Secondary Mitral Regurgitation in Heart Failure with Reduced or Preserved Left Ventricular Ejection Fraction

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Secondary MR in HFrEF

 Independently of the etiology of HFrEF and its underlying mechanisms, secondary MR portends a poor clinical outcome [3]. Early after myocardial infarction, moderate or severe MR was found to be independently associated with an increased risk of HF and death (relative risk 3.44 and 1.55, respectively) in a large community-based cohort [4]. The downward spiral of MR that begets MR affects the progression of HFrEF [5]. Secondary MR in HFrEF reflects primarily the severity of LV dysfunction and is not related to structural alterations of the mitral valvular apparatus. Nevertheless, mitral valves from hearts collected at the time of cardiac transplantation are biochemically different from those from normal hearts. Mitral valve remodeling resulting from increased deoxyribonucleic acid, glycosaminoglycan and collagen concentration develops in patients with LV systolic dysfunction [6]. Mitral valve area increases over time as the left ventricle remodels in an experimental model of inferior myocardial infarction [7]. This suggests that secondary MR in these HF patients may not be purely functional.

Key Words
Secondary mitral regurgitation · Heart failure · Diastolic dysfunction · Echocardiography

Abstract
Secondary mitral regurgitation (MR) has been extensively studied in heart failure due to reduced ejection fraction. In contrast, the occurrence and the pathogenesis of secondary MR are much less known in heart failure with preserved ejection fraction (HFpEF). The present review aimed at describing this common but ignored feature of HFpEF.

As in patients with heart failure (HF) and reduced left ventricular (LV) ejection fraction (HFrEF), patients with HF and preserved LV ejection fraction (HFpEF) may develop secondary (or functional) mitral regurgitation (MR) [1, 2]. The aim of this article is to review the mechanisms and the clinical significance of secondary MR in HFrEF and HFpEF patients.
Secondary Mitral Regurgitation in Heart Failure

Apical displacement of the papillary muscles due to eccentric global and local LV remodeling and segmental wall motion abnormalities associated with papillary muscle dysfunction increase the tethering forces acting on the mitral valve. Reduced LV contractility, LV dysynchrony and reduced mitral annular contractility decrease the LV systolic pressure that in turn results in reduced mitral valve closing forces. Importantly, the hallmark of secondary MR in HFrEF is the formation of mitral valve tenting (a more apical position of the leaflets and their coaptation point during the systolic phase) that may be asymmetric if the tethering forces predominate on the posterior mitral leaflet [8]. It is currently accepted that the mitral valve tenting results from an imbalance between these increased tethering forces and reduced closing forces [9, 10].

The concept that heightened left atrial (LA) pressure may induce mitral valve tenting, and thereby secondary MR has recently been reported. Park et al. [11] showed in 144 patients with dilated cardiomyopathy that the severity of secondary MR most significantly correlates with the mitral valvular tenting area, which is in turn more closely related to mitral annular size and diastolic dysfunction severity than to LV volume. Conversely, the E/e’ ratio, a noninvasive estimate of LV filling pressures, is independently predicted by secondary MR severity irrespective of age, gender and LV ejection fraction in a large cohort of patients with coronary artery disease [12]. Even mild MR was associated with an increased E/e’ ratio [12]. Our group demonstrated that in addition to the posterior papillary muscle-intervallvular fibrosa distance, a key parameter of local LV remodeling, a higher E/e’ ratio, is an independent predictor of the systolic mitral tenting area and ensuing MR in patients with HFrEF [13]. Hence, diastolic dysfunction and thereby increased LA pressure appear to be important contributing factors for secondary MR development in patients with LV systolic dysfunction through the increased mitral valve tenting area owing to increased LA size and LA ‘pushing’ forces. Figure 1 summarizes the mechanisms that promote secondary MR in patients with HFrEF.

Previous studies have demonstrated that secondary MR is in part responsible for pulmonary hypertension in HFrEF, a major predictor of poor outcome [14]. In a recent study, Miller et al. [15] confirmed that, irrespective of the severity of diastolic dysfunction (E/e’ ratio ≥15, odds ratio: 3.31, p < 0.001; deceleration time ≤150 ms, odds ratio: 3.8, p < 0.001), secondary MR [effective regurgitant orifice area (EROA) ≥20 mm², odds ratio: 3.8, p < 0.001] was a powerful predictor of pulmonary hypertension.

Secondary MR depends heavily on loading conditions (therapeutic compliance and daily salt intake) and ventricular performance. The volume of mitral regurgitant flow is determined hydraulically by two factors: magnitude and duration of the systolic pressure gradient across the valve and size of the EROA. In acutely decompensated HF, both diuretic and venodilation with nitroglycerin lower pulmonary venous pressure, resulting in a fall in LA pressure that is greater than the reduction in LV systolic pressure, thereby increasing the gradient across the mitral valve.

**Fig. 1.** Mechanisms leading to secondary MR in HFrEF.
valve and reducing the size of the EROA [16]. The reduction in LV size and thereby in annular distension also accounts for a reduction in the EROA, especially in patients with HFrEF who are receiving ACE inhibition and β-adrenergic blockade therapy [17, 18]. Altogether, a decrease in regurgitant flow is associated with an improved forward stroke volume and thereby end-organ perfusion. Besides increased loading conditions, active myocardial ischemia contributes to worsening secondary MR, while medical and nonpharmacological treatments including revascularization and cardiac resynchronization therapy reduce the amount of MR [19–24]. A major feature of secondary MR in HFrEF is its dynamic nature with exercise. A large exercise-induced increase in secondary MR (>13 mm²) has been linked to poor outcome in previous reports involving patients with LV systolic dysfunction due to coronary artery disease [25], while the role of dynamic exercise MR has been found to be less important in nonischemic and revascularized ischemic HFrEF patients [26]. Patients with coronary artery disease and a recent history of pulmonary edema experience a greater increase in MR during exercise suggesting the importance of secondary ischemic MR in acute decompensation of HFrEF [27].

Secondary MR in HFpEF

Patients with HFpEF have a poor prognosis as those with HFrEF, and HFpEF is responsible for as many hospitalizations as HFrEF is [28, 29]. Although it imposes a huge burden on the healthcare system, HFpEF remains a poorly understood clinical entity that has no evidence-based therapy as illustrated by consistently negative clinical trials [30, 31]. A potential explanation for the failed cardiovascular therapeutic approach of HFpEF may be that a majority of the HFpEF patients (60%) died of noncardiovascular causes, while only 36% of the HFrEF patients died of noncardiovascular causes [29]. The phenotype of HFpEF is well known: elderly women with hypertension, diabetes and obesity as comorbid conditions [32]. However, its pathogenesis is multifaceted. Investigators have highlighted the role of combined ventricular and arterial stiffening, subtle longitudinal and torsional LV systolic dysfunction, chronotropic incompetence and renal impairment in HFpEF pathogenesis [32, 33]. Overall HFpEF is a less homogenous condition than HFrEF is. Comorbidities appear to play a greater role in the pathogenesis of HFpEF than they do in HFrEF [34–37]. In such contexts it is not surprising that a lot less is known regarding the potential role of secondary MR in HFpEF.

Symptomatic patients with HFpEF may present with MR without typical lesions of the mitral valve apparatus commonly observed in organic MR [1]. While mitral valve remodeling has been demonstrated in patients with HFrEF, no pathology data exist in patients with HFpEF. Nevertheless, similar as in patients with HFrEF, the mitral valve may or may not be strictly normal in HFpEF patients with secondary MR owing to the age of the patient population. An increased leaflet thickness especially at the basal third of the valve (greater stress localization) is noticed in these older patients. Mitral valve leaflets become less translucent with age, and adipocytes and lipid deposits accumulate within the leaflet tissue. Nodular thickening can often be seen along the lines of closure on both leaflets promoting a degree of leaflet miscoaptation [38]. It is important to note that due to aging, calcifications of the mitral annulus are a common occurrence in HFpEF [39].

Secondary MR is found in a significant proportion of patients with HFpEF [2]. Mitral regurgitant volume is usually in the range of that observed in mild MR owing to a small LV cavity [2]. It is of note that due to unreliable semiquantitative assessment by Doppler color flow mapping (exquisite sensitivity of the color Doppler jet area to driving pressure, chamber constraint, gain settings, LA size and compliance) MR may appear hemodynamically severe upon admission and some patients with HFpEF are referred for mitral valve surgery despite the absence of overt lesions of the mitral valve apparatus [40, 41]. Combined increased LA pressure and atrial fibrillation (which occurs frequently in HFpEF) produce enlarged LA volume, an important feature of HFpEF [42]. LA size affects mitral annular size independent of LV dimensions [43]. Mitral annulus dilatation as a result of LA enlargement promotes the development of secondary MR [43]. It is interesting to note that the concept of ‘atrial functional MR’ has recently been associated with hypertensive and older patients with atrial fibrillation who develop MR. Atrial fibrillation induces mitral annular distortion and dysfunction and loss of atrial synchrony both contributing to MR. Conversely MR is improved after successful atrial fibrillation ablation [44]. Concentric LV remodeling, a common feature of HFpEF, rules out that increased tethering forces play a major role in the development of MR in these HFpEF patients. Tethering forces may nevertheless play a role in the subgroup of HFpEF patients with eccentric LV remodeling [13]. Whether dysfunctional subendocardial longitudinal fibers (as assessed by the reduced diastolic and systolic mitral annular velocities e’ and s’) lower closing forces and thereby play a role in the pathogenesis of secondary MR in HFpEF has not been investigated. LV

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dyssynchrony has been reported in HFpEF patients with narrow QRS [45]. LV dyssynchrony is load dependent [46, 47] and associated with discoordination of papillary muscle contraction and impaired LV performance. Although the relationship between LV dyssynchrony and MR has been extensively studied in HFrEF, its role remains to be established in HFpEF. Mitral valve tenting and miscoaptation are likely consequences of increased LV filling pressure and of the resulting increased LA pressure that opposes mitral leaflet closure. Of note the $E/e'$ ratio is independently associated with mitral valve tenting after adjustment for LV remodeling (interpapillary muscle distance) in the subset of patients with HFpEF [13]. Consistently, for a similar degree of LV remodeling or function, the increase in LA pressure determines mitral valve tenting [13]. Discrete mitral annular calcifications may restrict leaflet motion and act as a substrate to secondary MR. Figure 2 summarizes the mechanisms that promote secondary MR in patients with HFpEF.

Figure 3 and video 1 (online suppl. video 1; for all online suppl. material, see www.karger.com/doi/10.1159/000350356) show the case of a 65-year-old hypertensive patient presenting with acute HF with secondary MR, increased LV filling pressure and normal LV ejection fraction. Unloading therapy was associated with a decrease in LV preload mirrored by a major decrease in MR [1]. Similar to patients with LV systolic dysfunction and secondary MR, analysis of the proximal flow convergence often displays peaks in the early and late systole and a midsystolic decrease. Midsystolic decreases in the regurgitant orifice area mirror increases in transmirtal pressure acting to close the valve (fig. 3) [48].

Although coronary artery disease is less prevalent in HFpEF than in HFrEF, myocardial ischemic disease should definitely be excluded as a cause of dynamic or transient MR in HFpEF patients. Myocardial infarction of small size (particularly in the posterior wall) or ischemia cause LV remodeling, subendocardial dysfunction, papillary muscles and segmental wall motion abnormalities and dyssynchrony, all factors known to facilitate acute MR and HF [49]. Nevertheless, coronary artery disease is commonly associated with mitral annular calcifications [50].

As previously found in HFrEF, secondary MR has been linked to pulmonary hypertension in HFpEF irrespective of the severity of LV diastolic dysfunction [2].
Indeed, MR reduces forward LV outflow and in turn increases LV filling pressure and pulmonary venous hypertension. Pulmonary pressures fluctuate in patients with HFpEF with secondary MR of varying severity. Overall, pulmonary hypertension is frequent in patients with HFpEF and portends a poor prognosis as in patients with HFrEF [51]. However, the severity of pulmonary venous hypertension (combined role of LV diastolic dysfunction and MR) does not fully account for the severity of pulmonary hypertension in HFpEF [2, 51]. Pulmonary vascular resistances may increase out of proportion to the rise in pulmonary venous pressure in these aged and hypertensive patients who exhibit increased vascular stiffness.

Two-dimensional Doppler echocardiography examination during exercise reveals the dynamic nature of secondary MR in HFpEF as in HFrEF patients (fig. 4) [52, 53]. Once myocardial ischemia is excluded [54, 55], an acute increase in LV diastolic stiffness and thereby in LV filling pressure during exercise (as estimated from the E/e' ratio [56]) may increase or produce secondary MR owing to mitral leaflet miscoaptation [51]. Several investigators have noted an abnormal LV response to exercise that may exacerbate MR [53, 57–60]. Whether LV dysynchrony plays a role in the worsening of secondary MR during exercise is under investigation [61].

The prognostic importance of secondary nonischemic MR in HFpEF is currently unknown. As in patients with HFrEF, unloading therapies that improve signs and symptoms of HFpEF patients usually reduce or even suppress MR [1]. Worsening renal function may limit the efficacy of unloading therapies owing to an excessive rise in cardiac preload. Eventually mitral valve replacement may be considered in HFpEF patients with persistent MR or severe inducible exercise MR. However, the outcome of mitral surgical procedures is unproven in this elderly population where comorbid conditions play a major role in prognosis [34]. Table 1 shows the comparison of secondary MR features between HFrEF and HFpEF patients.

### Clinical Implications of Loading Conditions: Importance in Secondary MR

Patients with acutely decompensated HF due to either HFrEF or HFpEF should be assessed for MR after stabilization. A comparison between echocardiographic findings at the time of acute decompensation and after stabilization may help to identify MR mechanisms: worsening of LV diastolic dysfunction and/or LV systolic dysfunction? Substantial concomitant decreases in pulmonary pressures are also observed after unloading therapy.

### Conclusion

Secondary MR occurs in patients with HFpEF as it does in those with HFrEF. Whether secondary MR is a bystander or an actor in HF remains a source of debate. Secondary MR associated with HFpEF or HFrEF appears

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<th>Table 1. Features of secondary MR in HFrEF and HFpEF patients</th>
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<td><strong>HFrEF</strong></td>
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<tr>
<td>Eccentric global LV remodeling</td>
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<td>Local LV remodeling</td>
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<td>Mitral annular dilation and dysfunction</td>
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<td>Structural mitral valve changes</td>
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<td>Active myocardial ischemia</td>
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<td>Linked to pulmonary hypertension</td>
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<td>Poor outcome</td>
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+++ = Highly related to secondary MR; ++ = moderately related to secondary MR; + = mildly related to secondary MR; ? = unknown.
to be highly dependent on cardiac loading conditions. Careful assessment of the mitral valve apparatus and subapparatus is needed to exclude organic lesions including focal prolapse, rheumatic or drug-induced lesions. Ischemic disease should be clearly ruled out as a cause of dynamic or transient MR in HF patients. Secondary MR is an independent determinant of pulmonary hypertension in both patients with HFpEF or HFrEF. Hence, the finding even of a mild secondary MR with HFpEF is likely to be viewed as an HF diagnostic criterion in patients with suspected HF despite a normal LV ejection fraction. Whether severe secondary MR may be a specific therapeutic target in HFpEF patients deserves further study.

**References**


Ennezet/Maréchaux/Pibarot/Le Jemtel