV will tend to decrease both systolic pressure and PP. The phenomenon is highly insidious, because without calculating SAC one could easily have concluded that the arterial hemodynamics of these patients are normal when, in fact, they are highly abnormal and have a significant impact on global LV afterload (Fig. 3). Hence, it would seem important to routinely calculate SAC in every patient evaluated for AS. This can be easily accomplished at little expense with regard to time, because BP measurements and SV calculations should already be an integral part of the echocardiographic examination of the patient evaluated for AS.

Evaluation of afterload and AS severity in patients with reduced SAC. Using an animal model, we recently reported that AS severity may actually be underestimated in the context of hypertension (9). The results of the present study tend to confirm these findings. Hence, despite similar degrees of AS severity on the basis of EOA and ELI, the gradients and stroke work loss observed in groups 2 and 4 were less than those observed in groups 1 and 3, likely due to lower SVs and mean transvalvular flow rates (Table 2). The practical implications of these observations are that BP measurements should be routinely performed when evaluating AS severity and that the evaluation of AS severity cannot be solely limited to gradient measurements, but should always include calculation of EOA and ELI. Moreover, if the BP is elevated, it would seem preferable to repeat the measurements once the BP has normalized.

Notwithstanding these considerations, the present findings also demonstrate that a reduced SAC contributes to increase the prevalences of LV dysfunction and symptoms. From these data, one can also hypothesize that patients with

Table 4. Independent Predictors of LV Systolic Dysfunction Defined as an LV Ejection Fraction <50%

Variable	Model Without Z_{va}		Model With Z_{va}	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Female gender	—	—	3.5 (1.2–10.3)	0.025
Coronary artery disease	25.2 (3.3–195.0)	0.001	16.7 (2.2–128.7)	0.007
ELI ≤0.50 cm^2/m^2	4.5 (1.8–11.5)	0.002	—	—
SVi/PP ≤0.50 $ml/m^2/mm$ Hg	2.9 (1.1–7.6)	0.025	—	—
Z_{va} ≥5.0 mm Hg/ml/m^2	N/A	N/A	4.2 (1.7–10.3)	0.001

Abbreviations as in Table 3.

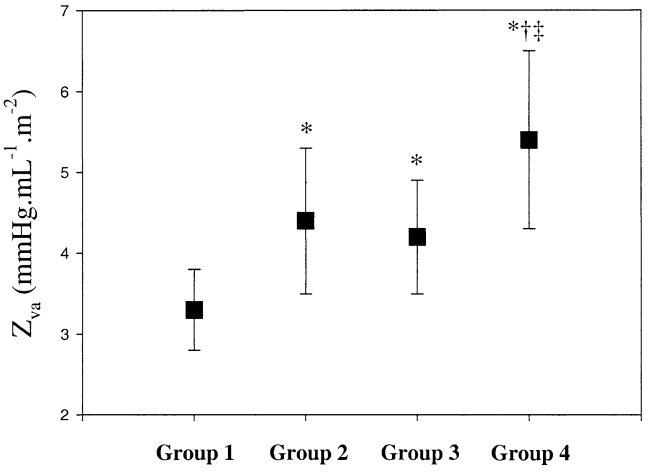

Figure 3. Comparison of the valvulo-arterial impedance (Z_{va}). *Significant difference versus group 1; †significant difference versus group 2; ‡significant difference versus group 3. Groups definitions as in Figure 2.

AS and reduced SAC probably become symptomatic earlier in the evolution of their disease than patients with pure AS. Indeed, this hypothesis would seem to be consistent with the results of Antonini-Canterin et al. (27), who observed that hypertensive patients who develop symptoms of AS have, on average, larger valve EOAs than normotensive patients referred with the same symptoms.

Management of patients with AS and reduced SAC. The logical first step in patients with AS and decreased SAC would evidently be to aggressively treat their hypertension and then to re-evaluate the situation. Further studies will be necessary, however, to determine whether significant improvement can be achieved with the intensification of medical treatment alone. Indeed, optimization of BP levels may have its limitations, because SAC may not be completely normalized by treatment. Indeed, patients with reduced SAC often have normal diastolic pressures but increased PPs (e.g., 160/60 mm Hg). Likewise, it may well be found that it is worthwhile to operate on some of these patients, although their criteria for AS severity do not meet current guidelines for operation. The rationale behind the latter attitude could be that total afterload of these patients is markedly increased and that any significant decrease may contribute to the improvement of their prognosis and well-being. If the surgical option were contemplated, one would have to ensure, however, that the projected operation would result in a significant reduction in afterload. In particular, proper care would have to be taken in order to avoid patient-prosthesis mismatch, as previously suggested (28).

In establishing proper clinical conduct, the calculation of the new parameter introduced in this study (i.e., Z_{va}) might prove useful to establish critical levels of afterload as well as to evaluate the effects of the various medical or surgical interventions. Hence, the results of this study would suggest that a value of $Z_{va} \geq 5.0$ mm Hg/ml/m^2 might represent a level of afterload that exceeds the limit of LV compensatory mechanisms and, therefore, leads to afterload mismatch and LV systolic dysfunction. As well, the value for Z_{va} could be confronted to the values of ELI and SVi/PP to determine the respective contributions of the aortic valve and of the SAC to the afterload excess.

Finally, the results of this study may also contribute to the explanation of the suboptimal results of aortic valve replacement with regard to postoperative normalization of LV diastolic and systolic function. Indeed, previous studies have reported that postoperative normalization of LV function may vary extensively from one patient to another and is often incomplete (29). The SAC is generally unchanged by aortic valve replacement because only the valve, but not the aorta, is replaced at the time of operation.

Study limitations. The study was retrospective in nature, and the data did not allow us to determine the exact time of symptom onset in the course of the disease. Likewise, the follow-up period was too short to draw any meaningful conclusions with regard to prognosis. Nonetheless, the data we present are very compelling in demonstrating that reduced SAC is a frequent occurrence in elderly patients with AS and that they pose important new challenges with regard to diagnostic evaluation and clinical decision making. Hence, it provides a strong impetus for the realization of further prospective longitudinal studies to determine whether the new quantitative indices we propose are better predictors of symptom onset and clinical outcome than conventional Doppler-echocardiographic indices. In particular, such studies would allow verifying whether patients with reduced SAC become symptomatic with less severity of AS as compared with patients with normal SAC.

Conclusions. Reduced SAC is a frequent occurrence in elderly patients with AS, where it contributes to increased afterload and independently contributes to the occurrence of LV dysfunction. This observation should be taken into consideration when examining such patients, because it may impact significantly on both diagnostic evaluation and ensuing clinical conduct.

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REFERENCES

1. Garcia D, Pibarot P, Dumesnil JG, Sakr F, Durand LG. Assessment of aortic valve stenosis severity: a new index based on the energy loss concept. Circulation 2000;101:765–71.
2. Garcia D, Dumesnil JG, Durand LG, Kadem L, Pibarot P. Discrepancies between catheter and Doppler estimates of valve effective orifice area can be predicted from the pressure recovery phenomenon: practical implications with regard to quantification of aortic stenosis severity. J Am Coll Cardiol 2003;41:435–42.

3. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. Hypertension 2001;38:429–33.
4. O'Rourke MF, Staessen JA. Clinical applications of arterial stiffness: definitions and references values. Am J Hypertens 2002;15:426–44.
5. Mitchell GF. Pulse pressure, arterial compliance and cardiovascular morbidity and mortality. Curr Opin Nephrol Hypertens 1999;8:335–42.
6. Schram MT, Kostense PJ, Van Dijk RA, et al. Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. J Hypertens 2002;20:1743–51.
7. de Simone G, Roman MJ, Koren MJ, Mensah GA, Ganau A, Devereux RB. Stroke volume/pulse pressure ratio and cardiovascular risk in arterial hypertension. Hypertension 1999;33:800–5.
8. Palmieri V, Bella JN, Roman MJ, et al. Pulse pressure/stroke index and left ventricular geometry and function: the LIFE Study. J Hypertens 2003;21:781–7.
9. Kadem L, Dumesnil JG, Rieu R, Durand LG, Garcia D, Pibarot P. Impact of systemic hypertension on the assessment of aortic stenosis. Heart 2005;91:354–61.
10. Bonow RO, Carabello BA, de Leon AC Jr., et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). Circulation 1998;98:1949–84.
11. Bermejo J, Odreman R, Feijoo J, Moreno MM, Gomez-Moreno P, Garcia-Fernandez MA. Clinical efficacy of Doppler-echocardiographic indices of aortic valve stenosis: a comparative test-based analysis of outcome. J Am Coll Cardiol 2003;41:142–51.
12. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
13. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 1992;19:1550–8.
14. Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Miller RR. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. Circulation 1981;64:744–53.
15. Dumesnil JG, Dion D, Yvorchuk K, Davies RA, Chan K. A new, simple and accurate method for determining ejection fraction by Doppler echocardiography. Can J Cardiol 1995;11:1007–14.
16. Dumesnil JG, Paulin C, Pibarot P, Arsenault M, Coulombe D. Mitral annulus velocities by tissue Doppler imaging: practical implications with regards to preload alterations, sample position, and normal values. J Am Soc Echocardiogr 2002;15:1226–31.
17. Rakowski H, Appleton C, Chan KL, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography. J Am Soc Echocardiogr 1996;9:736–60.
18. Chemla D, Hébert J-L, Coirault C, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol Heart Circ Physiol 1998;274:H500–5.
19. Nichols W, O'Rourke MF. Input impedance as ventricular load. In: Nichols W, O'Rourke MF, editors. McDonald Blood Flow in the Arteries. Theoretical, Experimental and Clinical Principles. London, England: Arnold, 1998:285–93.
20. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:H773–80.
21. Chemla D, Antony I, Lecarpentier Y, Nitenberg A. Contribution of systemic vascular resistance and total arterial compliance to effective arterial elastance in humans. Am J Physiol Heart Circ Physiol 2003;285:H614–20.
22. Baumgartner H, Steffenelli T, Niederberger J, Schima H, Maurer G. "Overestimation" of catheter gradients by Doppler ultrasound in patients with aortic stenosis: a predictable manifestation of pressure recovery. J Am Coll Cardiol 1999;33:1655–61.
23. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56–64.
24. Otto CM. Aortic Stenosis. In: Otto CM, editor. Valvular Heart Disease. Philadelphia, PA: Elsevier, 2003:197–246.
25. Holm AS. A simple sequentially rejective multiple test procedure. Scand J Statist 1979;6:65–70.
26. Rajamannan NM, Gersh B, Bonow RO. Calcific aortic stenosis: from bench to the bedside—emerging clinical and cellular concepts. Heart 2003;89:801–5.
27. Antonini-Canterin F, Huang G, Cervesato E, et al. Symptomatic aortic stenosis: does systemic hypertension play an additional role? Hypertension 2003;41:1268–72.
28. Blais C, Dumesnil JG, Baillot R, Simard S, Doyle D, Pibarot P. Impact of prosthesis-patient mismatch on short-term mortality after aortic valve replacement. Circulation 2003;108:983–8.
29. Hess OM, Villari B, Krayenbuehl HP. Diastolic dysfunction in aortic stenosis. Circulation 1993;87 Suppl IV:73–6.