Therapeutic implications of contractile reserve elicited by dobutamine echocardiography in symptomatic, low-gradient aortic stenosis

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Key words:
Aortic stenosis;
Heart failure;
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Background. **In patients with heart failure, poor ejection fraction and estimated severe aortic stenosis because of a reduced aortic valve area (AVA) and low gradients, dobutamine echocardiography (DE) was proposed to distinguish afterload mismatch from primary left ventricular dysfunction. In this setting the feasibility and safety of DE and the outcome following management based on DE results were investigated.**

Methods. **Forty-eight patients (mean age 73 ± 9 years; 79% males; AVA 0.7 ± 0.2 cm^2; mean aortic gradient 22 ± 6 mmHg; ejection fraction 0.28 ± 0.07; NYHA functional class 2.9 ± 0.8) underwent DE and were followed up for 24 ± 21 months. Aortic valve replacement (AVR) was offered to patients with left ventricular contractile reserve (ejection fraction increase ≥ 30% at peak DE) and fixed aortic stenosis (AVA increase ≤ 0.25 cm^2).**

Results. **DE elicited a left ventricular contractile reserve in 38 patients (79%). Among these, fixed aortic stenosis was present in 28 patients, among whom 19 underwent AVR and 9 declined surgery. The 20 patients without contractile reserve or with relative stenosis (AVA increase > 0.25 cm^2) were not considered eligible for surgery. During follow-up, 23 cardiovascular deaths occurred: 2/19 among operated patients, 7/9 among patients who declined surgery and 14/20 among non-eligible patients. Patients with AVR showed a significantly more favorable outcome and improved functional status as compared to the other two groups (NYHA class 1.2 ± 0.4 vs 2.7 ± 0.6 at baseline; p < 0.001). Conversely, non-surgical management was the strongest independent predictor of an adverse outcome (relative risk 3.6, 95% confidence interval 1.8-7.3; p < 0.0001).**

Conclusions. **In patients with heart failure and estimated severe aortic stenosis, DE could identify a subgroup with a left ventricular contractile reserve and fixed aortic stenosis who gained great benefit from AVR. The clinical outcome of patients who were not operated upon was unfavorable.**

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Introduction

In patients with heart failure and left ventricular (LV) dysfunction who show a critically reduced aortic valve area (AVA) and a calcified valve, low transvalvular gradients may be recorded even in the presence of severe aortic stenosis (AS). Although the prognosis of this group of patients is usually poor in the absence of surgical treatment of AS, the optimal management strategy is far from being resolved, and the identification of those who may benefit from aortic valve replacement (AVR) remains challenging[1-7]. This is a relevant issue, as AS is often diagnosed late, with many patients already in NYHA functional class III-IV when first observed in referral centers[8].

Dobutamine echocardiography (DE) has been proposed as a useful tool in patients with LV dysfunction and a reduced AVA, as it may allow the distinction between a reversible impairment of LV function secondary to afterload mismatch and a primary, irreversible dysfunction due to cardiomyopathy[9-13]. Still, the outcome of patients with heart failure associated with severe AS and managed on the basis of DE requires further understanding.

The aims of the present study were 2-fold: 1) to assess the feasibility and safety of DE in patients presenting with heart failure and previously unrecognized severe AS; 2) to evaluate their outcome following management based on DE results.

Methods

Patient selection. Patients were consecutively recruited from February 1995 to Jan-

uary 2001 among those referred for evaluation of symptoms or signs consistent with heart failure, in accordance with the European Society of Cardiology criteria[14]. Two-dimensional and color Doppler echocardiography was performed in all patients. Standard measurements and LV wall motion analysis were performed in accordance with the American Society of Echocardiography recommendations[15]. Hemodynamic assessment of AS was performed by measuring the aortic valve gradients and AVA using the modified Bernoulli equation and the continuity equation respectively[16,17]. Patients with estimated critical AS were considered for DE according to the following criteria: LV ejection fraction ≤ 0.40, mean aortic gradient ≤ 30 mmHg, AVA ≤ 1.0 cm^2. Eligible patients were excluded in the presence of systolic blood pressure < 90 or > 160 mmHg, unstable angina, complex ventricular arrhythmias, moderate-to-severe aortic regurgitation, or poor acoustic window.

Fifty patients were consecutively enrolled in accordance with the above criteria. In 2 patients (4%) DE was prematurely interrupted for technical reasons, as outlined below. Thus, the final study group consisted of 48 patients, in whom clear images of LV wall motion and flow could be maintained up to the end of the protocol. The patients' mean age was 73 ± 9 years (range 36-87 years); 38 patients were male (79%). AVA was 0.7 ± 0.2 cm^2, the mean aortic gradient was 22 ± 6 mmHg, ejection fraction was 0.28 ± 0.07, the average NYHA class was 2.9 ± 0.8. Thirty-one patients (64%) had some degree of mitral insufficiency, which was graded as mild in 27 patients, moderate in 3 and severe in 1.

Dobutamine echocardiography. Following written informed consent and baseline echocardiographic evaluation, dobutamine infusion was started at 5 μg/kg/min, increasing to 10 and then to 20 μg/kg/min at 5-min intervals, under 12-lead electrocardiographic and echocardiographic monitoring. The aim of the test was to elicit LV contractile reserve, i.e. an ejection fraction increase ≥ 30% over its original value. The transvalvular aortic and LV outflow tract mean and peak gradients as well as AVA were recalculated and compared to baseline values. A relative (pseudo) AS was considered present if AVA increased ≥ 0.25 cm^2; otherwise AS was labeled as fixed (true). Even though no valve has a truly "fixed" orifice, as orifices are all flow-dependent and can only be "relatively" fixed, the term "fixed" is used to improve readability.

DE interruption criteria included the following: 1) onset of new symptoms such as angina or severe dyspnea; 2) unbearable side effects; 3) ST elevation or depression ≥ 2 mm; 4) marked fall (< 90 mmHg) or rise (> 200 mmHg) in the systolic blood pressure; 5) new onset of wall motion abnormalities; 6) new onset of complex arrhythmias; 7) satisfactory diagnostic information. DE was conducted up to the minimum dose which elicited LV contractile reserve, or else until completion of the 20 μg/kg/min level.

Patient management and follow-up. AVR was suggested by the cardiologist when LV contractile reserve and true AS were documented at DE. The decision to proceed to AVR was then based on a joint evaluation by the clinical cardiologist and the surgeon, and on the patient's consent. Even though surgery was strongly suggested when LV contractile reserve and true AS were documented, several patients refused the operation because of the relatively high surgical risk, and preferred standard medical treatment for heart failure. Patients with relative AS, or without a demonstrable LV contractile reserve, were all treated medically. A total of 31 patients underwent coronary angiography, including all of the 19 patients who were subsequently operated. After DE patients were followed up prospectively for 24 ± 21 months (range 1-74 months). The clinical endpoints included cardiovascular mortality and functional status at the end of follow-up (NYHA class).

Statistical analysis. Data are expressed as mean ± standard deviation. Statistical analyses were performed using the Student's t-test or ANOVA, as appropriate, for comparison of normally distributed data. The χ^2 test or Fisher's exact test, as appropriate, were utilized to compare non-continuous variables expressed as proportions. Univariate analysis for survival and event-free curves were performed using Kaplan-Meier estimates; univariate and multivariate analyses for the assessment of independent risk predictors were performed using the Cox regression model.

Results

Feasibility and safety of dobutamine echocardiography. Fifty consecutive patients with a good acoustic window were enrolled. In 2 (4%) DE was interrupted prematurely because of deteriorating images due to hyperpnea. Thus, the final study group consisted of 48 patients, in whom clear images of LV wall motion, LV outflow tract and aortic flow could be maintained up to the end of the protocol, with a 96% overall feasibility for DE. The relevant echocardiographic data obtained during DE are shown in table I.

DE was interrupted at the first step (5 μg/kg/min) in 2 patients (4%), at the second step (10 μg/kg/min) in 20 patients (42%) and at the final step (20 μg/kg/min) in 26 patients (54%). No major complication occurred. In the 2 patients in whom DE was interrupted at the first step, this was due to sinus bradycardia (40 b/min) and a short run of 5 ventricular ectopic beats, without consequences. Of the 10 patients without a contractile reserve (see next paragraph), 5 had submaximal testing (the maximum dose employed was 5 μg/kg/min in 1 patient and 10 μg/kg/min in 4) due to side effects. Therefore,

Table I. Overall dobutamine echocardiography results.

	Dobutamine echocardiography		p
	Baseline	Peak	
Heart rate (b/min)	77 ± 13	100 ± 16	< 0.001
Systolic blood pressure (mmHg)	121 ± 25	128 ± 31	< 0.05
Diastolic blood pressure (mmHg)	76 ± 13	74 ± 27	0.3
Ejection fraction	0.28 ± 0.07	0.43 ± 0.12	< 0.001
Peak aortic gradient (mmHg)	40 ± 11	62 ± 21	< 0.001
Mean aortic gradient (mmHg)	22 ± 6	38 ± 15	< 0.001
Aortic valve area (cm^2)	0.69 ± 0.20	0.82 ± 0.27	< 0.001
Indexed aortic valve area (cm^2/m^2)	0.38 ± 0.09	0.44 ± 0.12	< 0.001
Maximum aortic velocity (m/s)	3.16 ± 0.35	3.93 ± 0.63	< 0.001
Mean aortic velocity (m/s)	2.34 ± 0.43	3.08 ± 0.45	< 0.001
Maximum outflow tract velocity (m/s)	0.64 ± 0.16	0.84 ± 0.25	0.001
Mean outflow tract velocity (m/s)	0.23 ± 0.18	0.32 ± 0.30	0.001

even if the technical feasibility was 96%, there was an additional 10.4% of non-diagnostic tests, thus yielding an overall feasibility of 85.6%.

Dobutamine echocardiography results and clinical management. DE results are summarized in tables I and II. LV contractile reserve was elicited in 38 patients (79%), whereas the remaining 10 had no significant increase in ejection fraction (Fig. 1). Among the 38 patients with LV contractile reserve, 28 (74%) had fixed AS (average AVA at peak DE 0.71 ± 0.19 cm^2) and 10 (26%) had relative AS (AVA 1.12 ± 0.21 cm^2; Fig. 1). An AVA > 1.0 cm^2 at peak DE has also been used to define relative AS[13]: in our subgroup with relative AS, this criterion was reached in all patients but 2, who nevertheless showed an increase in AVA much greater than 0.25 cm^2 compared to baseline (0.46 and 0.72 cm^2 respectively). Conversely, among the 28 patients with true AS, only 2 had an AVA > 1.0 cm^2 at peak DE, with an AVA increase of 0.01 and 0.20 cm^2 respectively.

The 28 patients with LV contractile reserve and fixed AS were referred for surgery. In 19 (68%) AVR was performed within 3 months of DE. All valves were judged as being severely stenotic by the surgeon. The

Table II. Baseline demographic, clinical and echocardiographic features based on the management strategy following dobutamine echocardiography.

	Aortic valve replacement (n=19)	Medical treatment (n=29)	p
Age (years)	67 ± 10	77 ± 5	0.001
Male	17 (89%)	21 (72%)	NS
Follow-up (months)	36 ± 22	17 ± 16	0.001
NYHA class	2.7 ± 0.6	3.0 ± 0.8	NS
History of AMI	1 (5%)	6 (21%)	NS
Angiographic evidence of critical CAD	3/19 (16%)	7/12 (58%)	0.02
One vessel	2	3	
Two vessels	1	3	
Three vessels	0	1	
History of APE	8 (42%)	12 (29%)	NS
Heart rate (b/min)	78 ± 10	80 ± 11	NS
Systolic blood pressure (mmHg)	121 ± 13	124 ± 26	NS
Diastolic blood pressure (mmHg)	81 ± 8	76 ± 13	NS
Mean aortic gradient (mmHg)	26 ± 13	22 ± 7	NS
Peak aortic gradient (mmHg)	45 ± 22	39 ± 12	NS
Aortic valve area (cm^2)	0.6 ± 0.2	0.7 ± 0.2	NS
Ejection fraction	0.30 ± 0.13	0.30 ± 0.10	NS
Maximum outflow tract/aortic velocity ratio	0.17 ± 0.04	0.22 ± 0.05	< 0.02
LV end-diastolic volume (ml)	170 ± 47	173 ± 77	NS
LV end-diastolic diameter (mm)	61 ± 9	61 ± 8	NS
Left atrial diameter (mm)	47 ± 11	42 ± 9	NS
LV mass index (g/m^2)	220 ± 57	213 ± 48	NS
LV contractile reserve	19 (100%)	19 (65%)	< 0.005

AMI = acute myocardial infarction; APE = acute pulmonary edema; CAD = coronary artery disease; LV = left ventricular.

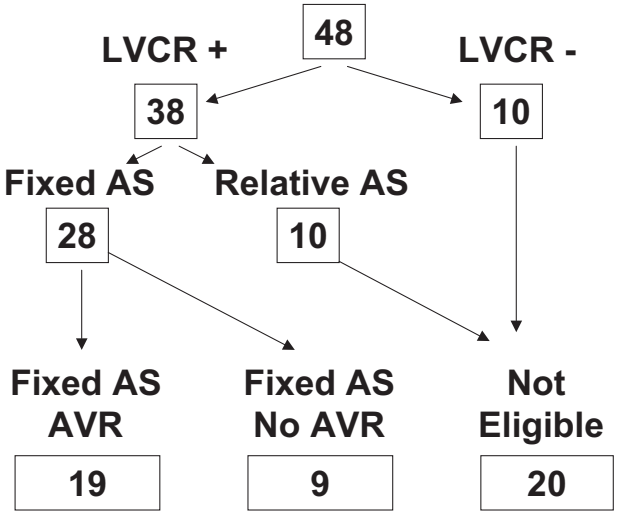

Figure 1. *Management strategies based on dobutamine echocardiography for the 48 study patients. AS = aortic stenosis; AVR = aortic valve replacement; LVCR = left ventricular contractile reserve.*

remaining 9 patients (32%) declined surgery because of the high surgical risk, and were therefore treated medically. Their clinical and demographic features did not significantly differ from those who gave their consent to surgery. The remaining 20 patients with relative AS or without LV contractile reserve were considered not eligible for AVR, and were treated medically (Fig. 1).

Impact of coronary artery disease and individual clinical features on decision making. The 19 surgically treated patients were younger and had a lower prevalence of angiographically critical coronary artery disease or of a history of myocardial infarction compared to the medically treated patients (Table II); all other clinical and echocardiographic variables were similar between the two groups. Thus, the independent predictors of AVR were LV contractile reserve (by study design), age and the absence of documented coronary artery disease ($p < 0.05$ for each variable). Of note, critical coronary artery disease was relatively infrequent in patients without as compared to those with prior myocardial infarction (7/28 or 25% versus 3/3 or 100% respectively; $p < 0.03$).

Cardiovascular mortality. During a mean follow-up of 24 ± 21 months, 23 cardiovascular deaths and 3 noncardiac deaths (2 cancer, 1 chronic obstructive airway disease) occurred. The cardiovascular mortality was 48%, with a 24% annual mortality rate. Of the 23 cardiovascular deaths, only 2 occurred among the 19 patients submitted to AVR: one patient died 17 days after surgery due to a low output state; the other one died suddenly 6 months later. Thus, the total cardiovascular mortality in the surgical group was 10%, and the perioperative mortality 5%. The remaining 21 cardiovascular deaths occurred among the 29 patients who were managed medically, with similar mortality rates among the 9 patients with fixed AS who declined AVR (n = 7; 78%) and the 20 patients who were not eligible for surgery (n = 14; 70%).

At survival analysis, patients undergoing AVR showed a significantly lower cardiovascular mortality as compared to those who declined or were not eligible for surgery (Fig. 2). The independent predictors of outcome at multivariate analysis were AVR and NYHA class at baseline (Table III). Non-surgically treated patients had a more than 3-fold increased risk compared to operated patients (relative risk 3.6; 95% confidence interval 1.8-7.3; $p < 0.0001$). Neither angiographic evidence of critical coronary artery disease nor a history of prior myocardial infarction were associated with an increased risk of cardiovascular death (Table III).

Functional status. NYHA functional class improved significantly in the 19 surgically treated patients (1.2 ± 0.4 at the end of follow-up vs 2.7 ± 0.6 at baseline, $p < 0.001$). Specifically, 16 patients (84%) improved ≥ 1 class, and all patients originally in class III-IV passed to class I or II. Only 2 patients originally in class II showed no improvement, and one additional patient, also in class II, developed a low-output state postoperatively (class IV) and died (Fig. 3). Conversely, medically treated patients showed no improvement (2.5 ± 0.9 at the end of follow-up vs 2.6 ± 0.7 at baseline, $p = 0.7$).

Discussion

The incidence and prevalence of heart failure are increasing, mainly because of population aging and because of the improved outcome for patients with coronary artery disease and hypertension[18]. Degenerative valvular lesions are increasing too, accounting for 20-25% of all causes of heart failure[19]. A sclerotic and/or calcified aortic valve is present in 30% of individuals aged ≥ 65 years[20].

Among valvular diseases associated with heart failure, AS is often diagnosed late[8], as too many patients

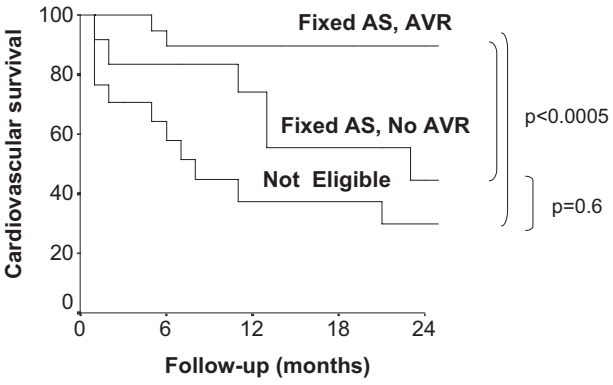

Figure 2. *Cumulative survival of the 48 study patients based on the management strategy. AS = aortic stenosis; AVR = aortic valve replacement.*

Table III. Predictors of cardiovascular mortality (Cox regression analysis).

	Univariate analysis		Multivariate analysis	
	p	OR (95% CI)	p	OR (95% CI)
Age	0.05	1.06 (0.99-1.12)	0.8	
Male	0.5			
NYHA class	< 0.02	2.0 (1.14-3.69)	< 0.02	2.2 (1.2-4.2)
History of AMI	0.4			
History of APE	0.5			
Diabetes	0.2			
History of smoking	0.18			
Hypertension	0.4			
History of syncope	0.3			
History of angina	0.6			
Heart rate	0.4			
Systolic blood pressure	0.8			
Diastolic blood pressure	0.2			
Aortic valve replacement	< 0.002	0.09 (0.02-0.38)	< 0.005	0.08 (0.01-0.40)
Angiographic evidence of critical CAD	0.13			
Mean gradient at baseline DE	0.7			
Peak gradient at baseline DE	0.4			
AVA at baseline DE	0.7			
Ejection fraction at baseline DE	0.4			
LV contractile reserve	< 0.05	0.4 (0.16-0.98)	0.6	
LV end-diastolic volume	0.4			
LV end-diastolic diameter	0.9			
Left atrial diameter	0.4			
LV mass index	0.8			
Mean gradient at peak DE	0.07	0.95 (0.91-1.0)	0.18	
Peak gradient at peak DE	0.17			
AVA at peak DE	0.11			
Ejection fraction at peak DE	0.2			

AMI = acute myocardial infarction; APE = acute pulmonary edema; AVA = aortic valve area; CAD = coronary artery disease; CI = confidence interval; DE = dobutamine echocardiography; LV = left ventricular; OR = odds ratio.

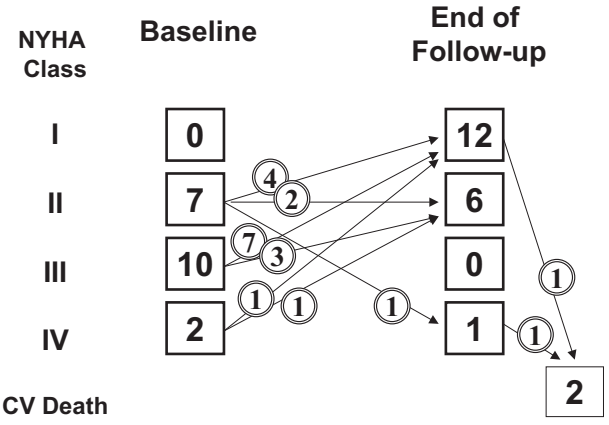

Figure 3. *Variations in NYHA functional class among the 19 patients with fixed aortic stenosis submitted to aortic valve replacement. CV = cardiovascular.*

with critical AS and heart failure are referred to tertiary centers in advanced NYHA class. This may be due to the presence of comorbidities which draw greater attention, or to the lack of the classical clinical signs of AS. Moreover, an "inappropriate *fixation* on gradient" has been highlighted in the literature[8]. Since all gradients are flow-dependent, the quantitative assessment of AS requires a direct calculation of AVA. However, regardless of whether the Gorlin formula or the continuity equation is employed, AVA measurements are also flow-dependent and show a linear relation with the transvalvular volume flow rate[21]. Thus, while severe AS may be underestimated in patients with LV dysfunction, patients with an estimated critically reduced AVA may be found to have only moderate disease at surgery.

Therapeutic implications of dobutamine echocardiography. DE has been shown to offer a method of flow correction allowing more accurate estimation of the severity of AS[22,23]. Therefore, in patients with a reduced ejection fraction, low aortic gradients and an estimated reduced AVA, DE can help distinguishing between a primary cardiomyopathy with a calcified aortic valve but no or only mild AS, and LV dysfunction secondary to true severe AS. Following the seminal study by deFilippi et al.[9], the rationale for using DE results in clinical decision making in patients with AS was supported by other authors[10-13]. DE is capable of distinguishing patients with fixed as opposed to relative AS. The former are more likely to benefit from AVR, but it is still unclear whether surgery can be effective in the

latter[10,11]. A recent paper by Nishimura et al.[24] proposed dobutamine stimulation at the time of cardiac catheterization in order to elicit LV contractile reserve. Their results also support the use of dobutamine challenge for the selection of patients with estimated severe AS who may benefit from surgery.

In the present study, DE allowed for the identification of a subgroup of patients with heart failure and symptomatic, low-gradient estimated severe AS, who definitely gained benefit from aggressive treatment. In patients with LV contractile reserve, considered the *sine qua non* pathophysiologic substrate for improvement following AVR, surgery was strongly recommended when a fixed AS could be demonstrated at DE. Although not all patients with LV contractile reserve and fixed AS gave their consent to surgery, our study could demonstrate a clear benefit of AVR as compared to medical treatment. Indeed, the 2-year mortality after AVR was very low (10%), despite a relatively high estimated surgical risk. At multivariate analysis, surgery proved to be the strongest independent predictor of survival.

Our findings are consistent with those of recent studies[6,7] showing a more favorable outcome following AVR in patients with LV dysfunction than had been reported earlier[3,4]. In addition, most patients showed a marked improvement in functional status; by the end of the follow-up period, all surviving patients submitted to AVR were in NYHA class I-II. Thus, patients with LV contractile reserve and fixed AS should be strongly encouraged to undergo surgery even in the presence of a relatively high operative risk.

The question as to whether patients with relative AS or without LV contractile reserve may also benefit from AVR remains open to debate[10,11]. Specifically, in the absence of LV contractile reserve it is impossible to distinguish between an irreversible cardiomyopathy or an excess afterload mismatch, and thus to foretell the benefits of AVR. Therefore, a negative DE study should not be used to deny AVR, if otherwise indicated, although the lack of contractile reserve is associated with a higher operative mortality[13].

Methodologic considerations. In the first paper focusing on this topic, LV contractile reserve was assessed by evaluating the changes of the wall motion score index[9]. In the present study, in order to avoid variability in segmental analysis, we chose to employ ejection fraction, the most widely used index of LV function. This parameter is characterized by variations following inotropic stimulation which allow an accurate estimation of LV contractile reserve[25,26]. A low-dose dobutamine protocol (maximum 20 μg/kg/min) was chosen in order to achieve: 1) an ejection fraction increase by inotropic stimulation and recruitment of the contractile reserve without a significant rise in heart rate, potentially at risk of myocardial ischemia[13]; 2) maximum safety, without the risk of complications related to high dobutamine doses[9-13].

In addition, as even patients with a limited AVA increase at DE (average 0.16 cm^2) may be found to have severe anatomic AS at the time of surgery[10], in the present study a higher cut off (AVA increase ≥ 0.25 cm^2) was chosen in order to improve sensitivity.

The study was not randomized for two reasons. The first is ethical: one could argue against the decision to deny surgery to a patient with severe AS and heart failure. The second is a consequence of daily clinical practice, as not all cardiologists and surgeons in our institution felt that the risk of surgery in this setting was lower than that of conservative management in each individual patient. Therefore, although great care was taken in exposing the potential advantages of surgery and recommending AVR to all patients with fixed AS, one cannot exclude that patients believed to be at lower operative risk may have been more inclined to accept, as compared to those at higher risk. In addition, medically treated patients were on average older and had more severe coronary artery disease. Therefore, the benefit of AVR might have been somewhat overestimated. However, the striking difference in outcome between surgically versus medically treated patients cannot be explained by the baseline differences between the two groups, which had similar clinical and demographic features, and indicate that surgery itself had a decisive influence on outcome.

In conclusion, DE had an 85.6% overall feasibility (in the presence of a good acoustic window) and a 100% safety in a group of consecutive patients with heart failure and estimated severe AS. In this setting DE allowed the identification of patients with LV contractile reserve and fixed AS in whom AVR turned out to be highly beneficial at a 2-year follow-up. Conversely, the outcome of patients who declined or were not eligible for surgery was unfavorable.

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