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Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction Is Associated With Higher Afterload and Reduced Survival

Zeineb Hachicha, MD; Jean G. Dumesnil, MD; Peter Bogaty, MD; Philippe Pibarot, DVM, PhD

Background—Recent studies and current clinical observations suggest that some patients with severe aortic stenosis on the basis of aortic valve area may paradoxically have a relatively low gradient despite the presence of a preserved left ventricular (LV) ejection fraction. The objective of the present study was to document the prevalence, potential mechanisms, and clinical relevance of this phenomenon.

Methods and Results—We retrospectively studied the clinical and Doppler echocardiographic data of 512 consecutive patients with severe aortic stenosis (indexed aortic valve area $\leq 0.6 \text{ cm}^2 \cdot \text{m}^{-2}$) and preserved LV ejection fraction ($\geq 50\%$). Of these patients, 331 (65%) had normal LV flow output defined as a stroke volume index $> 35 \text{ mL} \cdot \text{m}^2$, and 181 (35%) had paradoxically low-flow output defined as stroke volume index $\leq 35 \text{ mL} \cdot \text{m}^2$. When compared with normal flow patients, low-flow patients had a higher prevalence of female gender ($P < 0.05$), a lower transvalvular gradient (32 ± 17 versus $40 \pm 15 \text{ mm Hg}$; $P < 0.001$), a lower LV diastolic volume index (52 ± 12 versus $59 \pm 13 \text{ mL} \cdot \text{m}^{-2}$; $P < 0.001$), lower LV ejection fraction ($62 \pm 8\%$ versus $68 \pm 7\%$; $P < 0.001$), a higher level of LV global afterload reflected by a higher valvulo-arterial impedance (5.3 ± 1.3 versus $4.1 \pm 0.7 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$; $P < 0.001$) and a lower overall 3-year survival (76% versus 86%; $P = 0.006$). Only age (hazard ratio, 1.04; 95% CI, 1.01 to 1.08; $P = 0.025$), valvulo-arterial impedance $> 5.5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$ (hazard ratio, 2.6; 95% CI, 1.2 to 5.7; $P = 0.017$), and medical treatment (hazard ratio, 3.3; 95% CI, 1.8 to 6.7; $P = 0.0003$) were independently associated with increased mortality.

Conclusion—Patients with severe aortic stenosis may have low transvalvular flow and low gradients despite normal LV ejection fraction. A comprehensive evaluation shows that this pattern is in fact consistent with a more advanced stage of the disease and has a poorer prognosis. Such findings are clinically relevant because this condition may often be misdiagnosed, which leads to a neglect and/or an underestimation of symptoms and an inappropriate delay of aortic valve replacement surgery. (*Circulation*. 2007;115:2856-2864.)

Key Words: echocardiography ■ hemodynamics ■ hypertension ■ valves

We have recently shown that reduced systemic arterial compliance (SAC) is a frequent occurrence in elderly patients with aortic stenosis (AS), in which SAC independently contributes to increased afterload and decreased left ventricular (LV) function.¹ In particular, patients with a markedly increased afterload as a result of the combination of severe AS and reduced SAC were observed to have decreased cardiac output, which resulted in lower transvalvular gradients and pseudonormalization of peripheral blood pressure. The same patients also tended to have a lower ejection fraction (EF) but not of the same order of magnitude as the observed changes in cardiac output.

In the same context, we have long been intrigued by the clinical observation that an important proportion of elderly patients with severe AS on the basis of aortic valve area (AVA) calculations (eg, indexed AVA $< 0.6 \text{ cm}^2 \cdot \text{m}^{-2}$) tend to

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have low gradients (eg, mean gradient $< 30 \text{ mm Hg}$) despite a preserved LVEF (ie, $> 50\%$). The clinical conduct in these patients can also be problematic given that this paradoxical combination of measurements may raise questions with regard to the validity of the Doppler measurements although the same patients are often symptomatic. The problem may be further compounded by the fact that, to resolve this apparent discrepancy, many of these patients may be sent to cardiac catheterization, where the signs of AS severity may be masked by the presence of concomitant hypertension.^{2,3} This may lead to a situation in which symptomatic patients without a clear indication for surgery are left with no evident treatment to alleviate their symptoms.

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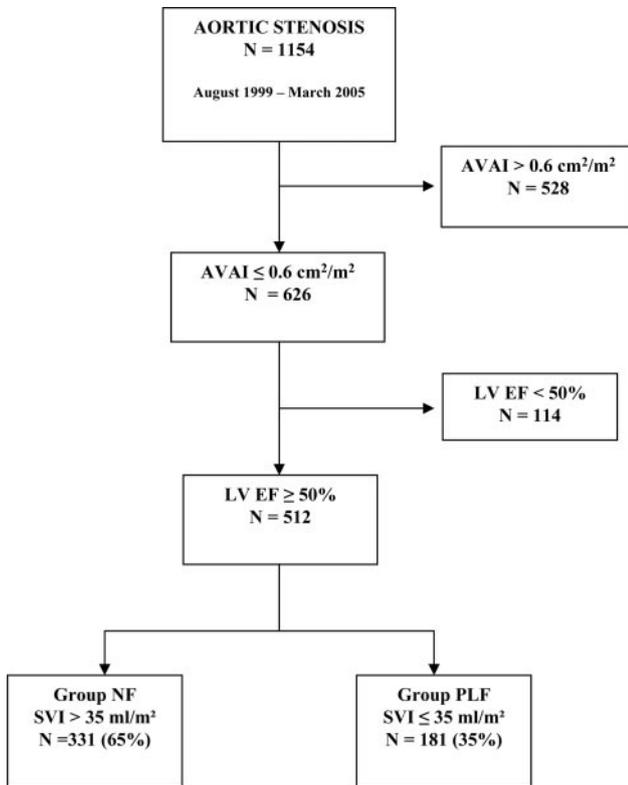


Figure 1. Description of the patient population. AVAI indicates indexed aortic valve area; SVI, stroke volume index; NF, normal flow; and PLF, paradoxical low flow.

The objective of the present study was to document the prevalence, potential mechanisms, and clinical relevance of this paradoxical cluster of findings. In particular, we sought to determine the pathophysiology of this phenomenon and its significance in terms of the severity of the disease and its prognosis.

Methods

Patient Population

From August 1999 to March 2005, 1154 patients were referred to the echocardiographic laboratory of the Quebec Heart Institute for the evaluation of AS (Figure 1). From this cohort, we included in the present study only the patients who had evidence of severe AS (defined as an indexed AVA $\leq 0.6 \text{ cm}^2 \cdot \text{m}^{-2}$) and a preserved LVEF (defined as LVEF $\geq 50\%$). The study group consisted of 512 consecutive patients (290 men and 222 women) with a mean age of 70 ± 14 years (range 22 to 100 years) (Figure 1).

These patients were then further subdivided into 2 groups depending on whether they had normal LV flow output defined as a stroke volume index (SVI) $> 35 \text{ mL/m}^2$ (NF group) or paradoxical low flow (ie, low flow in the context of normal LVEF defined as SVI $\leq 35 \text{ mL/m}^2$) (PLF group).

Clinical Data

Clinical data included age, gender, history of smoking, documented diagnosis of hypertension (patients on antihypertensive medications or with known but untreated hypertension [blood pressure $\geq 140/90 \text{ mm Hg}$]), hypercholesterolemia (patients on cholesterol-lowering medication or, in the absence of such medication, documentation of plasma low-density lipoprotein cholesterol level $> 160 \text{ mg} \cdot \text{dL}^{-1}$), diabetes, obesity (body mass index $\geq 30 \text{ kg} \cdot \text{m}^{-2}$), and coronary heart disease (history of myocardial infarction, coronary artery

stenosis on coronary angiography, or regional wall motion abnormality on echocardiogram). These data were complete in all patients.

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 measured in the left ventricular outflow tract (LVOT stroke volume). The ratio of SVI to brachial pulse pressure (PP) was used as an indirect measure of total systemic arterial compliance:¹

$$(1) \quad \text{SAC} = \frac{\text{SVI}}{\text{PP}}$$

The systemic vascular resistance was estimated by the formula

$$(2) \quad \text{SVR} = \frac{80 \times \text{MAP}}{\text{CO}}$$

where MAP is the mean arterial pressure defined as diastolic pressure plus one third of brachial pulse pressure and CO is the cardiac output.

Doppler Echocardiographic Data

Aortic Valve Stenosis Severity

The Doppler echocardiographic indices 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 dimensionless velocity index calculated as the ratio of LVOT velocity-time integral to aortic jet velocity-time integral. The valvular resistance (RES) was obtained with the formula

$$(3) \quad \text{RES} = \frac{(1333 \times \text{MG})}{\text{Q}_{\text{mean}}}$$

where MG is the mean gradient and Q_{mean} is the mean transvalvular flow rate (ie, the stroke volume divided by LV ejection time). The energy loss index (ELI) was determined with the following formula:

$$(4) \quad \text{ELI} = \frac{\text{AVA} \times A_A / A_A - \text{AVA}}{\text{BSA}}$$

where AVA is the valve effective orifice area, A_A is the aortic cross-sectional area, and BSA is body surface area.⁴

LV Geometry

Two-dimensionally directed LV M-mode dimensions were measured in the left parasternal long-axis view according to the recommendations of the American Society of Echocardiography. Left ventricular minor axis internal dimension (LVID), posterior wall (PWT) and septal thickness were measured at end-diastole (d) and at end-systole (s). Left ventricular mass was calculated with the corrected formula of the American Society of Echocardiography and indexed for body surface area. The relative wall thickness (RWT) was calculated with the formula

$$(5) \quad \text{RWT} = 200 \times \frac{\text{PWTd}}{\text{LVIDd}}$$

and LV hypertrophy was defined as LV mass index $> 115 \text{ g} \cdot \text{m}^{-2}$ in men and $> 95 \text{ g} \cdot \text{m}^{-2}$ in women as recommended in the 2005 report of the American Society of Echocardiography.

LV Diastolic Function

Early (E) transmitral filling peak velocity and transmitral atrial (A) wave velocity were measured at rest and during the second phase of the Valsalva maneuver.⁵ Early diastolic velocity of the lateral aspect of the mitral annulus (E_a) was measured by Doppler tissue imaging at rest. Diastolic function was classified according to the recommendations of the Canadian Consensus on Diastolic Dysfunction: normal, impaired relaxation, pseudonormal, and restrictive pattern. A pseudonormal pattern was defined as present if 2 of the 3 criteria

TABLE 1. Comparison of Clinical and Systemic Arterial Data in NF and PLF Groups

	NF Group (n=331)	PLF Group (n=181)	P	Adjusted P*	Overall Adjusted P†
Gender, %					
Females	39	51	<0.05	NS	NS
Males	61	49			
Age, y	69±14	73±13	0.004	NS	NS
Body surface area, m	1.8±0.2	1.8±0.2	NS	NS	NS
Risk factors and concomitant diseases, %					
Obesity	34	31	NS	NS	NS
Hypertension	68	74	NS	NS	NS
Diabetes	26	28	NS	NS	NS
Hypercholesterolemia	57	52	NS	NS	NS
Coronary artery disease	56	65	NS	NS	NS
Previous myocardial infarction	21	26	NS	NS	NS
Systemic arterial hemodynamics					
Systolic arterial pressure, mm Hg‡	134±22	131±21	NS	NS	NS
Diastolic arterial pressure, mm Hg‡	72±10	74±11	NS	NS	NS
Systemic vascular resistance, mm Hg · min · L ⁻¹ ‡	1508±380	1986±677	<0.001	<0.001	0.002
Systemic arterial compliance, mL · mm Hg ⁻¹ · m ⁻² ‡	0.8±0.3	0.6±0.2	<0.001	<0.001	<0.001
Systemic arterial compliance<0.6, %‡	30	57	<0.001	<0.001	<0.001

Values are expressed as mean±SD or %. NS indicates not significant.

*P value adjusted for age and gender.

†P value adjusted for age, gender, clinical, systemic arterial, and Doppler echocardiographic data.

‡Data available in 426 of the 512 patients.

were met: (1) Resting $E_a \leq 12.5$ cm/s, (2) E/A ratio <1 with the Valsalva maneuver, and (3) decrease in E/A ratio >25% with the Valsalva maneuver.⁵

LV Systolic Function

The LVEF was assessed in all patients with the Quinones method, the Dumesnil method,⁶ and by visual estimate. In the case of a disagreement among these methods, the reviewing cardiologist selected the value that appeared the most representative. We also retrospectively measured the LVEF and the LV stroke volume with the use of the biplane Simpson method in 320 of 512 (62.5%) patients in whom adequate quality images were available. The mid-wall fractional shortening (MWFS) was calculated as a percentage:

$$(6) \quad MWFS = 100 \times \frac{(LVID_{d/2} + PWT_{d/2}) - (LVID_{s/2} + PWT_{s/2})}{LVID_{d/2} + PWT_{d/2}}$$

The LV cardiac output was calculated as the product of heart rate and stroke volume and was indexed for body surface area. The LV stroke work (SW) was calculated with the formula⁷

$$(7) \quad SW = (MAP + MG) \times SV \times 0.0136,$$

where MAP is the mean arterial pressure, MG is the mean transvalvular pressure gradient, and SV is the stroke volume measured in the LVOT. The SW was also indexed to LV mass.

Global LV Afterload

As a measure of global LV afterload, we calculated the valvulo-arterial impedance:¹

$$(8) \quad Z_{va} = \frac{SAP + MG}{SVI},$$

where SAP is the systolic arterial pressure and MG is the mean transvalvular pressure gradient. Hence Z_{va} represents the valvular and arterial factors that oppose ventricular ejection by absorption of

the mechanical energy developed by the left ventricle.¹ The measurement of systemic arterial pressure was not performed at the time of the Doppler echocardiographic study in 86 patients. Systemic vascular resistance, SAC, and Z_{va} could thus not be determined in these patients. However, there was no significant difference in the missing rates of these variables as well as those of the LVEF and stroke volume measured by the Simpson method between the NF and PLF groups.

Clinical Outcomes

The primary end point for the present study was overall death regardless of whether there was aortic valve replacement surgery (AVR). Hence, this includes the deaths that occurred in patients who did not undergo AVR as well as those that occurred after operation in patients who underwent AVR. The last evaluation of patient survival status was performed in October 2005 (the closing follow-up date). Status could not be confirmed in 19 of 512 (3.7%) patients; these patients were excluded from the survival analyses. There was no difference between PLF and NF groups with regard to the percentage of patients lost to follow-up.

Statistical Analysis

Continuous data of NF and PLF groups were expressed as mean±SD and compared with a Student *t* test. Categorical data were given as a percentage and compared with a χ^2 test. The comparisons of data between NF and PLF groups were adjusted for age, gender, and other relevant variables with a logistic regression model that used NF/PLF status as dependent variable and the clinical, systemic arterial, and Doppler echocardiographic measurements as independent variables. Overall survival function was obtained by Kaplan-Meier estimates for the NF and PLF groups and for the levels of various risk factors. Differences among the groups or among the levels of risk factors were compared with the log-rank test. The effect of the clinical and Doppler echocardiographic variables on survival was assessed with the use of Cox proportional hazard model. All the variables presented in Tables 1 and 2 as well as the type of treatment (medical versus

TABLE 2. Comparison of Doppler Echocardiographic Data in NF and PLF Groups

	NF Group (n=331)	PLF Group (n=181)	P	Adjusted P*	Overall Adjusted P†
Aortic stenosis severity					
Aortic valve area, cm ²	0.84±0.18	0.76±0.23	<0.001	<0.001	NS
Indexed aortic valve area, cm ² · m ⁻²	0.46±0.08	0.42±0.11	<0.001	<0.001	NS
Peak aortic velocity, m · s ⁻¹	4.0±0.7	3.5±0.9	<0.001	<0.001	<0.001
Mean gradient, mm Hg	40±15	32±17	<0.001	<0.001	<0.001
Mean gradient ≤30, %	30	55	<0.001	<0.001	<0.001
Energy loss index, cm ² · m ⁻²	0.51±0.10	0.47±0.14	<0.001	0.027	NS
Valvular resistance, dyne · s · cm ⁻⁵	224±89	239±146	NS	NS	NS
Dimensionless velocity index	0.23±0.05	0.24±0.07	NS	NS	NS
LV global afterload					
Valvulo-arterial impedance, mm Hg · mL ⁻¹ · m ⁻² ‡	4.1±0.7	5.3±1.3	<0.001	<0.001	<0.001
Valvulo-arterial impedance ≥5.5, %‡	3	37	<0.001	<0.001	<0.001
LV geometry					
LVOT diameter, mm	22±2	20±2	<0.001	<0.001	0.04
LV end-diastolic interventricular septum thickness, mm	13±3	13±3	NS	NS	NS
LV end-diastolic posterior wall thickness, mm	11±2	11±2	NS	NS	NS
LV end-diastolic internal diameter, mm	48±5	45±5	<0.001	<0.001	0.015
LV end-diastolic volume index, mL · m ⁻²	59±13	52±12	<0.001	<0.001	0.017
LV end-diastolic volume indexed to height ^{2.7} , mL · m ^{-2.7}	28±7	25±6	<0.001	<0.001	0.03
LV mass index, g · m ⁻²	121±33	111±29	0.005	0.007	NS
LV mass indexed to height ^{2.7} , g · m ^{-2.7}	57±17	53±15	0.02	0.02	NS
LV hypertrophy, %	64	52	0.015	0.05	NS
Relative wall thickness	51±10	54±14	0.003	0.03	NS
Relative wall thickness >45, %	69	75	NS	NS	NS
LV diastolic function, %					
Normal	11	12	NS	NS	NS
Abnormal relaxation	56	62	NS	NS	NS
Pseudo-normal	31	24	NS	NS	NS
Restrictive	1	3	NS	NS	NS
LV systolic function					
Ejection fraction, %§	68±7	62±8	<0.001	<0.001	0.03
Ejection fraction by Simpson method, %¶	69±7	65±11	<0.001	<0.001	NS
Midwall fractional shortening, %	23±6	20±15	0.012	0.013	NS
LVOT stroke volume, mL	79±14	56±10	<0.001	<0.001	...
Stroke volume by Simpson method, mL¶	73±18	61±16	<0.001	<0.001	...
LVOT stroke volume indexed to height ^{2.7} , mL · m ^{-2.7}	20±3	15±2	<0.001	<0.001	...
Stroke work, g · m	145±33	96±24	<0.001	<0.001	NS
Stroke work per 100g of LV mass g · m	69±19	51±13	<0.001	<0.001	NS
Heart rate, bpm	65±11	71±13	<0.001	<0.001	NS
Cardiac output, L · min ⁻¹	5.12±1.12	3.90±0.93	<0.001	<0.001	...
Cardiac index, L · min ⁻¹ · m ⁻²	2.80±0.54	2.15±0.42	<0.001	<0.001	...
LV ejection time, ms	329±35	311±33	<0.001	<0.001	NS
Mean transvalvular flow rate, mL · s ⁻¹	243±49	180±39	<0.001	<0.001	...

Values are expressed as means±SD or %. NS indicates nonsignificant.

*P value adjusted for age and gender.

†P value adjusted for age, gender, clinical, systemic arterial, and Doppler echocardiographic data.

‡Data available in 426 of the 512 patients.

§Composite EF obtained from the EF values measured in all patients by Quinones method, Dumesnil method, and visual estimate.

¶Data measured retrospectively in a subset of 320 patients.

surgical [ie, AVR]) were tested in univariate analysis, and those with a P value <0.25 on univariate analysis were incorporated into the multivariate model. Age, gender, coronary artery disease, and hypertension were forced into the model.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Among the 512 patients with preserved LVEF, 331 (65%; NF group) had normal LV outflow (SVI 36 to 68 mL/m²) and 181 (35%; PLF group) had paradoxically low flow (SVI 14 to 35 mL/m²). Table 1 provides a comparison of the clinical and systemic arterial pressure data in the NF and PLF groups. When compared with the NF group, the PLF group comprised older patients and a higher proportion of females. The prevalence of risk factors and concomitant diseases was nonetheless similar in both groups.

Systemic Arterial Hemodynamics

Although the SAC was markedly lower and the systemic arterial resistance was higher in the PLF group than in the NF group, the values of arterial pressure were similar in both groups (Table 1). The lower LV output associated with the PLF pattern may have caused a "pseudo-normalization" of systemic arterial pressure in the PLF group.¹

Aortic Stenosis Severity

Table 2 shows the comparison of the Doppler echocardiographic indices of stenosis severity. Noticeably, the peak aortic velocity and the transvalvular gradients were significantly lower in the PLF group than in the NF group. However, the relatively flow-independent indices of AS severity such as the AVA and the energy loss index were significantly lower in the PLF group, and the dimensionless velocity index and the valvular resistance were similar in both groups, which suggests that the stenosis is in fact at least as severe in the PLF group as in the NF group.

Global Left Ventricular Afterload

The PLF patients had markedly higher values for Z_{va} as compared with NF patients, consistent with a markedly higher degree of global afterload in these patients. Based on the previous observations, this excessive afterload can be seen as frequently resulting from the combination of a more severe valvular obstruction and a greater reduction in SAC.

Left Ventricular Geometry

Table 2 shows the comparison of indices of LV geometry and function. Overall, the NF and PLF patients generally had concentric LV hypertrophy or remodelling. The concentric remodelling was more pronounced in the PLF group than in the NF group. The PLF patients indeed had a smaller cavity size, similar wall thickness, and thus a greater relative wall thickness ratio compared with the NF patients. The LV mass index was lower in the PLF group but the proportion of patients with LV hypertrophy was similar in both groups. This discrepancy is likely related to the higher proportion of females in the PLF group.

Left Ventricular Diastolic Function

Impaired relaxation was the predominant pattern in all groups. There was no significant difference between NF and PLF groups with regard to presence and severity of LV diastolic dysfunction.

Left Ventricular Systolic Function

Mid-wall fractional shortening, composite LVEF, and LVEF measured by Simpson method in a subset of 320 patients were significantly lower in the PLF group compared with the NF group. As well, SVI, stroke work, cardiac index, cardiac output, and mean transvalvular flow rate were markedly lower in the PLF group than in the NF group. There was a good agreement (mean absolute difference = 2 ± 14 mL and mean relative difference = $4 \pm 20\%$) between the stroke volume measured in the LVOT and the stroke volume measured by the Simpson method, and the latter was also significantly lower ($P < 0.001$) in the PLF group than in the NF group.

Thus, the higher global afterload in the PLF group is associated with reduced myocardial contractility and more pronounced LV concentric remodelling, which results in reductions of stroke volume and cardiac output, as well as a compensatory increase in heart rate.

Clinical Outcomes

Follow-up was complete for 493 of 512 (96%) patients and mean follow-up time was 25 ± 19 months (minimum 0.03; 25% quartile 11; median 18; 75% quartile 36; maximum 74 months). A total of 290 (59%) patients had AVR (210 of 322 [65%] in the NF group and 80 of 171 [47%] in the PLF group). Sixty-nine (14%) patients died during follow-up (37 of 322 [11%] in the NF group and 32 of 171 [19%] in the PLF group). Cause of death was cardiovascular in 38 patients, noncardiovascular in 19 patients, and unknown in 12 patients. There were 46 deaths in the subset of 203 patients (23%) who were treated medically (20 of 112 [18%] in the NF group and 26 of 91 [29%] in the PLF group) and 23 deaths in the 290 patients (8%) who underwent AVR (17 of 210 [8%] in the NF group and 6 of 80 [7.5%] in the PLF group). Among these 23 deaths, 11 occurred in the perioperative period.

Predictors of Survival

PLF patients had lower overall survival compared with the NF patients (PLF versus NF: 1 year, $87 \pm 3\%$ versus $94 \pm 1\%$; 2 years, $79 \pm 4\%$ versus $90 \pm 2\%$; 3 years, $76 \pm 4\%$ versus $86 \pm 3\%$; $P = 0.006$; P value adjusted for age and gender = 0.045) (Figure 2). Moreover, PLF patients treated medically had markedly lower survival compared with those who underwent AVR (PLF medical versus PLF surgical: 2 years, $65 \pm 7\%$ versus $93 \pm 3\%$; 3 years, $58 \pm 8\%$ versus $93 \pm 3\%$; $P = 0.001$; P value adjusted for age and gender = 0.002) (Figure 3). Survival was also lower in PLF patients treated medically compared with NF patients treated medically (PLF versus NF: 2 years, $65 \pm 7\%$ versus $84 \pm 4\%$; 3 years, $58 \pm 8\%$ versus $68 \pm 8\%$; $P = 0.049$); this difference was no longer significant ($P = 0.15$) after adjustment for age and gender.

The factors significantly associated with increased overall mortality on univariate analysis were older age, hypertension, $LVEF \leq 55\%$, $SVI \leq 35$ mL/m², $SAC \leq 0.6$ mL/mm Hg · m⁻²,

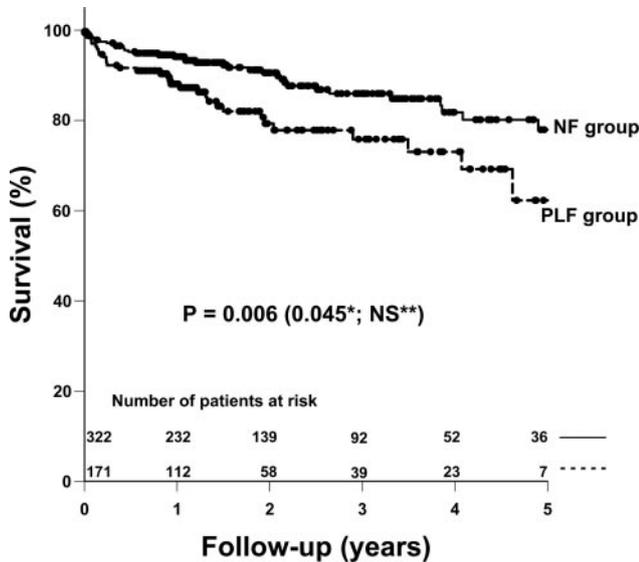


Figure 2. Overall survival in the patients with NF and in those with PLF. Numbers at the bottom indicate the number of patients at each follow-up interval. The circles on the curves indicate the censoring times. **P* value adjusted for age and gender. ***P* value adjusted for age, gender, valvulo-arterial impedance, and type of treatment.

$Z_{va} > 5.5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$, and medical treatment instead of AVR. On multivariate analysis, only older age (hazard ratio, 1.04; 95% CI, 1.01 to 1.08; $P=0.025$), $Z_{va} > 5.5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$ (hazard ratio, 2.6; 95% CI, 1.2 to 5.7; $P=0.017$), and medical treatment (hazard ratio, 3.3; 95% CI, 1.8 to 6.7; $P=0.0003$) were independently associated with increased mortality (Table 3). Thus, AVR was associated with a highly protective effect. Three-year survival was 62% for patients

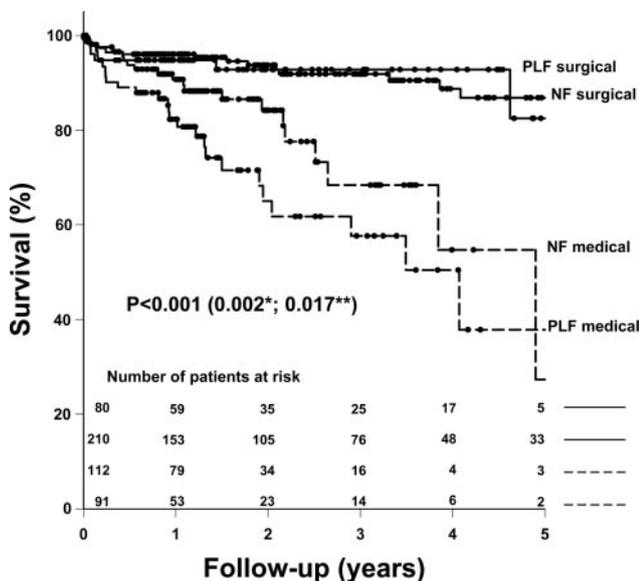


Figure 3. Overall survival in the patients with NF and in those with PLF as a function of the type of treatment: medical versus surgical. Numbers at the bottom indicates the number of patients at each follow-up interval. *P* values are for the comparison among all 4 groups. **P* value adjusted for age and gender. ***P* value adjusted for age, gender, and valvulo-arterial impedance.

with $Z_{va} \geq 5.5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$ versus 85% for those with $Z_{va} < 5.5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$ ($P=0.003$; *P* value adjusted for age and gender=0.02) (Figure 4). Consistent with the results of the multivariate analysis presented in Table 3, the survival difference observed between the PLF and NF groups (Figure 2) was no longer significant after adjustment for age, gender, valvulo-arterial impedance, and type of treatment.

Discussion

The present study confirms the clinical impression that the paradoxical combination of low-flow, low-gradient severe AS despite preserved EF is a frequent occurrence. This cluster of clinical findings occurred in 35% of the patients in this consecutive series. Compared with the patients with the more classic features of severe AS, the most striking findings in the PLF patients are a markedly increased global LV afterload as evidenced by the valvulo-arterial impedance values 29% higher than those observed in the NF group as well as a low output state as evidenced by mean transvalvular flow rates comparable to those observed in patients with low-flow AS associated with low EF.^{8,9} Further analysis also shows that the greater increase in global LV afterload is associated with a combination of a similar stenosis severity and a lower systemic arterial compliance in the PLF group compared with the NF group. The disease severity of this entity is also independently corroborated by the observation of a greater decrease in mid-wall fractional shortening than the NF group and a markedly lower survival in medically rather than surgically treated patients.

Potential Mechanisms of Low-Flow AS in Patients With Normal EF

The combination of a higher global afterload and a decreased output in the PLF group is suggestive of a decrease in cardiac reserve whereby the chronic exposure to a high level of afterload eventually exceeds the limit of LV compensatory mechanisms and leads to an intrinsic impairment of myocardial function and a decrease in cardiac output. This concept is further illustrated by the results of our recent study in which a value of the valvulo-arterial impedance $> 5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$ was independently associated with a 4-fold increase in the risk of LV systolic dysfunction defined as a LVEF $< 50\%$.¹ However, the apparent discrepancy in the present study is that the PLF patients all had a LVEF $\geq 50\%$ and on this basis could be presumed to have normal LV function. Nonetheless, the same patients also had significantly lower mid-wall fractional shortening and stroke work index, suggesting a significant impairment in intrinsic myocardial function.

Interpretation of LV Function Parameters in Patients With AS

As opposed to mid-wall fractional shortening, the LVEF is influenced by both intrinsic myocardial function and LV cavity geometry. We have previously demonstrated an independent relationship between LVEF and relative wall thickness ratio^{10,11}; thus, for a similar extent of intrinsic myocardial shortening, the LVEF or any parameter based solely on endocardial displacement will tend to increase in relation to the extent of LV concentric remodelling. Hence, as is often

TABLE 3. Predictors of Overall Death on Univariate and Multivariate Analysis

Variable	Percentage of Patients With Variable	Univariate Analysis		Multivariate Analysis	
		<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)
Age	100	<0.0001	1.06 (1.04 to 1.1)	0.025	1.04 (1.01 to 1.08)
Hypertension	70	0.02	2.0 (1.1 to 3.8)	NS	...
LVEF ≤55%*	12	0.02	2.1 (1.2 to 3.7)	NS	...
Stroke volume index ≤35, mL · m ⁻²	35	0.01	1.9 (1.2 to 3.0)	NS	...
Systemic arterial compliance ≤0.6, mL · mm Hg ⁻¹ · m ⁻²	38	0.04	1.7 (1.1 to 3.4)	NS	...
Valvulo-arterial impedance ≥5.5, mm Hg · mL ⁻¹ · m ⁻²	14	0.006	2.5 (1.2 to 4.5)	0.017	2.6 (1.2 to 5.7)
Medical treatment (vs surgical treatment)	70	<0.0001	4.3 (2.6 to 7.4)	0.0003	3.3 (1.8 to 6.7)

NS indicates nonsignificant. The multivariate analysis was performed in the 413 patients for whom all data were available and follow-up was complete. Only the variables that were significantly associated with survival on univariate analysis are shown in this table. Age was analyzed as a continuous variable. The other continuous variables were dichotomized with the cut-off values previously proposed in the literature.

*Composite LVEF obtained from the EF values measured in all patients by Quinones method, Dumesnil method, and visual estimate.

observed, patients with AS and significant concentric remodelling tend to have hypernormal EFs (ie, >70%), whereas similar patients with EFs usually considered normal (ie, 50% to 60%) may have significant reductions in intrinsic myocardial shortening as reflected by decreased values for mid-wall radius shortening.^{11,12} In the interpretation of LVEF in patients with AS, we believe what is normal for a left ventricle with normal geometry may be abnormal for a left ventricle with concentric remodelling. Thus, in this context a LVEF>50% cannot exclude the presence of intrinsic myocardial dysfunction. In the present study, the patients in the PLF group had smaller and relatively thicker ventricles as well as lower values for mid-wall radius shortening and EF. These findings are further evidence of severe disease. They also emphasize that the evaluation of patients with AS should include a more comprehensive assessment of LV function

and not be based solely on parameters that reflect LV endocardial displacement.

Relation Between LV Structural Changes and LV Function in AS

The PLF patients had smaller LV cavities and a greater degree of concentric remodelling. The strikingly lower values for SVI and transvalvular flow observed in this group are presumably caused by the association of both a lower LVEF and a smaller ventricle. These observations offer independent evidence that these patients are at a more advanced stage of their disease from both a structural and a functional standpoint. Indeed, it can be readily conceived that a greater and more longstanding increase in afterload will result in more pronounced LV concentric remodelling, a smaller LV cavity size, and a decrease in intrinsic myocardial function as evidenced by the lower values for mid-wall radius shortening. The fact that the PLF patients were older would be consistent with more longstanding disease. A gender-specific response to the increased afterload cannot be excluded given the significantly higher proportion of women in the PLF group.

Clinical Implications

The results of the present study have important implications with regard to both diagnosis and treatment of patients with AS. Our characterization suggests that the PLF pattern is associated with a cluster of findings that reflect advanced disease and poor prognosis. Moreover, the data presented in Figure 3 and Table 3 raises the provocative possibility that these patients have a better prognosis if treated surgically than medically. At present, physicians may be somewhat reluctant to recommend surgery in patients with low gradient and preserved EF even if they are symptomatic and have poor exercise tolerance, and in this sense, if not identified, the condition could frequently be misdiagnosed and inappropriately treated. The low-flow state might also contribute to an underestimation of hypertension. Indeed, systemic arterial compliance was significantly lower in the PLF group than in the NF group, but the recorded arterial pressures were nonetheless similar and within the normal range in both groups (Table 1). This result suggests that blood pressure

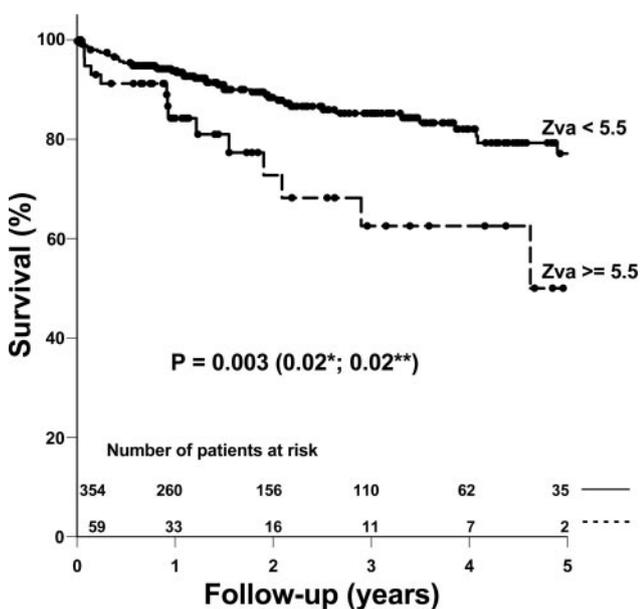


Figure 4. Overall survival according to valvulo-arterial impedance (Z_{va}). Numbers at the bottom indicate the number of patients at each follow-up interval. **P* value adjusted for age and gender. ***P* value adjusted for age, gender, and type of treatment.

tends to be pseudo-normalized in the PLF group because of the low-flow state. Hence, based on routine measurements of gradients and blood pressure, afterload might be evaluated as normal when it is in fact markedly elevated. Moreover, these patients may be quite symptomatic and the appropriate treatment (ie, medical treatment of hypertension and/or surgical treatment of AS) may not be readily apparent.

Comprehensive Evaluation of AS Severity

These results strengthen the need for a more comprehensive evaluation of AS severity that goes beyond the classic measurements to include parameters that are less flow-dependent such as AVA, energy loss index, velocity index, systemic arterial compliance, and valvulo-arterial impedance. The latter parameter would appear particularly important because it was the only independent predictor of mortality besides age and medical as opposed to surgical treatment, with a risk ratio of 2.6 when its value was $\geq 5.5 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{m}^{-2}$. To make these calculations, blood pressure should be measured at the time of the Doppler examination. Because hypertension may mask the signs of AS severity, Doppler examination is ideally performed when blood pressure control is optimal.^{2,3,13} Other measurements should include LV mass, relative wall thickness, EF, and mid-wall radius shortening because they provide essential corroboration of the flow-derived measurements and may be useful in the establishment of appropriate clinical conduct.

Management of Patients With Low-Flow AS and Preserved EF

The present results further confirm that AS cannot be viewed as an isolated disease of the valve, but that it is often just one manifestation of an atherosclerotic process that involves various components of the vascular system, such as the aorta.^{1,3} In many patients, the increased global LV afterload has a valvular component but also an arterial component. Treatment should therefore be directed to address both components. From a diagnostic and therapeutic standpoint, the logical first step would be to optimize blood pressure levels. However, this approach has its limitations because reduced arterial compliance that results from a more rigid aorta cannot be completely normalized by medical treatment. Indeed, patients with reduced arterial compliance often have normal diastolic pressures but increased pulse pressure (eg, 160/60 mm Hg), and treatment may be further limited because, as we have observed, blood pressure tends to be pseudo-normalized in patients with PLF because of the low-flow state. On the other hand, the present results also demonstrate that the apparently paradoxical combination of low-flow, low-gradient severe AS with normal LVEF is indeed an indicator of severity and has a worse prognosis than that of patients with more classic findings. Hence, in the presence of typical symptoms and in the absence of contraindications, surgical treatment would appear to be the appropriate option. It should however be recognized that the increased afterload may not be completely alleviated with surgery in patients with markedly reduced systemic arterial compliance. Insofar as these patients also have intrinsic LV dysfunction, it would appear especially important in this

context to avoid prosthesis-patient mismatch to optimize postoperative afterload.^{14,15} Finally, because these patients have transvalvular flow levels comparable to those observed in patients with low-flow AS and low EF, it is possible that some of these patients have pseudo-severe AS. In this context, the performance of dobutamine stress echocardiography might be worthwhile. Such considerations will need to be further validated by prospective studies.

Limitations of the Study

The present study was retrospective, and the data did not allow us to determine the exact time of symptom onset in the course of the disease. Nonetheless, the evaluation of symptoms is often subjective, and we believe symptoms to be more often a consequence of the evolution of AS rather than an independent determinant per se. We therefore elected for the purpose of the present study to identify objective Doppler echocardiographic variables that were independently related with a more robust end point (ie, overall survival).

We did not exclude the patients who were symptomatic at the time of the baseline Doppler echocardiographic study for the following reasons: (1) It was essential to include a cohort of patients that was representative of the entire spectrum of the disease to establish the prevalence of the PLF pattern; (2) the patients who are likely the most difficult to manage from a clinical standpoint are the symptomatic patients who have the PLF pattern because there is an apparent discrepancy between the symptomatic status of the patient and the severity of the disease as assessed with the conventional Doppler echocardiographic indices. In addition, we used overall survival rather than AVR as the primary end point for the present study because the decision for AVR may be influenced not only by the presence of symptoms but also by the perception of disease severity by the patient's physician.

Indeed, one of the main points that becomes apparent from these results is that, because AS severity tends to be underestimated on the echocardiogram, symptoms are probably neglected and/or underestimated in a good proportion of PLF patients. It is most likely for this reason that a lesser proportion of the PLF patients underwent AVR than the NF group although they had in fact a more advanced form of the disease.

It might be argued that the PLF pattern reported in the present study could be the result of an error in measurement, particularly of LVOT stroke volume, that is included in the calculation of many parameters, notably valvulo-arterial impedance. However, this pattern is associated with a cluster of other findings independent of this measurement that provide compelling evidence that this entity represents a severe form of valvulo-arterial disease. Hence, independent of LVOT measurement, our patients with the PLF pattern had smaller and relatively thicker ventricles with reduced mid-wall fractional shortening and had a poorer prognosis when treated medically rather than surgically. The measurements performed with Simpson's rule as well as the dimensionless index also provide independent evidence that the low gradients in these patients are the result of low flow in the presence of severe AS and preserved EF.

Conclusions

The main findings of the present study are that: (1) An important proportion of patients with severe AS have low transvalvular flow rates and low transvalvular gradients despite preserved values for LVEF; (2) this pattern is associated with higher global LV afterload, more pronounced concentric remodelling, evidence of intrinsic myocardial dysfunction, and lower survival, which suggests this pattern is not caused by artifact but represents a more advanced stage of disease; (3) this condition may often be misdiagnosed, which leads to underestimation or neglect of symptoms and inappropriate delay of AVR. These results thus reinforce the need for more comprehensive evaluations of patients with aortic stenosis. In particular, blood pressure should be systematically measured at the same time as Doppler echocardiography measurements, and valvulo-arterial impedance should be routinely calculated. This parameter may provide a more accurate estimate of global LV afterload and is a strong independent predictor of survival. It should thus prove useful both for risk stratification and clinical decision making.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In the present study, we report that a significant proportion (35%) of patients with severe aortic stenosis on the basis of echocardiographically determined aortic valve area may have a pattern characterized by paradoxically low-flow and low transvalvular gradients despite a normal left ventricular ejection fraction. The pattern is associated with higher global left ventricular afterload, more pronounced concentric remodelling, evidence of intrinsic myocardial dysfunction, and lower survival, which suggests that these patients are at a more advanced stage of their disease than their counterparts with the more classical normal flow pattern of aortic stenosis. Surgical treatment was also associated with a much better prognosis than medical treatment. Nonetheless, in this series only 47% of patients with paradoxically low-flow pattern were treated surgically as compared with 65% of patients with normal flow pattern. Hence this condition may often be misdiagnosed, which leads to underestimation or neglect of symptoms and inappropriate delay of aortic valve replacement. These results reinforce the need for more comprehensive evaluations of patients with aortic stenosis. In particular, blood pressure should be systematically measured at the same time as the Doppler echocardiography examination, and valvulo-arterial impedance should be routinely calculated to more accurately assess global left ventricular afterload and ensure proper clinical conduct.