EDITORIAL COMMENT

Doing Away With Dogma: Increasing Afterload To Reduce Mitral Regurgitation*

Thomas Wisenbaugh, MD, FACC
Tulsa, Oklahoma

As heart failure due to coronary and other nonvalvular heart disease becomes more prevalent in the urbanized world, functional mitral regurgitation will become a problem of increasing importance (1). Functional mitral regurgitation, which decreases effort tolerance and worsens prognosis in cardiomyopathy (2,3), is present in most patients referred for cardiac transplantation (4). It is therefore appropriate to direct efforts toward understanding and treating functional mitral regurgitation in cardiomyopathy.

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In this and a recent issue of the Journal of the American College of Cardiology, the cardiac ultrasound team from Massachusetts General Hospital (MGH) is challenging traditional concepts about mitral valve function in dilated cardiomyopathy. In severely dilated, poorly contracting ventricles, the mitral valve sometimes appears on ultrasound to be barely moving from a “tented” configuration somewhere between its normal fully closed position and normal fully open position. We have always assumed this to reflect a low flow state, and there were data in the literature to support this intuitive notion. However, in the August issue of the Journal of the American College of Cardiology (5), these investigators showed that mitral leaflet excursion was reduced despite normal transmirtal flow in patients who had both incomplete mitral leaflet closure and severely dilated ventricles, but was nearly normal despite reduced flow in patients with less severely dilated ventricles. They concluded that it is not low flow that accounts for reduced diastolic excursion of the mitral leaflets in dilated cardiomyopathy, but rather reduced chordal “slack,” that is, leaflet tethering (5).

Tethering is a result of, or interacts with, several other nonleaflet parameters to cause functional mitral regurgitation. These parameters include transmirtal systolic pressure and the sizes, geometries and contraction patterns of the left ventricle and mitral annulus. Depression of contractility has been presumed to be the initiating factor. Secondary dilation of the left ventricular chamber and to a lesser extent the mitral annulus (8) then cause apical and lateral displacement of the papillary muscles which, in turn, alters the location and degree of coaptation of the mitral leaflet edges (7,8). Experimentally increasing left ventricular size and transmirtal systolic pressure with angiotensin increased regurgitation (9). Nitroprusside infusion, which reduced ventricular volume, reduced mitral regurgitation without changing transmirtal systolic pressure (10). Despite its vasoconstrictor effect, norepinephrine did not increase regurgitation because it reduced regurgitant orifice size, presumably because of a positive effect on contractility of either the left ventricle or mitral annulus or both (9).

With so many variables simultaneously affecting mitral regurgitation, it has been difficult to be certain which is the most fundamental one. In this issue of the Journal of the American College of Cardiology (11), the MGH team has used the Doppler proximal flow convergence technique, at which they are expert, to study the time-course of functional mitral regurgitation throughout the cardiac cycle in patients with cardiomyopathy. These investigators confirmed their previous finding of a midsystolic decrease in regurgitant orifice area that mirrored increases in systolic transmirtal pressure, a pattern that seems to be unique to functional and ischemic mitral regurgitation. Because systolic decreases in mitral annular area did not correlate as well with dynamic regurgitant orifice area, and because there was also a midsystolic decrease in regurgitant orifice area in four patients with rigid mitral annular rings, they concluded that systolic transmirtal pressure—and not ventricular or annular contractility—was of fundamental importance in mitral valve closure. They also state that “decreased left ventricular pressure with vasodilator therapy could potentially exacerbate regurgitation” and, conversely, that “increased left ventricular pressure with increased afterload could . . . reduce mitral regurgitation.”

I consider their data interesting but their conclusions faulty for two reasons. The first and most obvious reason is that regurgitant orifice area is only one of two variables that determine regurgitant flow. The second determinant is transmirtal systolic pressure: the higher the left ventricular systolic pressure, the higher the regurgitant flow for any given orifice area and left atrial pressure. This helps explain why an earlier study of patients with functional mitral regurgitation due to cardiomyopathy showed that 80% of regurgitant flow occurs during midsystole even though mitral regurgitant orifice area decreased by 20% during the ejection phase of systole, and only 20% of total regurgitation occurred during the prejection and postejection phases (12). Thus, systolic pressure forces regurgitation through the mitral orifice at a time when its size is decreasing. This distinction is important because it is the amount of regur-

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From the Cardiology of Tulsa, St. Francis Hospital, Tulsa, Oklahoma.
gitant flow and not orifice size that determines left atrial pressure and symptoms.

The data of Hung and coworkers (11) suggest a second flaw in their eagerness to do away with dogma: they found that the rate of change of transmitral pressure had an even greater effect on regurgitant orifice area than pressure itself. The rate of change of transmural pressure, or dP/dt, is a measure of contractility. Thus, even though they have concluded otherwise, this finding suggests that contractility is the most important determinant of systolic mitral valve function. This is corroborated by the findings of others (13). Increasing contractility shortens the pre-ejection phase of systole, and this is the period of the cardiac cycle when the mitral valve is still closing and when most of the decrease in regurgitant orifice size occurs. This is illustrated nicely in Figures 3 and 5 of Hung et al., which seem to show very little change in orifice size during the ejection phase of systole.

So what should we make of their suggestion that increasing left ventricular pressure and afterload might be used to reduce functional mitral regurgitation? The answer to this question has two facets because left ventricular pressure can be manipulated in two ways: 1) peripheral resistance, and 2) contractility. There is already evidence that currently used vasodilator therapies for heart failure reduce functional mitral regurgitation. Short-term treatment with diuretic agents and vasodilating drugs reduced total stroke volume but increased forward stroke volume in 15 patients with cardiomyopathy, indicating that load reduction reduces functional mitral regurgitation (14). Two additional studies have shown afterload reduction with an angiotensin-converting enzyme inhibitor to be beneficial in reducing functional mitral regurgitation (15,16). More recently, Kizibash and coworkers (17) found that load reduction with nitroprusside unexpectedly increased mitral regurgitation in approximately a fourth of their patients with mitral regurgitation. Hung et al. (11) cite this as evidence to support their conclusions. However, mitral regurgitation was reduced by nitroprusside in all nine of their patients with cardiomyopathy (18). Thus, the weight of available evidence supports the traditional concept that reducing left ventricular pressure by reducing peripheral resistance reduces functional mitral regurgitation in cardiomyopathy.

An increase in left ventricular pressure by increasing contractility can be achieved with short-term infusion of dobutamine, which reduces left ventricular diastolic volume and significantly reduces mitral regurgitant fraction (18). Conversely, with long-term beta-blockade using metoprolol in cardiomyopathy, there was an increase in ejection fraction, a decrease in the grade of mitral regurgitation and an increase in systolic blood pressure (19). Thus, long-term treatments that we now know to remodel (angiotensin-converting enzyme inhibitors) and rest (beta-blockers) the myocardium both reduce functional mitral regurgitation while having opposite effects on left ventricular (and probably transmitral) pressure. All these interventions probably reduce functional mitral regurgitation by the same mechanism, namely, by partially reversing the abnormalities in ventricular contractility and geometry that caused it, and allowing earlier and more complete coaptation of the mitral leaflet edges. That “tethering distances were not statistically different throughout systole” in the present study may be due to an inability of echo to measure small (20) but hemodynamically important differences.

In summary, increasing left ventricular and transmitral systolic pressure can indeed be accompanied by a reduction in functional mitral regurgitation through a reduction in regurgitant orifice size. However, these increases in pressure should be effected only through treatments that restore left ventricular size and contractility, as these are the fundamental determinants of normal mitral and pump function. Thus, the MGH group has challenged our thinking about mitral valve function in cardiomyopathy, but the data supplied in the present article should not alter the sound concept that afterload reduction reduces the burden of functional mitral regurgitation.

REFERENCES

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