Ten-Year Clinical Laboratory Follow-Up After Application of a Symptom-Based Therapeutic Strategy to Patients With Severe Chronic Aortic Regurgitation of Predominant Rheumatic Etiology

Flavio Tarasoutchi, MD, Max Grinberg, MD, Guilherme S. Spina, MD, Roney O. Sampaio, MD, Luís F. Cardoso, MD, Eduardo G. Rossi, MD, Pablo Pomerantzeff, MD, Francisco Laurindo, MD, Protásio L. da Luz, MD, FACC, José Antônio F. Ramires, MD, FACC

São Paulo, Brazil

OBJECTIVES This study was designed to assess the feasibility and the long-term results of a symptom-based strategy of aortic valve replacement in a Brazilian population with predominant rheumatic etiology.

BACKGROUND Optimal criteria for valve replacement in aortic regurgitation (AR) are still not entirely clear. The appearance of symptoms is an indication for surgery, but may be associated with myocardial damage. Although cardiac imaging data have provided a safer guide for such decisions, the use of symptom-based surgical indication has not been validated and might conceivably be better in populations with predominant rheumatic etiology and younger age.

METHODS Echocardiography and rest-exercise radionuclide ventriculography were performed in 75 patients with severe AR, age 28±9 years, over a period of 10±0.69 years. Thirty-seven patients developed symptoms and underwent aortic valve replacement surgery within six months. Thirty-eight patients remained asymptomatic and were managed medically.

RESULTS Survival was 100% in asymptomatic patients and 82% in symptomatic. Surgical treatment caused marked ventricular remodeling, with ventricular diameter involution and an improvement of rest-exercise ejection fraction percent variation. Multivariate analysis showed that the probability of developing symptoms within 10 years was 58% for a patient with a left ventricular end-diastolic diameter ≥70 mm and 76% for a patient with left ventricular end-systolic (LVESD) ≥50 mm. Logistic regression identified LVESD and age as the most predictive and specific, but not sensitive, indicators of symptom development.

CONCLUSIONS Application of a standardized therapeutic strategy to patients with severe AR and predominant rheumatic etiology resulted in 90.6% survival after 10 years of follow-up. (J Am Coll Cardiol 2003;41:1316–24) © 2003 by the American College of Cardiology Foundation

Optimal criteria for valve replacement in aortic regurgitation (AR) are still not entirely clear (1–3). The natural history of AR is characterized by a long asymptomatic period during which significant eccentric left ventricular (LV) hypertrophy as well as large vessel remodeling take place as an adaptive response to pressure-volume overload (4–7).

The appearance of symptoms is generally viewed as an exhaustion of such adaptive mechanisms, which may lead to permanent damage to cardiomyocyte structure and function and/or alterations of the extracellular matrix (8,9). Such damage can preclude recovery of myocardial function after valve replacement (10,11).

During the past two decades (12–18), prognostic assessment studies based primarily on LV dimensions and/or systolic function have led to echocardiographic-based guidelines to define the ideal timing of surgical intervention, designed to interrupt the natural history of AR while minimizing the exposure to the complications of valvular prosthesis. Clinical decisions in such cases, however, remain controversial (19).

In Brazil, and likely in many other communities in which valvular heart disease is widely prevalent, the major etiology of AR is rheumatic fever. Such patients are much younger than the average patient covered by guidelines mentioned earlier and are more likely to reach the suggested cutoff values for LV size and function much earlier in the course of their disease (18). As long as myocardial function is significantly affected by age, the recovery of myocardial function after AR correction might conceivably be better in younger patients. In this situation, the echocardiographic variables defined as class IIa indication for AR in the guidelines issued, for example, by the American College of Cardiology (ACC) and American Heart Association (AHA) (19) might lead to early exposure to the complications of valvular
prosthesis without concomitant gain in the recovery of LV function. Indeed, it has been noted previously that many such patients operated soon after the onset of symptoms are capable of a full short-term recovery despite left ventricular end-systolic diameters (LVESDs) well above the cutoff of 55 mm (18,20,21). This is an indication that these patients might tolerate considerably larger increases in their LV size without detectable compromise in later function. The long-term results of such an approach, however, have not been assessed in our population. In addition to a welcome positive economic impact, the possibility of a delayed intervention could improve the long-term patient outcome because of decreased morbidity/mortality associated with valvular prosthesis and reoperations. The present study prospectively assessed the feasibility of a symptom-based indication for aortic valve replacement in severe chronic AR by examining the 10-year follow-up of a cohort of 75 patients in whom operation was indicated at the onset of clinical symptoms rather than based on the degree of LV enlargement.

METHODS

Study population. Severe chronic AR was defined according to the modified criteria of Spagnuolo et al. (22), which demanded a cardiothoracic index >0.50, electrocardiographic evidence of LV hypertrophy, a pulse pressure ≥80 mm Hg, diastolic arterial pressure ≤60 mm Hg, and Doppler echocardiography, which allows one to define the degree of AR. Seventy-five consecutive asymptomatic patients who met these criteria between January 1988 and December 1989 were prospectively enrolled and followed as outpatients at the Heart Institute (InCor) of the University of São Paulo. Exclusion criteria consisted of patient age <18 or >60 years, coexisting AF, or any cardiac condition other than AR. Thirty percent of the patients were receiving drugs, including digitalis, diuretics, or both. Asymptomatic patients did not receive any arterial or venous vasodilator during the study.

Informed consent was obtained for each patient and the study was approved by the local scientific/ethics committee. Radioisotopic ventriculography. Multiple-gated acquisition radioisotopic ventriculography was performed at rest and during exercise. All medications including diuretics were interrupted for at least three days before the test.

Images were obtained with the patients seated at a 45° angle in the left anterior oblique projection for optimal distinction between the LV and right ventricle. Images were acquired by manually selected areas of interest in the LV, at maximal diastole and systole, after subtracting background radiation. Exercise was performed on a bicycle and followed the Heart Institute protocol (18). A starting load of 25 W was increased by 25 W every 4 min. The speed was kept constant at 70 rotations per min. The extent of exercise was guided by generalized fatigue or the appearance of the first sign of dyspnea. Cardiac rhythm and blood pressure were monitored throughout the test. Images acquired during exercise were overlaid on those obtained at rest. The left ventricular ejection fraction (LVEF) at rest, LVEF at maximal exercise, and total effort time were recorded. A normal exercise response was defined as an increase in the LVEF of 5% or more from rest to maximal exercise (17,23).

Echocardiography. Echocardiographic examinations were performed using either an Aloka SSD, model 860, with a 2.5 MHz transducer (Aloka, Japan) or an Aloka SSD, model 725, with 2 and 3 MHz transducers. Interpretation followed the American Society of Echocardiography standards (24). The following LV variables were evaluated: end-diastolic diameter (LVEDD) in mm; LVESD in mm, and shortening fraction (SF). The cutoff values used for data analysis were drawn from well-accepted guidelines previously defined in the literature (12,13,15,19).

Follow-up. Once enrolled, each patient underwent complete clinical and cardiologic examination and was then followed for at least 120 months. Clinical examinations were repeated every 6 months and noninvasive cardiac tests every 12 months. Both procedures were performed earlier if symptoms occurred. Cardiac assessment included exercise testing, chest roentgenogram, resting echocardiography, and rest-exercise radionuclide ventriculography.

Particular attention was paid to assess the etiology of AR, which was determined on the basis of clinical history as well as echocardiographic evidence of mitral valve thickening in the majority of rheumatic patients, although none had the mitral stenosis and morphology of valves removed from patients during surgery.

Some patients remained asymptomatic throughout the 120-month study. Asymptomatic patients were defined as those not exhibiting symptoms of dyspnea, chest pain, dizziness, syncope, or extreme effort dyspnea. Symptomatic patients developed symptoms of congestive heart failure, such as dyspnea during habitual physical activities and at rest, chest pain, easier-than-normal fatigue, and/or syncope. Patients who developed symptoms were immediately scheduled for aortic valve surgery, which was performed within the ensuing six months. Patients who underwent valve replacement were followed postoperatively.

The minimal follow-up period was 120 months. Comparisons between patients remaining asymptomatic and
developing symptoms were performed at the beginning of the study, at the onset of symptoms, and at the final evaluation. Preoperative cardiac catheterization was performed in all patients, and macro/microscopic examination of all extracted aortic valves was performed.

**Statistical analysis.** Statistical analysis was performed with SAS software. Significance was defined at the 0.05 level. The mean ± SD is reported for quantitative variables and absolute and relative frequency for qualitative variables. Both the paired and unpaired Student t tests were used. Qualitative data were compared using the equivalence of proportions hypothesis, the chi-square test or, when this was limited, Fisher exact test (25). Multivariate profile analysis (26,27) was used to analyze changes in echocardiography and radioisotopic ventriculography data during follow-up.

Factors predictive of specific events were analyzed through a logistic regression model. The time interval to the occurrence of such specific events was analyzed through Kaplan-Meier curve and compared by log-rank tests.

**RESULTS**

**Clinical follow-up.** The minimum follow-up period was 10 years and the average follow-up period was 10.42 ± 0.69 years.

Thirty-eight patients (50.6%) remained asymptomatic throughout the follow-up; all such patients were alive at the
end of the study. The other 37 patients (49.4%) constituted the symptomatic group (Fig. 1). Of these patients, 30 became asymptomatic after surgical correction of the aortic valve. Thus, symptomatic patients can be divided in three clinical phases: an initial asymptomatic period, a symptomatic surgical period, and a postoperative period. Therefore, at the end of that period, 68 (90.6%) of the 75 patients were alive and asymptomatic (Fig. 2). Table 1 displays baseline characteristics of the patients.

The average time from study enrollment to the development of symptoms was 4.6 ± 1 year and mean postoperative follow-up period 5.2 ± 1.3 years. The reported symptoms were dyspnea or intolerance to effort (56%), angina (28%), and syncope (2%).

**Laboratory parameters.** Table 2 and Figure 3 show that there were significant differences (p < 0.05) in the mean LVEDD, LVESD, SF, LVEF, and the rest-exercise variation in LVEF (ΔEF r-ex) between groups at the beginning of the study (baseline). The LVEDD did not significantly change between baseline and final assessment in asymptomatic patients. However, significant changes (p < 0.05) in other parameters of LV function (LVESD, SF, LVEF, and ΔEF r-ex) occurred. In the symptomatic patients, there was marked remodeling of the LV after surgery, with a significant (p < 0.0001) reduction in both LVESD and LVEDD and an increase in the ΔEF r-ex.

Initially, 50% of the asymptomatic patients had LVEDD >70 mm, and 15.8% had LVESD >50 mm. At the end of the study, 52.7% patients had LVEDD >70 mm (p = ns vs. baseline values, chi-square test) and 47.3% had LVESD >50 mm (p = 0.021 vs. baseline values) (Tables 3 and 4).

<table>
<thead>
<tr>
<th>Table 1. General Data at Baseline</th>
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<tr>
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<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Male gender (%)</td>
</tr>
<tr>
<td>Heart-rate (beats/min)</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
</tr>
<tr>
<td>Cardiothoracic index</td>
</tr>
<tr>
<td>Rheumatic etiolog (%)</td>
</tr>
<tr>
<td>Time of diagnosis (yrs)</td>
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*pStudent’s test; †Chi-square test.

DAP = diastolic arterial pressure; SAP = systolic arterial pressure.

In the symptomatic patients, there was initially higher prevalences of LVEDD >70 mm (73%, p = 0.0006 vs. asymptomatic group) and LVESD >50 mm (51.3%, p = 0.0006 vs. asymptomatic group). In the symptomatic patients (91.8%) undergoing surgery there was marked decrease in LV size, so that at the end of the study, only 10% of patients in this group had LVEDD >70 mm (p = 0.0001 vs. baseline) and only 10% had LVESD >50 mm (p < 0.0001 vs. baseline) (Tables 3 and 4).

We observed no increase in diameters or reductions in systolic performance indexes at the time patients became symptomatic (Fig. 3).

Systolic LV was also lower in symptomatic patients at the beginning of the study (5.4% patients with SF <0.25 vs. none of the asymptomatic patients, p = 0.04). At the end of the study, 5.3% of the asymptomatic patients and 16.7% of the symptomatic patients had SFs <0.25. Overall, the SF remained stable in the symptomatic patients (p = ns) but significantly changed over time in asymptomatic ones (p = 0.0029) (Table 5, Fig. 3).

An analogous behavior was observed for the LVEF at rest (Table 6, Fig. 3), which decreased from average of 0.64 to 0.59 (p = 0.0005) in asymptomatic patients.

We observed that of the 37 patients who had LVEDD ≥75 mm or LVESD ≥55 mm (Tables 3 and 4), 20 needed surgery and 7 remained asymptomatic. All seven with LVEDD ≥75 mm or LVESD ≥55 mm who remained asymptomatic had normal ventricular function at the end of the study.

The rest-exercise percentile variation of the LVEF (ΔEF r-ex) was >0.05 at the initial (baseline) evaluation in 28.6% of the symptomatic patients and 42.7% of the asymptomatic patients (p = 0.0972). After surgical treatment, at the final evaluation, 63.3% of the symptomatic patients had ΔLVEF >0.05, a significant (p = 0.0001) change between evaluations. In asymptomatic patients, the ΔLVEF remained stable over time (p = 0.0976) (Table 7).

**Surgical follow-up.** Thirty-five aortic prostheses were implanted in 33 initial operations and 2 re-operations, including 31 bioprostheses (80.5%) and 4 metallic prostheses (11%). A conservative technique was used to repair the aortic valve in one patient. Two patients required re-operation after 60 and 65 months, respectively. Nine pa-
Figure 3. Evolution of left ventricular end-systolic diameter, left ventricular end-diastolic diameter, shortening fraction, left ventricular ejection fraction (LVEF), and percentile variation of the rest-exercise ejection fraction in the symptomatic group and asymptomatic group over time. For symptomatic group, four years follow-up was preoperative phase.
patients had mild dysfunction of the bioprosthesis at the end of the study and were in functional class (FC) I/II. Six prosthesis-related complications occurred during the late postoperative period.

**Deaths.** Three patients died while awaiting surgery; one of them had refused-surgery, FC III heart failure and one had FC II and syncope (Fig. 1, Table 8). There was no immediate surgical mortality (Table 9).

The medium interval between surgery and death was 1.97 ± 1.18 years. All four patients were asymptomatic at the time of their last evaluation. One patient with a metallic prosthesis developed acute thrombosis and died. The remaining five complications involved bioprostheses and consisted of two cases of fatal endocarditis and three spontaneous ruptures. Two of them had favorable outcomes after repeated surgery, and one patient died. The patients who died had ventricular diameters and systolic function similar to asymptomatic survivors (Table 9).

**Logistic regression.** Univariate analysis identified rest LVESD (p = 0.0015), rest LVEDD (p = 0.0003), SF (p = 0.0384), LVEF at rest (p = 0.0054), ΔEF r-ex (p = 0.0034), and age (p = 0.0030) as predictors of symptom development. These variables were then evaluated through a logistic regression model, with a stepwise selection process to obtain risk factors predictive of symptoms. Results from this multivariate analysis suggest that the LVEDD at rest (p = 0.0001) and age (p = 0.0003) are the best predictors of symptoms.

The probability that a patient with an initial LVESD >70 mm became symptomatic after 10 years was 58%, with an odds ratio of 2.70, sensitivity 73.0%, specificity 50.0%, and accuracy 61.3%. The probability that a patient with an initial LVEDD >50 mm became symptomatic after 10 years was 76%, with an odds ratio of 5.63, sensitivity 51.4%, specificity 84.2%, and accuracy 68.0%.

**DISCUSSION**

**Clinical follow-up.** During the 1970s, Spagnuolo et al. (22) proposed predictive clinical criteria for the natural evolution of AR. Further studies suggested specific values for echocardiographic as prognostic indication; for example, indexes of poor postsurgical results include an LVEDD ≥60 mm, LVESD ≥55 mm, SF ≤0.25, final systolic volume ≥90 ml/m², LVEF <0.50, and LV radius-thickness ratio >3.8 (7–16).

The clinical follow-up of patients with chronic AR at our institution (18) for 36 months suggested a different view from that reported by Henry et al. (12,13). Results showed that the use of symptoms as a guide to the transition from clinical to surgical treatment was appropriate. Although the LVEDD and LVESD were >70 mm and >55 mm, respectively, the postoperative outcome of most patients was favorable. One explanation for the divergent findings between our study and that of Henry et al. (12,13) is that they used an older population with significantly fewer rheumatic patients.

In contrast, the prevalence of a rheumatic etiology of AR in our patients (92%) was nearly three times higher than that reported in other series, which averaged 30%. Furthermore, the mean age of patients in the present study (30 years) was nearly half of that (55 years) previously reported in analogous reports series (28–30).

<table>
<thead>
<tr>
<th>Table 3. Distribution of End-Diastolic Diameters at the Baseline and Final Evaluations</th>
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</thead>
<tbody>
<tr>
<td><strong>LVEDD</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>&lt; 60 (mm)</td>
</tr>
<tr>
<td>60–69 (mm)</td>
</tr>
<tr>
<td>70–74 (mm)</td>
</tr>
<tr>
<td>≥75 (mm)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

*The difference reflects the seven patients who died. LVEDD = left ventricular end-diastolic diameter.

<table>
<thead>
<tr>
<th>Table 5. Distribution of Shortening Fraction at the Baseline and Final Evaluations</th>
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<tbody>
<tr>
<td><strong>SF</strong></td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>&lt; 0.25</td>
</tr>
<tr>
<td>0.25–0.29</td>
</tr>
<tr>
<td>≥0.30</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

*The difference reflects the seven patients who died. SF = shortening fraction.
Patients who died.

The higher mortality in the symptomatic patients reflects in part the presence of a valvular prosthesis. In fact, all post surgery complications as well four of the seven deaths resulted from prosthesis dysfunction caused by endocarditis, thrombosis, or failure. It is interesting to stress that there were no postoperative deaths due to heart failure. The remaining three patients died within six months of the onset of symptoms while awaiting surgery. These data indicate that surgery must be performed immediately after the development of symptoms.

Our study identified three outcomes of the implanted prostheses: 1) normal morphology in 49% (85% bioprostheses and 15% metallic prosthesis); 2) severe prosthesis dysfunction in 20% (6 patients); and 3) mild prosthesis dysfunction in 31% (9 patients).

Because of our patients' poor socioeconomic status and difficulties in adequate anticoagulation, bioprostheses were preferred over metallic prostheses, leading to better quality of life.

The present study was started before the use of vasodilators was introduced, and none of our asymptomatic patients received vasodilators. Therefore, it should be kept in mind that use of vasodilators could affect the reliability of symptoms as markers for therapy.

**Ventricular function.** The strategy proposed by the present study effectively reduced eccentric hypertrophy. Seventy percent of the survivors versus none at baseline in the symptomatic groups had a final LVEDD < 60 mm (90% < 70 mm). Similarly, 30 survivors in the symptomatic group had a final LVESD < 40 mm.

Our data agree with data reported by Fioretti et al. (20) and Daniel et al. (21), that is, there is a weak relationship between laboratory criteria and postsurgical evolution. The four patients who died after surgical correction demon-

### Table 7. Distribution of the ΔEF r-ex at the Baseline and Final Evaluations

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔEF r-ex Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>&lt; 0</td>
<td>16</td>
</tr>
<tr>
<td>0-0.04</td>
<td>9</td>
</tr>
<tr>
<td>≥ 0.05</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
</tr>
</tbody>
</table>

*Four patients were unable to perform the tests at the baseline evaluation and one was unable to perform the tests at the final evaluation; †The difference reflects the seven patients who died.

ΔEF r-ex = percentile variation of the rest-exercise left ventricular ejection fraction (LVEF).

In particular, older age has previously been reported as an index (29–32) of poor prognosis. Our findings support and strengthen this concept (Table 1), as the age of symptomatic patients was ≥20% higher than the age of asymptomatic ones.

According to the ACC/AHA guidelines (19), surgical indication when there is manifestation of FC II without ventricular dysfunction is Class IIa. Klodas et al. (29) reported in patients with average age of 50 years, that FC II (New York Heart Association) heart failure should be indicative for surgery. As a result, FC II patients had a better postsurgical prognosis than those with FC III/IV. We observed a lower mortality rate than Klodas et al. (29), who reported 82% survival in patients with FC I/II and 45% in those with FC III/IV. In our study, survival in patients with FC I/II was 100% (Fig. 2) and, in patients with symptoms, 82%. The difference in these mortality rates probably reflects differences in the populations studied, mainly regarding the etiology of AR and mean patient age, in a likely parallel with LV overload duration.

The 90.6% survival rate and relatively normal LV function observed at the end of our 10-year study is consistent with results reported by other authors (3,29,33).

The marked LV remodeling observed postoperatively further validates the recognition of progression to FC III or the manifestation of angina pectoris as cardinal signs of the need for surgery. Overall, the low incidence of complications and the homogeneous return to degree FC I/II heart failure give larger credence to this observation. This indication is shared with the ACC/AHA valve disease guidelines (19).

**Survival and mortality.** It is noteworthy that, even with a high LVEDD (73 ± 8.3 mm) at the beginning of the study, half (51%) of the asymptomatic patients experienced a natural evolution similar to that reported by Bonow et al. (3). Similarly, in both studies the excellent evolution of patients with severe AR, as long as normal function was present, emphasizes the findings that irreversible LV dysfunction preceding symptoms is infrequent. Similar behavior has been described in the literature (2,3,19), where the frequency of sudden death during the natural evolution of AR is reportedly only 0.2% per year.

The higher mortality in the symptomatic patients reflects in part the presence of a valvular prosthesis. In fact, all post surgery complications as well four of the seven deaths resulted from prosthesis dysfunction caused by endocarditis, thrombosis, or failure. It is interesting to stress that there were no postoperative deaths due to heart failure. The remaining three patients died within six months of the onset of symptoms while awaiting surgery. These data indicate that surgery must be performed immediately after the development of symptoms.

**Cardiac Imaging Parameters for Four Patients Who Died During the Late Postoperative Period**

<table>
<thead>
<tr>
<th>Baseline Evaluation</th>
<th>Final Evaluation</th>
</tr>
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<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>77 ± 4</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>52 ± 4</td>
</tr>
<tr>
<td>SF</td>
<td>0.32 ± 0.04</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.54 ± 0.09</td>
</tr>
<tr>
<td>ΔEF r-ex</td>
<td>-1.2 ± 10</td>
</tr>
</tbody>
</table>

*The mean interval between surgery and the final evaluation was 1.97 ± 1.18 years.

LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; SF = shortening fraction; V/MI = volume-mass index; ΔEF r-ex = percentile variation of the rest-exercise LVEF.

### Table 8. Mortality Before Surgery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>LVEDD (mm)</th>
<th>LVESD (mm)</th>
<th>SF</th>
<th>LVEF</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>54</td>
<td>0.33</td>
<td>0.58</td>
<td>FC III refused surgery</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>48</td>
<td>0.33</td>
<td>0.68</td>
<td>Syncpe</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>48</td>
<td>0.38</td>
<td>0.58</td>
<td>FC III/IV</td>
</tr>
</tbody>
</table>

FC = functional class; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SF = shortening fraction.
strated similar involution of cardiac diameters, and their
deaths were due to prosthesis-related complications.

An LVESD >50 mm was associated with a 76% chance of
experiencing symptoms, which is a five-fold increase
versus that associated with a LVESD <50 mm.

Furthermore, our data show that asymptomatic patients
with AR with normal ventricular function can be safely
followed clinically even after developing values of LVEDD
≥75 mm or LVESD ≥55 mm—a class IIa indication for
valve replacement according to the ACC/AHA guidelines
(19). In the 27 patients who had LVEDD ≥75 mm or
LVESD ≥55 mm (Tables 3 and 4), 20 were followed for an
average of four years before needing surgery on the basis of
symptom development, with no further deterioration of LV
function at this time. The other seven patients remained
asymptomatic with normal ventricular function at the end of
the 10-year follow-up.

The rest-exercise variation in LVEF (ΔEF r-ex) in our
study was dissociated from clinical symptoms (17). With a
cutoff value for ΔEF r-ex of 0.05, 22.2% of the asymptom-
atic patients had a negative ΔEF r-ex at baseline (decrease of
LVEF at exercise).

Contrary to what occurs in other cardiopathies, the fall in
the LVEF during exercise does not seem to signify intrinsic
myocardial dysfunction or loss of cardiac reserve, as initially
reported by Borer et al. (17). The LVEF at exercise tends to
decrease with the natural evolution of AR, without a change
in FC. Possibly such behavior does not necessarily reflect
actual reduction in the cardiac reserve, because we found an
increased variation of the index (>0.05) in symptomatic
patients at the final evaluation (34,35).

In conclusion, our study showed that in a population of
younger patients with higher prevalence of rheumatic fever,
the indication for valve replacement based on the onset of
clinical symptoms was associated with a favorable outcome.
These results reinforce the class I indications of the ACC/
AHA guidelines and provide further basis for clinical
decision-making in class IIa indications. In the latter cases,
we showed that the indication for AVR based on the onset of
clinical symptoms rather than on specific values of LV
dimensions might be more appropriate for such population.

Reprint requests and correspondence: Dr. Flavio Tarasoutchi,
Instituto do Coração, (InCor), University of São Paulo School of
Medicine, Valcular Heart Disease Unit, Av. Enéas de C. Aguiar,
44, São Paulo, SP 05403-000, Brazil. E-mail: tarasout@uol.com.br.

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