What to Do About Ischemic Mitral Regurgitation?*

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Mitral regurgitation (MR) can be classified as either degenerative or functional. Degenerative MR is due to disease, deformity, or damage of the mitral valve or its supporting apparatus. Functional MR is caused by improper coaptation of normal leaflets and apparatus and is due primarily to abnormalities of the left ventricle. Ischemic MR is a subset of functional MR (papillary muscle rupture, a mechanical complication of acute myocardial infarction [MI], is a rare exception). MR is commonly observed in patients with heart failure, recent or remote MI, and ischemic cardiomyopathy. The prevalence ranges from 10% to 70% (1). This broad range is due to differences in the method used to define MR, the population studied, and the time frame after MI that analysis was performed. Although the exact prevalence is unknown, some degree of MR is clearly common. Most patients have mild regurgitation. Moderate to severe regurgitation is reported in 10% to 20% of patients with ischemic heart disease (2–5). MR is also seen after non–ST-segment elevation myocardial infarction with 1 report observing MR in 40% of non–ST-segment elevation myocardial infarction patients with <5% exhibiting severe MR (6).

The presence of MR in patients with ischemic heart disease is a powerful predictor of adverse events (2–4,7). An analysis of 303 patients several weeks after transmural infarction found some degree of MR in 64% of patients (2). Patients with MR had a greater mortality than those without regurgitation and this was independent of other variables and was specifically independent of the degree of left ventricular dysfunction. Furthermore, the degree of MR was related to mortality; even patients with mild to moderate regurgitation experienced worse outcomes than did patients without regurgitation. Similar findings were reported in a large cohort of patients studied within 30 days of MI (3). Moderate or severe MR was associated with a large increase in risk of heart failure or death and mild degrees of regurgitation were associated with a greater likelihood of death.

Contrary to previous beliefs, ischemic MR is not due to ischemia and dysfunction of the papillary muscle. Instead, regurgitation is due to heterogeneous and complex mechanisms that ultimately prevent closure of the leaflets, thereby creating the characteristic central jet of functional MR. These complex mechanisms have been described (5,8). To summarize, ischemic MR may be due to: 1) alterations in left ventricular geometry; 2) distortion and enlargement of the mitral annulus; and 3) dyssynchrony of ventricular contraction that can interfere with normal valve closure. The most important of these are the alterations of left ventricular geometry that occur with infarction.

Closure of the mitral valve depends on 2 opposing forces. A tethering force from the papillary muscles and chordae pulls the leaflets away from the annulus during systole. A closing force occurs during systole and pushes the leaflets closed. An imbalance in these forces prevents proper closure. Infarction and ventricular remodeling distort the papillary muscles and surrounding myocardium, thereby increasing the tethering forces.

Tethering is the most important mechanism for ischemic MR, and additional mechanisms contribute. Severe left ventricular dysfunction reduces the force of systolic contraction and reduces the closing force. Ventricular enlargement stretches and enlarges the mitral annulus preventing proper coaptation of the
leaflets. Left ventricular dyssynchrony leads to reduced closing force and disturbed coordination of papillary muscle contraction affecting its tethering function. These mechanisms are important to understand when contemplating therapies to reduce MR in patients with ischemic cardiomyopathy.

In this issue of JACC: Cardiovascular Interventions, Zeng et al. (9) offer a novel method to treat ischemic MR. An injection of polyvinyl alcohol hydrogel polymer into infarcted myocardium adjacent to the papillary muscles would, in theory, stabilize the zone and prevent the geometric changes that occur from remodeling, thereby preventing tethering and reducing MR. Using an experimental model of infarction in sheep, the investigators injected the infarct zone with the polymer; a control group was injected with saline. Eight weeks later, the sheep injected with polymer had less MR, improved left ventricular function, and improved indices of remodeling and mitral valve geometry. These parameters did not change in control animals.

Now that we understand its prevalence, prognostic implications, and mechanisms, what do we do about ischemic MR? Despite its association with worse prognosis, it is entirely unclear whether reducing the degree of MR will change prognosis as there is little to no data to support this concept. To date, treatment has been mostly medical therapy or surgical repair with mitral annuloplasty at the time of coronary revascularization surgery (10). Percutaneous approaches have been proposed. The Monarc device (American Medical Systems, Minnetonka, Minnesota) is a transcatheter method relying upon the proximity of the coronary sinus to the mitral annulus in an effort to achieve a percutaneous annuloplasty. This device, however, was associated with coronary artery compression and MI and only modestly affected the degree of MR (11). The mitral clip (MitraClip, Abbott Vascular, Santa Clara, California), a percutaneous edge-to-edge repair, shows more promise. In terms of mechanism, the mitral clip might prove useful in functional MR by targeting the distorted annulus associated with this condition. In fact, the mitral clip has been shown to reduce mitral annular dimensions in functional MR, and this is associated with clinical improvement (12). Although there are no randomized data to support its use in the functional MR subset, it is widely used for this indication in Europe. In fact, 72% of patients treated with the mitral clip in a European registry had functional MR (13). Procedural success, reduction of MR, and 1-year mortality were similar for patients with functional and degenerative MR. Interestingly, the 1-year rehospitalization rate for heart failure was higher for patients with functional versus degenerative MR, suggesting that the underlying left ventricular dysfunction might be a more important determinant of outcome than the degree of MR. The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial (NCT01626079) is designed to specifically address the role of the mitral clip in this population.

By stabilizing the infarction zone and limiting remodeling, the method proposed in this issue by Zeng et al. (9) is particularly attractive as it addresses the most important mechanism of ischemic MR: distortion of ventricular geometry and abnormal tethering. However, implementing this strategy in humans and designing a clinical trial will prove extremely challenging. The clinical device must be percutaneous, and the operator would need to identify the precise location to inject the polymer, thus requiring advanced imaging during the procedure. Unanswered questions include the optimal volume of polymer, the optimal location in the ventricle, and the most effective time frame after MI. Additionally, which patients are candidates for this therapy? It is not clear whether efforts should focus only on those with severe MR or on patients with lesser degrees of MR. Remember though, as stated earlier, it is not entirely clear that reducing MR will change prognosis in patients with ischemic MR. Perhaps that question should be answered first.

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