

# The Prognostic Impact of Exercise-Induced Worsening of Mitral Regurgitation in Patients With Left Ventricular Dysfunction and Myocardial Ischemia

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“Ischemic mitral regurgitation (MR)” is convenient shorthand for functional MR caused by changes in ventricular structure and function, ultimately—but not necessarily directly—related to the effects of ischemia.<sup>1</sup> In the vast majority of cases, ischemic MR is essentially post-infarction MR, caused by progressive left ventricular (LV) remodeling rather than reversible ischemia. Lancellotti and Pierard have found exercise-induced increases in mitral regurgitant orifice areas in patients with systolic left ventricular dysfunction in the absence of ischemia defined as newly developed or significantly worsening wall motion abnormalities.<sup>2,3</sup> The observation of an exercise-induced deterioration of MR in itself is therefore never evidence of ischemia as the underlying cause of it. The terms “transient” “reversible,” and “dynamic” are not equivalent to the term “ischemia.” As the mitral valve is anchored to the ventricular myocardium through the papillary muscles, variations in LV volume and shape (more spherical during exercise) caused by changes in loading conditions will directly affect the tethering forces that oppose valve closure. For example, myocardial segments with substantial scar tissue, which lack the contractile force to withstand the rise in left ventricular pressure and load that occurs with exercise, may simply be strained in an outward direction, thus increasing tethering of the mitral valve. Therefore, scar tissue can behave quite dynamically even in the absence of any ischemia. However, the fact that exercise-induced worsening of MR in patients with LV dysfunction may occur in the absence of transient ischemia does not imply that its presence may not be important.

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In the current issue of the *Revista*, Peteiro et al provide valuable data from a large consecutive group of patients, which strongly suggest, that ischemia may be a significant contributor to worsening of MR during exercise.<sup>5</sup> Importantly, the authors demonstrate that such worsening of MR is independently associated with cardiac death and provides therefore incremental prognostic information both to the degree of resting MR as well as to other exercise echocardiographic predictors of events.

A possible prerequisite for the phenomenon of significant increases in ischemic MR during exercise is the presence of LV remodeling and dysfunction at baseline, which sets the stage for mitral valve tethering. Consequently, almost 2/3 of patients had already some degree of MR at rest, which was moderate or severe in more than a quarter. Without such baseline remodeling and baseline MR, significant MR during exercise is rarer (despite the impressive example of Figure 1), as shown by the group from A Coruña itself in a previous paper,<sup>6</sup> where only one of 42 patients without mitral regurgitation at rest developed severe MR during exercise, associated with ischemia (6 developed a moderate degree of MR). A word of caution with respect to the methodology: as the authors themselves are aware, jet size is not only dependent on regurgitant flow and orifice area, but also on driving pressure. The same increase in mitral regurgitant flow may therefore result in a larger increase in planimetered jet area in a patient with a more hypertensive blood pressure response. Confirmation by alternative techniques, such as the proximal flow convergence technique or the vena contracta method, would have been desirable, but these techniques may be more difficult to apply in combination with a treadmill stress test than with bicycle ergometry.

## What Is the Mechanism of Ischemic Worsening of Mitral Regurgitation?

Obviously, ischemia may transform segments which are normokinetic and hypokinetic at rest into noncontracting segments, particularly in case of myocardial tissue with patchy necrosis. Such segments

cannot withstand the increase in LV pressure and load that occurs during exercise and may therefore behave like scar tissue, which is passively distended or displaced (akinetic or dyskinetic), thus increasing mitral tethering, especially following posterior wall myocardial infarction. In other words, ischemia might cause transient LV remodeling on top of the distortion of LV geometry already present at rest in the post-infarct ventricle. This also explains why ischemia in the vicinity of the infarct area—contiguously extending the area of akinesis that caused the MR in the first place—is more likely to worsen MR than ischemia at a distance (Table 3). Once ischemia subsides, and loading conditions normalize the degree of LV shape distortion returns to baseline values.

### Is it Really All Ischemia?

A de novo wall motion abnormality in a myocardial segment with normal contraction at rest, and which does not border to an infarct zone, is clearly evidence of ischemia. However, normal segments next to an infarct zone may mimic ischemia during exercise, when they become tethered by neighboring scar tissue that becomes dyskinetic. Moreover, worsening of a preexisting wall motion abnormality could also be due to contractile dysfunction in a segment with patchy necrosis from previous microinfarctions; the contractions of such a segment may deteriorate directly as the result of an increasing load during exercise, even in the absence of significant ischemia. The use of validated criteria by a very experienced group and the clinical context strongly suggest that ischemia was indeed the cause of exercise-induced wall motion deterioration in the majority of cases. Nevertheless, deterioration of wall motion may occur more easily, and with a lesser degree of ischemia in myocardial segments already dysfunctional at rest.

### Why Is it Prognostically Important?

Does exacerbation of MR in itself increase the likelihood of a hard event, or is it simply the marker of ischemia in a dysfunctional post-infarct ventricle, which may precipitate death through a variety of mechanisms, including ventricular arrhythmias. *Prima facie*, the stepwise regression analysis would suggest that MR exacerbation independently contributes to the risk of death, in addition to parameters of ischemia and myocardial dysfunction (such as the extent of wall motion abnormality during exercise and exercise ejection fraction), and this is indeed a possible explanation. However, pathophysiological questions can usually not be settled by multivariate analysis, even if carefully performed as in the present paper. Statistics cannot establish causality; “independent predictor” is not a synonym for “cause of event.” MR exacerbation may have emerged unrejected from the stepwise regression analysis simply because it may be easier to assess than

wall motion abnormalities, the assessment of which may show substantial interobserver variability even between experts from leading core laboratories.<sup>7</sup> Interestingly, and as the authors clearly state, exacerbation of MR was only of prognostic importance in patients with an abnormal exercise echocardiographic response. Therefore, an alternative explanation might be that exacerbation of MR measured by color Doppler is simply a more robust and readily assessable expression of the degree of myocardial ischemia and dysfunction than visual assessment of wall motion abnormality and ejection fraction. It is probably both, an independent contributor as well as a marker of underlying disease severity. In any case, “whether the pitcher hits the stone or the stone hits the pitcher, it goes ill with the pitcher” (Don Quixote, Vol. II, Ch. XXII): Exacerbation of MR during exercise is an independent predictor of an adverse prognosis.

### Can We Treat it?

In order to answer this question, on the other hand, we do need to know who hits whom, the pitcher the stone, or vice versa. Is ischemic MR only the result of remodeling, or does it also promote further remodeling with all of its detrimental consequences for prognosis. Experimental data indicate that mitral regurgitant volume-overload reversibly promotes remodeling at the whole-heart, cellular, and molecular level.<sup>8</sup> Results of surgical annuloplasty in patients with MR and systolic LV dysfunction were so far disappointing.<sup>9</sup> However, these were not necessarily patients with exercise-induced ischemia. Moreover, mitral annuloplasty alone may not be the optimal repair strategy; although usually successful immediately post repair, it is associated with a relatively high failure rate at 6 months.<sup>10</sup> Revascularization in patients with significant ischemia and left ventricular dysfunction can improve prognosis and may therefore be indicated irrespective of the presence of MR.<sup>11,12</sup> Despite the fact that revascularization—coronary bypass grafting or percutaneous coronary interventions—may improve prognosis in patients with ischemic MR<sup>12</sup> the effect of revascularization alone on the degree of baseline MR itself has been disappointing.<sup>13</sup> This does not come as a great surprise, in patients whose baseline MR is caused by post-infarct remodeling. The potential effect of revascularization on the exercise-induced component of MR in patients with significant LV dysfunction needs still to be systematically studied.

### What Should We Do in the Meantime?

Patients with LV dysfunction, inducible significant ischemia and worsening of MR during exercise are a high-risk population, as clearly shown in the present study. They should receive optimal medical therapy, including beta-blocking agents and ACE-inhibitors, which have been shown to improve survival. In many of these

patients there will be an indication to coronary revascularization based on current guideline recommendations irrespective of the degree of MR. If these patients are referred for surgical revascularization, and when baseline MR is at least moderate, mitral valve repair (usually ring annuloplasty) should be performed. A recommendation to perform ring-annuloplasty also in patients referred for surgical coronary revascularization who have mild regurgitation at rest, but significant regurgitation during exercise, cannot be given at this point.

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