

Functional Mitral Regurgitation and Transcatheter Mitral Annuloplasty

The Carillon Mitral Annuloplasty Device European Union Study in Perspective

David S. Bach, MD

In this issue, Schofer and colleagues present findings from the Carillon Mitral Annuloplasty Device European Union Study (AMADEUS), an uncontrolled multicenter trial in which percutaneous placement of a cinching device in the coronary sinus is used to treat functional mitral regurgitation (MR) of ischemic and nonischemic etiologies.¹ Of 48 patients enrolled, the device was successfully implanted in 30. Major adverse events occurred in 6 (13%) of 46 patients based on intent-to-treat. The severity of MR, based on 4 echocardiography/Doppler measures, decreased between 22% and 32%. There was substantial functional improvement (assessed by New York Heart Association functional class, 6-minute walk test, and the Kansas City Cardiomyopathy Questionnaire) at 1-month and 6-month follow-up. The study is at once exciting and provocative; it is the extrapolation of its results to clinical practice that may be controversial.

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Implications of Functional MR

Functional MR occurs as a result of malcoaptation of anatomically normal mitral leaflets caused by restricted systolic motion in the setting of dilation and/or geometric distortion of the left ventricle (LV), with or without mitral annular dilation. Its causes and outcomes are inherently different from organic MR that occurs as a result of anatomic abnormalities of the mitral apparatus.

Functional MR has been associated with an adverse prognosis among patients with dilated² and ischemic cardiomyopathy,³ with increased risks of heart failure and death. Surgical intervention has been associated with improved symptoms of heart failure and LV reverse remodeling.^{4,5} However, intervention for functional MR has not been shown to improve survival.⁶ The reasons for this may be complex, but possibilities include a true absence of survival benefit associated with intervention; inadequate reduction of MR or recurrence of MR with the use of existing techniques; or an

inability to detect a potentially small survival benefit in patients with confounding risks of coronary artery disease and LV systolic dysfunction in studies limited to relatively few patients and relatively short follow-up duration. At present, the absence of data supporting mortality benefit leads to strong opinions but no consensus as to whether, and in whom, functional MR should be addressed.

Surgical Therapies for Functional MR

Most surgeons favor mitral valve repair rather than replacement for the treatment of functional MR. The most common surgical repair technique is reduction annuloplasty, in which a prosthetic ring is used to decrease the dimension and sometimes alter the shape of the mitral annulus.^{4,5} A variety of annuloplasty devices exist for this purpose, of various shape, rigidity, and symmetry. An edge-to-edge suture between the anterior and posterior mitral leaflets (the "Alfieri stitch"), creating a double-orifice mitral valve, has been used in the treatment of functional MR.⁷ Therapies directed at restraining or directly changing the shape of the LV also have been investigated.

What lessons have been learned from surgical intervention for functional MR? First, intervention is feasible. Past theories that functional MR was a beneficial "pop-off" for the weakened LV have fallen by the wayside, and concerns that the LV would fail with the correction of functional MR have proven untrue.⁴ Second, intervention has been shown to result in LV reverse remodeling^{4,5} and stable or improved LV ejection fraction.⁴ Third, intervention appears to be associated with functional improvement.^{4,5} Fourth, as already noted, survival benefit has not been demonstrated.⁶

Mitral valve repair appears to effectively treat many but not all patients with functional MR. Opinions run strong, and debate continues as to what, if any, factors can predict the recurrence of MR after mitral repair; whether any one ring is superior to another; whether chordae tendineae should be severed, lengthened, or left alone; whether concomitant therapies aimed at directly reshaping the LV are required; and even whether mitral valve replacement should be used instead of valve repair. However, as it has evolved, technical lessons also have been learned about surgical mitral repair for functional MR, and some conclusions now are generally accepted. On the basis of compelling data showing that mitral annular dilation in cardiomyopathy is not limited to the posterior annulus,^{8,9} current reduction annuloplasty typically involves a "complete" ("D")-shaped annuloplasty ring rather than a "partial" ("C")-shaped ring that extends only from

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From the Department of Internal Medicine, Division of Cardiovascular Medicine; University of Michigan, Ann Arbor.

Correspondence to David S. Bach, MD, University of Michigan, CVC Room 2147, SPC 5853, 1500 E Medical Center Dr, Ann Arbor, MI 48109-5853. E-mail dbach@umich.edu

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trigone to trigone. In addition, edge-to-edge mitral repair appears to require concomitant mitral annuloplasty to reliably treat functional MR.⁷

Percutaneous Therapies for Functional MR

In general, strategies for the transcatheter treatment of functional MR fall into 1 of 4 groups: percutaneous edge-to-edge techniques that aim to simulate the Alfieri stitch, remodeling of the mitral annulus with a device implanted in the coronary sinus, remodeling of the mitral annulus with sutures or the application of radiofrequency energy, and remodeling of the mitral apparatus by intervention on the LV or the left atrium. With lessons already learned about surgical techniques for the treatment of functional MR, how will these be applied to transcatheter therapies?

Surgical edge-to-edge repair for functional MR typically requires concomitant annuloplasty.⁷ Although percutaneous edge-to-edge repair has been shown to be feasible and result in statistical improvement in MR, the amount of resulting MR would be seen as a procedural failure after surgical intervention.¹⁰ Surgical mitral annuloplasty typically relies on a complete ring to reshape the entire mitral annulus, whereas partial annuloplasty is believed to be ineffective. If transcatheter therapies are limited to modifying the posterior annulus, they may be trying to emulate a procedure already abandoned in the operating room. Furthermore, implantation of a device in the coronary sinus has additional limitations. In more than half of patients, the coronary sinus is superior to the mitral annulus, and the distance between the 2 is directly proportional to the severity of MR.¹¹ In more than two thirds of patients, the circumflex artery or 1 of its branches courses between the coronary sinus and the mitral annulus.¹¹ Finally, implantation of hardware in the coronary sinus presumably precludes its use in pacing for resynchronization therapy, and vice versa.

However, there are reasons to pursue transcatheter therapies for MR. MR is common; by 1 estimate, moderate or severe ischemic MR occurs in 12% of patients after acute myocardial infarction.³ As such, favorable results of intervention potentially could affect many people. Functional MR is associated with an adverse prognosis in terms of both heart failure and death.^{3,4} Although it is not known to what, if any, degree MR needs to be reduced to affect prognosis, it is an attractive field for investigation.

AMADEUS in Perspective

The AMADEUS trial is a description of the early use in humans of a cinching device implanted in the coronary sinus with the intent to treat functional MR. The investigators are to be congratulated on the study. Favorable results include a rate of major adverse events that was not prohibitive, evidence of a statistical reduction in MR severity, and functional improvement among subjects in whom the device was successfully implanted. However, the results also raise concern.

Although feasibility was demonstrated, device implantation was possible in only 30 (62%) of 48 patients. The rate of major adverse events (13% of subjects), although perhaps acceptable for an early feasibility trial, was not low. The reduction in MR severity, similar to other trials of transcath-

eter therapies for MR, was significant but not profound. (For 2 of the 4 echocardiography/Doppler measures of MR severity, the clinical grade of MR for the majority of patients remained unchanged before and after intervention, at mild or moderate MR.) The decrease in MR was unaccompanied by any evidence of LV reverse remodeling.

Although designed as a trial of feasibility and safety, the most provocative data regard improvement in functional status. Unfortunately, the trial was performed with no control group, and the known and powerful procedure-associated placebo effect cannot be discounted. (A hallmark study published in 1959 found that sham surgery in patients with severe angina pectoris was associated with 43% subjective improvement, 42% reduction in nitroglycerin use, and 36% increase in exercise tolerance time.¹²) Armed with objective data, it is tempting to conclude that the mitral procedure in the AMADEUS trial was responsible for improved functional status. However, the absence of a control group leaves this open to question.

The Future Role of Transcatheter Therapy for Functional MR

Will transcatheter intervention increase the recognition of and appropriate therapy for functional MR? Will the ability to perform a percutaneous procedure lead to its widespread use without validation of its efficacy? Does reduction in MR constitute an adequate end point? Because functional MR is common, because functional MR is associated with an adverse prognosis, and because it may be feasible to develop transcatheter treatments for it, future research is important. However, challenges lie ahead.

Transcatheter therapies are nascent, and continued refinement is inevitable. Trials with mortality outcomes would require years or even decades to perform, delaying access to data on which present therapies could be based. Measuring surrogate and secondary end points (including functional status) requires inclusion of a control group—a not insignificant (but not unprecedented¹³) challenge when the intervention is procedural rather than medical. Realistically, devices and techniques will continue to evolve even before outcome data are available. (In the present study, the design of the device was altered in the course of the trial because of issues with the distal anchor.) The cardiac surgical community has become accustomed to this scenario of trying to (therapeutically) hit a moving target using constantly evolving devices and techniques. In its new role of performing transcatheter interventions for heart valve disease, the evidence-based cardiology community may find that, in addition to trying to invent and apply new therapies, it needs to adapt to—but still operate responsibly in—a new world of therapies based on incomplete and missing data.

Disclosures

None.

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