NIFEDIPINE IN ASYMPTOMATIC PATIENTS WITH SEVERE AORTIC REGURGITATION AND NORMAL LEFT VENTRICULAR FUNCTION

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Abstract Background. Vasodilator therapy with nifedipine reduces left ventricular volume and mass and increases the ejection fraction in asymptomatic patients with severe aortic regurgitation.

Methods. To assess whether vasodilator therapy reduces or delays the need for valve replacement, we randomly assigned 143 asymptomatic patients with isolated, severe aortic regurgitation and normal left ventricular systolic function to receive either nifedipine (20 mg twice daily, 69 patients) or digoxin (0.25 mg daily, 74 patients).

Results. By actuarial analysis, we determined that after six years a mean (±SD) of 34±6 percent of the patients in the digoxin group had undergone valve replacement, as compared with only 15±3 percent of those in the nifedipine group (P<0.001). In the digoxin group, valve replacement (in a total of 20 patients) was performed because of left ventricular dysfunction (ejection fraction <50 percent) in 75 percent, left ventricular dysfunction plus symptoms in 10 percent, and symptoms alone in 15 percent. In the nifedipine group, all six patients who underwent valve replacement did so because of the development of left ventricular dysfunction. In addition, all the patients in both groups who underwent aortic-valve replacement had an increase of 15 percent or more in the left ventricular end-diastolic volume index. After aortic-valve replacement, 12 of the 16 patients (75 percent) in the digoxin group and all six patients in the nifedipine group who had had an abnormal left ventricular ejection fraction before surgery had a normal ejection fraction.

Conclusions. Long-term vasodilator therapy with nifedipine reduces or delays the need for aortic-valve replacement in asymptomatic patients with severe aortic regurgitation and normal left ventricular systolic function. (N Engl J Med 1994;331:689-94.)

The role of long-term vasodilator therapy in the care of asymptomatic patients with severe aortic regurgitation is of considerable interest. Aortic regurgitation results in an increase in left ventricular volume and thus in afterload; the left ventricle adapts by increasing left ventricular mass.1 In patients with aortic regurgitation, vasodilators produce arteriolar vasodilatation, thereby increasing forward flow and reducing the amount of regurgitation,2 which results in a short-term improvement in hemodynamics and left ventricular function.3,4 In one symptomatic patient, hydralazine therapy for 14 months produced beneficial effects in terms of left ventricular function and symptoms,5 but this finding was not confirmed in a larger number of patients.6

Nevertheless, the possibility remained that the early administration of a vasodilator — that is, its administration when patients were asymptomatic and when left ventricular systolic pump function was also normal — might have a beneficial effect on the natural history of the disorder and on the need for valve surgery. In two trials — one of hydralazine given for two years7 and one of nifedipine given for one year8 — in patients with aortic regurgitation, these agents were shown to have a beneficial effect. Nifedipine was superior to hydralazine because the reduction in left ventricular volume at 12 months was greater with nifedipine, as was the increase in the ejection fraction, and there was a reduction in left ventricular mass; moreover, the side-effect profile of nifedipine was more favorable than that of hydralazine, and almost all the patients completed the trial.9 The next step was to evaluate whether these beneficial effects resulted in a reduction or delay in the need for valve surgery.

We therefore performed a long-term randomized trial of nifedipine in asymptomatic patients with chronic, severe aortic regurgitation and normal left ventricular systolic function. Our goal was to determine whether this therapy delayed or reduced the need for aortic-valve replacement.

Methods

We evaluated consecutive asymptomatic patients with isolated, chronic, severe aortic regurgitation and normal left ventricular systolic function who were seen at the University of Padua, Italy. Aortic regurgitation was quantitated in all patients by mapping of the regurgitant jet into the left ventricle by Doppler color-flow img-
ing. The severity of the regurgitation was graded with use of the ratio of the height of the jet to that of the left ventricular 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 greater than 45 percent were categorized as indicating grade 3+ aortic regurgitation, and those greater than 65 percent as grade 4+.10

Patients with any of the following characteristics were excluded: recent development or worsening of aortic regurgitation (within the preceding six months), diastolic blood pressure above 90 mm Hg, a history of coronary artery disease, mixed aortic stenosis and regurgitation (valve gradients >=20 mm Hg), evidence of additional valvular or congenital heart disease on echocardiographic or Doppler study, absence of a high-quality echocardiographic study of the left ventricle, and an abnormal left ventricular ejection fraction (<50 percent). The initial studies included a complete clinical evaluation (history, physical examination, 12-lead electrocardiogram, and chest roentgenogram in the posteroanterior and lateral projections) and a complete echocardiographic study.

On completion of the base-line studies, 143 patients were considered eligible for the study; 74 patients were randomly assigned to treatment with digoxin (0.25 mg daily) and 69 to treatment with nifedipine (20 mg twice daily). The characteristics of the 143 patients enrolled in the trial are listed in Table 1. The cause of aortic regurgitation was rheumatic in 87 of the 143 patients (61 percent) and nonrheumatic in 56 (39 percent). The nonrheumatic causes were aortic-valve prolapse in 24 of the 56 (43 percent) and a bicuspid aortic valve in 32 (57 percent). The complete clinical evaluation and echocardiographic studies were repeated and compliance with the drug regimen was assessed every six months. If a substantial increase in the left ventricular end-diastolic volume index or a decrease in the left ventricular ejection fraction was found, the echocardiographic study was repeated one month later. The use of angiotensin-converting–enzyme inhibitors was not allowed in any patient.

Echocardiographic Analysis

Two-dimensional echocardiograms were recorded with a Hewlett-Packard phased-array ultrasonoscope and a 2.5-MHz or 3.5-MHz transducer. Left ventricular endocardial and epipapillary echocardiograms in apical four-chamber and parasternal short-axis views in at least three to five cardiac cycles were digitized at end-diastole (the peak of the R wave) and at end-systole (the time when the cavity area was smallest). Each echocardiographic study was read by two independent observers who did not know the patient's identity or treatment assignment or the order of the studies. If these readings differed by 10 ml or more for left ventricular volume and 10 g or more for left ventricular mass, the echocardiographic data were analyzed by a third observer. Agreement was achieved by consensus. In our laboratory, the degree of interobserver and intraobserver correlation for left ventricular area (r = 0.98 and r = 0.97, respectively) and for left ventricular length (r = 0.98 and r = 0.96, respectively) was reasonable.8

Left ventricular volumes were calculated by an ellipsoid biplane area–length method11; the ejection fraction was calculated as (EDV - ESV)/EDV, where EDV is the left ventricular end-diastolic volume and ESV the end-systolic volume. Left ventricular myocardial mass was calculated by multiplying the myocardial volume by the specific weight of myocardial muscle (1.05 g per milliliter).12

At our institution, the results of cardiac catheterization and echocardiographic findings could be compared for 82 patients with aortic regurgitation who over the years had undergone both procedures within a short period of time. The mean (± SD) cardiac-catheterization and echocardiographic values for the left ventricular end-diastolic volume index were 144±26 ml per square meter and 136±27 ml per square meter, respectively (P not significant), and those for the left ventricular ejection fraction were 56±11.1 percent and 54±9.2 percent, respectively (P not significant).

In the comparison of echocardiographic with angiographic values, the left ventricular end-diastolic volume index, the regression equation was Y = 0.899X + 6.49, the standard error was 13.39, the correlation coefficient (r) was 0.88, and the P value was <0.01. In the comparison of echocardiographic with angiographic values for the left ventricular ejection fraction, the regression equation was Y = 0.70X + 16.4 (SE = 5.7; r = 0.84; P <0.01).

In patients who underwent valve replacement, the echocardiographic study was repeated at the time of valve replacement and two to three months thereafter. There was one perioperative death; in this patient, the echocardiographic evaluation had been performed in the first week after valve replacement.

Criteria for Aortic-Valve Replacement

Aortic-valve replacement was recommended for patients who met any of the following predetermined criteria: appearance of left ventricular systolic dysfunction, defined as a left ventricular ejection fraction of less than 50 percent that was confirmed by an echocardiographic study one month later; a clinically important deterioration in the patient's condition (subjectively determined), defined as an increase to New York Heart Association functional class II or higher, the development of angina, or both; and progressive left ventricular dilatation, defined as an increase of 15 percent or more in the left ventricular end-diastolic volume index that was confirmed by an echocardiographic study one month later.

Statistical Analysis

All data are expressed as means ± 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 paired t-tests. The probability of valve replacement during follow-up was calculated by the Kaplan–Meier method. A P value <0.05 by the two-tailed test was considered to indicate statistical significance.

RESULTS

Base-Line Comparison

The clinical characteristics of the patients and the values for left ventricular size and function obtained from the base-line echocardiogram were not significantly different in the two groups (Table 1). All the patients had left ventricular end-diastolic volume indexes greater than the mean value ±1.5 SD for normal subjects in our laboratory. The ejection fraction was normal (>50 percent) in all patients; the lowest ejection fraction value was 56 percent. In our laboratory, the mean values and 95 percent confidence intervals for these variables in normal subjects are as follows:
left ventricular end-diastolic volume index, 64 ml per square meter (54 to 74); left ventricular end-systolic volume index, 29 ml per square meter (24 to 34); and ejection fraction, 58 percent (53 to 63).8

Follow-up and Progression to Aortic-Valve Replacement

Four patients who had been randomly assigned to receive nifedipine and four patients assigned to receive digoxin were excluded from the analysis because they did not return for the scheduled follow-up visits. There was one perioperative death in the digoxin group. The remaining patients completed the six-year follow-up evaluation.

The rate of progression to aortic-valve replacement was significantly lower in the nifedipine group at all times after the first-year follow-up evaluation (Fig. 1). There were no valve replacements in the first two years in the nifedipine group. By actuarial analysis, at the end of the six years of follow-up, a mean (±SD) of 34±6 percent of the patients randomly assigned to the digoxin group and 15±3 percent of those assigned to the nifedipine group had undergone valve replacement (P<0.001). All these patients underwent cardiac catheterization and angiography before surgery; none had coronary artery disease that required coronary bypass surgery. All patients who met the predetermined criteria for surgery underwent valve replacement.

Table 2 shows the criteria for surgery and the baseline, preoperative, and postoperative values, determined echocardiographically, for the left ventricular end-diastolic volume index, end-systolic volume index, and ejection fraction.

Table 2. Left Ventricular Volume and Ejection Fraction in Patients Who Underwent Aortic-Valve Replacement, According to Treatment Group.*

<table>
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<tr>
<th>PATIENT NO.</th>
<th>EDVI BY ECHOCARDIOGRAPHY</th>
<th>ESVI BY ECHOCARDIOGRAPHY</th>
<th>EJECTION FRACTION</th>
<th>CRITERIA FOR SURGERY†</th>
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<td>POSTOPERATIVE</td>
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<td>percent</td>
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<td>116±12</td>
<td>147±17</td>
<td>89±24</td>
<td>43±6</td>
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*EDVI denotes left ventricular end-diastolic volume index; ESVI left ventricular end-systolic volume index; LVSD left ventricular systolic dysfunction (ejection fraction <50 percent); and NYHA II New York Heart Association functional class II or higher, angina, or both.

†All patients had an increase of 15 percent or more (range, 15 to 40 percent) in the left ventricular end-diastolic volume index, in addition to the criteria listed.
dex, and ejection fraction in the patients who underwent aortic-valve replacement. The table also shows the left ventricular ejection fraction determined angiographically in each patient before surgery. Aortic-valve replacement was performed in 20 patients in the digoxin group; 1 patient (5 percent) died during the perioperative period (10 days after surgery [Patient 20]). Six patients in the nifedipine group underwent aortic-valve replacement; there were no perioperative deaths. Total perioperative mortality among the patients who underwent valve replacement was 4 percent (1 of 26). No additional deaths occurred during follow-up.

Of the 20 patients in the digoxin group who underwent aortic-valve replacement, 15 (75 percent) did so because they had left ventricular ejection fractions below 50 percent, 2 (10 percent) because of an abnormal left ventricular ejection fraction and the development of symptoms, and 3 (15 percent) because symptoms developed in spite of their having a normal left ventricular ejection fraction. In the nifedipine group, all six patients who underwent aortic-valve replacement did so because of a persistently abnormal left ventricular ejection fraction despite the absence of clinical symptoms. In the patients with left ventricular dysfunction, the ejection fraction had fallen by more than 10 percentage points, and the abnormal value (<50 percent) was confirmed by preoperative angiographic study. The left ventricular end-diastolic volume index increased significantly (by 15 percent or more; range, 15 to 40 percent) in all the study patients in whom the ejection fraction had become abnormal or who had become symptomatic and subsequently underwent aortic-valve replacement.

Table 3 shows the left ventricular end-diastolic volume, end-systolic volume, ejection fraction, and mass in the digoxin and nifedipine groups both before randomization and at the end of the study (or at the time of valve replacement). As compared with those in the digoxin group, the patients in the nifedipine group had lower left ventricular end-diastolic and end-systolic volume indexes and mass and higher ejection fractions; this was the case because the patients in the nifedipine group had reductions in volume and mass, whereas those in the digoxin group had increases.

### Changes in Left Ventricular Size and Function after Aortic-Valve Replacement

After valve replacement, there was a decrease in the left ventricular end-diastolic volume index from 143±22 to 77±19 ml per square meter (P = 0.001) in the nifedipine group and from 147±16 to 89±24 ml per square meter (P = 0.001) in the digoxin group; the left ventricular end-systolic volume index also decreased, from 77±13 to 27±6 ml per square meter (P = 0.001) in the nifedipine group and from 77±14 to 39±17 ml per square meter (P = 0.001) in the digoxin group. The left ventricular ejection fraction increased in both groups: from 46±1 percent to 65±4 percent (P = 0.001) in the nifedipine group and from 48±6 percent to 58±9 percent (P = 0.001) in the digoxin group. After the procedure, the left ventricular end-diastolic volume index was not significantly lower, but the postoperative ejection fraction was significantly higher in the patients in the nifedipine group (65±4 percent vs. 58±8 percent, P = 0.04). In all the patients in the nifedipine group, the left ventricular ejection fraction returned to normal after valve replacement, whereas it remained abnormal in four patients (20 percent) treated with digoxin (Table 2). A total of 63 patients in the nifedipine group and 54 patients in the digoxin group who did not have valve replacement completed the six-year follow-up.

### Side Effects

A total of 42 percent of the 69 patients in the nifedipine group and 12 percent of the 74 patients in the digoxin group (P<0.001) had at least one new mild symptom during the first three months of the study. The most common side effects were tachycardia and headache in the nifedipine group and fatigue in the digoxin group. At the 12-month follow-up visit, side effects were still present in 6 percent of both groups. After six years of follow-up, 5 percent of patients in the nifedipine group had adverse effects, as had 6 percent in the digoxin group (P not significant). No patient in either study group refused to take the trial medication or to return for follow-up visits because of side effects.

### Discussion

This randomized trial demonstrates that in asymptomatic patients with chronic, severe aortic regurgitation and normal left ventricular ejection fractions, treatment with nifedipine, as compared with digoxin, results in a lower incidence of left ventricular dysfunction and of symptoms for up to six years and thus reduces the need for aortic-valve replacement (rate of
valve replacement, 34±6 percent vs. 15±3 percent at six years; P<0.001). Left ventricular dysfunction that occurred during nifedipine therapy was uniformly reversible if treated promptly with surgery.

The life-table event curve in the digoxin group in our study is similar to that reported for asymptomatic patients receiving no medical therapy.13,14 Routine therapy with digoxin has been recommended for all asymptomatic patients with severe aortic regurgitation15 on the basis of data from studies of animals; however, its efficacy in patients with this condition has not been documented. In a one-month trial in asymptomatic patients, digoxin increased the ejection fraction both at rest and during exercise.16 Because of its many actions,17 including those on the myocardium, digoxin might be expected to have the beneficial effect of reducing the incidence or delaying the onset of left ventricular dysfunction or symptoms. Thus, we chose to test nifedipine against another potentially useful medication rather than against a placebo.

Nifedipine, administered in a previous randomized trial for one year,8 was found to reduce systolic and diastolic blood pressure and to produce an important reduction in left ventricular volume and mass and a large increase in the ejection fraction. Therefore, the hypothesis on which our study was based was that these changes would result in a reduction or delay in the need for valve replacement. In our trial, nifedipine had similar beneficial effects on left ventricular function during up to six years of follow-up, and no patient in the nifedipine group needed valve replacement for the first two years. Moreover, the indications for valve replacement were defined before the trial, and the hemodynamic criterion for valve replacement was an objective one (left ventricular ejection fraction <50 percent); this was the indication for aortic-valve replacement in 85 percent of the digoxin-treated patients and in all the nifedipine-treated patients who underwent the procedure. Previously, it had been shown that patients with chronic, severe aortic regurgitation could have normal left ventricular ejection fractions in spite of having symptoms.18 Consequently, the development of symptoms with normal left ventricular function was also an indication for surgery.

As it increases in severity, aortic regurgitation produces an increasing volume load on the heart, which compensates by a progressive increase in left ventricular volume and hypertrophy, while left ventricular systolic function remains normal. Patients may remain asymptomatic for a long period of time. In those with severe regurgitation, the subsequent clinical course is usually characterized by the onset of left ventricular systolic dysfunction, symptoms, or both. With the development of left ventricular dysfunction, the outcome for patients treated medically is unsatisfactory, and with valve replacement it is also less satisfactory than when valve replacement is performed in the presence of normal left ventricular function19-22; this finding indicates the need for valve replacement before the development of irreversible myocardial damage. However, there is no reliable evidence that early valve replacement is of benefit in asymptomatic patients with normal left ventricular function.23-28

The chief indication for valve replacement in patients with severe aortic regurgitation is therefore the onset of symptoms, and in the absence of symptoms the chief indication is the development of left ventricular systolic dysfunction.23-27 Left ventricular systolic dysfunction is usually completely reversible if successful valve replacement is performed within 12 to 14 months of its onset,30 indicating that the probable initial cause of the dysfunction is afterload mismatch or reversible myocardial dysfunction rather than irreversible myocardial dysfunction.24,25,27 Thus, the main goals of secondary prevention in asymptomatic patients with severe, chronic aortic regurgitation and normal left ventricular systolic function are the reduction of left ventricular volume and mass and the preservation of left ventricular function. These effects translate into a substantial prolongation of the asymptomatic period and of normal ventricular function, thereby reducing or delaying the need for valve replacement.

One concern about the use of any agent that appears to preserve the ejection fraction is that it may mask progressive myocardial dysfunction; thus, when the ejection fraction falls or becomes abnormal, myocardial dysfunction may have progressed to such a degree that successful valve replacement may no longer improve the ejection fraction. This was not the case in our patients, since all those in the nifedipine group in whom the ejection fraction had become abnormal had normal values after surgery; 20 percent of patients in the digoxin group, however, continued to have abnormal values. This finding indicates that when patients are treated with nifedipine, left ventricular dysfunction is detectable by careful follow-up at the stage of afterload mismatch and before irreversible myocardial damage has occurred. It should be emphasized, however, that valve replacement has to be performed as soon as possible after the onset of ventricular dysfunction.30

In our study, the vasodilator calcium-channel-blocking agent nifedipine was effective in delaying the need for surgery and thus represents an advance in the management of severe, chronic aortic regurgitation.

References


