

# Usefulness of Vasodilator Therapy in Regurgitant Valvular Diseases

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Mitral and aortic valve regurgitation both lead to left ventricle volume overload, but have different pathophysiology. Preload is increased in mitral regurgitation whereas afterload is normal since part of the ejection flow goes to the left atrium; however, both pre- and afterload are increased in aortic regurgitation. When the regurgitations are chronic, the ventricle adapts by increasing the volumes and causing eccentric left ventricular hypertrophy. Nevertheless, when the adaptation mechanisms fail, in the long term left ventricular filling pressures increase and, finally, the ejection fraction decreases, leading to signs and symptoms of heart failure. In acute regurgitations these adaptation mechanisms may not be sufficiently rapid, and although the left ventricle responds with greater hypercontractility, the acute increase in preload can increase filling pressures and trigger pulmonary edema.

The regurgitant volume directly depends on the regurgitant orifice, the duration of regurgitation and the pressure gradient between the cavities where regurgitation occurs.<sup>1</sup> There are few studies on variations in the regurgitant orifice, but they seem to be associated with the presence or absence of structural valve disease and loading conditions. Although mitral regurgitation is more dynamic than aortic regurgitation, experimental studies have shown that the aortic regurgitant orifice area decreases during diastole and also depends on the loading conditions.<sup>2</sup>

Clearly, changes in the regurgitant orifice area are associated with the etiology of valvular regurgitation and the degree of structural changes. In aortic regurgitation secondary to valvular thickening or calcification, the

regurgitant orifice area is relatively constant. Nevertheless, when regurgitation is due to valvular prolapse or aortic root dilatation, the regurgitant orifice area can vary considerably, depending on the loading conditions. The duration of aortic regurgitation is always pandiastolic which means that bradycardia increases the regurgitant volume significantly.

In addition to the regurgitant orifice area (ROA) and the duration of regurgitation (T), which depends on heart rate, the other determinant of regurgitant volume (RV) is the diastolic pressure gradient between the aorta ( $AO_{PD}$ ) and left ventricle ( $LV_{PD}$ ).<sup>1</sup>

Although this could be a mechanism to reduce regurgitant volume, the benefit of decreasing the gradient is very slight since it should be reduced by the square root according to the following equation:  $RV = ROA \times C \times \sqrt{AO_{PD} - LV_{PD}} \times T$ . This would imply that a 25% reduction in diastolic pressure would only lead to a 13% reduction in regurgitant volume. Taking into account that in severe aortic regurgitation the aortic diastolic pressure is low, achieving greater reductions could be difficult and also dangerous regarding coronary perfusion.

In non-rheumatic mitral regurgitation the regurgitant orifice is frequently dynamic and depends on the size of the left ventricle. In patients with obstructive hypertrophic cardiomyopathy or mitral valve prolapse, reducing preload via vasodilators can increase the severity of mitral regurgitation. On the other hand, in patients where regurgitation is secondary to severe ventricular dilatation, due to changes in subvalvular apparatus functional anatomy or to papillary muscle dysfunction associated with ischemic heart disease or dilated cardiomyopathy, reducing preload reduces the severity of mitral regurgitation.<sup>3</sup>

## Effect of Vasodilators

Vasodilators have been considered to prolong the stable phase in which valvular regurgitation does not lead to ventricular dysfunction, thus delaying or avoiding surgery. The mechanisms of the possible benefit of vasodilators are controversial. Hypothetically, they could

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**TABLE 1. Effects of Vasodilator Therapy on Severe Aortic Regurgitation\***

	Vasodilator	Duration	No. Treated Patients	No. Patients Placebo	S/D BP	D/S LV Volume	EF	Regurgitant Volume	LV Mass
Greenberg et al <sup>4</sup>	Hydralazine	24 months	45	35	0/0	↓/↓	↑	↓	—
Scognamiglio et al <sup>11</sup>	Nifedipine	12 months	38	34	↓/0	↓/↓	↑	—	↓
Lin et al <sup>6</sup>	Hydralazine	12 months	38	—	↓/↓	0/0	0	—	0
	Enalapril	12 months	38	—	↓/↓	↓/↓	0	—	↓
Schön et al <sup>8</sup>	Quinapril	12 months	12	—	↓/0	↓/↓	0	↓	↓
Scognamiglio et al <sup>14</sup>	Nifedipine	6 years	69	74	—/—	↓/↓	↑	—	↓
Sondergaard et al <sup>9</sup>	Felodipine	12 weeks	8	8	0/0	0/0	0	↓	0
Evangelista et al <sup>13</sup>	Nifedipine	7 years	32	31	0/0	0/0	0	0	0
	Enalapril	7 years	32	31	0/0	0/0	0	0	0

\*D indicates diastole; EF, ejection fraction; BP, systemic blood pressure; S, systolic; LV, left ventricle; ↓, reduction; ↑, increase; 0, no change; —, no data.

achieve their effects in three ways: *a*) by reducing regurgitant volume; *b*) by reducing the ventricular loading conditions with improvements in ventricular remodelling; and *c*) by reducing ventricular filling pressures. Some studies have shown that vasodilators reduce preload and afterload, maintain ejection volume, and reduce regurgitant volume in the short term.<sup>4,5</sup> Others consider that there is no reduction in regurgitant volume, but by reducing the ventricular loading conditions there is reduced wall stress thus promoting ventricular remodelling with reductions in volumes and hypertrophy.<sup>6-8</sup> The most consistent hemodynamic effect on left ventricular volume overload is, without doubt, the reduction in ventricular filling pressures.<sup>3</sup> Nevertheless, when left ventricular filling pressures are high due to valvular regurgitations surgical treatment should be considered.

### Aortic Regurgitation

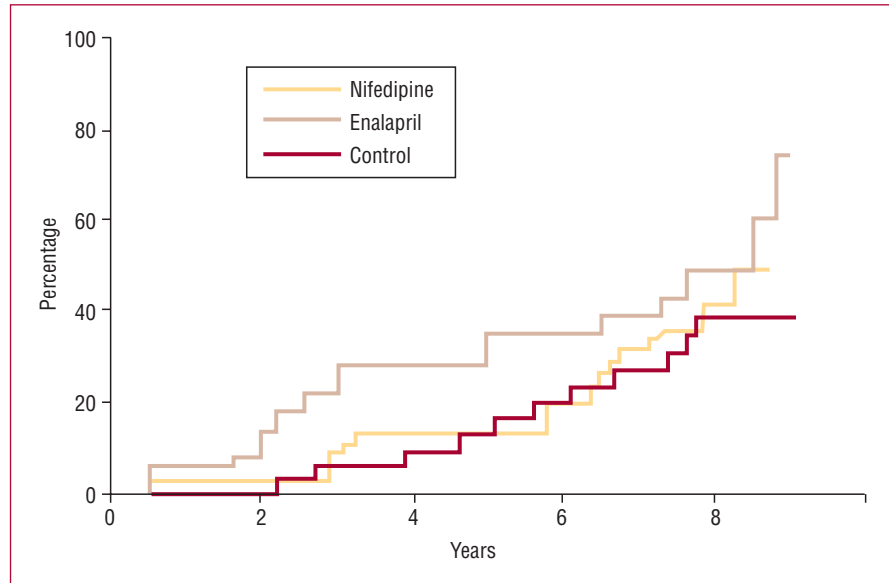
Even though the beneficial effect of long-term vasodilator therapy is well-established, there were less than 300 patients in the series described in the literature.<sup>1</sup> Most of the published series include low numbers of patients and have relatively short follow-up. On the other hand, different vasodilators have been used and sometimes yield contradictory results.<sup>5-14</sup> The drugs most frequently used are hydralazine,<sup>4,6</sup> nifedipine<sup>7,11</sup> and other dihydropyridines,<sup>9</sup> and enalapril.<sup>6</sup> The most consistent results in these studies have been reductions in ventricular end-diastolic and end-systolic volumes. On the other hand, there is greater heterogeneity regarding the increase in ejection fraction and the reduction in ventricular mass (Table 1). A striking aspect is that, in most of these studies, the reduction in ventricular volumes recorded via two-dimensional echocardiography is reported, but not the diameters measured in M-mode. Intraobserver variability regarding two-dimensional echocardiography measurements without harmonic imaging was relatively high.

Some authors<sup>12</sup> have assumed that the vasodilator effect is mediated by reducing blood pressure and consider that

if vasodilator therapy is effective there should be a reduction in systolic blood pressure. If this was the case, rather than giving a fixed dose of vasodilator, the dose should be increased until the hypotensive effect is obtained. However, the results demonstrate that the reductions in systolic blood pressure are related to pre-treatment baseline pressure values.<sup>1</sup> Thus, there can be little reduction in blood pressure when this is normal at baseline.<sup>4,8-11</sup> In this sense, the study by Lin et al<sup>6</sup> clearly shows the greatest reduction in blood pressure, but 47% of the patients included in their series had systolic blood pressure values higher than 180 mm Hg. In our study,<sup>13</sup> hemodynamic response to vasodilator therapy in the long term did not show a reduction in blood pressure, although patients with systemic hypertension were excluded from the study.

Only 2 randomized studies have analyzed the beneficial effect of vasodilators using clinical endpoints and not surrogate variables.<sup>13,14</sup> In the study by Scognamiglio et al<sup>14</sup> the need for surgical treatment was 34 (6%) in the digoxin group compared to only 15 (3%) in the nifedipine group at 6-year follow-up. Compared to the digoxin group, the nifedipine group had reductions in ventricular volumes and increased left ventricular ejection fraction. Nevertheless, this study suffered major shortcomings.

The lack of a control group means that a deleterious effect of digoxin cannot be ruled out. In pharmacodynamic studies,<sup>15</sup> a 10% reduction in heart rate has been verified in healthy subjects in sinus rhythm, which could lead to an increase in regurgitant volume. With the aim of confirming the beneficial effect of vasodilators while avoiding the shortcomings of using digoxin as placebo, our group<sup>13</sup> randomized 95 asymptomatic patients with severe aortic regurgitation and preserved ventricular function to treatment with nifedipine (20 mg/12 h), enalapril (20 mg/day), or no treatment (control group). At 7-year follow-up, the need for aortic valve replacement was similar in the 3 groups: 35% in the control group, 50% in the enalapril group, and 38% in the nifedipine group (Figure). Furthermore, the 3 groups showed a similar trend in the progression



**Figure.** Probability of needing surgical treatment in the 3 medical treatment groups analyzed via the Kaplan-Meier method.

of ventricular volumes and reductions in ejection fraction, although the scores were strongly scattered. One year after surgery, ejection fraction and ventricular diameters were normal in all patients in the three groups. One of the study's possible drawbacks is that 22% of the patients treated with nifedipine had to stop treatment due to side effects such as symptoms of peripheral vasodilatation or edema. There were no significant differences between the groups of patients who complied with the assigned treatment to the end of the study. Although these results do not deny a beneficial effect of vasodilator therapy, they bring into question their usefulness in delaying or avoiding valve replacement surgery. Given the lack of better evidence, this study implies modifying the class I to IIb recommendations in the clinical practice guidelines.<sup>16</sup>

In a recent study,<sup>17</sup> the Scognamiglio group suggested that reductions in afterload are associated with a long-term benefit in ventricular function that persists after surgery, including in patients with depressed ventricular function. In our opinion, it is difficult to accept that the improvement due to nifedipine persists for years after stopping treatment.

### Mitral Regurgitation

The aim of vasodilator therapy for mitral regurgitation is to reduce regurgitant volume, increase ejection volume, and reduce pulmonary congestion. It is well known that vasodilators reduce peripheral resistance and end-diastolic pressures in the short term, in both mitral and aortic regurgitation. However, in mitral regurgitation the ejection volume increases and ejection fraction does not change, whereas in aortic regurgitation the ejection fraction increases but the ejection volume does not change. Initial studies<sup>18</sup> showed that treatment with nitroprusside reduced

functional mitral regurgitation by reducing the left ventricular volume. This beneficial effect was stronger in functional mitral regurgitation secondary to ischemic heart disease or dilated cardiomyopathy.<sup>19</sup> These results seem reasonable since the reduction in afterload leads to less resistance to blood ejected into the aorta, which promotes a reduction in left ventricular volume and mitral annulus size and, thus, in regurgitant orifice area and regurgitant volume.

Although angiotensin-converting enzyme inhibitors are clearly effective in the long-term treatment of heart failure,<sup>20</sup> their long-term effect on mitral regurgitation is less clearly defined. A study conducted by our group<sup>21</sup> showed that in patients with dilated/ischemic cardiomyopathy, captopril 75-150 mg/day led to greater benefit in reduced ventricular volume, increased ejection volume and exercise tolerance in patients with significant mitral regurgitation than in those with none. Other studies<sup>22</sup> have shown that vasodilator therapy is more beneficial in patients with severe mitral regurgitation with ventricular dilatation and depressed systolic function.

Up to now, there has been little information on the benefit of vasodilators in asymptomatic primary mitral regurgitation<sup>23-26</sup> (Table 2). Just one group has reported preliminary results on the benefit per year of treatment with candesartan or ramipril in reducing regurgitant volume and left atrial volume compared to placebo.<sup>27</sup> Nevertheless, no vasodilator therapy has proven beneficial in delaying the appearance of symptoms or ventricular dysfunction. One aspect to consider is that reductions in afterload should be less effective in mitral regurgitation associated with normal afterload than in aortic regurgitation. On the other hand, recent experimental studies<sup>28</sup> suggest that despite apparent improvements in ejection fraction, ACE inhibitors, and angiotensin II

**TABLE 2. Effect of Vasodilator Therapy on Asymptomatic Severe Mitral Regurgitation\***

	Vasodilator	Duration	No. Treated Patients	No. Patients Placebo	S/D BP	D/S LV Volume	EF	Regurgitant Volume	LV Mass
Wisnibaugh et al <sup>10</sup>	Captopril	6 months	12	16	0/0	-/-	0	-	-
Schön et al <sup>23</sup>	Quinapril	12 months	12	-	↓/↓	↓/↓	0	↓	-
Tischler et al <sup>25</sup>	Enalapril	12 months	38	-	↓/↓	0/0	↑	↓	↓
Dujardin et al <sup>26</sup>	Losartan	1 month	24	-	↓/↓	-/-	0	↓	↓

\*D indicates diastole; EF, ejection fraction; BP, systemic blood pressure; S, systolic; LV, left ventricle; ↓, reduction; ↑, increase; 0, no change; -, no data.

receptor blockers could not improve or even reduce left ventricular contractility in severe mitral regurgitation. Thus, in severe mitral regurgitation, the beneficial effect of vasodilators is foreseeable only in cases of left ventricular dysfunction.

## Conclusions

In left ventricular volume overload, vasodilators have a beneficial effect on systolic dysfunction, when there is an increase in ventricular filling pressures or when they are accompanied by systemic hypertension. There is no evidence for using these agents in asymptomatic and normotensive patients with severe valvular regurgitation and normal ventricular function. Nevertheless, the disparity in the published results suggests that there may be subgroups of patients who could benefit from this therapy. More studies are needed that analyze the beneficial effect of this therapy on subgroups of patients with more homogeneous characteristics, taking into consideration not only the severity of the valvular heart disease, but its etiology, the structural valve disease, blood pressure values and arterial distensibility.

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