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Usefulness of the Valvuloarterial Impedance to Predict Adverse Outcome in Asymptomatic Aortic Stenosis

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Objectives This study was designed to examine the prognostic value of valvuloarterial impedance (Z_{va}) in patients with aortic stenosis (AS).

Background We previously showed that the Z_{va} is superior to standard indexes of AS severity in estimating the global hemodynamic load faced by the left ventricle (LV) and predicting the occurrence of LV dysfunction. This index is calculated by dividing the estimated LV systolic pressure (systolic arterial pressure + mean transvalvular gradient) by the stroke volume indexed for the body surface area.

Methods We retrospectively analyzed the clinical and echocardiographic data of 544 consecutive patients having at least moderate AS (aortic jet velocity $\geq$2.5 m·s^{-1}) and no symptoms at baseline. The primary end point for this study was the overall mortality regardless of the realization of aortic valve replacement (AVR).

Results Four-year survival was significantly ($p < 0.001$) lower in the patients with a baseline Z_{va} $\geq$4.5 mm Hg·ml^{-1}·m^2 (65 ± 5%) compared with those with Z_{va} between 3.5 and 4.5 mm Hg·ml^{-1}·m^2 (78 ± 4%) and those with Z_{va} $\leq$3.5 mm Hg·ml^{-1}·m^2 (88 ± 3%). The risk of mortality was increased by 2.76-fold in patients with Z_{va} $\geq$4.5 mm Hg·ml^{-1}·m^2 and by 2.30-fold in those with a Z_{va} between 3.5 and 4.5 mm Hg·ml^{-1}·m^2 after adjusting for other risk factors and type of treatment (surgical vs. medical).

Conclusions Increased Z_{va} is a marker of excessive LV hemodynamic load, and a value >3.5 successfully identifies patients with a poor outcome. These findings suggest that beyond standard indexes of stenosis severity, the consideration of Z_{va} may be useful to improve risk stratification and clinical decision making in patients with AS.
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Reduced arterial compliance is a frequent occurrence in patients with degenerative aortic stenosis (AS), where it independently contributes to increase afterload and decrease left ventricular (LV) function (1,2). Congenital bicuspid AS is also associated with impaired aortic elasticity, independent of stenosis severity or aortic size (3,4). Hence, the LV of AS patients often faces a double load: valvular plus arterial, and in these patients, the presence of symptoms and occurrence of adverse events should logically better correlate with the global burden faced by the ventricle than with the transvalvular gradient and/or aortic valve area (AVA). To this effect, we recently proposed a new index of global LV hemodynamic load, that is, the valvuloarterial impedance (Z_{va}), which is calculated by dividing the estimated LV systolic pressure (systolic arterial pressure + mean transvalvular gradient) by the stroke volume index (SVI) (1). This index, in fact, represents the cost in mm Hg for each systemic milliliter of blood indexed for the body size, pumped by the LV during systole. And, indeed, we have shown that Z_{va} is superior to the standard indexes of AS severity in predicting LV dysfunction (1). The objective of this study was to examine the relevance of Z_{va} with regard to prognosis, and in particular, to define reference values that could be used in routine clinical practice.

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Methods

Patient population. We retrospectively reviewed the clinical and echocardiographic data that were prospectively collected in 544 asymptomatic patients (320 men and 224 women; mean age 70 ± 14 years; range 21 to 98 years) with at least a

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Abbreviations and Acronyms

AS = aortic stenosis
AVA = aortic valve area
AVR = aortic valve replacement
CABG = coronary artery bypass graft
CI = confidence interval
ELI = energy loss index
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
PP = pulse pressure
SV = stroke volume
SVI = stroke volume index
Z_{va} = valvuloarterial impedance

moderate AS, defined as peak aortic jet velocity ≥2.5 $m \cdot s^{-1}$. The exclusion criteria were concomitant moderate or severe aortic insufficiency or mitral valve disease, left ventricular ejection fraction (LVEF) <50%, and the presence of symptoms at baseline.

Clinical data. Clinical data included age, sex, history of smoking, documented diagnosis of hypertension, hypercholesterolemia, diabetes, obesity (body mass index ≥30 kg/m^2), and coronary heart disease (5).

Systemic arterial hemodynamics. Systemic arterial pressure was measured with the use of an arm cuff sphygmomanometer at the same time as the Doppler measurement of stroke volume (SV) was measured in the left ventricular outflow tract. The ratio of SVI to brachial pulse pressure (PP) was used as an indirect measure of total systemic arterial compliance: SAC = SVI/PP (1). The systemic vascular resistance was estimated by the formula: SVR = (80 × MAP)/CO, where MAP is the mean arterial pressure defined as diastolic pressure plus one-third of PP and CO is the cardiac output.

Doppler echocardiographic data. AORTIC VALVE STENOSIS SEVERITY. The Doppler echocardiographic indexes of AS severity included: the mean transvalvular pressure gradient obtained with the use of the modified Bernoulli equation, the AVA obtained with the use of the standard continuity equation, and the energy loss index (ELI) as previously described in Garcia et al. (6). Severe AS was defined as an AVA ≤1.0 cm^2.

LV GEOMETRY. Two-dimensionally directed LV M-mode dimensions were measured in the left parasternal long-axis view following the recommendations of the American Society of Echocardiography. Left ventricular minor axis internal dimension (LVID), posterior wall thickness (PWT), and interventricular septal thickness (IVST) were measured at end-diastole (d). The LV mass was calculated using the corrected formula of the American Society of Echocardiography and was indexed for body surface area. Significant LV hypertrophy was defined as LV mass index >134 g/m^2 in men and >110 g/m^2 in women. The relative wall thickness (RWT) was calculated with the formula: RWT = (PWTd + IVSTd)/LVIDd.

LV SYSTOLIC FUNCTION. Diastolic function was assessed as previously described (7). The LVEF was determined in all patients using the Quinones method, the Dumesnil method (8), and visual estimate. In the case of a disagreement among these methods, the reviewing cardiologist selected the value that seemed the most representative.

GLOBAL LV HEMODYNAMIC LOAD. As a measure of global LV load, we calculated the valvuloarterial impedance: Z_{va} = (SAP + MG)/SVI, where SAP is the systolic arterial pressure and MG is the mean transvalvular pressure gradient (1). Hence, Z_{va} represents the valvular and arterial factors that oppose ventricular ejection by absorbing the mechanical energy developed by the LV.

Clinical outcomes. The primary end point for this study was overall death regardless of whether or not there was aortic valve replacement (AVR). Hence, this includes the deaths occurring in patients who did not undergo AVR as well as those occurring after operation in patients who underwent AVR. The outcome data were retrospectively obtained from patients' charts or death certificates.

Statistical analysis. We subdivided the patients into 3 groups according to the level of Z_{va}: 1) Z_{va} ≤3.5 mm $Hg \cdot ml^{-1} \cdot m^2$ (low Z_{va} group, n = 172; 32%); 2) 3.5 < Z_{va} <4.5 mm $Hg \cdot ml^{-1} \cdot m^2$ (medium Z_{va} group, n = 192; 35%); and 3) Z_{va} ≥4.5 mm $Hg \cdot ml^{-1} \cdot m^2$ (high Z_{va} group, n = 180, 33%). These 3 groups correspond approximately to the tertiles of Z_{va}.

Continuous data were expressed as mean ± SD and compared among the 3 Z_{va} groups using a 1-way analysis of variance followed by a Tukey test. Categorical data were given as a percentage and compared with a chi-square test. Cumulative probability of survival was estimated with the Kaplan-Meier method and compared between groups using a log-rank test. The survival observed in these groups was also compared with that of the general population in the Québec province matched for age and sex. The survival data of this control population were derived from the 2002 life tables of Canada Statistics. The effect of the clinical and Doppler echocardiographic variables on survival was assessed with the use of a Cox proportional hazards model. All of the variables presented in Tables 1, 2, and 3 as well as the type of treatment (medical vs. surgical, i.e., AVR) were tested in univariate analysis, and those with a p value <0.20 on univariate analysis were incorporated into the multivariate models. Age was forced into the model. To avoid colinearity among a subset of several variables measuring the

Table 1 Baseline Clinical Characteristics of the Patients According to the Level of Z_{va}

Group	Low Z_{va} (n = 172)	Medium Z_{va} (n = 192)	High Z_{va} (n = 180)	p Value
Age, yrs	66 ± 15	70 ± 12*	73 ± 13*†	<0.001
Female sex	69 (40)	73 (38)	82 (46)	NS
Body surface area, m^2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	NS
Body mass index, kg/m^2	27 ± 6	27 ± 5	28 ± 5	NS
Obesity	39 (23)	53 (27)	55 (31)	NS
Hypertension	96 (56)	138 (72)*	128 (71)*	0.02
Hypercholesterolemia	93 (54)	109 (57)	76 (42)	NS
Diabetes	39 (23)	40 (21)	34 (19)	NS
Coronary artery disease	96 (56)	128 (67)	106 (59)	NS

Values are mean ± SD or n (%). *Significant difference versus low Z_{va} group. †Significant difference versus medium Z_{va} group.
NS = not significant; Z_{va} = valvuloarterial impedance.

Table 2 Doppler Echocardiographic and Systemic Arterial Indexes of Valvular Load, Arterial Load, and Global LV Hemodynamic Load According to the Level of Z_{va}

Group	Low Z_{va} (n = 172)	Medium Z_{va} (n = 192)	High Z_{va} (n = 180)	p Value
Valvular load				
Aortic valve area, cm^2	1.2 ± 0.2	1.0 ± 0.3*	0.8 ± 0.2*†	<0.0001
Aortic valve area index, $cm^2 \cdot m^{-2}$	0.66 ± 0.13	0.56 ± 0.15*	0.45 ± 0.12*†	<0.0001
Energy loss index, $cm^2 \cdot m^{-2}$	0.78 ± 0.18	0.65 ± 0.23*	0.51 ± 0.15*†	<0.0001
Peak gradient, mm Hg	44 ± 16	46 ± 20	56 ± 26*†	<0.0001
Mean gradient, mm Hg	25 ± 10	27 ± 12	34 ± 17*†	<0.0001
Vascular load				
Systolic arterial pressure, mm Hg	122 ± 16	135 ± 19*	145 ± 23*†	<0.001
Diastolic arterial pressure, mm Hg	68 ± 9	73 ± 10*	78 ± 10*†	<0.0001
Systemic arterial compliance, $ml \cdot m^{-2} \cdot mm\ Hg^{-1}$	0.94 ± 0.24	0.69 ± 0.18*	0.57 ± 0.18*†	<0.0001
Systemic vascular resistance, $dyne \cdot s \cdot cm^{-5}$	1,303 ± 287	1,605 ± 361*	1,824 ± 398*†	<0.001
Global LV hemodynamic load				
Valvuloarterial impedance, $mm\ Hg \cdot ml^{-1} \cdot m^2$	3.1 ± 0.4	4.0 ± 0.3*	5.2 ± 0.9*†	<0.0001

*Significant difference versus low Z_{va} group. †Significant difference versus medium Z_{va} group.
LV = left ventricular; other abbreviation as in Table 1.

same phenomenon (e.g., AVA, peak gradient, mean gradient, ELI), we entered in the multivariate models the variable that had the strongest association with mortality on univariate analysis. We constructed a first series of multivariate models with independent variables entered in continuous format and then a second series with these variables entered in dichotomous formats.

Results

Table 1 shows the baseline characteristics of the patients in the 3 Z_{va} groups. Patients with high and medium Z_{va} were significantly older and had a higher prevalence of systemic arterial hypertension compared with those with low Z_{va}. There was no significant difference among the 3 groups with regard to sex distribution, body surface area, body mass index, and prevalence of hypercholesterolemia, diabetes, and coronary artery disease.

Table 2 shows the data of the Doppler echocardiographic and systemic arterial indexes reflecting the valvular load (i.e., AS severity) and the arterial load. As expected, patients with high Z_{va} had a higher valvular load, that is, more severe valvular stenosis, as reflected by smaller AVA and ELI and

Table 3 Doppler Echocardiographic Data of LV Geometry and Function According to the Level of Z_{va}

Group	Low Z_{va} (n = 172)	Medium Z_{va} (n = 192)	High Z_{va} (n = 180)	p Value
LV geometry				
IVSTd, mm	12 ± 3	12 ± 2	13 ± 3*†	<0.001
PWTd, mm	10 ± 2	11 ± 2	11 ± 2*	0.02
LVIDd, mm	48 ± 5	47 ± 5	45 ± 5*†	<0.001
LVEDV, ml	111 ± 27	106 ± 27	96 ± 25*†	<0.001
LVEDV index, $ml \cdot m^{-2}$	61 ± 13	58 ± 13*	52 ± 12*†	<0.001
Relative wall thickness, %	44 ± 10	46 ± 10*	49 ± 10*†	<0.001
LV mass, g	210 ± 73	209 ± 56	210 ± 64	NS
LV mass index, g/m^2	116 ± 34	114 ± 27	115 ± 32	NS
LV systolic function				
LV ejection fraction, %	67 ± 7	66 ± 7	65 ± 7*	0.025
Stroke volume, ml	87 ± 16	75 ± 12*	65 ± 15*†	<0.001
Stroke volume index, $ml \cdot m^{-2}$	48 ± 8	41 ± 5*	35 ± 7*†	<0.001
Cardiac output, $l \cdot min^{-1}$	5.5 ± 1.2	4.8 ± 1.0*	4.6 ± 1.1*†	<0.001
Cardiac index, $l \cdot min^{-1} \cdot m^{-2}$	3.1 ± 0.7	2.6 ± 0.5*	2.5 ± 0.5*†	<0.001
Mean transvalvular flow rate, $ml \cdot s^{-1}$	268 ± 61	232 ± 49*	210 ± 55*†	<0.001
LV diastolic function, %				
Normal	20	13	11	NS
Abnormal	80	87	89	<0.001

*Significant difference versus low Z_{va} group. †Significant difference versus medium Z_{va} group.
IVSTd = interventricular septal thickness in diastole; LVEDV = left ventricular end-diastolic volume; LVIDd = left ventricular internal dimension in diastole; PWTd = posterior wall thickness in diastole; other abbreviations as in Tables 1 and 2.

higher transvalvular gradients compared with patients with medium or low Z_{va} (Fig. 1). Patients with medium Z_{va} also had significantly smaller AVA but similar gradients compared with patients with low Z_{va}. Patients with higher levels of Z_{va} also had a higher vascular load as reflected by reduced systemic arterial compliance, increased systemic vascular resistance, and higher systolic and diastolic arterial pressures.

Table 3 shows the echocardiographic data of LV geometry and function. Patients in the high Z_{va} group had thicker LV walls, a smaller LV cavity, and a higher relative wall thickness ratio compared with those in the medium and low Z_{va} groups. Patients with high Z_{va} also had a lower LVEF, SV, cardiac output, and mean transvalvular flow rate compared with patients with lower Z_{va}. The indexes of LV systolic function, except LVEF, were also significantly lower in the medium Z_{va} group than in the low Z_{va} group.

Moreover, as shown in Figure 1, the proportion of patients with a paradoxical low flow pattern, defined as stoke volume index ≤35 ml·m^{-2} in the setting of LVEF ≥50%, was much higher ($p < 0.001$) in the high Z_{va} group (n = 90, 50%) than that in the medium Z_{va} group (n = 28, 15%) or in the low Z_{va} group (n = 7, 4%), which is consistent with our previous study showing that patients with paradoxical low flow are characterized by a markedly increased Z_{va} (5). Hence, among the 125 patients with paradoxical low flow, 90 (72%) had a high Z_{va}, and of these patients 74 (82%) had a severe AS.

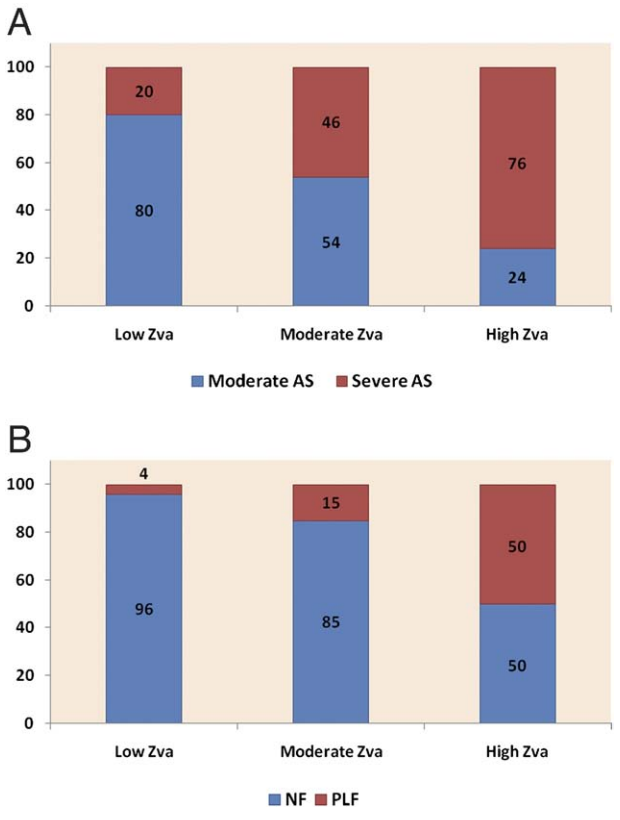

Figure 1 Distribution of Stenosis Severity and Paradoxical Low-Flow Pattern Versus Z_{va}

Percentage of patients with moderate versus severe aortic stenosis (AS) **(A)** and with normal flow (NF) versus paradoxical low flow (PLF) **(B)** according to the level of valvuloarterial impedance (Z_{va}) (low Z_{va} ≤3.5, moderate 3.5 < Z_{va} <4.5, high Z_{va} ≥4.5). The **numbers in the bars** are percentages.

Type of treatment. Aortic valve replacement was performed during follow-up in 54 (31%) patients in the low Z_{va} group, 58 (30%) in the medium Z_{va} group, and 64 (36%) in the high Z_{va} group. Coronary artery bypass grafting (CABG) was performed concomitantly in 75 of 176 (43%) patients. Among the 176 patients undergoing AVR, 166 (94%) had severe AS at the time of operation (67 of these patients underwent CABG) and 10 (6%) had moderate AS (8 underwent CABG).

Clinical outcome. The mean follow-up time in the total cohort was 2.5 ± 1.8 years (median 2.1 years). The follow-up was complete in all patients, and there was no significant difference between groups with regard to the duration of follow-up.

Overall, there were 91 deaths: 15 (9%) in the low Z_{va} group, 36 (19%) in the medium Z_{va} group, and 40 (22%) in high Z_{va} group. Among them 51 (56%) were from a cardiovascular cause: 7 (4%) in low Z_{va} group, 19 (10%) in the medium Z_{va} group, and 25 (14%) in the high Z_{va} group. Seventy-eight of the 91 deaths occurred in patients treated medically, whereas 13 occurred after AVR. Six of these post-operative deaths occurred in the early post-operative period (<30 days).

Four-year survival was significantly ($p < 0.001$) lower in the high Z_{va} group (65 ± 5%) than in the medium (78 ± 4%) and low (88 ± 3%) Z_{va} groups. Survival was also significantly ($p = 0.007$) lower in the patients with medium Z_{va} compared with those with low Z_{va} (Fig. 2). Patients with low Z_{va} had similar survival compared with that of the general population in Quebec, whereas patients in the medium and high Z_{va} groups had lower ($p < 0.05$) survival than in this control population.

Figure 3 shows the survival as a function of the 3 levels of Z_{va} and the type of treatment. Particularly noteworthy is the fact that survival of patients in the 3 groups treated surgically was similar or better than that of the control population, albeit there was a statistical difference ($p = 0.02$) between the high and low Z_{va} groups treated surgically. Likewise, survival of patients in the low Z_{va} group treated medically was no different from that of the control population. Conversely, patients with high and moderate Z_{va} treated medically had markedly lower survival compared with the control population ($p = 0.002$ and $p = 0.002$, respectively) and with the patients with low Z_{va} ($p = 0.0003$ and $p = 0.02$, respectively). Moreover, although significantly different in both groups, the magnitude of the protective effect of AVR was most important in patients with higher Z_{va} (4-year survival: 87 ± 5% vs. 42 ± 9% for patients treated medically, $p < 0.001$) than in patients with moderate Z_{va} (4-year survival: 89 ± 5% vs. 74 ± 4% for patients treated medically, $p = 0.001$). Overall, these results

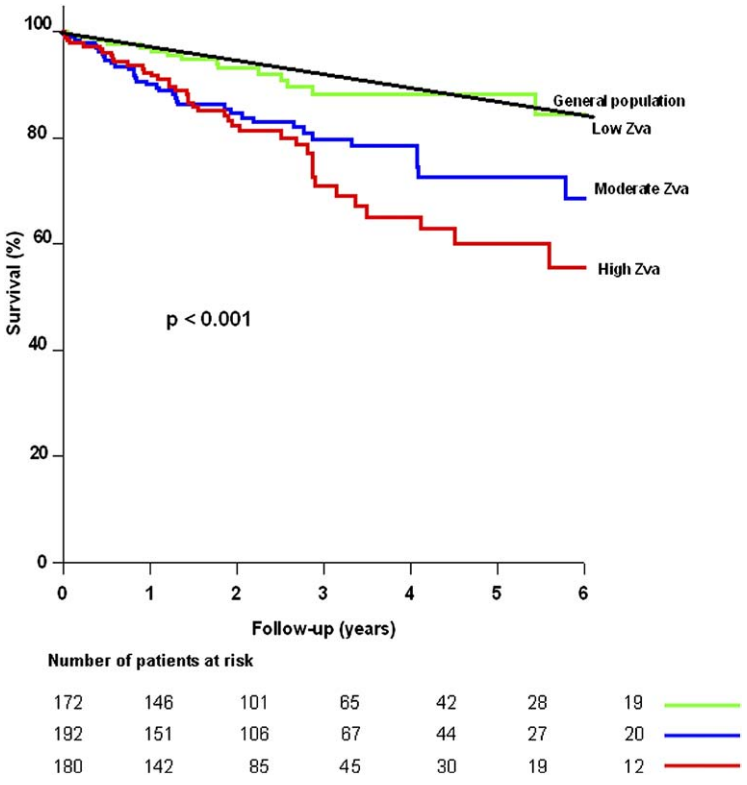

Figure 2 **Overall Survival Versus Z_{va}**

Overall survival as a function of the level of valvuloarterial impedance (Z_{va}) (low $Z_{va} \leq 3.5$ **[green line]**, moderate $3.5 < Z_{va} < 4.5$ **[blue line]**, high $Z_{va} \geq 4.5$ **[red line]**). Survival was compared with that in the general population in Quebec matched for age and sex (control group; **black line**).

seem to identify Z_{va} >3.5 mm Hg·ml^{-1}·m^2 as the logical threshold to identify patients likely to be at higher risk if treated medically rather than surgically.

Predictors of outcome. Table 4 shows the univariate and multivariate predictors of mortality. Mortality risk increased by 1.41-fold (95% confidence interval [CI]: 1.17 to 1.67, p = 0.0004) per 1-U increase in Z_{va} on univariate analysis and by 1.36-fold (95% CI: 1.03 to 1.75, p = 0.03) on multivariate analysis (Model 1 in Table 4). When Z_{va} was expressed in a categorical format, a value of $Z_{va} \geq 4.5$ mm Hg·ml^{-1}·m^2 was associated with a hazard ratio for mortality of 2.95 (95% CI: 1.67 to 5.53, p = 0.0001), whereas a value of Z_{va} >3.5 and <4.5 mm Hg·ml^{-1}·m^2 was associated with a hazard ratio of 2.24 (95% CI: 1.25 to 4.22, p = 0.006). On multivariate analysis, the independent risk factors for mortality were older age, increased LV mass index, and increased Z_{va}, whereas the surgical treatment (AVR with or without CABG) was highly protective (models 1 and 2 in Table 4). The risk of mortality was increased by 2.76-fold (95% CI: 1.32 to 5.92; p = 0.01) in patients with $Z_{va} \geq 4.5$ mm Hg·ml^{-1}·m^2 and by 2.30-fold (95% CI: 1.16 to 4.71; p = 0.03) in those with a Z_{va} comprised between 3.5 and 4.5 mm Hg·ml^{-1}·m^2 after adjustment for other risk factors and type of treatment (surgical vs. medical) (Model 2 in Table 4). With regard to the risk of cardiovascular mortality, a value of $Z_{va} \geq 4.5$ mm Hg·ml^{-1}·m^2 was associated with a hazard ratio for mortality of 3.71-fold (95% CI: 1.47 to 10.17; p = 0.001) whereas a value of Z_{va} >3.5 and <4.5 mm Hg·ml^{-1}·m^2 was associated with a hazard ratio of 3.11 (95% CI: 1.28 to 8.20, p = 0.014).

Discussion

The most important finding of the present study is that Z_{va} predicts adverse outcome in asymptomatic patients with at least moderate AS, even after adjustment for standard indexes of stenosis severity, LV geometry and function, and type of treatment. A value of $Z_{va} \geq 4.5$ mm Hg·ml^{-1}·m^2 was indeed associated with a 2.76- and a 3.71-fold increase in the risk of overall and cardiovascular mortality, respectively, whereas a value of Z_{va} between 3.5 and 4.5 was associated with 2.30- and 3.11-fold increases of the same risks. The fact that the adverse impact of Z_{va} on survival was most evident in patients with moderately (>3.5 and <4.5 mm Hg·ml^{-1}·m^2) or severely (≥ 4.5 mm Hg·ml^{-1}·m^2) increased Z_{va} treated medically whereas survival of patients treated surgically or with a low Z_{va} (≤ 3.5 mm Hg·ml^{-1}·m^2) was similar or better than that of the general population in Quebec is also compelling evidence that this parameter should be highly useful for risk stratification and clinical

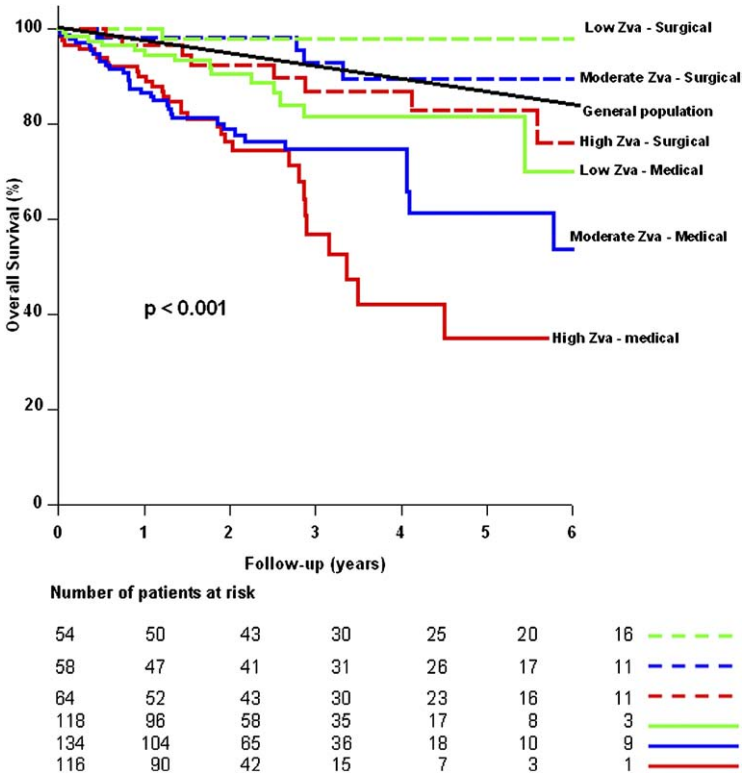

Figure 3 **Overall Survival Versus Z_{va} and Type of Treatment**

Overall survival as a function of the level of valvuloarterial impedance (Z_{va}) (low $Z_{va} \leq 3.5$ **[green lines]**, moderate $3.5 < Z_{va} < 4.5$ **[blue lines]**, high $Z_{va} \geq 4.5$ **[red lines]**) and the type of treatment: medical **(solid lines)** versus surgical **(dashed lines)**. Survival was compared with that in the general population in Quebec matched for age and sex (control group; **black line**).

decision making and that the logical reference value for this purpose would seem to be a $Z_{va} > 3.5$ mm Hg·ml^{-1}·m^2.

The valvuloarterial impedance provides an estimate of the global LV hemodynamic load that results from the summation of the valvular and vascular loads, and the concept is very useful because it incorporates stenosis severity, volume flow rate, body size, and systemic vascular resistance. Moreover, Z_{va} can easily be calculated using Doppler echocardiography from 3 simple measurements, that is, the SVI in the LV outflow tract, the transvalvular mean gradient, and systolic arterial pressure, and as previously shown (1), it is superior to the standard indexes of AS severity in predicting LV dysfunction. These results have been independently corroborated by a substudy of the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial (9), in which increased Z_{va} was a powerful independent predictor of myocardial systolic dysfunction in asymptomatic patients with mild to severe AS. Moreover, in a recent study (5) including only patients with severe AS, a value of $Z_{va} > 5.5$ mm Hg·ml^{-1}·m^2 was associated with a 2.5-fold increase in the risk of overall mortality, regardless of the type of treatment (AVR or medical). An important limitation of that study, however, is that many patients were already symptomatic at baseline.

Comparison with previous studies. Previous studies of patients with asymptomatic AS have identified older age, hemodynamic severity of AS, severe aortic valve calcification, physical inactivity, coronary artery disease, and renal failure as independent predictors of adverse events generally defined as AVR (or onset of symptoms) and death (10–12). In the present study, we identified some of these factors, such as age and baseline AVA, as predictors of mortality. It should also be emphasized that Z_{va} was not determined in previous studies. Moreover, we selected overall mortality as the end point for the present study rather than a combined end point of AVR or death as used in some previous studies.

AS: a disease not only limited to the valve. There is now a strong body of evidence suggesting that degenerative AS is an active disease akin to atherosclerosis (13,14), and in this context, it is not surprising that many patients with degenerative AS also have manifestations of atherosclerosis in other target organs. Many patients with degenerative AS thus also may present with concomitant systolic hypertension, and indeed, a markedly reduced arterial compliance was previously found to be present in up to 40% of patients with at least moderate AS (1). As well, such patients also

Table 4 Univariate and Multivariate Analysis of Predictors of Overall Death in the Total Cohort (544 Patients)

	Univariate Analysis		Multivariate Analysis	
	p Value	HR (95% CI)	p Value	HR (95% CI)
Model 1: continuous				
Age, yrs	<0.0001	1.07 (1.04–1.09)	0.0002	1.05 (1.02–1.08)
Hypertension	0.007	1.97 (1.19–3.44)	NS	—
AVA, cm^2	0.0015	0.30 (0.14–0.64)	NS	—
LVEF, %	0.02	0.97 (0.94–0.99)	NS	—
SAC, $ml \cdot m^{-2} \cdot mm\ Hg^{-1}$	0.0004	0.19 (0.07–0.49)	NS	—
LVMI, g/m^2	0.0016	1.01 (1.00–1.02)	0.004	1.01 (1.01–1.02)
Z_{va}, $mm\ Hg \cdot ml^{-1} \cdot m^2$	0.0004	1.41 (1.17–1.67)	0.03	1.36 (1.03–1.75)
Surgical treatment	<0.0001	0.21 (0.11–0.38)	<0.0001	0.22 (0.11–0.43)
Model 2: categorical				
Age >70 yrs	<0.0001	3.86 (2.31–6.87)	0.0001	2.94 (1.50–6.17)
Hypertension	0.007	1.97 (1.19–3.44)	NS	—
AVA ≤1.0 cm^2	0.015	1.67 (1.10–2.54)	NS	—
LVEF ≤55%	0.005	2.23 (1.29–3.65)	NS	—
SAC <0.6 $ml \cdot m^{-2} \cdot mm\ Hg^{-1}$	0.026	1.60 (1.05–2.42)	NS	—
LV hypertrophy	0.03	1.65 (1.03–2.59)	0.05	1.66 (1.01–2.73)
Z_{va} ≤3.5 $mm\ Hg \cdot ml^{-1} \cdot m^2$	—	1.00 (referent)	—	1.00 (referent)
$3.5 < Z_{va} < 4.5\ mm\ Hg \cdot ml^{-1} \cdot m^2$	0.006	2.24 (1.25–4.22)	0.03	2.30 (1.16–4.71)
Z_{va} ≥4.5 $mm\ Hg \cdot ml^{-1} \cdot m^2$	0.0001	2.95 (1.67–5.53)	0.01	2.76 (1.32–5.92)
Surgical treatment	<0.0001	0.21 (0.11–0.38)	<0.0001	0.20 (0.10–0.36)

For model 1, all variables except hypertension and surgical treatment were entered in continuous format. The hazard ratio (HR) represents the increase in mortality risk per 1-U increase in the variable. For model 2, all variables were entered in a dichotomous format.

AVA = aortic valve area; CI = confidence interval; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; SAC = systemic arterial compliance; other abbreviations as in Table 1.

may have alterations of LV function that might not only be caused by AS as such but also by hypertension and/or associated coronary artery disease and in varying proportions depending on the severity of each entity. Thus, degenerative AS cannot be viewed as an isolated disease strictly limited to the valve, but rather as part of a continuum that may also include a reduction in systemic arterial compliance and/or alterations of LV function. From the results of the present study, it would indeed seem that the pathophysiology of adverse outcomes in AS is primarily related to an imbalance between the global increase in LV overload, independent of whether it be of valvular and/or vascular origin, and LV reserve both at rest and during exercise; as well, it becomes evident that Z_{va} is the best-suited and most relevant parameter to clinically quantify this "global or total" increase in LV hemodynamic load.

The chronic exposure to a high level of afterload may eventually lead to a reduction in the coronary vasodilatory reserve, an intrinsic impairment of myocardial contractile function, and a decrease in cardiac output (1,5,9,15). To this effect, previous studies from our laboratory (1,5) and from the SEAS investigators (9) have reported that patients with a markedly increased Z_{va} often have decreases in LVEF, mid-wall fractional shortening, and cardiac output. The consequences of a reduction in cardiac output are a reduction of transvalvular gradients and a pseudo-normalization of peripheral blood pressure, which may occur in up to 30% of patients (1,5). 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, whereas, in fact, these patients are at a more advanced stage of their disease. In this regard, the calculation of Z_{va} may be useful for identifying the patients in whom disease severity is masked by this pseudo-normalization phenomenon.

Clinical implications. These results strengthen the need for a more comprehensive evaluation of AS that should include indexes such as: 1) AVA and ELI (in patients with a small aorta) for the assessment of valvular load; 2) systemic arterial compliance and vascular resistance for the assessment of arterial load; and finally, 3) Z_{va} to quantify global LV load. The consideration of these indexes easily measurable by Doppler echocardiography allows the clinician to better quantify the severity of the disease and could be particularly helpful in the 3 following clinical situations.

ASYMPTOMATIC PATIENTS WITH SEVERE AS. Management of these patients remains a source of debate (16,17), and recent studies have suggested that those treated surgically may have better survival than those treated medically (18–20). This difference may be related to underestimation of symptoms and/or stenosis severity in some patients, especially in the elderly sedentary patients (5,19,20). Moreover, it has been argued that a "wait for symptoms" strategy may result in some patients undergoing surgery too late (i.e., at a stage of the disease when myocardial impairment has become, at least in part, irreversible) (21). On the other

hand, AVR is not without risk (22), and the decision to operate on such patients therefore requires careful weighing of benefits against risks. To this effect, Z_{va} may be useful for identifying patients who are at higher risk and may be an indication for closer follow-up and further investigation. In this context, exercise stress testing may be particularly useful to corroborate symptomatic status in patients with a Z_{va} >4.5 mm Hg·ml^{-1}·m^2 who claim to be asymptomatic. If the exercise test is abnormal (exercise-limiting symptoms, decrease in blood pressure), AVR can be contemplated (16), whereas in the case of a normal test, the patient can be followed up more closely with a clinical brain natriuretic peptide level and/or echocardiographic evaluation every 6 to 12 months (23).

SYMPTOMATIC PATIENTS WITH MODERATE AS. Patients with moderate AS may become symptomatic because of concomitant hypertension. The calculation of Z_{va} may thus help to reconcile the apparent discrepancy between stenosis severity and symptomatic status. If the Z_{va} is <3.5 mm Hg·ml^{-1}·m^2, the symptoms could be related to a concomitant disease such as coronary artery disease, whereas if it is >3.5 mm Hg·ml^{-1}·m^2, the symptoms could be caused by the additive effects of the moderate AS and reduced arterial compliance and/or increased vascular resistance.

In such patients, the logical first step would be to treat their hypertension and then to re-evaluate symptomatic status and Z_{va} under treatment. Traditionally, vasodilator therapy has been considered relatively contraindicated in patients with AS because of its hypotensive effects, but recent studies, however, suggest that except in patients with very severe disease, it can be applied both safely and beneficially (23,24). Nonetheless, therapy should be introduced cautiously, particularly in patients with severe AS. Further studies will, however, be necessary to determine whether symptomatic status and outcome can be significantly improved in this fashion. Indeed, because AS patients often have reduced arterial compliance (1), blood pressure levels may not be completely normalized by treatment.

PARADOXICAL LOW-FLOW, LOW-GRADIENT, SEVERE AS. We recently reported that an important proportion of the patients with severe AS on the basis of AVA paradoxically have a low transvalvular flow rate (SVI <35 ml/m^2) and thus a low gradient (<40 mm Hg) despite the presence of a preserved LVEF (≥50%) (5). When compared with patients with severe AS, normal LV output and thus high gradient, these patients with paradoxical low flow were characterized by a higher degree of LV concentric remodeling, a lower LVEF (although still within the normal range), a reduced mid-wall shortening, a markedly higher level of LV global load reflected by a higher Z_{va}, and a worse prognosis if treated medically. Hence, it can be conceived that a greater and more longstanding increase in afterload may result in more pronounced LV concentric remodeling, a smaller LV cavity size, and a decrease in intrinsic myocardial function. This paradoxical low-flow, low-gradient AS pattern may bring some uncertainty about the actual severity of AS and may lead clinicians to erroneously conclude that the stenosis is not severe and that surgery is not indicated. Hence, the consideration of Z_{va} may be helpful in these patients to determine the actual level of global LV hemodynamic load that is often underestimated because of a reduction of transvalvular gradients and a pseudo-normalization of arterial pressures inherent to the low-flow state. If the Z_{va} is high, it is likely that the excessive hemodynamic load imposed by AS and/or hypertension contributed to the alteration of LV geometry and function that, in turn, led to the paradoxical low-flow state. In the present series, the vast majority (72%) of patients with paradoxical low flow had high Z_{va}, and among these patients >80% had a severe AS. In the subset of patients with moderate AS, the severe augmentation of Z_{va} is most likely caused by the coexistence of hypertension. On the other hand, if Z_{va} is low, the alteration of the LV geometry and function leading to a paradoxical low-flow state may be caused by concomitant risk factors or diseases such as diabetes, metabolic syndrome, or hypertrophic cardiomyopathy.

Study limitations. One limitation of this study is its retrospective design. The baseline data were prospectively collected in consecutive patients with asymptomatic AS referred to the echocardiographic laboratory. However, the outcome data were retrospectively obtained from patients' charts or death certificates. Consequently, we did not have the information on: 1) the exact timing of symptom onset during follow-up; 2) the proportion of patients in whom severe symptomatic AS developed and who were not referred to AVR because of advanced age, comorbidities, or inappropriate management; and 3) the primary reason that motivated AVR. These limitations were, at least in part, compensated by the fact that we used overall survival (and not AVR) as the primary end point for this study and that we adjusted for the type of treatment in the multivariate analyses.

Patients with more than mild aortic insufficiency were excluded from the study. In the presence of significant aortic insufficiency, both the numerator (transvalvular gradient) and the denominator (SVI measured in the LV outflow tract) of Z_{va} may increase, which may reduce the ability of this index to correctly quantify the severity of the hemodynamic load in patients with mixed valvular dysfunction, and further studies are thus needed to examine the applicability and utility of Z_{va} in patients with mixed dysfunction.

Conclusions

Increased Z_{va} is a marker of excessive LV hemodynamic load and identifies patients with a poor outcome. These findings suggest that beyond standard indexes of stenosis severity, LV geometry, and function, the consideration of

Z_{va} may be useful to improve risk stratification and clinical decision making in patients with AS.

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