

ORIGINAL ARTICLE

Long-Term Vasodilator Therapy in Patients with Severe Aortic Regurgitation

Artur Evangelista, M.D., Pilar Tornos, M.D., Antonia Sambola, M.D.,
Gaietà Permanyer-Miralda, M.D., and Jordi Soler-Soler, M.D.

ABSTRACT

BACKGROUND

Vasodilator therapy can reduce the left ventricular volume and mass and improve left ventricular performance in patients with aortic regurgitation. Accordingly, it has been suggested that such therapy may reduce or delay the need for aortic-valve replacement.

METHODS

We randomly assigned 95 patients with asymptomatic severe aortic regurgitation and normal left ventricular function to receive open-label nifedipine (20 mg every 12 hours), open-label enalapril (20 mg per day), or no treatment (control group) to identify the possible beneficial effects of vasodilator therapy on left ventricular function and the need for aortic-valve replacement.

RESULTS

After a mean of seven years of follow-up, the rate of aortic-valve replacement was similar among the groups: 39 percent in the control group, 50 percent in the enalapril group, and 41 percent in the nifedipine group ($P=0.62$). In addition, there were no significant differences among the groups in aortic regurgitant volume, left ventricular size, left ventricular mass, mean wall stress, or ejection fraction. One year after valve replacement, the left ventricular end-diastolic diameter and end-systolic diameter had decreased to a similar degree among the patients who underwent surgery in each of the three groups, and all the patients had a normal ejection fraction.

CONCLUSIONS

Long-term vasodilator therapy with nifedipine or enalapril did not reduce or delay the need for aortic-valve replacement in patients with asymptomatic severe aortic regurgitation and normal left ventricular systolic function. Furthermore, such therapy did not reduce the aortic regurgitant volume, decrease the size of the left ventricle, or improve left ventricular function.

From the Servei de Cardiologia, Hospital Universitari Vall d'Hebron, Barcelona. Address reprint requests to Dr. Evangelista at the Servei de Cardiologia, Hospital Universitari Vall d'Hebron, P. Vall d'Hebron 119-129, 08035 Barcelona, Spain or at aevangel@vhebron.net.

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AORTIC REGURGITATION RESULTS IN left ventricular volume overload, leading to progressive dilatation of the chamber and eventual deterioration in left ventricular function.¹ Vasodilator therapy has been used to reduce the regurgitant volume,²⁻⁴ afterload,⁴⁻⁷ left ventricular volumes,^{2-5,8,9} and wall stress^{8,9} in an effort to preserve left ventricular function and reduce left ventricular mass.^{3,8-10}

Vasodilators have been considered useful for treating asymptomatic, chronic, severe aortic regurgitation since Scognamiglio et al.¹¹ reported that nifedipine reduced or delayed the need for valve surgery. One important limitation of their study was that digoxin was used in the control group. Studies of various doses of several vasodilators involving small numbers of patients and short-term follow-up have reported highly heterogeneous effects of these agents on echocardiographic variables.^{12,13} Despite limited evidence of their efficacy,¹⁴ vasodilators have been included as a class I recommendation in the guidelines of the American College of Cardiology–American Heart Association¹⁵ and the European Society of Cardiology¹⁶ for the treatment of asymptomatic, chronic, severe aortic regurgitation. Nonetheless, since a beneficial effect of vasodilators is far from certain, reassessment of their long-term effect in asymptomatic patients with this condition is warranted.¹⁷

The current long-term trial was designed in 1995, three years before the American guidelines were published.¹⁵ We attempted to ascertain whether either nifedipine or enalapril reduces or delays the need for valve surgery and whether these drugs exert any effect on the size and function of the left ventricle in patients with asymptomatic, chronic, severe aortic regurgitation.

METHODS

A randomized, open-label trial was designed to compare nifedipine, enalapril, and no treatment in patients with asymptomatic, chronic, severe aortic regurgitation. This study was conducted at the Cardiology Service, Hospital Universitari Vall d'Hebron, from January 1995 to January 2004. The protocol was approved by the ethics committee of the hospital. All patients provided written informed consent.

STUDY PATIENTS

All consecutive patients with asymptomatic, chronic, severe aortic regurgitation and normal left ven-

tricular function who were seen at our outpatient clinic between January 1995 and January 2000 were considered eligible for the study. These patients were part of a cohort followed since 1982 and were treated according to an established protocol.^{18,19} Aortic regurgitation was quantified as severe when the jet width exceeded 10 mm and the apical jet area exceeded 7 cm² on color Doppler ultrasonography or when the regurgitant fraction exceeded 60 percent with the use of previously described methods.²⁰ Patients with any of the following characteristics were excluded: a decreased left ventricular ejection fraction (less than 50 percent) during the preceding six months, other clinically significant associated valvular disease, associated valvular aortic stenosis (aortic mean gradient, more than 20 mm Hg), a diastolic blood pressure of more than 90 mm Hg, atrial fibrillation, or a history of coronary heart disease or other associated diseases that could affect the prognosis or functional class (including Marfan's syndrome or an ascending aortic aneurysm).

RANDOMIZATION

Eligible patients were randomly assigned to receive 20 mg of nifedipine every 12 hours, 20 mg of enalapril daily, or no treatment. The computer-generated randomization scheme used random permuted blocks of six patients to ensure balanced assignment of patients to each of the three groups. Randomization codes were provided by the hospital pharmacy only when patients gave their informed consent to participate.

STUDY PROTOCOL

Before treatment, each patient's clinical history was obtained; a physical examination, echocardiography, 12-lead electrocardiography, chest radiography, and radionuclide angiography while the patient was at rest were performed. Clinical and echocardiographic evaluations were conducted by the same two investigators the day before treatment, at one month and six months during the first year, and annually thereafter. Clinical follow-up included specific inquiry about the presence of symptoms and treatment compliance.

ECHOCARDIOGRAPHIC ANALYSIS

Echocardiographic studies were performed by a single echocardiographer who was unaware of the patients' treatment assignments and used a GE System V apparatus with a 2.5-MHz transducer. Left

ventricular end-diastolic diameter and end-systolic diameter were measured by M-mode echocardiography from two-dimensional echocardiography, according to the recommendations of the American Society of Echocardiography.²¹ The left ventricular end-diastolic volume and end-systolic volume were determined in the apical four-chamber view with the use of Simpson's rule. The ejection fraction was calculated with the use of the following equation: $\text{ejection fraction} = (\text{end-diastolic volume} - \text{end-systolic volume}) \div \text{end-diastolic volume}$. The left-ventricular-mass index and mean wall stress were calculated by two-dimensional M-mode echocardiography as previously described.^{22,23} Aortic regurgitation was quantified by the width of the regurgitant jet at the subvalvular aortic level from the parasternal long-axis view. Aortic regurgitant volume was determined from the difference between the stroke volumes of the left and right ventricular outflow tracts.

AORTIC-VALVE REPLACEMENT

The recommendation for aortic-valve replacement was strictly based on our preestablished protocol¹⁹: the presence of symptoms (angina or syncope or dyspnea, defined as an increase in the New York Heart Association functional class to class II or higher) or left ventricular dysfunction or enlargement (defined as an ejection fraction of less than 50 percent on echocardiography and confirmed by radionuclide ventriculography or as an end-systolic diameter of more than 50 mm on two consecutive echocardiograms). All candidates for surgery who had depressed left ventricular function or who were more than 50 years of age underwent coronary angiography. All patients who underwent aortic-valve replacement underwent a clinical and echocardiographic reassessment one year after surgery.

STATISTICAL ANALYSIS

Descriptive analysis was performed with the use of means and ranges for continuous variables and the absolute and relative frequencies of patients in each category for categorical variables. Analysis of variance was used to compare continuous variables among the three groups in the case of repeated measurements, and the chi-square test was used for categorical variables.

Kaplan–Meier actuarial analysis was used to determine the probability of valve replacement during follow-up, and the resulting survival curves were

compared with use of the Mantel–Cox log-rank test. A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with the use of SPSS software, version 11.0.

RESULTS

A total of 108 consecutive patients were considered eligible for participation. Seven of them declined to participate, and six were excluded owing to a poor-quality echocardiogram. Thus, 95 patients were enrolled: 32 were randomly assigned to receive nifedipine, 32 to receive enalapril, and 31 to receive no treatment.

BASELINE CHARACTERISTICS

The baseline clinical characteristics of the three groups were similar, and there were no significant differences among the groups with respect to echocardiographic variables (Table 1). At baseline, all patients had a left ventricular ejection fraction of at least 50 percent and a left ventricular end-systolic diameter of less than 50 mm.

FOLLOW-UP AND SURVIVAL

The mean (\pm SD) duration of follow-up was 7 ± 2 years (range, 0.6 to 8.8 years), with a median of 7.3 years. Only one patient did not complete the follow-up owing to a change of residence. One patient in each group died. One patient in the nifedipine group and one patient in the control group died of cardiac causes (sudden death and heart failure, respectively); both had an ejection fraction exceeding 50 percent and a left ventricular end-systolic diameter of 50 mm. Surgery had been indicated in both patients because of dyspnea but had been declined. A third patient (in the enalapril group) died from Parkinson's disease.

EFFECT OF VASODILATORS ON HEMODYNAMIC AND ECHOCARDIOGRAPHIC VARIABLES

Clinical and echocardiographic values at baseline were compared with those obtained at the final follow-up visit (for patients who did not undergo surgery) or at the last assessment preceding the evaluation that led to surgery (for those who underwent aortic-valve replacement) (Table 2). Systolic blood pressure, diastolic blood pressure, and heart rate did not change significantly in any of the three groups between baseline and follow-up. No signif-

icant differences were found in any echocardiographic variables at the end of follow-up among the groups.

AORTIC-VALVE REPLACEMENT

During follow-up, aortic-valve replacement was indicated in 41 patients: 12 (39 percent) in the control group, 16 (50 percent) in the enalapril group, and 13 (41 percent) in the nifedipine group (P=0.62). Aortic-valve replacement was indicated in 7 patients owing to the presence of symptoms (2 in the control group, 2 in the enalapril group, and 3 in the nifedipine group), in 15 patients because of asymptomatic left ventricular dysfunction or enlargement (4 in the control group, 6 in the enalapril group, and 5 in the nifedipine group), and in 19 patients on the basis of both criteria (6 in the control group, 8 in the enalapril group, and 5 in the nifedipine group). An ejection fraction of less than 50 percent was identified by echocardiography and confirmed by radionuclide angiography in 18 patients.

Patients underwent valve replacement after a mean of 4.2±2.8 years in the enalapril group, 5.4±2.3 years in the nifedipine group, and 5.4±1.9 years in the control group. These differences were not significant. The rate of progression leading to the need for surgery was similar in the three groups (Fig. 1). There were no significant differences among the groups with respect to the need for aortic-valve replacement during follow-up: the relative risk was 1.19 (95 percent confidence interval, 0.5 to 2.6) in the nifedipine group as compared with the control group, 1.77 (95 percent confidence interval, 0.8 to 3.7) in the enalapril group as compared with the control group, and 0.71 (95 percent confidence interval, 0.3 to 1.4) in the nifedipine group as compared with the enalapril group.

During the study, 10 patients dropped out. In view of the high dropout rate (11 percent), an on-treatment analysis was performed. The rate of progression leading to surgery was similar in the three groups (P=0.32). There were no significant differences among the groups regarding the need for aortic-valve replacement in the on-treatment analysis: the relative risk was 1.12 (95 percent confidence interval, 0.5 to 2.5) in the nifedipine group as compared with the control group, 1.69 (95 percent confidence interval, 0.8 to 3.4) in the enalapril group as compared with the control group, and 0.73 (95 percent confidence interval, 0.3 to 1.7) in the nifedipine group as compared with the enalapril group.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Control Group (N=31)	Enalapril Group (N=32)	Nifedipine Group (N=32)
Age (yr)	42±15	44±10	44±14
Sex (no. of patients)			
Male	21	28	25
Female	10	4	7
Blood pressure (mm Hg)			
Systolic	143±19	142±15	147±18
Diastolic	74±10	75±10	78±11
Heart rate (beats/min)	67±8	68±10	68±8
Left ventricular variables			
End-diastolic diameter (mm)	64±5	68±6	65±7
End-systolic diameter (mm)	44±5	45±5	44±5
Mass index (g/m ²) [†]	135±3	140±4	141±4
Mean wall stress (kdyn/cm ²)	310±47	308±40	310±61
End-diastolic volume (ml)	196±64	208±61	181±49
End-systolic volume (ml)	81±35	90±33	75±27
Ejection fraction (%)	60±6	58±6	59±7
Severity of aortic regurgitation			
Jet width (mm)	11±3	11±3	11±4
Regurgitant volume (ml)	82±36	89±43	81±33
Morphologic appearance of aortic valve (no. of patients)			
Normal	12	5	7
Bicuspid	10	16	14
Degenerative	6	7	10
Rheumatic	3	4	1

* Plus-minus values are means ±SD. There were no significant differences among the groups.

[†] The left-ventricular-mass index is the left ventricular mass divided by the body-surface area.

There was no operative mortality. One year after valve replacement, the left ventricular end-diastolic diameter and end-systolic diameter had decreased to a similar degree in each of the three groups, and the ejection fraction was normal in all the patients (Table 3).

SIDE EFFECTS

During the study period, 10 patients (11 percent) dropped out of their assigned treatment group owing to side effects: 3 (9 percent) dropped out of the enalapril group (2 because of cough and 1 because of hypotension), and the other 7 (22 percent) dropped out of the nifedipine group (because of

Table 2. Comparison of Baseline and Final Values.*

Study Group and Assessment	Systolic Blood Pressure mm Hg	Diastolic Blood Pressure mm Hg	Heart Rate beats/min	LVEDD mm	LVEDS mm	LVMl g/m ²	LVMWS kdyn/cm ²	LVEDVI ml/m ²	LVESVI ml/m ²	LVEF %	Jet Width mm	Regurgitant Volume ml
Control group												
Baseline	143±19	74±10	67±8	64±5	44±5	135±31	307±48	109±35	45±19	60±6	11±3	82±36
Final†	141±18	70±9	68±16	69±7	46±7	168±42	310±38	114±33	49±16	57±8	11±3	85±38
Change‡	-1±8	-4±13	1±13	3.9±5	2.6±5	33±40	3.0±10	15±29	8.5±18	-2.5±8	-0.4±3	3.3±18
Enalapril group												
Baseline	142±15	75±10	68±10	68±6	46±5	141±44	307±38	114±33	49±16	58±6	11±3	89±43
Final†	140±20	69±10	69±10	70±7	48±6	162±50	311±63	124±37	53±17	57±6	11±3	93±51
Change‡	-1±7	-4±13	1±10	2.2±4	2.0±4	21±6	4.0±25	8.2±30	2.6±15	-1.0±9	-0.2±3	4.5±24
Nifedipine group												
Baseline	147±18	78±11	68±8	65±7	44±5	139±44	311±61	94±27	40±14	59±7	11±4	81±33
Final†	141±20	77±11	69±8	68±6	46±6	151±37	310±61	104±36	46±18	58±7	11±4	81±35
Change‡	-6±4	-1±13	1±8	2.9±4	2.1±4	12±7	-1±0	9.8±3	8.2±15	-1.8±9	0.2±3	0.9±20

* Plus-minus values are means ±SD. LVEDD denotes left ventricular end-diastolic diameter, LVEDS left ventricular end-systolic diameter, LVMl left ventricular mass index (the left ventricular mass divided by the body-surface area), LVMWS left ventricular mean wall stress, LVEDVI left ventricular end-diastolic volume index, LVESVI left ventricular end-systolic volume index, and LVEF left ventricular ejection fraction.

† For patients who did not undergo aortic-valve replacement, the final evaluation is the last assessment obtained during follow-up. For patients who underwent surgery, the final evaluation is the last assessment preceding the evaluation that led to surgery.

‡ Changes are those between baseline and final values in each group. There were no significant differences among the groups in any of the changes.

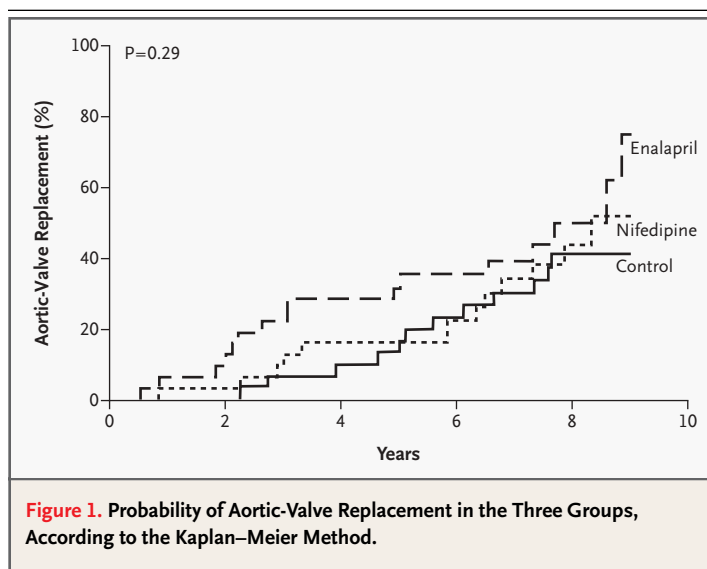
headache, flushing, edema, epigastric pain, or a combination thereof). These patients stopped taking enalapril at a mean of 5 ± 4 months and nifedipine at a mean of 2 ± 7 months but were followed and analyzed throughout the study in accordance with the established protocol.

DISCUSSION

In this randomized trial, vasodilator therapy with nifedipine or enalapril did not reduce or delay the need for aortic-valve replacement in patients with asymptomatic, chronic, severe aortic regurgitation and a normal left ventricular ejection fraction. Moreover, such treatment did not decrease the size of the left ventricle, improve left ventricular function, or reduce the severity of aortic regurgitation.

The clinical course of chronic aortic regurgitation is characterized by a prolonged phase of stability during which the left ventricle adapts to the volume overload, with increasing end-diastolic volume, compliance, and hypertrophy.^{13,19,24-27} It has been suggested that vasodilator therapy in the stable plateau phase of the disease delays decompensation of the left ventricle and thus postpones the need for surgery.^{11,28} Several studies that involved small numbers of patients and short-term follow-up have reported various beneficial effects of vasodilators on echocardiographic indicators of left ventricular function,^{3-7,10} but only one group has reported that long-term nifedipine therapy reduced left ventricular dimensions and increased the left ventricular ejection fraction.^{8,11} Recently, the same group suggested that the benefit of nifedipine treatment persisted after aortic-valve replacement.²⁹ A few studies^{3,5-7,9} have demonstrated an improvement in hemodynamic variables with vasodilator therapy, although this has not been a universal finding.³⁰ The study of long-term nifedipine therapy did not examine hemodynamic variables.¹¹

The mechanism of the possible benefit of vasodilator treatment remains a matter of controversy.³¹ Several studies have reported a reduction in aortic regurgitant volume with short-term therapy.^{5,32-34} Since regurgitant volume is determined by the diastolic aortoventricular pressure gradient, regurgitant orifice area, and diastolic filling time, the effect of vasodilators has been assumed to be mediated by a reduction in aortic pressure.^{9,13,35} Some studies have shown the effect of nifedipine on blood pressure to be related to pretreatment values (i.e., the higher the pressure, the greater the reduction



in blood pressure).³⁶ Other studies^{2,4,30} have found no significant decrease in blood pressure or change in heart rate with long-term vasodilator therapy.

In view of the available information, the need for clinical trials using hard outcome variables became evident. Only one previous clinical trial, by Scognamiglio et al.,¹¹ used clinical end points rather than surrogate variables alone, such as the function or size of the left ventricle, to assess the value of vasodilators. In that study, a mean of 34 ± 6 percent of the patients in the digoxin group required aortic-valve replacement at six years, as compared with 15 ± 3 percent of the patients in the nifedipine group. As compared with the digoxin group, the nifedipine group had reductions in left ventricular volume and mass. In contrast to these benefits, an earlier, smaller study suggested that stopping vasodilator therapy had no apparent adverse consequences on the size or function of the left ventricle and did not influence the rate of progression to valve replacement.³⁷

Furthermore, several limitations of the trial by Scognamiglio et al. have been noted. The lack of a placebo or no-treatment control group has been considered a major shortcoming, especially because the ejection fraction decreased and left ventricular volume and mass increased in the digoxin group, suggesting a possible deleterious effect of digitalis.^{38,39} In addition, the echocardiographic criteria for valve replacement may not have been optimal, given that 81 percent of the patients undergoing surgery did so because of an ejection fraction of less than 50 percent (assessed by two-dimen-

Table 3. Comparison of Left Ventricular Variables before and One Year after Surgery.*

Left Ventricular Variable	Control Group (N=11)	Enalapril Group (N=16)	Nifedipine Group (N=12)
End-diastolic diameter (mm)			
Preoperative	73±6†	75±5†	71±8†
Postoperative	51±4	54±4	53±5
End-systolic diameter (mm)			
Preoperative	51±3†	53±3†	51±3†
Postoperative	35±4	36±5	38±5
Ejection fraction (%)			
Preoperative	48±4‡	53±6§	51±5
Postoperative	56±6	61±8	56±6

* Plus-minus values are means ±SD. All P values are for the comparison of the mean preoperative values with the mean postoperative values.

† P<0.0001.

‡ P=0.006.

§ P=0.02.

sional echocardiography without harmonic imaging). By contrast, in a study by Bonow et al.,²⁴ only 17 percent of the patients who required surgery underwent surgery because of asymptomatic left ventricular dysfunction, whereas in our study, 37 percent required surgery for either left ventricular dysfunction or enlargement.

Our study has two main limitations. First, the clinician in charge of the patients was not blinded to the treatment prescribed. However, it is unlikely that knowledge of the treatment prescribed would have modified the decision to recommend aortic-valve replacement, since patients with aortic-valve disease have been systematically treated in our hospital since 1982 according to a strict protocol for recommending surgery.^{18,19} In fact, in only seven patients was surgery recommended owing to symp-

toms without left ventricular dysfunction or enlargement, and the indications were similarly distributed in each group. With regard to the echocardiographic findings, the echocardiographer was unaware of patients' treatment assignments and thus could not have given biased information. The second shortcoming of the study is that it had insufficient statistical power to definitively support the hypothesis that vasodilator therapy has no benefit in patients with severe aortic regurgitation. In any event, our trial failed to replicate the results of Scognamiglio et al.,¹¹ even though the patient populations were similar. Furthermore, we observed no beneficial trend in the clinical or echocardiographic variables in patients who completed vasodilator therapy. Both findings provide a basis to question whether vasodilator therapy should be given a class I recommendation for asymptomatic severe aortic regurgitation. Our results suggest that any role of vasodilators in potentially delaying the need for valve replacement must be small or limited to a small proportion of patients.

In conclusion, we found that vasodilator treatment with nifedipine or enalapril did not decrease or delay the need for valve replacement in patients with chronic aortic-valve regurgitation. Furthermore, such treatment did not decrease the size of the left ventricle or improve left ventricular function. These results, though not ruling out the possibility of a beneficial effect of vasodilators in some subgroups of patients, do at least cast some doubt as to their broad clinical effect in patients with asymptomatic, chronic, severe aortic regurgitation.

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