EDITORIAL COMMENT

Is Mitral Regurgitation a Viable Treatment Target in Heart Failure?
The Plot Just Thickened*
Mandeep R. Mehra, MD, FACC,†
Bartley P. Griffith, MD‡
New Orleans, Louisiana; and Baltimore, Maryland

The traditional cautious attitude towards surgical correction of mitral regurgitation in the presence of severe left ventricular failure recently has been vigorously challenged (1,2). Recognition that mitral regurgitation occurs as part and parcel of the cardiomyopathic state has focused attention towards its amelioration as a viable therapeutic target. Several observational studies have pointed out the high prevalence of significant mitral regurgitation in chronic systolic heart failure as well its association with a poor five-year survival (3–5). Thus, the notion that treatment of systolic heart failure as well as its association with a poor five-year survival (3–5). Thus, the notion that treatment directed towards correcting the mitral valve could favorably alter outcome in heart failure has been advanced. Some researchers have even advocated the use of such a surgical approach as an alternative to transplantation (6). Observational investigations by experienced surgical teams have reported an improvement in symptoms and cardiac function. These results, however, suffer from lack of evaluation of a control group.

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In this issue of the Journal, Wu et al. (7) present perhaps the largest experience of mitral valve annuloplasty repair in patients who have severe left ventricular dysfunction. The primary objective of this retrospective analysis was to ascertain the effect of surgical annuloplasty on the end point of long-term mortality in patients. Using their echocardiographic database, these investigators studied 682 patients and excluded those who did not meet criteria for surgical intervention (n = 263). Of the remaining 419 patients, 126 underwent mitral valve annuloplasty and 293 did not. No improvement in long-term survival (or the combined end point of mortality or urgent transplantation) was evident in the surgical group, irrespective of heart failure etiology (either ischemic or nonischemic).

Unfortunately, this observational investigation suffers from the classical limitation of “confounding by indication,” which the authors sought to overcome by developing a propensity score and using it in the Cox model multivariable analysis. The propensity score is the conditional probability of exposure to a treatment given observed covariates. In a cohort study, matching or stratifying treated and control subjects on a single variable, the propensity score, tends to balance all of the observed covariates; however, unlike the random assignment of treatments, the propensity score may not balance unobserved covariates. In the simplest randomized experiment, the propensity score is 0.5 for every patient. In contrast, in an observational study, without random assignment, the chance of being assigned to one treatment or another may vary from patient to patient depending on prognostic variables. Propensity scores remove overt biases but do not account for hidden biases because of unrecorded differences between treated and control patients (8).

Other limitations of this study include the single center experience (largely contributed to by a single surgeon); the lack of follow-up on indices of ventricular structural remodeling; absence of any quantitative analysis of symptom or functional improvement; the inadequate control of appropriateness of medical therapy and, finally, little information on the long-term durability of the repair. Despite these analytical limitations, this review calls into serious question what many clinicians now refer to as an “alternative or bridge to transplantation” strategy. The reported five-year event-free survival is unaffected by whether the patients suffered from an ischemic or nonischemic etiology of heart failure and is much lower than the known outcomes at this time point from cardiac transplantation (9). In Bolling’s previous communications, he has stressed improvement in New York Heart Association functional class as a “winning” outcome even if long-term outcomes might include the need for transplantation or less strikingly improved survival (1). The present report, however, does little to clarify the important issue of possible symptomatic improvement.

Anatomy of the mitral valve. A normal mitral valve is characterized by apposition of the mitral valvular leaflet coaptation point at the annular plane during systole. In ventricular dysfunction, this point of coaptation shifts towards the ventricular apex (10). The ability to achieve appropriate leaflet coaptation is a function of a properly aligned leaflet, an optimally sized annulus, and a geometrically coordinated subvalvular apparatus (chordae tendinae and papillary muscles). Ventricular dysfunction is accompanied by annular dilation, an increase in the interpapillary muscle distance, amplified leaflet tethering, and decreased closing forces (11). Assessment of all these aberrations is vital because treatment options that attend to only one aspect are likely to lead to partial benefits. Although the report of Wu et al. (7) does not provide information on the durability of the repair, we know that annuloplasty alone for

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From the †Department of Cardiovascular Medicine, Ochsner Clinic Foundation, New Orleans, Louisiana; and the ‡Division of Cardiothoracic Surgery, University of Maryland at Baltimore, Baltimore, Maryland.
ischemic mitral regurgitation may be associated with recurrence of ≥2+ mitral regurgitation in as many as one-third of patients (12).

**Pharmacologic and cardiac resynchronization therapy effects on mitral regurgitation.** The treatment of heart failure has evolved from the neurohormonal model to devices that attempt to resynchronize focal areas of discordant contractility (13). Thus, pharmacological treatment with beta-blockers diminishes mitral regurgitation by favorable ventricular remodeling (14–16). Similarly, in the setting of decompensated heart failure, vasodilator therapy enhances forward stroke volume by decreasing mitral regurgitant fraction and reducing the mitral valve orifice area (17). However, cardiac resynchronization therapy improves mitral regurgitation by improving ventricular asynergy (18–20). This benefit is related to an increase in mitral valve closing forces generated by resynchronization therapy (19). These lines of evidence point to the importance of optimization of medical and nonsurgical device intervention in treating mitral regurgitation before surgery is entertained.

**Surgical aspects of mitral valve repair.** Although an “undersized” annuloplasty repair is believed to effectively correct mitral regurgitation in heart-failure patients, questions of its durability remain. Recurrent mitral leak is often due to progressive lateral displacement of the papillary muscles and attendant chordal tethering (12). Severe displacement of the anterior muscle may be predictive of recurrence. From a surgeon’s viewpoint, it is critical to plan the operative approach by being anatomically well informed. This includes knowledge of the presence of leaflet malapoprtation (failure to meet), malapposition (failure to close at the same plane), annulus diameter, interpapillary distance, and chordal length. The mode of repair selected must then address these multiple aberrations. This is why, some argue, that functional ischemic mitral regurgitation cannot be treated adequately with annuloplasty (12,21).

In the remodeled ventricle, the papillary muscle tethering distance and angle must also be rectified. Menicanti et al. (22), on behalf of the RESTORE surgical remodeling group, has emphasized intraventricular imbrication or “pexy” to realign displaced papillary muscles. Kron et al. (23) have surgically relocated the posterior papillary muscle in chronic ischemic mitral regurgitation. However, others have demonstrated the efficacy of secondary chordal cutting to relieve the tethering caused by papillary muscle displacement (24). Moainie et al. (25) have demonstrated that external infarct restraint attenuates remodeling and mitral regurgitation in an ovine model of posterior lateral infarction. Ongoing surgical clinical trials evaluating cardiac restraint devices with and without correction of mitral regurgitation are underway and should provide important information about this approach (26). Finally, lest interventional cardiologists fear they may remain idle while surgical options evolve, we know that percutaneous options are being assessed as well (27,28). Although these percutaneous options are not likely to improve beyond simple annuloplasty, they might help advance the field with tandem procedures such as adjunctive minimally invasive application of external restraint devices.

Although the investigation of Wu et al. (7) suggests that patients receive little benefit from mitral valve annuloplasty, several questions are raised. Is this lack of benefit because mitral valve surgery does not work or because a different surgical approach is needed? Is annuloplasty sufficient? Are subannular three-dimensional repairs required? We simply do not know. As Wu et al. (7) admit, only well–designed, randomized controlled trials will answer these issues with finality. Until then, what is a clinician to do? First, we believe that pharmacological options, including widespread and aggressive neurohormonal inhibition and use of vasodilators should be employed when indicated. Device therapy (cardiac resynchronization) should also be used in appropriately selected candidates (Table 1). If surgery is considered as an alternative to transplantation, the patient should be informed of the uncertainties of the outcome with this approach. We strongly believe that a randomized clinical trial is feasible and endorse the development of registries that systematically evaluate surgical outcomes from this approach.

Reprint requests and correspondence: Dr. Mandeep R. Mehra, 1514 Jefferson Highway, New Orleans, Louisiana 70121. E-mail: mmehra@Ochsner.org.

**REFERENCES**


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