Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 4, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.09.046

EDITORIAL COMMENT

The Conundrum of Functional Mitral Regurgitation in Chronic Heart Failure*

Maurice Enriquez-Sarano, MD, FACC,†
Didier F. Loulmet, MD,‡
Daniel Burkhoff, MD, PHD§

Rochester, Minnesota; and New York, New York

Heart failure begets mitral regurgitation (MR); MR begets heart failure. This incestuous and insidious relationship has long been known to contribute to the positive feedback loop that underlies progressive, pathologic ventricular remodeling in chronic heart failure (CHF). Yet, despite decades of investigation and thought, important questions have gone unanswered, many with direct relevance to the care of CHF patients with MR. Fundamentally, these questions revolve around understanding how much MR contributes to symptoms and disease progression, whether to intervene and, if so, when to intervene surgically to eliminate MR. With lack of randomized clinical trials proving benefit, along with associated risks, surgical correction of MR is not performed

See page 476

frequently as a standalone procedure in patients whose primary problem is a dilated failing heart. However, several different approaches for percutaneous mitral repair are currently in development and will soon provide less invasive alternatives that could facilitate such questions being addressed. Therefore it is relevant and important to refocus attention on understanding the role of MR in the pathogenesis and progression of CHF. In this regard, the study reported by Beeri et al. (1) in this issue of the *Journal* provides an important contribution.

After an infarct or in early stages of dilated cardiomyopathies, ventricular remodeling (dilation and deformation) occurs and can be associated with mitral annular distortion and/or dilation. Papillary muscles might be infarcted or can be dysfunctional during periods of ischemia. Importantly, recent studies have revealed that apical and posterior displacement of one or both papillary muscles due to left ventricular (LV) dysfunction and remodeling are critical in initiating MR (2–4). Such displacement causes traction on the inextensible chordae tendinae, particularly the strut chords attached to the body of both mitral leaflets. This pulls the leaflets into the LV, resulting in "tenting" of the valve over the plane of the annulus and a reduced area of leaflet coaptation. In turn, the reduced coaptation leads to formation of a regurgitant orifice. Such MR occurring in the setting of LV dilation with structurally normal leaflets is referred to as functional mitral regurgitation (FMR). This is distinguished from organic mitral regurgitation, which occurs in the setting of primary valve pathology, as in rheumatic heart disease.

By the time most patients present with symptoms of heart failure, ventricular dilation and MR are typically both present. Although the degree of FMR can be reduced in some cases by optimizing medical therapies (afterload reduction and treatment of fluid overload), many patients persist with significant FMR. In the clinical setting, however, it is usually difficult if not impossible to tease out the relative contributions of the primary pump dysfunction and FMR to LV remodeling and patient symptoms. Consequently it is not known for a given patient whether fixing FMR will improve symptoms or play any role in reversing ventricular dilation and pump dysfunction.

Clinical studies of the role of FMR provide a somewhat confusing message. On the one hand, recent data suggest that even moderate FMR (≥30 ml/beat or effective regurgitant orifice ≥20 mm^2) has serious clinical consequences (5,6). Patients with FMR incur higher mortality (approximately twice) and have a greater risk of developing CHF (approximately 4 times) than those without. On the other hand, several prior observational and retrospective studies suggested that treating ischemic FMR did not lead to reverse remodeling (7), did not provide superior survival compared with bypass alone (8,9), and treating cardiomyopathy with FMR by valve repair did not seem to provide better survival than medical treatment (10). Therefore, some authors already consider surgery of FMR as a failed innovation (11). However, these observational results do not answer the question of whether FMR influences outcome in patients with LV dysfunction, particularly because mitral surgery has had limitations related to recurrence of FMR due to ongoing LV remodeling with reappearance of valve tenting after annuloplasty (12,13). The uncertainty regarding FMR is further complicated by the fact that patients with FMR also have, in general, worse LV function, remodeling, and clinical presentation (2,5). Even after matching patients with and without FMR for ejection

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Mayo College of Medicine, Rochester, Minnesota; ‡Lenox Hill Hospital, New York, New York; and §Columbia University, New York, New York. Dr. Enriquez-Sarano has a research contract with Edwards, Life Sciences, Pfizer, and AstraZeneca; is on the Scientific Advisory Board of Edwards Life Sciences, and has received honorarium from Edwards Life Sciences. Dr. Loulmet is on the Scientific Advisory Board and has stock in the Guided Delivery System. Dr. Burkhoff is an employee and owns stock in IMPULSE Dynamics; is on the Scientific Advisory Board and owns stock in Guided Delivery Systems; and owns stock in Mitralign.

JACC Vol. 51, No. 4, 2008
January 29, 2008:487–9

fraction, one might wonder whether lower LV intrinsic function (undetected by standard methods) is not the main driver for excess risk (5). Thus, controlled studies are needed in which the only difference between cases and control subjects is the treatment of FMR.

Such was the approach employed by Beeri et al. (1), who conducted a remarkable experimental study that eliminates some of the outstanding uncertainties of clinical studies. Techniques for inducing ventricular dilation and heart failure by myocardial infarction are well established in many animal species. However, these models don't always develop MR, even when special attention is given to try to infarct the papillary muscles and overlying apical and lateral walls (14). Furthermore, when it does occur, the degree of FMR is difficult to control. Rankin et al. (15) previously described an animal model of left ventricle-to-left atrial regurgitation (LVAR) as a surrogate for a model of FMR. The model was created by surgically placing an extracardiac artificial conduit between the LV and the left atrium in otherwise normal animals. It was shown that, over time, the presence of LVAR caused progressive ventricular dilation and myocardial dysfunction as signs of CHF developed. Beeri et al. (1) have now adapted this model to assess the additive role of FMR to the development of LV remodeling after a myocardial infarction. Key elements of the model are the consistently sized and located apical infarct and the relatively consistent, low-volume, 30% regurgitant fraction created by the LVAR. Methodologically, these researchers not only analyzed the changes of LV volumes during the experiment but also gathered complementary evidence of functional and biochemical changes that characterize ongoing LV remodeling. It was observed that the animals with LVAR incurred a much larger increase in LV volume and also incurred more severe systolic and diastolic LV alterations, reduced calcium cycling proteins, activation of prohypertrophic signaling pathways, cellular elongation, and activation of metalloproteinases and their inhibitors in the myocardium remote from the myocardial infarction. Thus, even a moderate-volume regurgitant fraction, similar to that typically seen clinically with FMR, is not a bystander from the point of view of progressive LV remodeling but is directly linked to excess LV remodeling and functional and biochemical markers thereof. Thereby, the present study establishes a firm link between FMR and excess LV remodeling, a well-established precursor of clinical events (16).

Certain limitations of the study should be acknowledged. First, the size of the myocardial infarctions seems to be relatively small and by itself leads to only modest dilation. It is not certain that the additive effect of MR in the setting of a larger infarct will equal that observed in the present study. Second, it would have been ideal to have included animals receiving only the LVAR shunt, so as to evaluate the final contribution of the original infarct to the remodeling. It is conceivable that the effects of the LVAR are so overwhelming that the initial infarct is actually inconsequential as it relates to the final amount of remodeling observed. Finally, and most importantly, it would have been most significant to have investigated the impact over time of eliminating the LVAR once the animals reached the final stable heart failure state. This would have answered the question, at least for this model, of whether elimination of MR in a dilated failing heart can have a beneficial effect on remodeling, LV function, and clinical status.

There are several important issues that need to be addressed in order to bring us closer to resolving the conundrum of FMR in the setting of CHF. Prospective clinical studies evaluating the impact of FMR and MR repair on outcomes are central to advancing understanding. Development of less invasive percutaneous therapies for treating FMR (17) might provide the means of addressing such questions without putting patients through the risks of surgery. Multiple designs are explored through coronary sinus, annular, or ventricular approaches, which are promising. Continued investigation through careful preclinical experimental work can help fill gaps in understanding that cannot be filled through clinical studies alone. In this regard, the comprehensive experimental study by Beeri et al. (1) in the present issue of the *Journal* is an important step in pursuing this important therapeutic pathway for patients with LV dysfunction and CHF who remain at high risk.

Reprint requests and correspondence: Dr. Daniel Burkhoff, Division of Cardiology, Columbia University, 177 Fort Washington Avenue, New York, New York 10032. E-mail: db59@columbia.edu.

REFERENCES

1. Beeri R, Yosefy C, Guerrero JL, et al. Mitral regurgitation augments post-myocardial infarction remodeling. J Am Coll Cardiol 2008;51:476–86.
2. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation 2000;102:1400–6.
3. Otsuji Y, Handschumacher MD, Schwammenthal E, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation 1997;96:1999–2008.
4. Watanabe N, Ogasawara Y, Yamaura Y, Kawamoto T, Akasaka T, Yoshida K. Geometric deformity of the mitral annulus in patients with ischemic mitral regurgitation: a real-time three-dimensional echocardiographic study. J Heart Valve Dis 2005;14:447–52.
5. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–64.
6. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
7. Enomoto Y, Gorman JH III, Moainie SL, et al. Surgical treatment of ischemic mitral regurgitation might not influence ventricular remodeling. J Thorac Cardiovasc Surg 2005;129:504–11.
8. Tolis GA Jr., Korkolis DP, Kopf GS, Elefteriades JA. Revascularization alone (without mitral valve repair) suffices in patients with advanced ischemic cardiomyopathy and mild-to-moderate mitral regurgitation. Ann Thorac Surg 2002;74:1476–80.
9. Harris KM, Sundt TM III, Aeppli D, Sharma R, Barzilai B. Can late survival of patients with moderate ischemic mitral regurgitation be

impacted by intervention on the valve? Ann Thorac Surg 2002; 74:1468–75.
10. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45:381–7.
11. Gorman JH III, Gorman RC. Mitral valve surgery for heart failure: a failed innovation? Semin Thorac Cardiovasc Surg 2006;18:135–8.
12. Hung J, Papakostas L, Tahta SA, et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. Circulation 2004;110:II85–90.
13. Zhu F, Otsuji Y, Yotsumoto G, et al. Mechanism of persistent ischemic mitral regurgitation after annuloplasty: importance of augmented posterior mitral leaflet tethering. Circulation 2005;112:I396–401.
14. Gorman JH III, Gorman RC, Plappert T, et al. Infarct size and location determine development of mitral regurgitation in the sheep model. J Thorac Cardiovasc Surg 1998;115:615–22.
15. Rankin JS, Nicholas LM, Kouchoukos NT. Experimental mitral regurgitation: effects on left ventricular function before and after elimination of chronic regurgitation in the dog. J Thorac Cardiovasc Surg 1975;70:478–88.
16. St. John SM, Pfeffer MA, Plappert T, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation 1994;89:68–75.
17. Webb JG, Harnek J, Munt BI, et al. Percutaneous transvenous mitral annuloplasty: initial human experience with device implantation in the coronary sinus. Circulation 2006;113:851–5.