Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 45, No. 7, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.06.081

Long-Term Survival and Functional Results After Aortic Valve Replacement in Asymptomatic Patients With Chronic Severe Aortic Regurgitation and Left Ventricular Dysfunction

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OBJECTIVES We examined the influence of medical treatment on the results of surgery in terms of long-term survival and functional results in patients with chronic, severe aortic regurgitation (AR).

BACKGROUND Asymptomatic patients with AR and a reduced left ventricular ejection fraction (LVEF) are at high risk because of a higher-than-expected long-term mortality. The influence of preoperative medical therapy on the outcome after aortic valve replacement (AVR) is not well known.

METHODS Surgery was indicated for the appearance of a reduced LVEF (<50%). At the time of AVR, there were 134 patients treated with nifedipine (group A), and 132 received no medication (group B).

RESULTS Operative mortality was similar in the two groups (0.75% vs. 0.76%, p = NS). The LVEF normalized in all of group A, whereas it remained abnormal in 36 group B patients (28%). At 10-year follow-up, LVEF persisted higher in group A (62 ± 5% vs. 48 ± 4%, p < 0.001). Five-year survival was similar in the two groups (94 ± 2% vs. 94 ± 3%, p = NS). Group A showed a 10-year survival not different from expected and significantly higher than that in group B (85 ± 4% vs. 78 ± 5%, p < 0.001), which had a worse survival than expected.

CONCLUSIONS Unloading treatment with nifedipine in AR allows one to indicate AVR at the appearance of a reduced LVEF with a low operative mortality and an optimal long-term outcome. The concept of surgical correction of AR indicated for reduced LVEF may not be applied to all patients. Indeed, in a large amount of untreated patients, a reduced LVEF preoperatively is not reversed by prompt surgery, indicating irreversible myocardial damage, and 10-year survival is worse than expected. (J Am Coll Cardiol 2005;45:1025–30) © 2005 by the American College of Cardiology Foundation

The decision to recommend operative intervention to the asymptomatic patient with chronic, severe aortic regurgitation (AR) is very difficult because aortic valve replacement (AVR) continues to entail immediate risk, and biologic and mechanical valves still have problems resulting in significant morbidity and mortality. On the other hand, the mortality

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rate in asymptomatic patients with AR is very low, and surgery does not improve the quality of life. Thus, the indication in asymptomatic patients must be delayed until changes occur that will predict an increased risk of operative or long-term death after AVR.

It is not clear whether the occurrence of a reduced left ventricular ejection fraction (LVEF) in asymptomatic patients with AR represents the right moment to recommend surgery or whether this is a parameter that will predict a less-than-optimal result. The issue of patients with AR after deterioration of LVEF has occurred offers an intriguing clinical and pathophysiologic problem. Particularly, controversies exist about the questions of whether the risks of surgery are too high, and whether any improvement in LVEF and survival can realistically be expected after successful AVR. Several studies support the idea that asymptomatic patients with normal LVEF should undergo surgery without waiting for the development of symptoms or reduced LVEF. This conclusion is based on the demonstration that reduced LVEF has a marked influence on survival after aortic valve replacement (1–5). However, other studies indicate that there is no reliable evidence that early valve replacement is beneficial in asymptomatic patients with normal LVEF (6–9), and in the absence of symptoms, the chief indication is the development of reduced LVEF (5,10–15). Recently, a long-term follow-up study (5) showed that asymptomatic patients with normal LVEF had a 10-year mortality rate not different from expected, whereas those with reduced LVEF constituted a subgroup with excess mortality rates with conservative man-

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Manuscript received April 14, 2004; revised manuscript received June 10, 2004, accepted June 22, 2004.

JACC Vol. 45, No. 7, 2005
April 5, 2005:1025–30

Abbreviations and Acronyms

AR = chronic, severe aortic regurgitation
AVR = aortic valve replacement
LV = left ventricle/ventricular
LVEDVI = left ventricular end-diastolic volume index
LVEF = left ventricular ejection fraction
LVESVI = left ventricular end-systolic volume index

agement. The authors concluded that these patients should be considered at high risk and evaluated for prompt intervention. Unfortunately, data on postoperative survival derived from large series of these patients are not available. Moreover, the effects of medical treatment are largely unknown, because in these studies patients received, in variable proportion, calcium channel blockers, angiotensin-converting enzyme inhibitors, hydralazine, beta-blockers, digoxin, or none of these (1–12). In a previous study, unloading therapy with nifedipine in asymptomatic patients with normal LVEF delayed surgery (indicated by the appearance of reduced LVEF), and all patients responded favorably to aortic valve replacement with normalization of the ejection fraction (16).

The present study prospectively assessed operative mortality, long-term survival, and functional results in asymptomatic patients who underwent AVR after deterioration of LVEF. The effects of a preoperative unloading therapy with nifedipine or the absence of medical therapy were also evaluated.

METHODS

Patient selection. In order to assess the effect of pretreatment unloading therapy on surgical outcome, in the 1980s and during the first half of the 1990s, the policy of the "Valve Heart Disease Unit" of our University randomly assigned asymptomatic patients with AR and normal LVEF to nifedipine unloading therapy or no medical treatment. In both groups of patients, no other cardioactive drugs were administered. At the moment of randomization to nifedipine or no medication, the age was comparable in the two study groups (42 ± 16 years vs. 43 ± 18 years, p = NS). Patients were followed up with a return visit and echocardiographic and color Doppler evaluations every six months. They were enrolled into the present study at the moment of the first appearance of reduced LVEF and then operated on within three months. Left ventricular (LV) dysfunction was defined as a reduced LVEF (<50%) confirmed by an echocardiographic study one month later. Moderately severe (grade III/IV) or severe (grade IV/IV) AR was diagnosed with color flow Doppler echocardiography (17). Exclusion criteria were the following: recent development or worsening of AR (within the preceding six months), diastolic blood pressure above 90 mm Hg, significant (≥50% diameter reduction) stenosis of coronary vessels demonstrated by coronary angiography, mixed aortic stenosis and regurgitation (mean valve gradient ≥20 mm Hg), and evidence of additional valvular or congenital heart disease.

The events and cause of death were established by a review of medical, coroner, and autopsy records and death certificates. To avoid biases due to concomitant diseases able to influence survival, associated co-morbid conditions were summated as a co-morbidity index (18). Informed consent was obtained in all patients, and the study was approved by the ethical committee of our institution.

Echocardiographic analysis. Two-dimensional echocardiograms were recorded with a Hewlett-Packard (Andover, Massachusetts) ultrasonoscope (Sonos 2500, 4500, or 5500) and a 2.5- or 3.5-MHz or S3 transducer. Left ventricular echocardiograms in the apical four-chamber and parasternal short-axis views in at least three to five cardiac cycles were digitized at end diastole (peak of the R-wave) and at end systole (time when the cavity area was smallest). Each echocardiogram was read by two independent observers who did not know the patient's identity. If the readings differed by 10 ml or more for LV volume, data were analyzed by a third observer. Agreement was achieved by consensus. The degree of interobserver and intraobserver correlation for LV area (r = 0.98 and r = 0.97, respectively) and for LV length (r = 0.98 and r = 0.96, respectively) was reasonable.

The LV volumes were calculated by an ellipsoid biplane area-length method (19); LVEF was calculated as: (LVEDVI − LVESVI)/LVEDVI, where LVEDVI is left ventricular end-diastolic volume index and LVESVI is the left ventricular end-systolic volume index.

Aortic regurgitation was quantified in all patients by mapping of the regurgitant jet into the LV by color Doppler imaging. The severity of regurgitation was graded with use of the ratio of the height of the jet to that of LV outflow tract. The height of the regurgitant jet was measured at its origin, immediately beneath the aortic valve, in the parasternal long-axis view. Ratios >45% were categorized as indicating grade III/IV AR, and those >65% as grade IV/IV AR (17).

Echocardiographic study was repeated at the time of valve replacement, two months thereafter, and every year during follow-up.

Statistical analysis. All data are expressed as the mean value ± SD. Comparisons of continuous variables in the two groups were made by repeated measures analysis of variance. Within each group, we compared preoperative and postoperative values by means of the paired *t* test. Long-term survival analysis was carried out using the Kaplan-Meier method, and the two-tailed *k*-sample log-rank test was used to compare groups. The one-sample log-rank test was used to compare survival with expected survival of the age- and gender-matched 1990s Italian census sample. Generally, the census data do not truly constitute a relevant matched control group, allowing a specific conclusion. To minimize the limits of this approach, we followed this design: background mortality and excess mortality were estimated from life-table data (Central Bureau for Statistics)