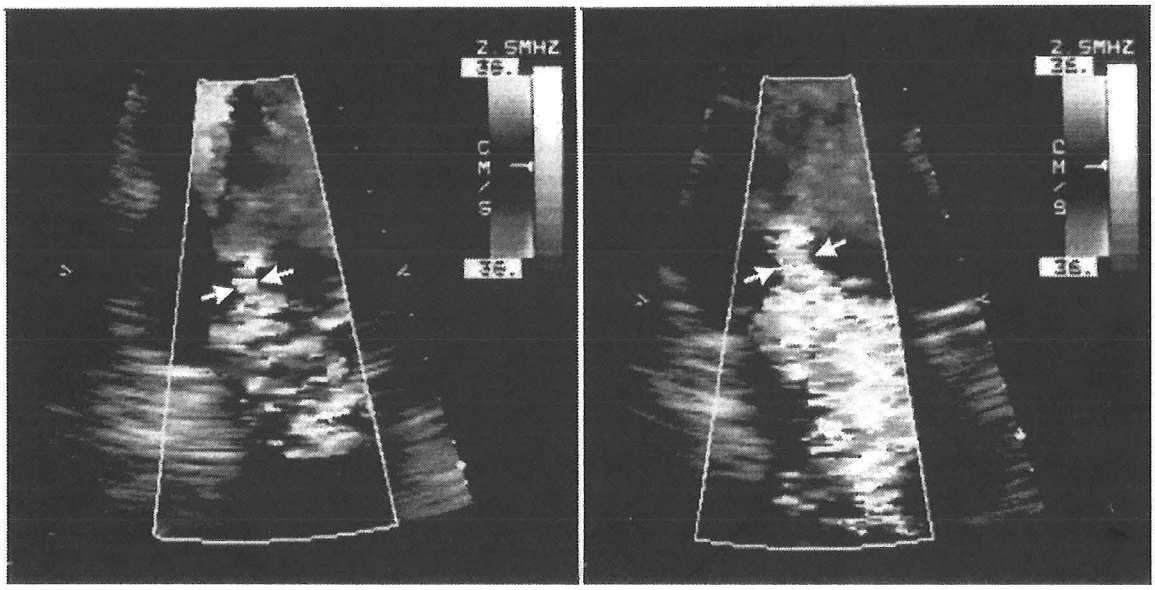
Vasodilator Therapy for Chronic Aortic and Mitral Regurgitation

Paul A. Grayburn, M.D.



Example of Worsened Mitral Regurgitation After Vasodilators In Mitral Valve Prolapse

Internal Medicine Grand Rounds

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Paul A. Grayburn, MD

Associate Professor of Medicine

Division of Cardiology

Interests: I am a clinical cardiologist with a special interest and expertise in echocardiography and cardiac imaging. At present, my major clinical research interest is studying the relation between myocardial perfusion and ventricular remodeling in heart failure, a project funded by NIH grant K24- HL03980. Other clinical research interests are valvular heart disease, myocardial viability, and contrast echocardiography. Collaborators on these clinical projects include Sheila Heinle, Ali Kizilbash, Eric Eichhorn, Beth Brickner, DuWayne Willett, and others. I have a animal research laboratory working on the development of a method of in vivo gene delivery using ultrasound-mediated destruction of microbubbles containing genetic material. Collaborators on this work include Ralph Shohet, Yan-Ting Zhou, Roger Unger, Shuyuan Chen, and others. Outside interests my family, the Dallas Cowboys, playing guitar and basketball. I particularly enjoy playing basketball with the housestaff on Thursday nights although I am getting a little too old and slow to be doing that.

Introduction

The issue of using vasodilators to treat chronic left-sided regurgitant lesions comes up often in the clinics and on the wards. For these Grand Rounds, I will discuss aortic and mitral regurgitation separately, beginning with the natural history and indications for surgery in both lesions because patients with clear indications for surgery should proceed to the operating room rather than receive vasodilators. Next, I will discuss the hemodynamic determinants of the regurgitant lesion with the goal of understanding how vasodilators might be beneficial or even harmful. Finally, we will discuss the published clinical studies of these drugs for treatment of chronic aortic and mitral regurgitation and derive current recommendations for their clinical use.

AORTIC REGURGITATION

Natural History of Aortic Regurgitation

Several studies have assessed the natural history of severe AR with remarkably consistent findings (1-4). Risk factors for a poor outcome in patients with severe AR are age, symptoms, functional class, atrial fibrillation, co-morbidity, left ventricular (LV) end-systolic dimension, and LV ejection fraction. Asymptomatic patients with normal LV size and function have an excellent prognosis. In such patients, the risk of death is <0.5% per year and the combined risk of death or aortic valve replacement is 4-5% per year (1-3). Thus, patients with severe AR who have no symptoms and normal LV size and function can be managed conservatively. The effects of symptoms and LV dilation on mortality are shown in Figure 1 (4). As can be seen in Figure 1A, even mild heart failure symptoms reduce the expected mortality in severe AR. An increase in LV end-systolic diameter dramatically decreases survival in asymptomatic patients (Fig 1B).

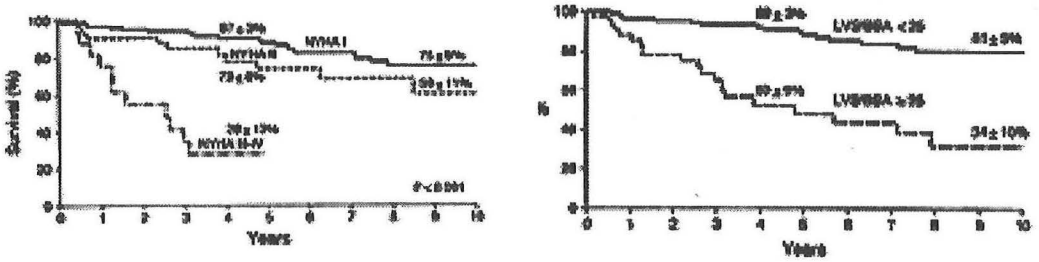


Fig 1. Left Panel. Survival of patients with chronic severe AR by symptoms (NYHA Class). Survival in asymptomatic patients (Class I) is no different than expected (p=0.38). However, patients with Class II symptoms have a significantly worse survival (p=0.02) and patients with Class II-IV symptoms have a markedly worse survival (p<0.001). **Right Panel.** Survival for patients stratified by LV end-systolic dimension. Patients with a LV end-systolic dimension <25 mm/m^2 have a markedly worse survival (p<0.001). Data from Dujardin et al (ref 4).

Indications for Surgery in Aortic Regurgitation

The indications for surgery in patients with severe AR (table 1) are based on the well-defined natural history of the disease as well as good studies on post-operative outcome (5-8). Once the LV has dilated beyond a certain point, LV dysfunction cannot be reversed by valve replacement. Thus, surgery should be considered before the LV end-systolic diameter reaches 55mm, the LV end-systolic volume reaches 55 ml/m^2, or the LVEF falls below 55%. This is

known as the "55 rule" (9). It is important to understand that these indications refer to patients with severe chronic AR; they do not apply to acute AR or infective endocarditis. In addition, it is clinically important to have accurate quantitation of the severity of AR since these indications apply to severe AR. Finally, patients with clear indications for surgery should not be treated with vasodilator therapy in hopes of postponing valve replacement, except in extenuating circumstances in which surgery is not feasible. The consideration of vasodilator therapy for AR will be limited to patients who are asymptomatic with normal LV size and function. In such patients, it is hoped that vasodilators may delay the onset of symptoms or LV dysfunction.

Table 1. Indications for Surgery in Severe Chronic Aortic Regurgitation

- Symptoms attributed to severe AR (even NYHA Class II symptoms)
- Asymptomatic with LV end-systolic dimension approaching 55 mm
- Asymptomatic with LV end-systolic volume approaching 55 ml/m^2
- Asymptomatic with LV ejection fraction < 55%

Hemodynamic Determinants of Aortic Regurgitant Volume

Conventional clinical "wisdom" dictates that afterload reduction by vasodilators causes a decrease in aortic regurgitant volume and therefore should be beneficial as a therapy for AR. However, to actually understand what afterload reduction does to regurgitant volume in AR, one must examine the hemodynamic determinants of regurgitant volume.

The Gorlin hydraulic orifice equation, which is most often used to evaluate aortic stenosis, can also be used to derive the hemodynamic determinants of regurgitant volume in AR (10,11). Thus, regurgitant volume in AR is determined by the regurgitant orifice area (ROA), a constant known as the discharge coefficient (C_d), the mean pressure gradient in diastole between the aortic root and the LV (MPG), and the time or duration of the AR in diastole (T).

$$RgV = ROA \bullet C_d \bullet \sqrt{MPG} \bullet T$$

Each aspect of this equation merits careful consideration. First, the regurgitant orifice area in AR is usually fixed rather than dynamic (12). In other words, the regurgitant orifice does not usually change in size during diastole. Since the regurgitant orifice in AR is usually fixed, it is unlikely to be affected in vasodilator therapy. A potential exception to this is AR due to a dilated aortic root and a structurally normal aortic valve. In this case, if vasodilator therapy reduces the size of the aortic root, the leaflets will coapt better and AR will decrease. The second part of the equation is a constant which accounts for contraction of the flow stream as it passes through the anatomic orifice. This discharge coefficient is dependent on orifice geometry, flow, and fluid viscosity (10). This constant is also unlikely to be affected by vasodilator therapy. The mean pressure gradient in the case of AR refers to the diastolic mean gradient between the aorta and the left ventricle. It is important to remember that in the classic case of severe AR, the aortic diastolic pressure is already quite low and further reducing it with vasodilators is difficult to do and may compromise coronary flow. Therefore, it is difficult to reduce the regurgitant volume by vasodilator therapy in chronic severe AR unless there is diastolic hypertension. The final part of the equation is the time during which AR occurs. This is not the diastolic filling period unless AR is holodiastolic. However, since increases in heart rate shorten the diastolic filling period, there is less time for AR to occur. Firth, et al (13) showed that rapid atrial pacing reduces regurgitant volume per beat but has no effect of regurgitant flow per minute (the number of increased beats compensates for the reduced flow per beat). These authors concluded that atrial pacing is unlikely to provide a long-term benefit in AR. Significant bradycardia should be

avoided because it can certainly worsen AR. Given these considerations, it is clear that in the majority of cases, vasodilator therapy probably does significantly decrease regurgitant volume unless there is diastolic hypertension. Therefore, it seems likely that any beneficial effects of vasodilator therapy may be related to improved LV function and geometry.

Effects of Aortic Regurgitation on LV Function and Geometry

If vasodilators do not significantly decrease regurgitant volume in AR, are there other mechanisms by which they might improve LV function and geometry? The answer to this question is unequivocably, yes. In diastole, the regurgitant volume entering the LV from the aorta combines with forward LV filling from the left atrium to cause an increased preload. In the setting of normal LV systolic function, most of this increased end-diastolic volume is then ejected into the aorta. It is this increased LV stroke volume that results in the well known peripheral manifestation of severe AR such as Corrigan's pulse, Quincke's pulse, Duroziez's sign, etc. This increased stroke volume causes systolic hypertension, thereby increasing LV afterload. In fact, it has been shown that afterload is often as high in AR as it is in aortic stenosis (13,14). Such afterload mismatch causes left ventricular hypertrophy and both systolic and diastolic dysfunction. Once LV function begins to deteriorate, compensatory neurohormonal activation contributes to further afterload mismatch and the development of irreversible LV failure as it does in heart failure of any cause (15,16).

The goal of vasodilator therapy for is to reverse afterload mismatch by reducing systolic blood pressure. This should lead to regression of hypertrophy, reduction in LV size, and preservation of LV systolic performance (Figure 2).

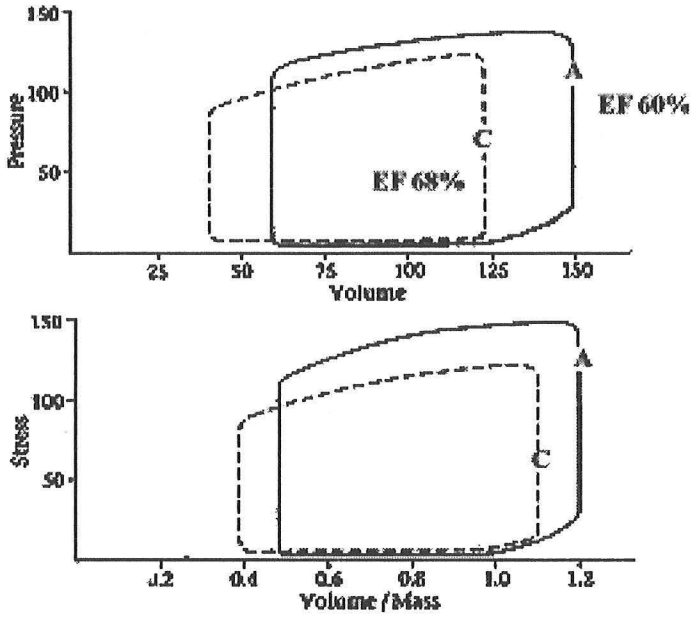


Fig 2. Top panel. Pressure-volume loops showing the effects of vasodilators on afterload mismatch in chronic AR. Preload and afterload are elevated at baseline (loop A) and LVEF is 60%. After vasodilator therapy (loop B), preload and afterload decrease and LVEF is 68% with little change in forward stroke volume. **Bottom panel.** Stress-volume.mass loops showing the effects of regression of LVH after chronic vasodilator therapy for AR. Favorable ventricular remodeling has occurred (loop B) with smaller end-systolic stress (afterload) and a smaller volume/mass ratio than at baseline (loop A). Adapted from Levine and Gaasch (ref 11).

Clinical Studies of Vasodilator Therapy in Aortic Regurgitation

It is well known that acute vasodilator therapy has beneficial hemodynamic effects in AR (11). A number of studies have also evaluated the effects of chronic vasodilator therapy for AR and these are listed in Table 2.

Study	Drug	No. of Pts	BP	EDV/EDD	ESV/EDD	LVEF
Kleaveland	HDRZ	6	↓	0	0	0
Grrenberg	HDRZ	45	0	↓	↓	↑
Dumesnil	HDRZ	7	0	↓	↓	
Lin	HDRZ	38	↓	0	0	0
Wisenbaugh	CAPT	11	0	0	0	0
Schon	QUIN	12	↓	↓	↓	0
Lin	ENAL	38	↓	↓	0	
Scognamiglio	NIFP	38	↓	↓		↑

HDRZ = hydralazine, CAPT = captopril, QUIN = quinapril, ENAL = enalapril, NIFP = nifedipine, EDV/EDD = LV end-diastolic volume or diameter, ESV/ESD = LV end-systolic volume or diameter, LVEF = LV ejection fraction, 0 = no change, ↓ = decrease, ↑ = increase.

The studies are conflicting to some degree. With hydralazine or ACE inhibitors, not all studies showed a decrease in blood pressure, a goal that must be achieved in order to affect afterload mismatch. Not all studies showed a reduction in LV size or an improvement in LVEF. In a follow-up to the above study on hemodynamics, Scognamiglio, et al (24) randomized 143 asymptomatic patients with chronic severe AR to either nifedipine 20mg BID or digoxin 0.25 mg QD. The patients were followed for a mean period of 6 years; 20 patients on digoxin required valve replacement compared to 6 patients on nifedipine ($p<0.001$). The incidence of progression to valve replacement in the two groups is shown in Fig 3).

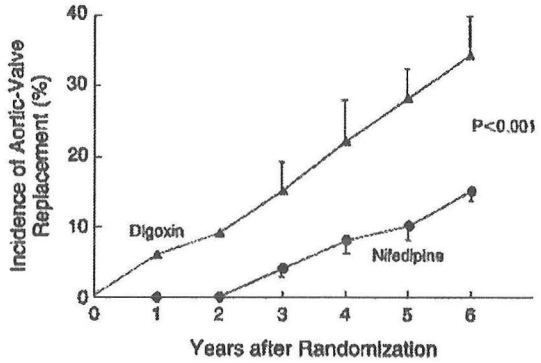


Fig 3. Cumulative incidence of progression to aortic valve replacement in patients randomized to digoxin vs nifedipine. From Scognamiglio et al (24).

Clinical Recommendations for Using Vasodilators in Aortic Regurgitation

Based on current knowledge, vasodilator therapy for chronic severe AR should be limited to patients who do not have an indication for surgery or cannot undergo surgery due to other risk factors. Nifedipine is the drug of choice, primarily because of the Scognamiglio data. The dose

of nifidipine used in the Scognamiglio study was 20 mg BID; however, hemodynamic considerations warrant increasing the dose if needed to effectively reduce systolic blood pressure. As noted before, the point of vasodilator therapy in AR is to reduce the systolic afterload mismatch and protect the LV. Vasodilators are not very effective at reducing the regurgitant volume in most patients with chronic severe AR because the orifice is fixed and the diastolic pressure gradient is already low.

MITRAL REGURGITATION

Natural History of Mitral Regurgitation

The natural history of chronic severe MR is difficult to precisely define because of the varying underlying disease processes and associated rates of progression. For example, the clinical course of patients with MR secondary to dilated cardiomyopathy differs substantially from that in patients with rheumatic MR or mitral valve prolapse. Since most of the early studies of the natural history of MR contained mixed etiologies and did not rigorously define the severity of MR, few conclusions can be drawn from them. However, more recent studies have begun to emerge that suggest that the prognosis of patients with severe MR treated conservatively is poor. Such patients may remain asymptomatic until after irreversible LV dysfunction has already occurred. Combining this information with surgical advances such as chordal preservation and valve repair that have dramatically improved surgical mortality and morbidity, a concensus is developing that favors early surgery for severe MR, even in asymptomatic patients.

Liang et al (25) reviewed the records of 229 patients with flail mitral leaflets by echocardiography. Of these, 86 had been treated medically and 143 underwent surgical correction. The mortality rate was 6.3% per year in the medically treated group and was significantly higher than the expected mortality based on U.S. census data ($p=0.016$). Predictors of mortality were age, symptoms, and LV dysfunction. In contrast, the 10 year survival of patients who were treated surgically was 79 ± 3% which was no different than expected ($p=0.68$). In a multivariate analysis, surgery reduced the mortality rate (hazard ratio 0.29, 95% CI 0.15-0.56).

Enriquez-Sarano, et al reviewed the records of 409 patients who underwent surgical correction of MR at the Mayo Clinic (26,27). They found that the operative mortality declined significantly over time (Table 3). Predictors of survival by multivariate analysis were age, year of operation, NYHA symptom class, atrial fibrillation, coronary artery disease, creatinine, LVEF, and LV end-systolic volume index. Figure 4 shows survival for patients grouped according to LVEF. These data indicate that once LVEF falls below 60%, prognosis worsens in MR. Other studies have shown that once LV end-systolic dimension rises above 45 mm, prognosis worsens (28-30).

Table 3. Relation of surgical mortality to surgical period, stratified by age.

Age (years)	Surgical period 1980-1984	Surgical period 1985-1989
≥ 75	31% (n=26)	12% (n=57)
< 75	7% (n=142)	1% (n=184)

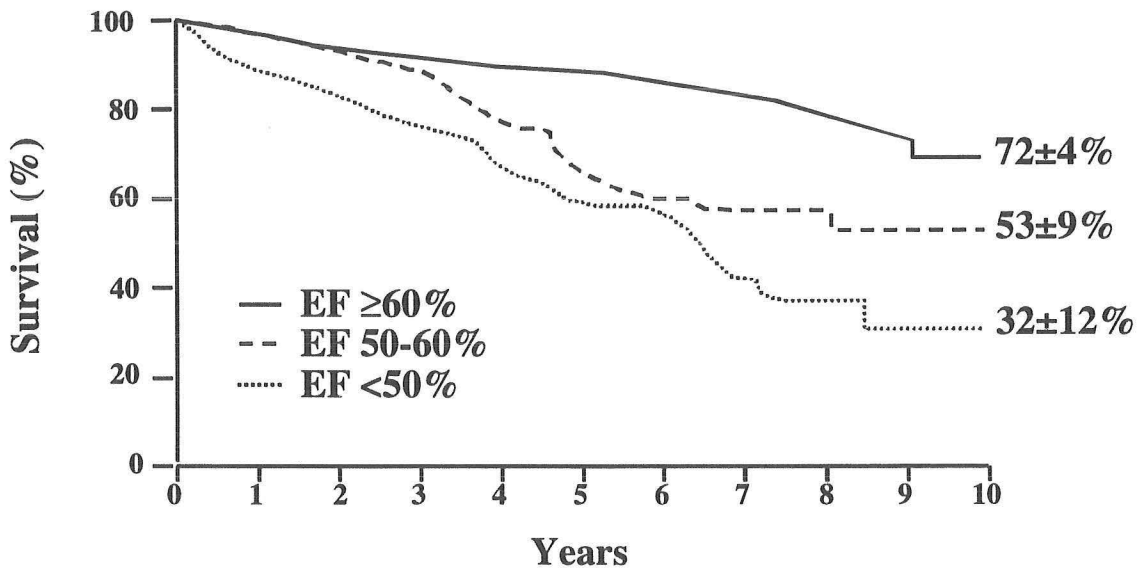


Fig 4. Survival curves of patients undergoing mitral valve surgery stratified according to LVEF. Data from Enriquez-Sarano, et al (ref 26).

Indications for Surgery in Mitral Regurgitation

Indications for surgery in severe MR are listed in Table 4. It is important to understand that prognosis worsens once LVEF falls below 60% or LV end-systolic volume reaches 45 mm. Therefore, surgery should be considered in asymptomatic patients before their LV function reaches these threshold values. This typically requires careful serial follow-up. It is also true that many of these patients gradually decrease their activities over time due to the regurgitant lesion. Therefore, a very careful history and exercise test may be useful in determining symptom status (i.e. functional class).

Table 4. Indications for Surgery in Severe Chronic Mitral Regurgitation

- Symptoms attributed to severe MR (even NYHA Class II symptoms)
- Asymptomatic with LV end-systolic dimension approaching 45 mm
- Asymptomatic with LV ejection fraction < 60%

Hemodynamic Determinants of Mitral Regurgitant Volume

To understand the effects of vasodilator therapy in MR, one must examine the hemodynamic determinants of mitral regurgitant volume by the Gorlin hydraulic orifice equation (11). According to this equation, mitral regurgitant volume is determined by the regurgitant orifice area (ROA), a constant known as the discharge coefficient (C_d), the mean pressure gradient in systole between the LV and the LA (MPG), and the time or duration of the MR in systole (T). Each aspect of this equation merits careful consideration.

First, unlike AR, the regurgitant orifice area in MR is often dynamic and highly dependent on loading conditions (11,31,32). Thus, the actual mechanism of MR is very important in determining whether the regurgitant orifice is dynamic or not. In rheumatic MR, the valve is generally fibrotic, calcified and immobile. The regurgitant orifice is fixed and unlikely to change with load manipulation. In patients with dilated cardiomyopathy, MR is a consequence of

annular dilatation and is very dynamic. Load manipulations that reduce LV size and hence, annular size will cause the regurgitant orifice to become smaller. On the other hand, reducing LV size in a patient with mitral valve prolapse may increase the regurgitant orifice and the severity of MR. Kizilbash, et al (33) studied the effects of acute administration of sodium nitroprusside on MR severity in 31 patients and found that MR improved in 16 (52%), worsened in 8 (26%), and was unchanged in 7 (22%). Figure 5 shows a example of a patient with mitral valve prolapse in whom MR severity is markedly worsened by acute vasodilation with sodium nitroprusside.

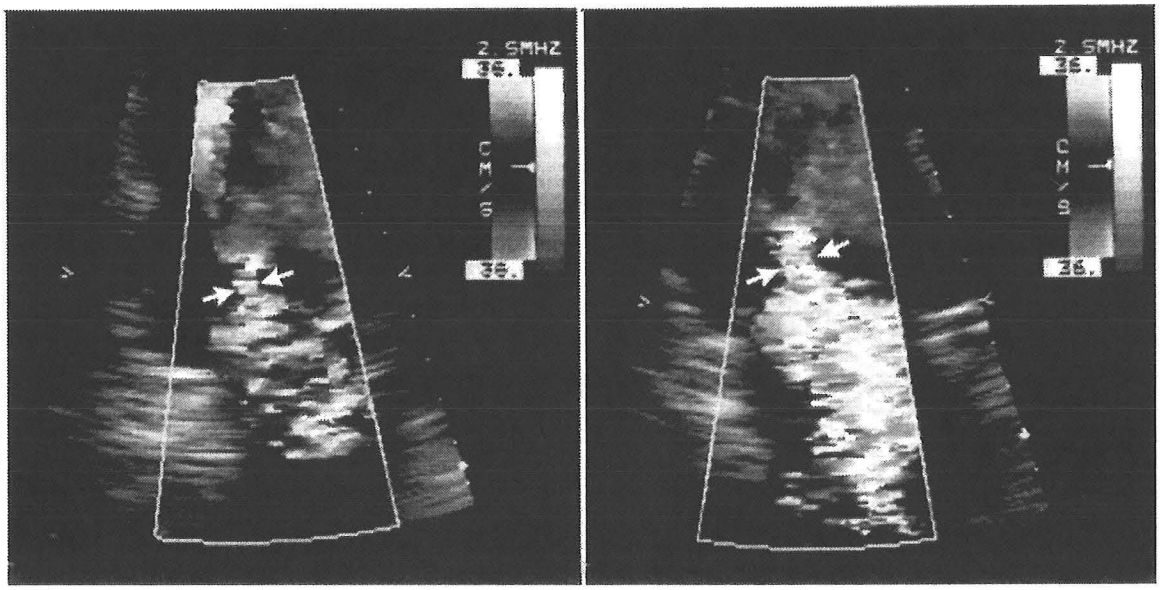


Fig 5. Left panel. MR jet across the mitral valve in a patient with mitral valve prolapse. **Right panel.** After nitroprusside, the MR jet is wider due to the dynamic nature of the mitral orifice in mitral valve prolapse.

The second part of the hydraulic orifice equation is a constant which accounts for contraction of the flow stream as it passes through the anatomic orifice. This discharge coefficient is dependent on orifice geometry, flow, and fluid viscosity. It is not likely to be significantly affected by vasodilator therapy.

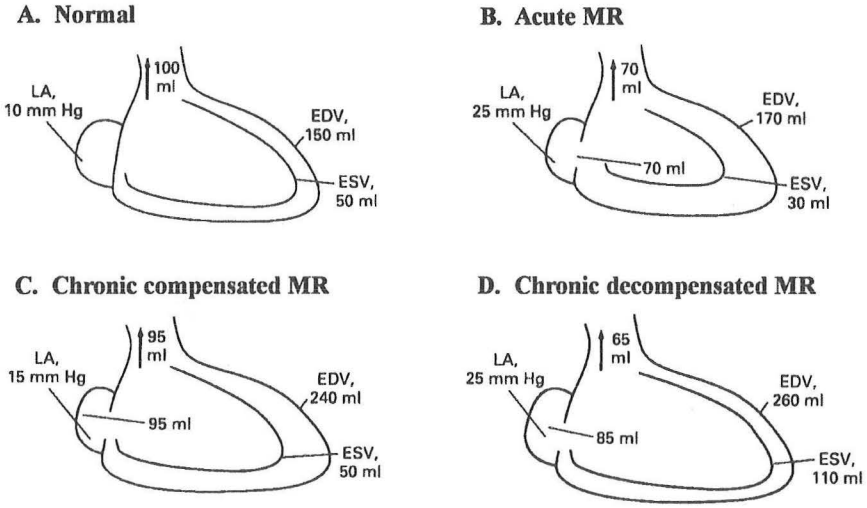
The mean systolic pressure gradient between the LV and LA may be reduced by vasodilator therapy but this effect is blunted by two factors. First, vasodilator therapy reduces both the LV and LA pressures such that the gradient is not reduced as much as the LV systolic pressure is. Second, a 25% reduction in gradient will only reduce regurgitant volume by 13% since the effect of gradient is a function of its square root.

Finally, systolic ejection time. Is not reduced by much even during tachycardia, so this parameter is not a therapeutic target for reducing mitral regurgitant volume.

Effects of Mitral Regurgitation on LV Function and Geometry

The effects of chronic MR on LV function and geometry have been well-studied in animal models and in humans (Fig 6). Acute MR causes supernormal LV ejection performance because of the increased preload of the MR regurgitant volume and the reduced afterload of ejecting into the left atrium. Over time, the LV begins to compensate by dilatation and eccentric hypertrophy.

Unlike concentric hypertrophy due to pressure overload in which sarcomeres are arranged in parallel with thickening of the myocardial walls, eccentric hypertrophy exhibits sarcomeres arranged in series with thin myocardial walls. Despite the fact that the LV is emptying into the low impedance left atrium, the gradual dilatation of the LV cavity without wall thickening causes wall stress (afterload) to increase over time. Eventually end-systolic wall stress becomes increased, there is loss of myocytes, and the LV decompensates with rapid progression to irreversible heart failure. It has been shown that afterload is actually increased in chronic severe MR with LV dilatation (34,35). Moreover, the unique loading conditions in chronic severe MR allow a situation in which LV ejection performance (i.e. LVEF) can be maintained in the "normal" range despite significantly impaired LV muscle function (34,35).



STAGE	PRE-LOAD SL μm	AFTER-LOAD ESS kdyn/cm²	CF	EF	RF	FSV ml
Normal	2.07	90	N	0.67	0.00	100
AMR	2.25	60	N	0.82	0.50	70

STAGE	PRE-LOAD SL μm	AFTER-LOAD ESS kdyn/cm²	CF	EF	RF	FSV ml
AMR	2.25	60	N	0.82	0.50	70
CCMR	2.19	90	N	0.79	0.50	95

STAGE	PRE-LOAD SL μm	AFTER-LOAD ESS kdyn/cm²	CF	EF	RF	FSV ml
CCMR	2.19	90	N	0.79	0.50	95
CDMR	2.19	120	↓	0.58	0.57	65

Fig. 6. Stages in the progression of MR (adapted from Carabello, ref 9).

Clinical Studies of Vasodilator Therapy in Chronic Mitral Regurgitation

Acute vasodilator therapy in MR is well known to produce salutary hemodynamic effects and has been reviewed by Gaasch and Levine (11). Unfortunately, there are few data regarding the effects of chronic vasodilator therapy in MR. Wisenbaugh (21) randomized 32 patients with rheumatic MR to captopril or placebo for a 6 month period. Blood pressure was not significantly changed by captopril and there was no difference between groups in LV volumes or LVEF. On the other hand, Schon et al (36) showed that quinapril reduced LV end-diastolic volume and regurgitant volume after 1 year of therapy. The small number of patients and non-randomized design make it impossible to draw any conclusions.

In a dog study of chronic (3 months) MR, it has been shown that beta-blocker therapy prevents myocyte loss and LV decompensation (39). This intriguing finding remains to be evaluated in patients with primary MR; however, Lowes et al (40) improved LV mass, geometry

and severity of MR in dilated cardiomyopathy. Future studies are needed to determine if beta-blockers will be effective for chronic MR due to primary diseases of the mitral apparatus.

Clinical Recommendations for Using Vasodilators in Chronic Mitral Regurgitation

There are two major concerns regarding the use of chronic vasodilator therapy in MR. One is that the use of vasodilators may mask the development of LV dysfunction and cause surgery to be delayed until it is too late (35). The other is that vasodilator therapy may worsen MR in some patients and accelerate the process of LV dysfunction (33). Both concerns are valid. Accordingly, vasodilator therapy for chronic severe MR should generally be avoided. It is particularly important not to give vasodilators to patients with MR secondary to mitral valve prolapse or hypertrophic cardiomyopathy. It is important to emphasize that these concerns apply to patients with MR due to primary disease of the mitral apparatus. Patients in whom MR is secondary to a dilated cardiomyopathy comprise a subset in whom vasodilator therapy is clearly beneficial (37,38). Thus, it should be clear that the mechanism and severity of MR need to be established in order to make rational decisions regarding surgical or medical therapy.

Summary

The use of vasodilator therapy in chronic aortic and mitral regurgitation may be beneficial in selected patients and harmful in others. The hemodynamics of the two lesions are different and must be taken into account. In AR, vasodilators reduce afterload mismatch and can preserve LV function and delay the need for surgery. However, if the patient has severely reduced diastolic blood pressure, vasodilators could potentially impair coronary perfusion. In mitral regurgitation, vasodilators may reduce regurgitant volume and hence, LV preload depending on the mechanism of MR. In patients with MR secondary to dilated cardiomyopathy, vasdilators reduce symptoms and improve functional class. However, in mitral valve prolapse or hypertrophic cardiomyopathy, vasodilators may worsen the MR and should be avoided. In other primary causes of MR, vasodilators could potentially mask the development of LV dysfunction and lead to unnecessary and harmful delays in surgery.

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