

Dobutamine-Stress Echocardiography in Asymptomatic Patients with Aortic Regurgitation

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Summary

Background: Decreased contractile reserve may already be present in asymptomatic patients with aortic regurgitation and normal ejection fraction (EF), thus indicating the need for frequent and accurate assessments of the left ventricular function for the early detection of systolic dysfunction.

Objective: To analyze if increments in EF with low dose dobutamine could predict surgery and/or death in patients with aortic regurgitation.

Methods: Dobutamine-stress echocardiography was performed in 24 patients with aortic regurgitation in order to analyze whether EF increments at low dobutamine doses could predict the need for surgery and/or death in this group of patients.

Results: Mean age was 37.8 ± 16.8 years and 16 patients (66%) were male. EF increased from a mean baseline value of $62.3 \pm 7.9\%$ to $71.5 \pm 10.5\%$ at a dobutamine dose of $20 \mu\text{g}/\text{kg}/\text{min}$ ($p < 0.001$). The patients were followed-up for 36.6 ± 20.1 months; two patients died (one of cardiovascular death) and five underwent cardiac surgery. Baseline EF was correlated with surgery and death in the follow-up of patients.

Conclusion: Baseline EF was correlated with surgery or death in the follow-up of young patients with aortic regurgitation. However, the percentage increase in EF at low dobutamine doses did not allow us to predict events in these patients. (Arq Bras Cardiol 2009;93(1):49-54)

Key words: Echocardiography, stress; dobutamine; patients; aortic valve insufficiency.

Introduction

It is difficult to define the surgical time for aortic valve replacement in patients with significant aortic regurgitation in the absence of symptoms. Previous studies suggest that asymptomatic patients have a good prognosis^{1,2}. However, the outcome of patients with mild symptoms or of asymptomatic patients that could nevertheless be exposed to a high risk of ventricular dysfunction is not established. It is necessary to assess early valve replacement accurately, since the natural history of aortic regurgitation is usually benign and the surgical mortality rate of valve replacement is low, but not negligible. Additionally, the long-term performance of valve prostheses is uncertain.

Several studies have demonstrated that even asymptomatic patients with aortic regurgitation and normal left ventricular

function can show an abnormal response of ventricular function to exercise. Left ventricular dysfunction during exercise is an important predictor of prognosis in chronic aortic regurgitation; however, this is not easy to define and its mechanism is not fully understood. It seems to be multifactorial, not necessarily indicating LV dysfunction. Radionuclide ventriculography is frequently performed in asymptomatic patients for the detection of early left ventricular dysfunction, although this study modality is a class IIb in the American guidelines³. Stress echocardiography has been often used for the diagnosis of coronary artery disease, and occasionally in the course of selected cases of heart valve diseases, such as aortic stenosis⁴⁻⁶, mitral stenosis^{7,8}, and aortic regurgitation⁹⁻¹¹.

Since dobutamine-stress echocardiography (DSE) is a reliable technique that is less expensive and usually more easily available than radionuclide ventriculography, the objective of the present study was to assess the changes in left ventricular function during dobutamine stress in patients with aortic regurgitation and to analyze whether these changes are correlated with events in the follow-up of the patients.

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Methods

A total of 24 patients with aortic regurgitation, most of which moderate, were studied. Exclusion criteria were: associated aortic stenosis, patients with > mild mitral stenosis or regurgitation, and previous aortic surgery. Clinical history and electrocardiogram (ECG) were obtained from all patients. The protocol was approved by the ethics committee and a written informed consent was obtained from all patients.

Aortic regurgitation was diagnosed and graded by Doppler and color Doppler as described elsewhere¹². Cardiac dimensions were measured by the two-dimensional guided M-mode, according to established criteria¹³. Ejection fraction (EF) was calculated using both the Teichholz and the area-length methods. The studies were performed in HP 2000 or 5500 (Hewlett Packard, Andover MA, USA) instruments, with 3.5 and 2.5 MHz transducers.

The low-dose dobutamine protocol was performed in all patients, with an initial dose of 5 µg/kg/min followed by incremental doses of 5 µg/kg/min every three minutes, up to the maximum dose of 20 µg/kg/min, since the objective was to assess the contractile reserve, and ischemia was not expected among this group of patients. Both ECG and blood pressure were monitored during the test. Left ventricular (LV) systolic and diastolic diameters, EF, and maximum and mean aortic gradients were obtained in all stages. The index expressing the percentage of EF elevation with the low dobutamine dose was calculated using the formula:

$$\frac{\text{EF at 20 } \mu\text{g/kg/min} - \text{baseline EF}}{\text{Baseline EF}}$$

The same index was obtained using EF at the 10µg/kg/min and 15µg/kg/min doses. The patients were followed-up and clinical history as well as resting Doppler echocardiography were repeated during the follow-up.

Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables and as frequencies for categorical variables. The Student's t test and analysis of variance were used, as appropriate, for comparison between groups of living patients not undergoing surgery and patients with events for continuous variables normally distributed (events were defined as valve replacement or cardiac death). Continuous non-parametric data were analyzed using the Wilcoxon or Kruskal-Wallis test, as appropriate. The differences between categorical variables were analyzed using the chi-square test. In all cases, the statistical significance was set at p<0.05.

Results

Clinical data of all patients at enrollment are shown in Table 1.

Rheumatic disease was the most prevalent cause (14 patients, 58%); in two patients (8%) the etiology was degenerative disease, one (4%) had annuloaortic ectasia, in one patient the aortic regurgitation was secondary to bicuspid aortic valve, and in another it developed after surgery for

Table 1 - Clinical characteristics of 24 patients with aortic regurgitation

Age (years)	37.8±16.8
Gender (M/F)	16/8
Moderate/severe AR	20/4
Functional class (NYHA I/II/III/IV)	18/5/1/0
Angina (n)	5
Syncope (n)	1

AR - aortic regurgitation, F - female, M - male; NYHA - New York Heart Association functional class.

correction of ventricular septal defect. In five patients the exact etiology could not be established.

Five patients (21%) less than 40 years old were taking penicillin for prophylaxis of rheumatic disease. Eight patients (33%) were not taking any type of medication; six (25%) were taking converting-enzyme inhibitors, four (17%) were taking calcium antagonists, four (17%) beta-blockers, eight (33%) digoxin and seven (29%) diuretics.

- *ECG* - Two patients (8%) had normal ECG. Of the remaining, only four did not present LV overload: two had ST-T segment changes, one had supraventricular extrasystoles, and one patient had right ventricular branch block alone. LV overload was present in 18 (75%) patients. Three of these patients also had supraventricular extrasystoles, three with right bundle branch block of varying degrees, three had some degree of left bundle branch block, one had first-degree AV block, one had right and left atrial overload, and one had atrial fibrillation.

- *Doppler echocardiography* - Mean baseline values of Doppler parameters of the 24 patients are shown in Table 2.

Table 2 - Baseline Doppler echocardiographic parameters in 24 patients with aortic regurgitation

Doppler echocardiographic parameters	Mean ± Standard deviation
LVd (mm)	64.5±7.9
LVs (mm)	42.4±7.1
VST (mm)	10.5±2.2
PW (mm)	11.6±2.9
FS	34.1±5.0
EF (%)	62.3±7.9
LA (mm)	38.5±7.6
AO (mm)	38.5±8.3
AVA (cm ²)	3.5±1.3
MG (mmHg)	12.6±5.2
mG (mmHg)	6.8±2.5

LA - left atrium; AO - aorta; AVA - aortic valve area; EF - ejection fraction; FS - fractional shortening; MG - maximum aortic gradient; mG - mean aortic gradient; mm - millimeters; mmHg - millimeters of mercury; PW - posterior wall thickness; VST - ventricular septal thickness; LVd - LV diastolic diameter; LVs - LV systolic diameter.

• *Dobutamine-stress echocardiography* - All patients underwent the low-dose dobutamine protocol with no complications. No collateral effects were observed and the 20 $\mu\text{g}/\text{kg}/\text{min}$ dose was reached in all patients. Comparative data on heart rate, EF, and mean gradient between baseline and dobutamine-stress test at the 20- $\mu\text{g}/\text{kg}/\text{min}$ dose are shown in Table 3.

• *Follow-up of the patients* - The patients were followed-up for 36.6 ± 20.1 months after the dobutamine-stress test. During follow-up, the events aortic valve replacement and cardiac death were observed, and a new Doppler echocardiogram was obtained at baseline conditions. Three patients did not attend the appointment for control. Two patients died: one with moderate regurgitation and dilated aorta died in a car accident before undergoing surgery; the other, who was in class III for dyspnea and had angina and syncope, died of the heart valve disease. Data at baseline, at 20- $\mu\text{g}/\text{kg}/\text{min}$ dobutamine stress test, and in the follow-up of the 20 patients from whom the control Doppler echocardiogram was obtained are shown in Table 4.

EF with dobutamine was correlated with baseline EF (Figure 1), but not with EF in the follow-up ($p=0.13$).

Five patients underwent surgery (two were in functional class I and three in functional class III at the moment the stress echocardiography was performed, and surgery was indicated

by the attending physician). Mean time for surgery after the dobutamine stress test was 11.5 ± 5.9 months. Age was not statistically different between patients undergoing surgery and those not undergoing surgery (46.6 ± 15.5 vs. 33.8 ± 16.5 years, $p=0.149$). Baseline EF values of patients undergoing surgery were among the lowest in the group. There was improvement of the functional class in three patients after surgery, and two patients who were in class I remained asymptomatic during the follow-up. Although both diastolic ($67.2 \pm 1.9 \rightarrow 50.8 \pm 1.1$; $p=0.043$) and systolic ($45.6 \pm 1.5 \rightarrow 35.2 \pm 2.7$; $p=0.042$) diameters had decreased with surgery, the EF measured in the follow-up of the patients undergoing surgery were not statistically different from the EF at the beginning of the study ($59.3 \pm 3.3\%$ vs $59.4 \pm 9.5\%$, $p=0.786$).

The initial diastolic diameter and at follow-up of the patients who survived without undergoing surgery (63.6 ± 9.5 and 63.4 ± 10.8 , respectively) were not statistically different ($p=0.636$). The same occurred with the systolic diameters (40.3 ± 8.1 and 41.1 ± 8.8 , respectively; $p=0.329$) and with EF ($67.0 \pm 7.3\%$ and $63.9 \pm 8.1\%$, respectively; $p=0.151$).

Table 3 - Dobutamine-stress echocardiography parameters at the 20 $\mu\text{g}/\text{kg}/\text{min}$ dose compared to baseline values

Parameters	Baseline	20 $\mu\text{g}/\text{kg}/\text{min}$	P
HR (bpm)	74.5 \pm 12.2	94.2 \pm 18.0	<0.001
EF (%)	62.3 \pm 7.9	71.5 \pm 10.5	<0.001
mG (mmHg)	6.8 \pm 2.5	14.7 \pm 9.3	<0.001

Bpm - beats per minute, HR - heart rate; EF - ejection fraction, mG - mean aortic gradient; min - minutes.

Table 4 - Doppler echocardiographic values at baseline, at dobutamine 20 $\mu\text{g}/\text{kg}/\text{min}$, and at follow-up of 20 patients of whom control was obtained

Parameters	Baseline	20 $\mu\text{g}/\text{kg}/\text{min}$	Follow-up
LVd (mm)	64.5 \pm 8.0	61.8 \pm 8.6	60.1 \pm 10.8
LVs (mm)	41.7 \pm 7.0	35.3 \pm 8.7	39.5 \pm 8.1
SF	35.3 \pm 4.6	43.5 \pm 8.1	34.5 \pm 5.5
EF (%)	64.0 \pm 7.4	73.8 \pm 9.8	62.4 \pm 8.3
MG (mmHg)	12.9 \pm 5.5	23.8 \pm 9.9	15.3 \pm 7.4
mG (mmHg)	7.0 \pm 2.7	15.7 \pm 9.7	8.7 \pm 4.3

EF - ejection fraction; FS - fractional shortening; MG - maximum aortic gradient; mG - mean aortic gradient; min - minutes; mm - millimeters; mmHg - millimeters of mercury; LVd - LV diastolic diameter; LVs - LV systolic diameter.

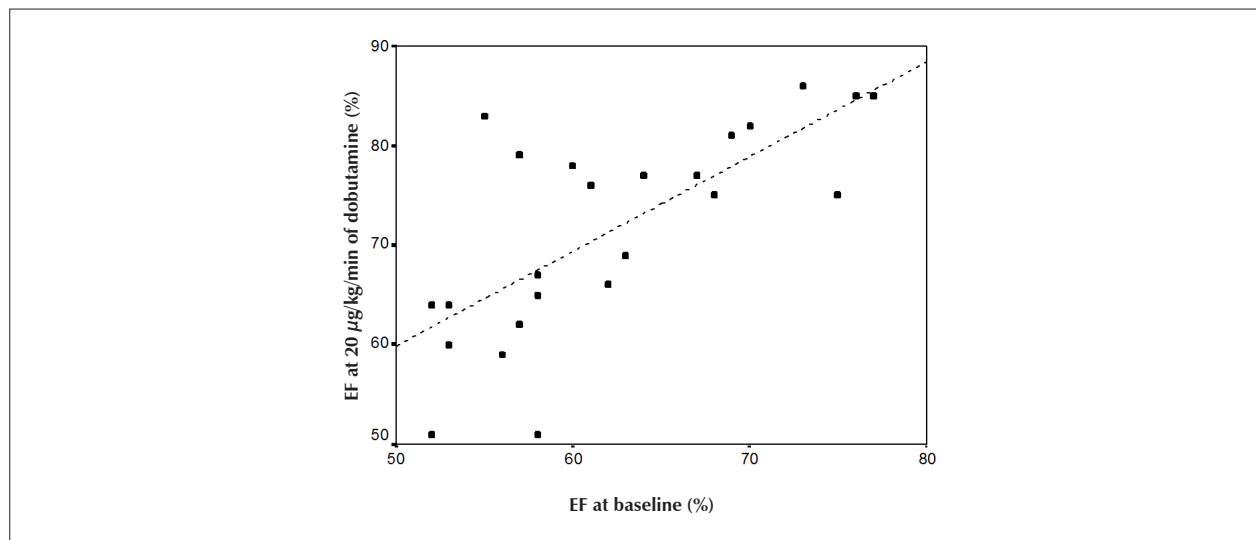


Figure 1 - Correlation between baseline EF and EF at peak-dobutamine dose.

In the 20 patients from whom echocardiographic data were obtained during follow-up, the initial EF was lower in patients who had events than in those who survived without surgery (59.3 ± 3.3 vs. 66.0 ± 7.9 ; $p=0.016$), as shown in Figure 2. However, the percentage increase of EF with dobutamine was not different between patients with events and those who survived without surgery, whether at the $10 \mu\text{g}/\text{kg}/\text{min}$ ($p=0.387$), $15 \mu\text{g}/\text{kg}/\text{min}$ ($p=0.703$) or $20 \mu\text{g}/\text{kg}/\text{min}$ ($p=0.467$) dose.

Discussion

The present study showed a correlation of baseline EF with the outcome of patients with aortic regurgitation. However, the EF response to dobutamine-stress echocardiography in this group of patients did not show efficiency at predicting events.

Due to the still high prevalence of rheumatic disease in developing countries, our group of patients with aortic regurgitation is relatively young in comparison with patients with this disease in developed countries. However, the results of this study may not apply to a group of older patients with degenerative aortic regurgitation.

In aortic regurgitation, it has been demonstrated that even patients with decreased EF may remain asymptomatic, thus reflecting the insidious development of left ventricular dysfunction and the need for frequent ventricular assessments in order to detect additional deterioration before a marked reduction occurs, because this may have severe consequences even after a successful valve replacement¹⁴. Studies on the natural history of aortic regurgitation have focused mainly on asymptomatic patients with normal systolic function; however, more recent studies demonstrated that the outcomes without surgery in patients even with mild dysfunction ($\text{EF} < 55\%$ or $\text{LVs} \geq 25 \text{mm}^2$) are poor. Even when asymptomatic at diagnosis, these patients incur excess long-term mortality if surgery is not performed¹⁵. The excessive afterload in aortic regurgitation caused by the combination of volumetric and pressure overload partly explains the improved ventricular function

after reduction of the afterload that follows valve replacement. Thus, both the short-term and long-term improvement in ventricular function after surgery is significantly related to the early reduction of ventricular dilation resulting from the correction of the volume overload³.

The increased EF following valve replacement in aortic regurgitation contrasts with the situation observed in mitral regurgitation, in which the EF commonly decreases after surgery, even when the valve repair is very successfully performed^{16,17}. In the present study, EF did not increase in patients undergoing surgery, which may suggest that, although they were in functional class I (two patients) and II (three patients) and their EF were normal or slightly decreased at the initial study, they probably already had a decreased contractile reserve.

In a study of 35 asymptomatic patients with grades 3 and 4 aortic regurgitation who underwent exercise echocardiography, 21 had EF increased by 7 units percent in comparison with baseline EF, thus indicating contractile reserve. The other 14 patients did not present contractile reserve. The mean follow-up period was 15 months; the systolic function of 13 out of the 21 patients with contractile reserve remained normal, whereas the EF of 13 out of the 14 patients without contractile reserve decreased from 60% to 54%. In this study, the baseline EF and contractile reserve with exercise were the only independent predictors of decreased systolic function during follow-up¹⁸, thus suggesting that exercise is a better tool for investigating these patients than dobutamine-stress echocardiography. However, this is a controversial finding, because there is evidence that even patients who present decreased EF at exercise may have a good outcome in the postoperative period^{19,20}, thus suggesting that the reduction in EF at exercise is multifactorial and should be analyzed with reservation, because it may not necessarily be due to ventricular dysfunction. Few studies using dobutamine-stress echocardiography in aortic regurgitation are available in the literature, and they usually analyze a small number of patients. In one of them which

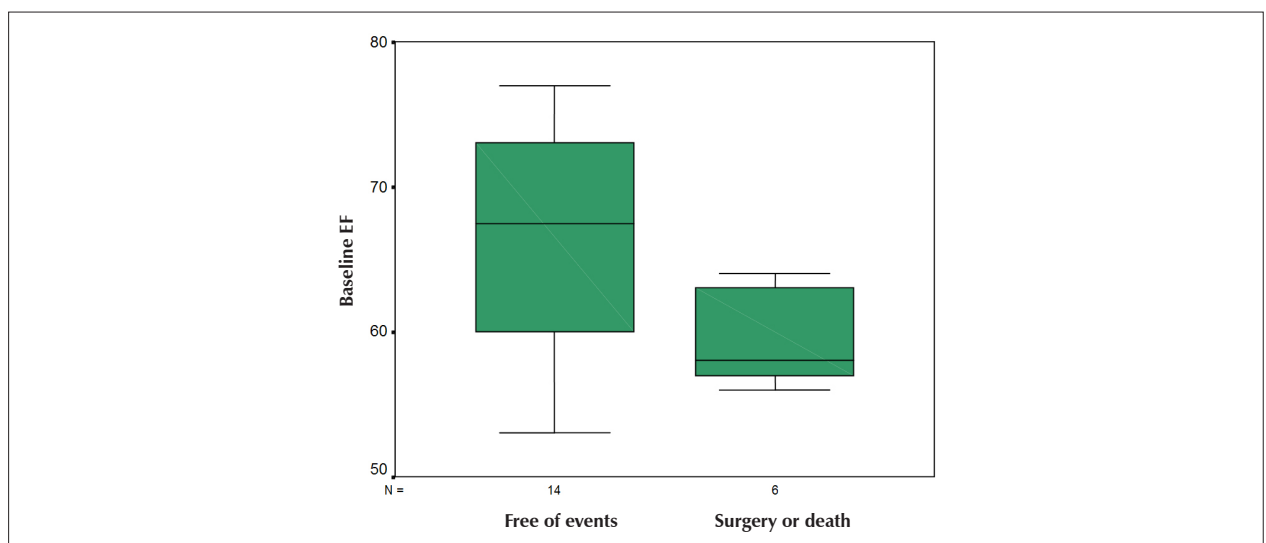


Figure 2 - Comparison between baseline EF of patients who had events and those of the other patients. EF - ejection fraction.

analyzed 11 patients with aortic regurgitation and decreased systolic function, dobutamine led to an elevation of baseline EF from 37 ± 9 to $43 \pm 12\%$, whereas the systolic wall stress and systolic pulmonary pressure did not change. Three patients underwent surgery and became asymptomatic. One patient whose EF did not increase with dobutamine died. The authors conclude that in patients with aortic regurgitation and decreased EF, dobutamine-induced elevation of EF and reduction of ventricular diameters and volumes are variables that indicate contractile reserve¹¹. However, the samples were very small to enable any statistical analysis.

In another study comparing dobutamine-stress echocardiography and exercise ventriculography in 26 patients with moderate to severe aortic regurgitation, De Rito et al¹⁰ showed concordance between these two modalities in the assessment of asymptomatic or minimally symptomatic patients.

Tam et al⁹ studied 16 patients who underwent elective surgery for aortic regurgitation and had echocardiograms obtained at baseline and at $7.5 \mu\text{g}/\text{kg}/\text{min}$ dobutamine. They compared patients with full recovery (normalization of ventricular size and function in the absence of symptoms at six months of follow-up) - Group I, to those without full recovery - Group II. Age, functional class and end-diastolic diameters were similar between the groups. However, patients in Group I had a lower preoperative end-systolic ventricular index and higher EF than patients in Group II. Dobutamine was useful in increasing the difference in ventricular size and function of patients of Groups I and II. The authors then concluded that EF during dobutamine infusion is highly predictive of postoperative EF, and that this modality of stress-echocardiography may play a role in the prediction of the clinical response of patients with aortic regurgitation who are undergoing aortic valve replacement. Differently from that study, the percentage increases of EF at $10 \mu\text{g}/\text{kg}/\text{min}$, $15 \mu\text{g}/\text{kg}/\text{min}$ or $20 \mu\text{g}/\text{kg}/\text{min}$ in our study did not permit prediction of surgery or death in the follow-up of the patients. All patients in Tam et al⁹ study were eligible for aortic valve replacement, a situation different from that of our patients, for most of whom surgery was not indicated. Dobutamine-stress echocardiography may have had a better performance to discriminate patients with contractile reserve among those who already required surgery than among those asymptomatic

or minimally symptomatic. In the latter, the knowledge of the natural progression of the disease, a well-performed history taking, and results of tests such as ECG, chest radiography, and transthoracic echocardiography with color flow mapping seem to be enough, provided that there is no dissociation between the clinical manifestations and the ancillary tests.

Study limitations

This is a small group of patients, especially for the analysis of follow-up events. Further studies including a larger number of patients are required to confirm the findings of the present study. Additionally, our group of patients was quite heterogeneous in terms of age, etiology of rheumatic disease, and follow-up duration, and these may have influenced the results.

Three patients were lost to follow-up and one patient died in a car accident. The results could be different if data on the follow-up of these four patients had been obtained.

Conclusion

Our findings showed that in young patients with aortic regurgitation baseline EF was correlated to surgery or death in the follow-up. However, EF elevation induced by dobutamine infusion at low-doses did not permit the prediction of events in these patients. Thus, based on these results, dobutamine-stress echocardiography does not seem to be a useful tool in risk stratification of young patients with aortic regurgitation. However, further studies with larger number of patients and events may show different results.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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