Randomized Trials in Moderate Ischemic Mitral Regurgitation
Many Questions, Limited Answers

Patrick T. O’Gara, MD

Ischemic mitral regurgitation (MR) occurs as a consequence of left ventricular (LV) remodeling after myocardial infarction and is a reproducible marker of reduced event-free survival over the intermediate to long term. Mortality risk increases as a function of MR severity and is higher among patients with moderate or severe ischemic MR compared with patients with trivial or mild MR. In this context, the mitral valve has been described as an anatomically normal innocent bystander, although structural changes in leaflet architecture consequent to abnormal stretching have been described. MR results from a combination of apical and lateral papillary muscle displacement, leaflet tethering, annular dilatation, and reduced closing forces. Ischemic MR and its natural history derive more from underlying LV dysfunction and less from primary (organic) valve failure, although both mechanisms may contribute in individual patients. The pathophysiological principles that underlie treatment recommendations for patients with organic MR from myxomatous degeneration (eg, fibroelastic deficiency or Barlow syndrome) are, therefore, not directly applicable to the management of patients with functional, ischemic MR. In addition, there are important differences in the Doppler echocardiographic thresholds used to define organic and functional MR severity. Although severe organic MR is usually characterized by an effective regurgitant orifice area ≥0.4 cm² and regurgitant volume (RV) >60 mL/beat, these cut points are significantly lower for patients with functional MR (effective regurgitant orifice area ≥0.2 cm² and RV >30 mL/beat, respectively). MR severity in any individual patient should not be defined solely on the basis of 1 or 2 quantitative parameters but rather on an integrative assessment that takes into account additional supportive findings, such as left atrial and LV chamber sizes, the density of the Doppler continuous wave regurgitant signal, mitral E wave height, and the pattern of pulmonary vein flow. Lastly, functional MR is an inherently dynamic lesion, the severity of which can vary as a function of LV loading conditions, heart rhythm, and intraventricular conduction. Exercise echocardiography is an important adjunct to the noninvasive evaluation of appropriate patients. Surgical planning is preferentially based on preoperative rather than intraoperative MR assessment, although apparent qualitative worsening of MR severity by transesophageal echocardiographic criteria under anesthesia is occasionally encountered.

Guidelines for the management of patients with valvular heart disease (VHD) have been heavily criticized for their lack of treatment recommendations based on randomized, controlled trials (RCTs). Consensus opinions regarding best practices rely heavily on studies that are retrospective, observational, and most often single centered. Propensity analyses cannot overcome all of the associated confounding and bias. An unspoken reality in the care of patients with VHD is the fact that thresholds for operative intervention have been lowered empirically over the past 2 decades largely in recognition of the very limited medical therapies available to alter the natural history of the disease and the extraordinary improvements in surgical technique and outcomes reported from major referral centers of excellence. In many respects, surgical advances have outpaced rigorous and unbiased assessment of their efficacy and safety. Shared decision making with patients should reflect these gaps and recognize that several areas of uncertainty remain.

The optimal approach to the management of individual patients with ischemic MR has not been established. Opinions vary strongly regarding the use of routinely adding mitral valve repair (MVRp) with a downsized rigid or semirigid annuloplasty ring to coronary revascularization in patients with moderate ischemic MR referred for coronary artery bypass graft (CABG) surgery. In a minority of patients, moderate ischemic MR improves or resolves after coronary revascularization alone, possibly in association with the viability of subjacent myocardium and absence of papillary muscle dyssynchrony. Efforts to identify these patients confidently have been sporadic. In most patients, however, moderate ischemic MR will persist or worsen after CABG alone and portend higher long-term mortality as a function of residual MR severity. Performance of MVRp with CABG increases aortic cross-clamp and cardiopulmonary bypass times and could adversely impact myocardial and functional recovery. Questions remain regarding not only the durability of MVRp for ischemic MR but also its impact on the hard clinical end points of death and rehospitalization for heart failure (HF). There is uncertainty as to whether MVRp or chord-sparing MV replacement is the preferred operative strategy for patients with severe ischemic MR. That the...
optimal management strategy for patients with chronic, ischemic MR is shrouded in uncertainty is reflected in the single class Ib level of evidence C recommendation and supporting paragraph devoted to this topic in the 2006 American College of Cardiology/American Heart Association VHD practice guidelines. The 2012 European Society of Cardiology VHD practice guidelines include more discussion and provide a greater number of treatment recommendations for patients with functional MR, although none with a level of evidence other than C.

The successful execution of RCTs in cardiac surgery has been challenged by many factors including biased expectations of referring cardiologists, lack of surgical equipoise, inadequate infrastructural support, nuanced inclusion/exclusion criteria that detract from the applicability of the findings to patients encountered in routine practice, and patient unwillingness or inability to consent to a procedure the technical details of which may not be adjudicated by his or her surgeon. Cardiologists may opt to perform percutaneous coronary intervention in selected patients with multivessel disease irrespective of the presence of MR or may feel pressure to offer their patients access to the latest innovations in cardiac surgery without full knowledge of their efficacy. Surgical champions may not embrace the notion that their individual results could be admixed with others. Random assignment to a treatment group in the context of open heart surgery is a process that many patients simply cannot accept even when they understand that there is uncertainty as to the better of the 2 options proposed. These factors differ in several ways from the typical constraints encountered in a randomized trial of 2 medical interventions. Yet, many such obstacles can be overcome and a culture created to foster randomized investigations in surgical practice.

Two small-sized RCTs in patients with moderate ischemic MR have now been completed, although it is clear from their execution that many questions remain.

Fattouch et al21 randomly assigned 102 patients with moderate ischemic MR to CABG plus MVRp versus CABG alone at a single surgical center between February 2003 and May 2007. Ischemic MR was defined as moderate on the basis of a proximal isovelocity area radius between 5 and 8 mm. Quantitative measures of MR severity were performed but not reported, and it was not specified whether the echocardiographic assessment necessary for trial inclusion occurred preoperatively with transthoracic echocardiography or intraproactively under anesthesia with transesophageal echocardiography. LV systolic function was moderately impaired (ejection fraction =0.42). MVRp was performed in all of the patients with a Carpentier–Edwards Physio Ring (Edwards Lifesciences, Irvine, CA); mean leaflet coaptation length was 7.1 ± 1.2 mm. Repair was considered successful if no or trivial MR remained on post-CPB transesophageal echocardiography. The number of coronary grafts per patient was comparable between the 2 groups. The primary outcome was the change in postoperative LV end-systolic dimension, an index of reverse remodeling, at transthoracic echocardiography follow-up, although the specific time point (1, 3, or 5 years) at which this comparison was made had the baseline value was also not specified. Compared with CABG alone, CABG plus MVRp resulted in a significant decrease in LV end-systolic dimension at follow-up, along with favorable changes in LV end-diastolic dimension, LV ejection fraction, pulmonary artery systolic pressure, and New York Heart Association class. Interestingly, at the time of their last follow-up, 40% of patients managed with CABG alone had trivial or mild MR, although approximately one third of patients in this CABG-only subgroup developed worsening MR on postoperative exercise testing. In 35% of the CABG-only patients, MR progressed to a moderate-to-severe grade. Aortic cross-clamp and CPB times were significantly longer in the CABG plus MVRp group, but there were no differences in perioperative mortality (1.8% CABG alone versus 4.0% CABG plus MVRp; \( P =0.12 \)) or 5-year survival, as would expected from this small, underpowered trial.

In this issue of Circulation, Chan et al22 report the United Kingdom National Institute for Health Research–sponsored, multicenter Randomized Ischemic Mitral Evaluation Trial composed of 73 patients with moderate ischemic MR randomly assigned to CABG plus MVRp versus CABG alone between March 2007 and July 2011. Moderate ischemic MR was defined by an effective regurgitant orifice area of 0.20 to 0.39 cm², RV of 30 to 59 mL/beat, and vena contracta width of 0.30 to 0.69 cm. RVs were measured with cardiac magnetic resonance imaging techniques. All of the qualifying transthoracic echocardiographies and cardiac magnetic resonance imaging images were analyzed in a core laboratory. MVRp was performed with insertion of a Carpentier-McCarthy-Adams IMR ETHlogix Annuloplasty Ring (Edwards Lifesciences) in 85% of patients and a Carpentier-Edwards Physio Annuloplasty Ring (Edwards Lifesciences) in 15% of patients. Mean mitral leaflet coaptation length was 7.1 ± 1.2 mm, and technical success was defined as no or trivial MR on separation from CPB. Similar numbers of CABGs were used in both groups. The primary end point was peak myocardial oxygen consumption at 1 year of follow-up. Secondary end points included LV end-systolic volume index measured by cardiac magnetic resonance imaging, RV, and plasma brain natriuretic peptide levels. The investigators had intended to randomly assign 100 patients but were forced to stop enrollment after 5 years for both physician- and patient-related reasons (eg, lack of equipoise and unwillingness to consent). Unfortunately, analyzable 1-year data were available for only 59 patients. The patient cohort was on average 6 years older than that reported by Fattouch et al,21 LV ejection fraction was moderately reduced at \( =0.45 \), and nearly all of the patients had New York Heart Association class 2 or 3 limitations. The addition of MVRp to CABG, compared with CABG alone, resulted in significantly longer aortic cross-clamp, CPB, total operating and endotracheal intubation times, more blood transfusions despite no differences in measured blood loss, and longer total lengths of stay. In addition, there were inexplicably high use rates of intra-aortic balloon counterpulsation (≈30%) and renal replacement therapy (≈10%), as well as an 8% rate of re-exploration for bleeding or tamponade (5% for CABG alone versus 12% for CABG plus MVRp; \( P =0.27 \)). Although standardized postoperative management protocols vary across institutions, these rates are far higher and the reported lengths of stay are far
longer than expected for surgery of this nature in this patient cohort. Such outcomes raise concerns regarding quality and processes of care at participating centers. The study nevertheless met its primary end point with significantly higher peak oxygen consumption at 1 year in patients randomly assigned to CABG plus MVRp compared with patients treated with CABG alone (18.1 ± 3.3 versus 15.9 ± 2.4 mL/kg per minute; P = 0.004). There were significant reductions in the secondary end points of LV end-systolic volume index, RV, and brain natriuretic peptide, as well as greater improvement in New York Heart Association class, with CABG plus MVRp versus CABG alone. As was noted in the study by Fattouch et al., 50% of patients in the CABG-only group had no (3%) or mild (47%) MR at 1 year. Longer-term follow-up of MR severity in both treatment groups would be of interest. Perioperative mortality rates (3%) did not differ between the groups. One-year mortality was not reported, although the small study size did not allow for meaningful assessment of survival. Data are not provided on the use of evidence-based medical therapies in either the study by Chan et al. or the study by Fattouch et al., including on the use of cardiac resynchronization therapy when appropriate, an intervention proven to reduce the severity of ischemic MR.

Firm conclusions regarding the efficacy and safety of MVRp at time of CABG surgery in patients with moderate ischemic MR cannot be drawn from these studies. Nevertheless, and despite the several important limitations and concerns noted, both groups of investigators are to be congratulated for conducting these RCTs. The addition of MVRp to CABG surgery does not appear to increase perioperative mortality risk but may adversely affect perioperative morbidity in some centers. The severity of ischemic MR decreases in some patients after revascularization alone. The improvements noted in the surrogate end points of LV reverse remodeling and exercise capacity with MVRp are directionally consistent with nonrandomized observations and provide a basis for the design and execution of a pivotal trial using the lessons learned from more definitive RCTs in patients with HF, arrhythmias, and acute coronary syndromes. Trials of this nature are clearly needed in patients with VHD including, most urgently, those patients with asymptomatic severe aortic stenosis, asymptomatic severe organic (myxomatous) MR, and functional MR with either ischemic or nonischemic LV systolic dysfunction. The challenges involved in the successful completion of such ambitious trials cannot be underestimated, as exemplified by previous well-intentioned efforts that have either failed or languished. The Effectiveness of Surgical Mitral Valve Repair Versus Medical Treatment for People With Significant Mitral Regurgitation and Non-Ischemic Congestive Heart Failure trial (www.clinicaltrials.gov identification No. NCT00608140) attempted to enroll 120 patients with symptomatic severe nonischemic MR and LV systolic dysfunction in a randomized trial of optimal medical therapy versus optimal medical therapy plus MVRp using an LV end-systolic volume index at 18 months as the primary end point but was terminated prematurely because of the inability to recruit patients. Recruitment has also been stalled in the Moderate Mitral Regurgitation in Patients Undergoing CABG trial (www.clinicaltrials.gov identification No. NCT00613548), an international multicenter study designed to assess the effect of MVRp added to CABG surgery on the combined end point of survival and rehospitalization for HF in 550 patients with moderate ischemic MR followed for 5 years. The National Heart Lung and Blood Institute-sponsored Cardiothoracic Surgery Network has completed enrollment of 250 patients in a study of MVRp versus chord-sparing MV replacement in patients with severe ischemic MR and will shortly complete enrollment of 300 patients in a companion study of CABG plus MVRp versus CABG alone in patients with moderate ischemic MR. Both studies rely on an integrative assessment of MR severity derived from preoperative transthoracic echocardiography images. Their common primary end point is the change in LV end-systolic volume index from baseline to 1 year. Several secondary outcomes related to other indices of LV function and MR severity, survival, exercise capacity, quality of life, and neurocognitive performance will also be reported. The trials are not powered to provide definitive answers regarding survival and rehospitalization for HF. It is not clear whether a future meta-analysis using patient-level data from the RCTs of moderate ischemic MR will be either feasible or enlightening. There may simply be too many discrepancies in trial design, patient and echocardiographic inclusion/exclusion criteria, surgical technique, and processes of care across trials to allow for valid assessment. There is also growing interest in the use of percutaneous MitraClip (Abbott Vascular, Redwood City, CA) therapy in high surgical risk patients with severe functional MR, a treatment modality that will require rigorous longitudinal study.

It is doubtful that surgical practice will change in the short term on the basis of the studies by Fattouch et al. and Chan et al. It remains to be seen whether the ongoing Cardiothoracic Surgery Network trials will provide incremental mechanistic insights. Perhaps these collective efforts will catalyze an even wider-scale effort to study patients with functional MR or to initiate additional randomized trials in patients with other types of VHD. Ways must be found to overcome the many imposing challenges of patient recruitment so that larger surgical studies aimed at hard clinical end points are completed more efficiently and at lower cost. Failure to do so will likely imperil future funding and result in continued uncertainty regarding optimal management of patients with VHD.

Disclosures
Dr O’Gara is the cochair of the National Heart, Lung, and Blood Institute–sponsored Cardiothoracic Surgery Network Steering Committee.

References

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