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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Secondary Mitral Regurgitation in Heart Failure

Pathophysiology, Prognosis, and Therapeutic Considerations

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ABSTRACT

The development of secondary mitral regurgitation (MR) due to left ventricular dysfunction, also known as functional MR, is strongly associated with a poor prognosis in patients with heart failure. The mechanisms underlying secondary MR are multifactorial; accurate imaging assessment of secondary MR may be challenging and nuanced; and the appropriate roles of medical, surgical, and interventional therapies for management of secondary MR are controversial and evolving. In this review, the pathophysiology, evaluation, and prognosis of secondary MR in patients with heart failure are discussed, and we evaluate in detail the evidence for the various therapeutic approaches for secondary MR, including guideline-directed medication for left ventricular dysfunction, cardiac resynchronization therapy and revascularization when appropriate, and mitral valve surgery and transcatheter interventions. The role of a multidisciplinary heart team in determining the optimal management strategy for secondary MR is also discussed. (J Am Coll Cardiol 2015;65:1231–48)
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Mitral regurgitation (MR) is among the most common valvular heart disorders, with an estimated prevalence in the United States of ~1.7%, increasing with age to ~9.3% in those >75 years of age (1). MR is classified as primary (also known as organic) when principally due to a structural or degenerative abnormality of the mitral valve (MV), whether of the leaflets, chordae tendineae, papillary muscles, or mitral annulus. Secondary (also known as functional) MR occurs in the absence of organic MV disease, usually from left ventricular (LV) dysfunction. It is more common than primary MR (2), is associated with a worse prognosis (compounded by the underlying cardiomyopathy), and (in contrast to primary MR) the benefits of MV surgery are uncertain. The present report reviews the etiology, pathophysiology, prognostic implications, and diagnosis of secondary MR, as well as potential therapeutic approaches.

PATHOPHYSIOLOGY OF SECONDARY MR

The MV consists of 2 leaflets (anterior and posterior) sitting within the annulus (**Figure 1**). The posterior mitral leaflet originates from the left atrial (LA) endocardium. A subvalvular apparatus, comprising 2 papillary muscles (anterolateral and posteromedial) arising from the LV myocardium and the chordae tendineae, supports the leaflets. LV dilation due to ischemic or nonischemic cardiomyopathy secondarily impairs leaflet coaptation of a structurally normal MV, resulting in secondary MR. Specifically, LV

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor(s)

CRT = cardiac resynchronization therapy

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HF = heart failure

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

MDCT = multidetector computed tomography

MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

dysfunction and remodeling lead to apical and lateral papillary muscle displacement, resulting in leaflet tethering (3), dilation and flattening of the mitral annulus, and reduced valve closing forces. Because these changes are dependent on loading conditions and the phase of the cardiac cycle, secondary MR is dynamic in nature.

Papillary muscle displacement occurs as a result of global LV enlargement or focal myocardial scarring, and can affect 1 or both papillary muscles, causing posteriorly directed or central MR (**Figure 2**) (4). With chronic MR, the mitral leaflet area may increase up to 35% over time, an adaptive response that minimizes the degree of regurgitation; insufficient leaflet remodeling may contribute to severe MR (5,6). However, even in patients with increased mitral leaflet area, papillary muscle displacement with subsequent decreased coaptation length may still result in significant MR (6).

The normal saddle-shape of the annulus is important for maintaining normal leaflet stress (7). Loss of this shape and annular flattening with LV remodeling result in increased leaflet stress with secondary MR. In addition, LV systolic dysfunction reduces the strength of MV closing, which opposes the leaflet tethering forces created by papillary muscle displacement. These pathological changes culminate in failure of leaflet coaptation and decreased valvular closing forces due to LV dysfunction, resulting in MR. The Carpentier classification, commonly used by surgeons to describe MV pathology, categorizes MR using a mechanistic and functional approach to the mitral leaflets (8). Secondary MR is most commonly Carpentier type IIIB, and occasionally type I.

ISCHEMIC VERSUS NONISCHEMIC MR. MR can be further classified as either ischemic or nonischemic. In ischemic MR (the more frequent etiology), LV remodeling after myocardial infarction (MI) results in papillary muscle displacement, causing systolic tenting of the MV. Global left ventricular ejection fraction (LVEF) does not have to be reduced; regional wall motion abnormalities with remodeling may result in sufficient MV tethering to cause severe MR, despite preserved LVEF (9). Symmetric or asymmetric leaflet tethering may occur. Symmetric tethering is associated with substantial systolic dysfunction, global remodeling, and increased LV sphericity with a central regurgitant jet. Asymmetric tethering most frequently results from localized remodeling affecting the posterior papillary muscle, with posterior tenting of both leaflets (most pronounced at the medial or P3 portion of the posterior leaflet) causing a posteriorly directed asymmetric regurgitant jet (Carpentier Type IIIB) (10). Mitral annular dilation typically occurs late in the pathophysiology of secondary MR, and is often asymmetric, with greater involvement of the posterior annulus (11). Papillary muscle infarction is rarely the cause of secondary MR (12).

Nonischemic MR, most commonly due to long-standing hypertension or idiopathic dilated cardiomyopathy, is characterized by global LV dilation with increased sphericity and (typically) a centrally located regurgitant jet. Symmetric mitral annular dilation is greatest in the septal-lateral direction, and correlates with the severity of LV dysfunction (13).

MR DUE TO ATRIAL FIBRILLATION. An additional, although relatively infrequent, cause of severe secondary MR is isolated LA enlargement, with or without atrial fibrillation, resulting in a dilated mitral annulus and reduced leaflet coaptation (without tenting or prolapse), with normal LV function and mitral leaflets (Carpentier Type I) (14). In patients with atrial fibrillation, improvement in MR severity may occur with restoration of sinus rhythm, suggesting a causal relationship (14).

PROGNOSTIC IMPLICATIONS OF SECONDARY MR

A strong association between secondary MR severity and both all-cause mortality and heart failure (HF) hospitalizations has been reported. Among 303 patients with a completed Q-wave MI, any ischemic MR was detected by echocardiography in 194 patients (64.0%) and was a powerful, independent correlate of long-term all-cause mortality (relative risk: 1.88 [95% confidence interval (CI): 1.23 to 2.86], $p = 0.003$) (15). In a study from the Duke Cardiovascular Databank, qualitatively assessed 3+ to 4+ MR on left ventriculography was present in 29.8% of 2,057 HF patients with an LVEF <40% and was an independent predictor of 5-year mortality (adjusted hazard ratio [HR]: 1.23 [95% CI: 1.13 to 1.34]) (16). Among 1,256 patients with dilated cardiomyopathy at the Mayo Clinic, quantitatively assessed severe secondary MR (defined as an effective regurgitant orifice area [EROA] >0.2 cm^2, a regurgitant volume >30 ml, or a vena contracta width >0.4 cm) was present in 24% of patients, and was an independent predictor of death or HF hospitalization at median 2.5-year follow-up (adjusted HR: 1.5 [95% CI: 1.2 to 1.9]), independent of LVEF (17). This relationship was present separately for death and HF hospitalizations, and in patients with ischemic and nonischemic MR (**Figure 3**). Secondary MR is a powerful predictor of death or transplant, even with less severe HF (18). However,

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