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REVIEW ARTICLES

# Vasoactive Drugs in Chronic Regurgitant Lesions of the Mitral and Aortic Valves

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**This review examines the results of vasodilator therapy in patients with chronic regurgitant lesions of the aortic and mitral valves. The analysis includes those studies which provide data on hemodynamic measurements, left ventricular systolic function, ventricular volumes and regurgitant flow. In patients with chronic aortic or mitral regurgitation, the short-term administration of nitroprusside, hydralazine, nifedipine or an angiotensin-converting enzyme (ACE) inhibitor produces salutary hemodynamic effects. The major difference in the response to combined preload and afterload reduction (i.e., nitroprusside) in patients with aortic versus mitral regurgitation was that forward stroke volume generally increased and ejection fraction remained unchanged in mitral regurgitation, whereas ejection fraction generally increased and forward stroke volume remained unchanged in aortic regurgitation. These observations suggest that a reciprocal relation between regurgitant and forward flow characterizes the response to preload and afterload reduction in mitral regurgitation (through a preload-dependent dynamic regurgitant orifice), whereas correction of afterload mismatch dominates the response in aortic regurgitation. In studies of long-term vasodilator therapy in patients with chronic aortic regurgitation, a reduction in left ventricular volumes and regurgitant fraction, with or without an increase in ejection fraction, has been observed during treatment with hydralazine, nifedipine and ACE inhibitors. Patients with the largest, sickest hearts generally benefit the most from treatment with vasoactive drugs. Nonetheless, favorable ventricular remodeling has been reported in asymptomatic patients, and long-term nifedipine use has delayed the need for operation in asymptomatic patients with chronic aortic regurgitation. For patients with chronic mitral regurgitation, definition of the etiology of the lesion is a prerequisite for choosing appropriate therapy. Excluding patients with obstructive hypertrophic cardiomyopathy and mitral valve prolapse, and some with fixed-orifice (i.e., rheumatic) mitral regurgitation, the signal importance of preload reduction suggests that the preferred long-term therapy for symptomatic chronic mitral regurgitation is an ACE inhibitor. There are no long-term studies that support the use of vasodilator therapy in asymptomatic patients with chronic mitral regurgitation.**

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The time-honored medical therapy for chronic valvular regurgitation has been to treat the major consequences of volume overload, namely, systolic dysfunction of the ventricle and congestive heart failure. For the most part, this therapy has been the same as that used for most patients with other causes of heart failure. During the past two decades, however, a more complete understanding of the specific ventricular loading conditions in aortic and mitral regurgitation and familiarity with a spectrum of vasoactive drugs have combined to provide the potential for altering hemodynamic abnormalities in regurgitant valve disease. In this manner, it becomes possible to offer symptomatic relief and potentially delay the development of ventricular dysfunction and heart failure. Such strategies are targeted to reduce the volume of regurgitant flow and to achieve favorable remodeling of the ventricle. Implicit in the latter is the goal of optimizing the loading conditions of the volume overloaded ventricle. To provide the rationale for effective medical therapy in patients with valvular regurgitation, it is appropriate to analyze the hemodynamic determinants of regurgitant flow and to examine the mechanisms by which ventricular remodeling may prove advantageous to the volume-overloaded heart.

## Determinants of Regurgitant Flow

The determinants of valvular regurgitation are best understood by examination of the variables of the orifice equation. This equation is based on the Torricelli principle, which states that turbulent flow through an orifice varies as the square root of the pressure gradient across that orifice (1). By solving the orifice equation for the regurgitant volume, one can directly examine the hydraulic determinants of regurgitant flow. This principle can be applied either to the aortic or mitral valve.

### *Aortic Regurgitation*

The hydraulic determinants of aortic regurgitant volume are described by the following equation:

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**Abbreviations and Acronyms**

ACE = angiotensin-converting enzyme
LV = left ventricular

$$ARV = AROA \times C \times \sqrt{AOdm - LVdm} \times T_d,$$

where ARV = aortic regurgitant volume; AROA = aortic regurgitant orifice area; C = constant; AOdm = aortic diastolic mean pressure; LVdm = LV diastolic mean pressure; and $T_d$ = time or duration of diastole. In primary disease of the aortic valve, it has been assumed that regurgitant orifice area is constant, although this assumption may not be valid in some patients with disease of the aortic root. The duration of diastole is primarily a function of heart rate, and thus, as pointed out by Corrigan (2) 160 years ago, bradycardia will increase aortic regurgitant flow. Several investigators (3–6) have examined the effect of increasing heart rate as a means of reducing regurgitant flow. In these studies, increasing heart rate was uniformly associated with a decrease in regurgitant volume/beat, but in most instances regurgitant volume/minute remained unchanged. Of note, however, left ventricular (LV) end-diastolic pressure and volume decreased in response to pacing-induced tachycardia (5,6). Despite these observations, Firth et al. (6), conclude that "pacing induced tachycardia offers little, if any, potential benefit in the therapy of patients with aortic regurgitation." Thus, although long-term manipulations of heart rate have relatively little potential for significant benefit, clinicians should be alert to the danger of profound bradycardia in this condition.

In addition to the regurgitant orifice area and heart rate, the other major determinant of regurgitant volume is the transvalvular pressure gradient throughout diastole. Although this variable provides a rationale for treating diastolic hypertension in aortic regurgitation, it should be recognized that most vasodilator therapies reduce the aortic diastolic pressure *and* LV diastolic pressure. As a result, there may be little change in the transvalvular pressure gradient. Moreover, the benefit of any reduction in pressure gradient is reduced by the square root sign in the orifice equation. Thus, a 25% reduction in the pressure gradient would be expected to reduce regurgitant volume by only 13%. Recently, it has been suggested (7) that in patients with aortic stenosis, valve resistance, calculated as the simple quotient of pressure gradient and flow per unit time, may more accurately reflect the hydraulics of a narrowed aortic valve than does the Torricelli principle. Cannon et al. (8), have demonstrated that such is the case in subjects with noncritical stenosis and small transaortic gradients, but whether this principle applies to the dynamics of aortic regurgitant flow remains to be shown.

The major determinants of aortic regurgitant volume are the regurgitant orifice area, the duration of diastole and the diastolic transvalvular pressure gradient. It should be noted that neither LV ejection fraction nor systemic vascular resistance are direct determinants of regurgitant volume. Thus, the notion that a greater forward stroke volume or a decrease in the regurgitant fraction means less regurgitant flow is not valid unless one of the variables of the orifice equation is altered.

Consideration of these hydraulic principles places substantial constraints on the potential for achieving a meaningful reduction in regurgitant volume in chronic aortic regurgitation. If, indeed, the aortic valve lesion is fixed or near fixed, nonsurgical methods have little potential to reduce the regurgitant orifice size. Likewise, in the absence of diastolic hypertension, a steady state reduction in aortic diastolic pressure sufficient to reduce regurgitant volume significantly will be difficult to accomplish with vasodilator therapy, particularly because aortic regurgitation itself is generally associated with a low aortic diastolic pressure, and a further reduction may compromise the high requirements for myocardial blood flow of a hypertrophied left ventricle. These constraints suggest that if medical therapy is to be effective in the management of chronic aortic regurgitation, it is not likely to do so through the mechanism of a reduced regurgitant volume alone.

### *Mitral Regurgitation*

The hydraulic determinants of mitral regurgitant volume are described by the following equation:

$$MRV = MROA \times C \times \sqrt{LVsm - LAsm} \times T_s,$$

where MRV = mitral regurgitant volume; MROA = mitral regurgitant orifice area; C = constant; LVsm = LV systolic mean pressure; LAsm = left atrial systolic mean pressure; and $T_s$ = time or duration of systole. Unlike chronic aortic regurgitation, the regurgitant orifice area in some forms of mitral regurgitation is dynamic and critically dependent on ventricular dimensions. This is of great importance in choosing appropriate therapy, and it provides special opportunities for effective therapy in mitral regurgitation that are not applicable to patients with chronic aortic regurgitation.

To examine the hydraulic determinants of regurgitant flow in mitral regurgitation, it is helpful to classify the etiology of the valve disease on the basis of whether the mitral regurgitant orifice is fixed or dynamic. The prototype of fixed orifice disease is the rheumatic lesion. Mitral regurgitation due to severe mitral annular calcification also falls into this category. In contrast, there are three conditions that characteristically exhibit wide variations in the severity of regurgitation that are closely coupled to changes in ventricular dimensions. For example, in patients with hypertrophic obstructive cardiomyopathy or mitral valve prolapse, interventions or vasoactive drugs that reduce ventricular preload *increase* the severity of mitral regurgitation and indeed serve as useful provocative tests for the clinical identification of these conditions. In contrast, in patients with dynamic papillary muscle dysfunction often associated with acute coronary syndromes or dilated cardiomyopathy, these same interventions *reduce* the severity of the mitral regurgitation. In such cases, the prompt reduction in regurgitant volume and often dramatic clinical improvement

seen with nitrate therapy is causally related to a decrease in ventricular volume. Experimental studies of acute mitral regurgitation using a canine model (9,10) have demonstrated convincing evidence of the dynamic nature of the mitral regurgitant orifice and its dependence on ventricular volume and contractile state. Thus, if one excludes patients with pure fixed orifice (i.e., rheumatic) disease and those with hypertrophic cardiomyopathy or mitral valve prolapse, the importance of reducing ventricular size as a means of lessening regurgitant volume may have clinical utility, not only in cases of mitral regurgitation due to papillary muscle dysfunction but also in some patients with prosthetic valve dysfunction or ruptured chordae tendinae.

As in patients with aortic regurgitation, the hemodynamic variables of the orifice equation offer ample reason for vigorous treatment of hypertension in patients with mitral regurgitation. Furthermore, as demonstrated by Jose et al. (11), the increase in mitral regurgitation produced by elevated blood pressures is often more than can be predicted by an increase in the transvalvular pressure gradient alone and can only be explained by an increase in the regurgitant orifice area. Thus, in patients who do not have fixed-orifice mitral regurgitation, the benefit of lowering blood pressure may be unexpectedly gratifying and greater than that predicted by a reduction in the transmitral systolic gradient alone.

## Ventricular Remodeling

The potential for improving LV performance in chronic mitral and aortic regurgitation need not involve a change in the size of the regurgitant volume. Indeed, there is reason to suspect that the long-term benefit of vasodilator therapy in chronic volume overload (particularly aortic regurgitation) may be independent of changes in regurgitant volume. A possible mechanism for this benefit is illustrated in Figure 1. Depicted are the acute and chronic effects of combined preload and afterload reduction in a hypothetical case. With short-term therapy, reduced fiber shortening associated with a decrease in preload is offset by a reduction in afterload and, as a result, the total stroke volume (forward plus regurgitant) is maintained. With long-term therapy and a gradual regression of hypertrophy as well as a leftward shift of the diastolic pressure–volume curve, the remodeled smaller ventricle functions much as it would have before dilation and expansive remodeling occurred. To some degree, preload reserve is reestablished, and a large total stroke volume is preserved by the continued unloading effect of vasodilator therapy. The effects of hypertrophy regression are also illustrated in Figure 1. The essence of this long-term response is a reduction in ventricular volume and wall stress, which need not require a change in heart rate, contractile state or regurgitant flow.

The proven benefit of ACE inhibitors or combined nonspecific vasodilator therapy in patients with heart failure (12–15) who do not have primary valvular regurgitation provides the framework for a similar effect in treating patients with chronic aortic or mitral regurgitation. If, indeed, reductions in wall

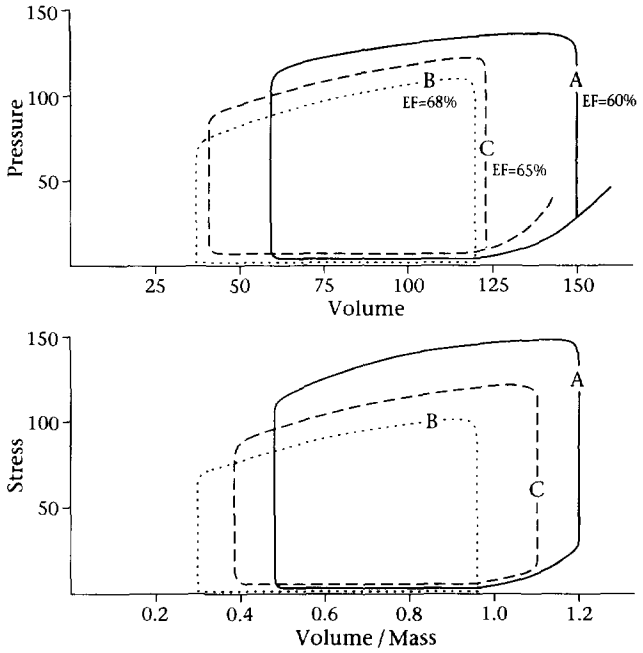


**Figure 1.** Effects of combined preload and afterload reduction on pressure–volume relations (**upper panel**) and stress–volume/mass relations (**lower panel**). **Upper panel, Loop A** represents the baseline state in a hypothetical patient with chronic aortic regurgitation. **Loop B** illustrates the acute effects of combined preload and afterload reduction; the negative heterometric effect of a decrease in preload is countered by a reduction in afterload, and stroke volume is unchanged. **Loop C** represents the results of long-term vasodilator therapy; the pressure–volume curve of the remodeled, smaller ventricle has shifted upward and to the left of that seen in the baseline (**loop A**) and acute (**loop B**) states; ejection fraction (EF) and stroke volume are maintained. **Lower panel,** The effect of regression of hypertrophy induced by chronic vasodilator therapy is shown by examining the stress–volume/mass relations. With regression of hypertrophy, the remodeled smaller ventricle (**loop C**) exhibits higher end-diastolic and end-systolic volume/mass ratios and higher systolic stress than are seen after acute load reduction (**loop B**), but still less than in the baseline state (**loop A**).

stress are closely coupled to the improvement observed in patients with congestive heart failure treated with vasodilators, it should be possible to predict responsiveness from baseline characteristics. For example, a reduced contractile state, graphically represented by a decrease in the slope of the systolic pressure–volume relation, would permit a greater increase in stroke volume for a given reduction in systolic pressure (Fig. 2). Thus, one would predict that the largest, sickest hearts would be the ones most likely to respond favorably to load reduction. In studies of vasodilator therapy for congestive heart failure, this phenomenon is well recognized. For example, Packer et al. (16), observed that the beneficial response to hydralazine in patients with severe heart failure was related to ventricular chamber size; it is not unlikely that the same would be true for patients with chronic valvular regurgitation. A particular benefit of ventricular volume reduction in valvular regurgitation is suggested by a study of the effect of nitroprusside in patients with severe ischemic cardiomyopathy (17). Those patients with clinically relevant mitral

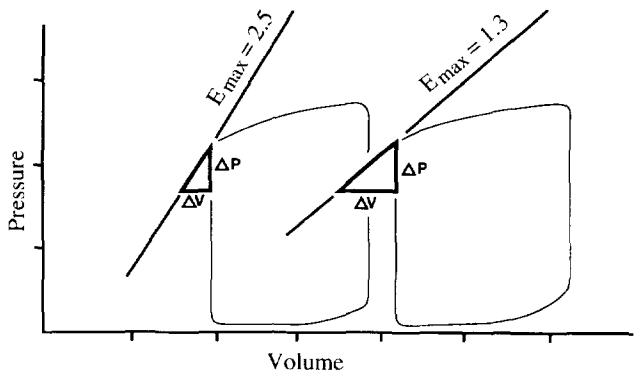


**Figure 2.** Pressure–volume loops and end-systolic pressure–volume relations in a mildly depressed and a myopathic ventricle. In the former, ejection fraction is ~50%, and the slope of the end-systolic pressure–volume relation ($E_{max}$) is 2.5. In the latter, ejection fraction is ~30%, and $E_{max}$ is only 1.3. In the case of the myopathic ventricle, a given reduction in end-systolic pressure (ΔP) effects a greater reduction in end-systolic volume (ΔV) than in the mildly depressed ventricle. In patients with chronic aortic or mitral regurgitation, the salutary hemodynamic effects of vasodilators are most marked in the most symptomatic patients with the largest hearts and the most depressed systolic function.

regurgitation had larger ventricles and responded to the vasodilator with a greater increase in forward cardiac output (coincident with a decrease in regurgitant volume) than did those without mitral regurgitation. Whether the larger ventricle or the mitral regurgitation was the major factor responsible for the more favorable response to preload and afterload reduction cannot be answered. In either case, a central role for reducing LV volume is apparent.

There are other possible explanations for the benefit of vasodilator therapy in chronic volume overload that may be particularly relevant to the patient with aortic regurgitation. Because the work and power of the normal ventricle is maximal at 50% to 60% of peak isometric force (18), and because peak systolic stress is characteristically elevated in aortic regurgitation (19,20), afterload reduction should enable such a volume-overloaded ventricle to perform more work merely by moving the work load relation to a more favorable and efficient operative load (21,22). A similar effect may be seen in severe decompensated mitral regurgitation in which systolic loads are elevated.

In this respect, it is also important to recognize the interaction of preload and afterload reduction. Although relief of venous congestion is directly related to preload reduction, the associated decrease in chamber volume effects a secondary decrease in afterload through the Laplace relation; such unloading is independent of any vasomotor effect on the peripheral resistance vessels. In this way, vasodilator therapy results in reduced venous congestion, restoration of preload reserve and lower systolic wall stress, which provides a stimulus for regression of hypertrophy and remodeling of a smaller, more efficient ventricle (Fig. 1).

## Short-Term Vasodilator Effects

The hemodynamic effects of short-term administration of vasodilators in chronic aortic (23–30) and mitral regurgitation (25,31–42) are summarized in Tables 1 and 2.

### *Aortic Regurgitation*

In three studies (23–25) of the effects of intravenous nitroprusside in patients with chronic aortic regurgitation, the hemodynamic responses were quite consistent. Heart rate changed little, if at all, and significant reductions in arterial pressure, LV end-diastolic pressure and volume and an increase in the systolic ejection fraction were observed. Cardiac index increased in two of the three studies. Examination of individual responses suggested that patients with high filling pressures, reduced LV systolic function and elevated systolic pressures were the most likely to benefit from nitroprusside infusion. Sasayama et al. (25) concluded that the beneficial effects of combined afterload and preload reduction (i.e., with nitroprusside) are most apparent in patients who have exhausted their preload reserve. In this circumstance, relief of venous congestion can be achieved with relatively little ven-

**Table 1.** Vasodilators in Aortic Regurgitation: Short-Term Effects

| Study (ref no.) | Year | Drug | No. of Pts | HR | BP (D/S) | SVR | EDV | ESV | EF | RegF | RegV | FSV | CI | EDP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bolen et al. (23) | 1976 | NP | 13 | 0 | ↓/↓ | | ↓ | | ↑ | ↓ | ↓ | | ↑ | ↓ |
| Miller et al. (24) | 1976 | NP | 12 | 0 | ↓/↓ | ↓ | ↓ | | ↑ | ↓ | | 0 | ↑ | ↓ |
| Sasayama et al. (25) | 1982 | NP | 7 | | ↓/ | | ↓ | ↓ | ↑ | 0 | 0 | 0 | 0 | ↑ |
| Greenberg et al. (26) | 1981 | HDZ | 10 | | (↓) | ↓ | ↓ | ↓ | ↑ | ↓ | ↓ | ↑ | ↑ | ↓ |
| Reske et al. (27) | 1985 | CAP | 10 | 0 | 0/0 | | | | 0 | ↓ | | | | |
| Rothlisberger et al. (28) | 1993 | CAP | 10 | ↓ | ↓/↓ | ↓ | 0 | 0 | 0 | 0 | | 0 | ↓ | ↓ |
| Fioretti et al. (29) | 1982 | NIF | 12 | | ↓/0 | ↓ | 0 | 0 | 0 | | | 0 | ↑ | ↓ |
| Shen et al. (30) | 1984 | NIF | 20 | ↑ | ↓/0 | ↓ | 0 | 0 | 0 | ↓ | | ↑ | ↑ | |
| Rothlisberger et al. (28) | 1993 | NIF | 10 | 0 | ↓/0 | ↓ | 0 | 0 | 0 | ↓ | | ↑ | ↑ | ↓ |

BP = blood pressure; CAP = captopril; CI = cardiac index; D = diastolic; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; FSV = forward stroke volume; HDZ = hydralazine; HR = heart rate; NIF = nifedipine; NP = nitroprusside; Pts = patients; ref = reference; RegF = regurgitant fraction; RegV = regurgitant volume; S = systolic; SVR = systemic vascular resistance; 0 = no change; ↓ = decrease; ↑ = increase; (↓) = decrease in mean pressure.

**Table 2.** Vasodilators in Mitral Regurgitation: Short-Term Effects

| Study (ref no.) | Year | Drug | No. of Pts | HR | BP (D/S) | SVR | EDV | ESV | EF | RegF | RegV | FSV | CI | EDP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chatterjee et al. (31) | 1973 | NP | 8 | ↓ | (↓) | ↓ | ↓ | ↓ | ↑ | ↓ | ↓ | ↑ | ↑ | ↓ |
| Goodman et al. (32) | 1974 | NP | 14 | 0 | (↓) | ↓ | ↓ | ↓ | 0 | ↓ | ↓ | ↑ | ↑ | ↓ |
| Harshaw et al. (33) | 1975 | NP | 7 | 0 | (↓) | ↓ | 0 | 0 | 0 | ↓ | ↓ | ↑ | ↑ | ↓ |
| Sasayama et al. (25) | 1982 | NP | 5 | 0 | ↓/ | | ↓ | ↓ | 0 | ↓ | ↓ | ↑ | ↑ | ↓ |
| Greenberg et al. (34) | 1978 | HDZ | 10 | 0 | (↓) | ↓ | 0 | 0 | 0 | ↓ | ↓ | ↑ | ↑ | 0 |
| Greenberg et al. (35) | 1982 | HDZ | 16 | ↑ | (0) | ↓ | | | | | | ↑ | ↑ | ↓ |
| Heck et al. (36) | 1985 | CAP | 10 | | ↓/↓ | | | | 0 | ↓ | | | | |
| Wisenbaugh et al. (37) | 1992 | CAP | 9 | ↓ | (↓) | 0 | 0 | | 0 | 0 | | 0 | ↓ | ↓ |
| Rothlisberger et al. (38) | 1994 | CAP | 8 | ↓ | ↓/↓ | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 |
| Schön et al. (39) | 1994 | QUIN | 12 | ↓ | ↓/↓ | | ↓ | ↓ | ↑ | ↓ | ↓ | | 0 | ↓ |
| Sniderman et al. (40) | 1974 | NTG | 9 | 0 | 0/ | | ↓ | 0 | ↓ | | | 0 | 0 | 0 |
| Elkayam et al. (41) | 1987 | NTG | 10 | ↓ | (↓) | 0 | ↓ | ↓ | ↑ | 0 | 0 | 0 | | |
| Jeang et al. (42) | 1986 | ISD | 7 | ↑ | (↓) | 0 | ↓ | | | 0 | | | 0 | ↓ |
| Rothlisberger et al. (38) | 1994 | NIF | 8 | 0 | ↓/↓ | ↓ | 0 | 0 | 0 | ↓ | | 0 | 0 | ↓ |

ISD = isosorbide dinitrate; NTG = nitroglycerin; QUIN = quinapril; other abbreviations and symbols as in Table 1.

tricular volume change, and the negative heterometric effect on systolic function is thus blunted. Similar findings were reported by Greenberg et al. (26) after intravenous hydralazine.

In two studies (27,28) of the effect of a single dose of captopril, the results were less consistent than those observed with nitroprusside or hydralazine. In neither study was a significant change in the ejection fraction observed. The responses to a single oral dose of nifedipine (20 mg) in three studies (28–30) were for the most part similar. Although there was no significant change in LV end-diastolic volume, there was a decrease in end-diastolic pressure. Ejection fraction did not change, but cardiac index increased in all three studies.

These data indicate that intravenous nitroprusside is the preferred agent for the immediate or short-term treatment of aortic regurgitation. Hydralazine can produce similar salutary results. Nifedipine produces an increase in cardiac index and a decrease in end-diastolic pressure (similar to that seen with nitroprusside or hydralazine) but has little effect on ventricular volume. On the basis of available data, there appears to be little rationale for the use of captopril in the short-term treatment of patients with aortic regurgitation.

### *Mitral Regurgitation*

The major effects of short-term vasodilator therapy in patients with chronic mitral regurgitation are summarized in Table 2. Not apparent from Table 2 is that the pooled patient population in these studies is much more heterogeneous than that encountered in studies of chronic aortic regurgitation. In some instances, the study group was composed entirely of patients with fixed orifice (i.e., rheumatic) mitral regurgitation. In others, primary myocardial disease was the etiology of the mitral regurgitation, whereas in others the etiology was mixed. Nonetheless, a pattern of response is apparent.

Intravenous nitroprusside (25,31–33) and hydralazine (34,35) had similar beneficial effects on forward stroke volume, cardiac index and regurgitant flow. There was no significant change in ejection fraction. Despite the widespread use of ACE inhibitors in patients with congestive heart failure, hemodynamic and volumetric data on the effects of these agents in chronic mitral regurgitation are relatively sparse and the results conflicting (36–39).

The short-term response to nitrate therapy in chronic mitral regurgitation consists of a reduction in LV end-diastolic volume but no change in forward or regurgitant flow (40–42). These results are most likely confounded by the inclusion of patients with fixed orifice and dynamic orifice lesions. Indeed, Jeang et al. (42), observed that regurgitant flow increased 72% in rheumatic mitral regurgitation and decreased 5% in patients with nonrheumatic mitral regurgitation after isosorbide dinitrate. In mitral valve prolapse, Takenaka et al. (43) found that changes in LV size (i.e., degree of prolapse) and pressure interact to determine the regurgitant volume. As was seen in chronic aortic regurgitation, the most consistent beneficial results of short-term vasodilator therapy are seen with the administration of nitroprusside.

## Differences in Short-Term Response to Vasodilator Therapy

Although consistent reductions in arterial pressure, systemic vascular resistance, regurgitant fraction and end-diastolic pressure and volume were observed in both mitral and aortic regurgitation after nitroprusside, forward stroke volume generally increased and ejection fraction remained unchanged in mitral regurgitation, whereas ejection fraction generally increased and forward stroke volume remained unchanged in aortic regurgitation. It would appear, therefore, that as a consequence of combined preload and afterload reduction with nitroprusside, a reciprocal relation between regurgitant and forward flow characterizes the response in mitral regurgitation. By contrast, in aortic regurgitation correction of after-

**Table 3.** Vasodilators in Aortic Regurgitation: Long-Term Effects

| Study (ref no.) | Year | Drug | No. of Pts | HR | BP (D/S) | EDV | ESV | EF | RegF | EDD | ESD | FS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jensen et al. (44) | 1983 | HDZ | 6 | ↑ | /0 | | | | | ↓ | ↓ | ↓ |
| Kleaveland et al. (45) | 1986 | HDZ | 6 | 0 | ↓/0 | 0 | 0 | 0 | 0 | 0 | ↑ | |
| Greenberg et al. (46) | 1988 | HDZ | 45 | 0 | 0/0 | ↓ | ↓ | ↑ | ↓ | 0 | 0 | 0 |
| Dumesnil et al. (47) | 1990 | HDZ | 7 | 0 | 0/0 | | | | | ↓ | ↓ | 0 |
| Lin et al. (48) | 1994 | HDZ | 38 | 0 | ↓/↓ | 0 | 0 | 0 | | | | |
| Heck et al. (36) | 1985 | CAP | 17 | | | | | 0 | ↓ | | | |
| Wisenbaugh et al. (49) | 1994 | CAP | 11 | | 0/0 | | | 0 | | 0 | 0 | |
| Schön et al. (48) | 1994 | QUIN | 12 | 0 | ↓/0 | ↓ | ↓ | 0 | ↓ | ↓ | ↓ | ↑ |
| Lin et al. (48) | 1994 | ENAL | 38 | 0 | ↓/↓ | ↓ | 0 | | | | | |
| Scognamiglio et al. (51) | 1990 | NIF | 38 | 0 | ↓/0 | ↓ | | ↑ | | | | |

EDD = end-diastolic dimension; ENAL = enalapril; ESD = end-systolic dimension; FS = fractional shortening; other abbreviations and symbols as in Tables 1 and 2.

load mismatch dominates the response, and a decrease in preload limits the increase in forward flow. This interpretation is supported by the fact that peak systolic stresses are substantially higher in chronic aortic regurgitation than in mitral regurgitation (19); thus, the substrate for afterload reduction in chronic aortic regurgitation makes this lesion more susceptible to favorable manipulation of the inverse force-shortening relation than is the case in chronic mitral regurgitation.

## Long-Term Effects of Vasodilator Therapy

The effects of long-term vasodilator therapy in chronic aortic regurgitation (36,44–51) and chronic mitral regurgitation (36,49,52) are summarized in Tables 3 and 4.

### *Aortic Regurgitation*

The results of five hydralazine studies (44–48) are shown in Table 3. In the largest randomized, placebo-controlled, double-blind trial of hydralazine (average dose 216 mg/day), Greenberg et al. (46) observed no significant changes in heart rate or blood pressure during drug therapy in 45 largely asymptomatic patients followed for up to 24 months. Despite this finding, significant and progressive reductions in end-diastolic and end-systolic volumes were observed. Similar changes were not observed in the 35 patients in the control group. Ejection fraction decreased slightly in the placebo group, whereas a small increase was observed in hydralazine-treated patients. In contrast to these salutary results, Lin et al. (48) did not find a salutary effect of this drug despite a significant decrease in systolic and diastolic pressures.

Wisenbaugh et al. (49) observed no effect upon LV dimensions or ejection fraction after 6 months of captopril therapy in 23 patients with severe chronic aortic regurgitation. However, Schön et al. (50) reported significant reductions in LV volume and an increase in ejection fraction in 12 patients with chronic aortic regurgitation after 1 year of quinapril therapy. Lin et al. (48) reported the results of a randomized, double-blind trial comparing enalapril and hydralazine therapy in 76 asymptomatic patients with mild to severe chronic aortic regurgitation. Arterial pressure decreased in both groups. At 1 year, patients receiving enalapril had a significant reduction in LV volume and mass, whereas no significant changes were found in the hydralazine group (Table 3).

Scognamiglio et al. (51), studied the effect of long-term nifedipine therapy in a randomized, double-blind, placebo-controlled trial in 72 asymptomatic patients with severe aortic regurgitation. After 12 months of nifedipine therapy (20 mg twice daily), significant reductions in LV end-diastolic volume, LV mass and LV mean systolic stress and a significant increase in ejection fraction were observed. In the placebo group, a small but significant decrease in ejection fraction was found; no changes were observed in the other variables. Except for a decrease in systolic blood pressure in the nifedipine group, no significant changes in heart rate, diastolic blood pressure or cardiothoracic ratio were observed during the trial. In a subsequent report, the same investigators (53) followed the course of 143 patients with chronic aortic regurgitation and normal left ventricular function who were randomized to receive either nifedipine (20 mg twice daily) or digoxin (0.25 mg daily). After 6 years, a significantly larger proportion of the digoxin group had undergone valve replacement, sug-

**Table 4.** Vasodilators in Mitral Regurgitation: Long-Term Effects

| Study (ref no.) | Year | Drug | No. of Pts | HR | BP (D/S) | EDV | ESV | EF | RegF | EDD | ESD | FS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heck et al. (36) | 1985 | CAP | 10 | | | | | 0 | ↓ | | | |
| Wisenbaugh et al. (49) | 1994 | CAP | 12 | | 0/0 | | | 0 | | 0 | 0 | 0 |
| Schön et al. (52) | 1994 | QUIN | 12 | ↓ | ↓/↓ | ↓ | ↓ | 0 | ↓ | ↓ | ↓ | 0 |

Abbreviations and symbols as in Tables 1 to 3.

gesting that nifedipine therapy reduces or delays the need for aortic valve replacement.

### *Mitral Regurgitation*

After studying the short-term effects of hydralazine in 16 symptomatic patients with severe mitral regurgitation, Greenberg et al. (35) followed their clinical course and found that 8 achieved a sustained symptomatic improvement over a mean follow-up period of 13 months. The remaining eight patients either experienced intolerable side effects or failed to experience symptomatic improvement; these patients were treated surgically. Heck et al. (36), treated 10 patients with captopril for 3 to 5 months and found a reduction in the regurgitant fraction. Schön et al. (52) studied the effect of quinapril in 12 symptomatic patients with chronic mitral regurgitation of mixed etiologies. After 1 year, there was a reduction in LV end-diastolic volume and regurgitant volume, and hemodynamic variables during exercise were improved. Wisenbaugh et al. (49) compared the effects of captopril versus placebo in 32 asymptomatic patients with chronic mitral regurgitation; most had rheumatic disease. After 6 months, there was no difference in arterial pressure, LV volume or ejection fraction between the two groups.

The different results in these latter two studies may be due in part to the fact that Schön et al. (52) studied patients who were more symptomatic and had slightly larger hearts than those treated by Wisenbaugh et al. (49). Moreover, the patients in the study by Schön et al. exhibited higher baseline arterial pressures that decreased significantly during treatment. By contrast, the patients in the study by Wisenbaugh et al. had lower arterial pressures that did not change during treatment. Certainly, vasodilator therapy provides the most benefit in patients with the largest hearts, the poorest systolic function and the most disabling symptoms (35). Some benefit can be seen in less symptomatic patients with only moderate LV enlargement, but there appears to be no detectable benefit in asymptomatic patients with only minimal LV enlargement (49,52).

## Discussion

The specific effects of vasodilators on regurgitant fraction, ejection fraction and forward flow depend on the nature of the regurgitant lesion, its etiology and the hemodynamic determinants of regurgitant flow. These determinants include the magnitude and duration of the pressure gradient across the valve and the effective orifice area.

The most consistent hemodynamic effect of vasodilator therapy in patients with chronic LV volume overload (both aortic and mitral regurgitation) is a reduction in ventricular filling pressures. This effect is observed not only with agents that reduce venous tone but also with vasoactive drugs that act primarily on the arterial resistance vessels (i.e., hydralazine and nifedipine). Although most vasodilators also produce a reduction in ventricular volume, this effect has been observed less consistently than the decrease in filling pressures, perhaps due to less accuracy in the volume measurements or to the steep operative portion of the diastolic pressure–volume relation in symptomatic patients with LV volume overload.

Specific changes in ejection fraction and regurgitant volume appear to depend importantly on the clinical substrate under study. That is, the response to combined preload and afterload reduction and, to a lesser extent, to all vasodilator therapy is different in patients with chronic aortic regurgitation than in those with chronic mitral regurgitation. For example, in aortic regurgitation, nitroprusside consistently effects a decrease in end-diastolic volume and an increase in ejection fraction; changes in regurgitant volume and forward stroke volume are less consistent. By contrast, in mitral regurgitation, nitroprusside invariably reduces regurgitant volume and increases forward stroke volume, whereas ejection fraction generally does not change. These observations suggest that the reciprocal relation between forward stroke volume and regurgitant volume in chronic mitral regurgitation is favorably influenced by ventricular volume reduction and a decrease in the mitral regurgitant orifice area, whereas the major benefit of vasodilator therapy in chronic aortic regurgitation is brought about by a reduction in the high levels of systolic stress that characterize this lesion. This reduction in afterload effects an increase in ejection fraction despite a decrease in preload.

The disappointing responses to single-dose ACE inhibitors reported in both chronic aortic regurgitation (27,28) and chronic mitral regurgitation (36–38) warrant special comment. In chronic mitral regurgitation, Wisenbaugh et al. (37) suggests that this lack of a favorable response is due to inhibition of the positive inotropic effect of angiotensin II. A decrease in heart rate may also contribute to the lack of improvement in cardiac index after single-dose ACE inhibitor therapy in aortic and mitral regurgitation. The failure of captopril to decrease LV dimensions and regurgitant fraction in the patients from South Africa with chronic mitral regurgitation (37,38) may be due in large part to the fact that most of the subjects studied had fixed orifice (rheumatic) mitral regurgitation. This distinction is especially important with the use of venodilators (nitrates) because the regurgitant volume may increase in rheumatic mitral regurgitation after nitrate administration (42). This increase may occur in mitral regurgitation associated with hypertrophic cardiomyopathy or mitral valve prolapse, but the reverse is generally observed in patients with papillary muscle dysfunction, dilated cardiomyopathy or coronary heart disease.

The results of long-term therapy with vasodilators in some respects are more impressive than those predicted by studies of single-dose drug administration. In chronic aortic regurgitation, significant reductions in ventricular volumes have been observed after chronic therapy with hydralazine (46), nifedipine (51), enalapril (48) and quinapril (50). Excluding patients with fixed orifice mitral regurgitation, long-term therapy with captopril (36) and with quinapril (52) has reduced regurgitant fraction in patients with chronic mitral regurgitation; in the latter instance, ventricular volumes were also measured and decreased significantly. The demonstration that long-term

vasodilator therapy can decrease systolic wall stress and LV mass in patients with chronic volume overload (48,50,51,52) has further contributed to enthusiasm for the use of these drugs.

## Conclusions

The choice of long-term vasodilator therapy in patients with chronic aortic or mitral regurgitation remains problematic. In chronic aortic regurgitation, convincing beneficial effects have been shown with nifedipine, ACE inhibitors and hydralazine. However, long-term hydralazine therapy is often poorly tolerated and, in one randomized study (48), was shown to be less effective than enalapril. A direct comparison of nifedipine (using a 24-h drug delivery system) and an ACE inhibitor would be both timely and appropriate.

For most patients with chronic mitral regurgitation, there is reason to believe that preload reduction is an important ingredient in mediating the benefit of vasodilator therapy. Thus, by reducing the effective regurgitant orifice area, a decrease in regurgitant volume can be achieved. A reduction in arterial pressure (i.e., LV systolic pressure) may also contribute to this salutary effect, especially if the patient is hypertensive. This latter mechanism is of primary importance in fixed orifice rheumatic mitral regurgitation. The available data, although very limited, support the use of an ACE inhibitor as the vasodilator of choice for most patients with symptomatic mitral regurgitation. It should be recognized that there are no published studies that support the use of oral vasodilator therapy in asymptomatic patients with chronic mitral regurgitation.

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## References

1. Gorlin R, Gorlin G. Hydraulic formula for calculation of stenotic mitral valves, other cardiac valves, and other circulatory shunts. Am Heart J 1951;41:1–29.
2. Corrigan DJ. On permanent patency of the aorta or inadequacy of the aortic valves. Edinburgh Med Surg J 1832;37:225–45.
3. Warner HR, Toronto AF. Effect of heart rate on aortic insufficiency as measured by a dye dilution technique. Circ Res 1961;9:413–7.
4. Brawley RK, Morrow AG. Direct determinants of aortic blood flow in patients with aortic regurgitation: effects of alterations in heart rate, increased ventricular preload or afterload, and isoproterenol. Circulation 1967;35:32–45.
5. Judge TP, Kennedy JW, Bennett LJ, Wills RE, Murray JA, Blackmon JR. Quantitative hemodynamic effects of heart rate in aortic regurgitation. Circulation 1971;44:355–67.
6. Firth BG, Dehmer GJ, Nicod P, Willerson JT, Hillis LD. Effect of increasing heart rate in patients with aortic regurgitation. Am J Cardiol 1982;49: 1860–6.
7. Ford LE, Feldman T, Chui YC, Carroll JD. Hemodynamic resistance: a measure of functional impairment in aortic valvular stenosis. Circ Res 1990;66:1–7.
8. Cannon JD, Zile MR, Crawford FA, Carabello BA. Aortic valve resistance as an adjunct to the Gorlin formula in assessing the severity of aortic stenosis in symptomatic patients. J Am Coll Cardiol 1992;20:1517–23.
9. Borgenhagen DM, Serur JR, Gorlin R, Adams D, Sonnenblick EH. The effect of ventricular load and contractility on mitral regurgitation orifice size and flow in the dog. Circulation 1977;56:106–13.
10. Yoran C, Yellin EL, Becker RM, Gabbay S, Frater RWM, Sonnenblick EH. Dynamic aspects of acute mitral regurgitation: effects of ventricular volume, pressure, and contractility on the effective regurgitant orifice area. Circulation 1979;60:170–6.
11. Jose AD, Taylor RR, Gerstein L. The influence of arterial pressure on mitral incompetence in man. J Clin Invest 1964;43:2094–103.
12. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of Veterans Administration cooperative study. N Engl J Med 1986;314:1547–52.
13. The CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
14. The SOLVD Investigators. Effect of enalapril in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991;325:293–302.
15. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction; results of the survival and ventricular enlargement trial. N Engl J Med 1992;327:669–77.
16. Packer M, Meller J, Medina N, Gorlin R, Herman MV. Importance of left ventricular chamber size in determining the response to hydralazine in severe chronic heart failure. N Engl J Med 1980;303:250–5.
17. Weiland DS, Konstam MA, Salem DN, Martin TT, Cohen SR, Zile MR. Contribution of reduced mitral regurgitant volume to vasodilator effect in severe left ventricular failure secondary to coronary artery disease or ideopathic dilated cardiomyopathy. Am J Cardiol 1986;58:1046–50.
18. Levine HJ, Forward SA, McIntyre KM, Schechter E. Effect of afterload on force-velocity relations and contractile element work in the intact dog heart. Circ Res 1966;18:729–44.
19. Gaasch WH, Levine HJ, Zile MR. Chronic aortic and mitral regurgitation: mechanical consequences of the lesion and the results of surgical correction. In: Levine HJ, Gaasch WH, editors. The Ventricle. Boston: Martinus Nijhoff 1985:237–58.
20. Wisenbaugh T, Spann JF, Carabello BA. Differences in myocardial performance and load between patients with similar amounts of chronic aortic versus chronic mitral regurgitation. J Am Coll Cardiol 1984;3:916–23.
21. Hill AV. The dimensions of animals and their muscular dynamics. Sci Prog 1950;38:209–29.
22. Levine HJ. Optimum heart rate of large failing hearts. Am J Cardiol 1988;61:633–6.
23. Bolen JL, Alderman EL. Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. Circulation 1976;53:879–83.
24. Miller RR, Vismara LA, DeMaria AN, Salel AF, Mason DT. Afterload reduction therapy with nitroprusside in severe aortic regurgitation: improved cardiac performance and reduced regurgitant volume. Am J Cardiol 1976; 38:564–7.
25. Sasayama S, Ohyagi A, Lee JD, et al. Effect of the vasodilator therapy in regurgitant valvular disease. Japanese Circ J 1982;46:433–41.
26. Greenberg B, Demots H, Murphy E, Rahimtoola S. Mechanism for improved cardiac performance with arteriolar dilators in aortic insufficiency. Circulation 1981;53:263–8.
27. Reske SN, Heck I, Kropp J, et al. Captopril mediated decrease of aortic regurgitation. Br Heart J 1985;54:415–9.
28. Rothlisberger C, Sareli P, Wisenbaugh T. Comparison of single-dose nifedipine and captopril for chronic severe aortic regurgitation. Am J Cardiol 1993;72:799–804.
29. Fioretti P, Benussi B, Scardi S, Klugmann S, Brower RW, Camerini F. Afterload reduction with nifedipine in aortic insufficiency. Am J Cardiol 1982;49:1728–32.
30. Shen WF, Roubin GS, Hirasawa K, et al. Noninvasive assessment of acute effects of nifedipine on rest and exercise hemodynamics and cardiac function in patients with aortic regurgitation. J Am Coll Cardiol 1984;4:902–7.
31. Chatterjee K, Parmley WW, Swan HJC, Berman G, Forrester J, Marcus HS. Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvular apparatus. Circulation 1973;48:684–90.
32. Goodman DJ, Rossen RM, Holloway EL, Alderman EL, Harrison DC. Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. Circulation 1974;50:1025–32.
33. Harshaw CW, Grossman W, Munro AB, McLaurin LP. Reduced systemic

vascular resistance as therapy for severe mitral regurgitation of valvular origin. Ann Intern Med 1975;83:312–6.

34. Greenberg BH, Massie BM, Brundage BH, Botvinick EH, Parmley WW, Chatterjee K. Beneficial effects of hydralazine in severe mitral regurgitation. Circulation 1978;58:273–9.
35. Greenberg BH, DeMots H, Murphy E, Rahimtoola SH. Arterial dilators in mitral regurgitation: effects on rest and exercise hemodynamics and long-term clinical follow-up. Circulation 1982;65:181–7.
36. Heck I, Schmidt J, Mattern H, Fricke G, Kropp J, Reske S. Reduktion der regurgitation bie aorten- und mitralinsuffizienz durch captopril im akut-und langzeitversuch. Schweiz Med Wochenschr 1985;115:1615–8.
37. Wisenbaugh T, Essop R, Rothlisberger C, Sareli P. Effects of a single oral dose of captopril on left ventricular performance in severe mitral regurgitation. Am J Cardiol 1992;69:348–53.
38. Rothlisberger C, Sareli P, Wisenbaugh T. Comparison of single dose nifedipine and captopril for chronic severe mitral regurgitation. Am J Cardiol 1994;73:978–81.
39. Schön HR, Schröter G, Blömer H, Schömig A. Beneficial effects of a single dose of quinapril on left ventricular performance in chronic mitral regurgitation. Am J Cardiol 1994;73:785–91.
40. Sniderman AD, Marpole DGF, Palmer WH, Fallen EL. Response of the left ventricle to nitroglycerin in patients with and without mitral regurgitation. Br Heart J 1974;36:357–61.
41. Elkayam U, Roth A, Kumar A, Kulick D, McIntosh N, McKay CR, Rahimtoola SH. Hemodynamic and volumetric effects of venodilation with nitroglycerin in chronic mitral regurgitation. Am J Cardiol 1987;60:1106–11.
42. Jeang MK, Petrovich LJ, Adyanthaya AV, Alexander JK. Effects of isosorbide dinitrate on rheumatic and non-rheumatic mitral regurgitation. Texas Heart Inst J 1986;13:453–7.
43. Takenaka K, Sakamoto T, Amano W, et al. Effect of amyl nitrite on mitral valve prolapse and mitral regurgitation. Am J Noninvas Cardiol 1991;5:257–61.
44. Jensen T, Kornerup HJ, Lederballe O, et al. Treatment with hydralazine in mild to moderate mitral or aortic incompetence. Eur Heart J 1983;4:306–12.
45. Kleaveland JP, Reichek N, McCarthy DM, et al. Effects of six-month afterload reduction therapy with hydralazine in chronic aortic regurgitation. Am J Cardiol 1986;57:1109–16.
46. Greenberg B, Massie B, Bristow JD, et al. Long-term vasodilator therapy of chronic aortic insufficiency: a randomized double-blinded, placebo-controlled clinical trial. Circulation 1988;78:92–103.
47. Dumesnil JG, Tran K, Dagenais GR. Beneficial long-term effects of hydralazine in aortic regurgitation. Arch Intern Med 1990;150:757–60.
48. Lin M, Chiang H-T, Lin S-L, et al. Vasodilator therapy in chronci asymptomatic aortic regurgitation: enalapril versus hydralazine therapy. J Am Coll Cardiol 1994;24:1046–53.
49. Wisenbaugh T, Sinovich V, Dullabh A, Sareli P. Six month pilot study of captopril for mildly symptomatic, severe isolated mitral and isolated aortic regurgitation. J Heart Valve Dis 1994;3:197–204.
50. Schön HR, Dorn R, Barthel P, Schömig A. Effects of 12 months quinapril therapy in asymptomatic patients with chronic aortic regurgitation. J Heart Valve Dis 1994;3:500–9.
51. Scognamiglio R, Fasoli G, Ponchia A, Dalla Volta S. Long-term nifedipine unloading therapy in asymptomatic patients with chronic severe aortic regurgitation. J Am Coll Cardiol 1990;16:424–9.
52. Schön HR, Schröter G, Barthel P, Schömig A. Quinapril therapy in patients with chronic mitral regurgitation. J Heart Valve Dis 1994;3:303–12.
53. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. N Engl J Med 1994;331:689–94.