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Cardiac Dyssynchrony as a Pathophysiologic Factor of Functional Mitral Regurgitation: Role of Cardiac Resynchronization Therapy

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Abstract

Functional mitral regurgitation, a common problem in patients with left ventricular systolic dysfunction, has a strong negative impact on prognosis. Beneficial effects of surgical treatment in functional mitral regurgitation are still a matter of debate. Thus, cardiac dyssynchrony, a factor involved in functional mitral regurgitation pathophysiology, may become a therapeutic target in patients with this condition. This part of the book presents the pathophysiology of functional mitral regurgitation as a dynamic process, with particular emphasis on cardiac dyssynchrony, as both a contributor to functional mitral regurgitation and a target for cardiac resynchronization therapy. The underlying mechanisms of success and failure in the resynchronization therapy are discussed, along with therapeutic approaches to symptomatic patients with severe left ventricular dysfunction and significant persistent functional mitral regurgitation.

Keywords: functional mitral regurgitation, left ventricular remodeling, cardiac dyssynchrony, cardiac resynchronization therapy

1. Introduction

Secondary (functional) mitral regurgitation (MR) is a common finding in patients with global left ventricular (LV) dilatation and dysfunction, in both ischemic and non-ischemic cardiomyopathy. This functional disorder of the mitral valve is more common and far more complex than organic MR. In secondary MR, mitral valve is structurally normal (or almost normal) but its geometry and function are disrupted due to an imbalance between closing and tethering...
forces secondary to alterations in the geometry and function of the left ventricle. Functional MR can promote progressive LV remodeling. This results in a vicious circle, with both LV dilatation and functional MR acting as self-perpetuating processes. While prognosis is affected only in severe organic MR, even a mild functional MR may significantly worsen the outcome. However, it is unclear whether the unfavorable impact of functional MR on prognosis is independent of underlying LV dysfunction. We still do not know if mitral valve surgery, effective in the treatment of organic diseases of the mitral valve, can be equally beneficial in functional MR, since the surgical correction of valve dysfunction does not reverse the underlying LV pathology. Thus, indications for mitral valve surgery in heart failure (HF) patients with functional MR are not well defined in any currently available guidelines. Also the role of other treatment modalities, such as medical and interventional therapies, still raises controversies because of their limited effectiveness in functional MR management. This is related to both the underlying heart disease and the complexity of functional MR phenomenon. Also, adequate assessment of functional MR mechanisms and severity by means of imaging studies prior to making any therapeutic decisions constitute a challenge for clinicians. Cardiac dyssynchrony is a mechanism that provides a pathophysiologic basis for potential improvement of functional MR after the use of cardiac resynchronization therapy (CRT).

This part of the book presents the pathomechanism of functional MR with particular emphasis on the influence of cardiac dyssynchrony on mitral valve function, as well as the mechanisms of MR improvement after implantation of a CRT device, and prognostic value of both functional MR and its regression in response to CRT in patients with chronic heart failure.

2. Incidence and importance of functional mitral regurgitation in left ventricular dysfunction

Functional MR is a common, but often ‘silent,’ finding in heart failure patients [1–6]. Reported prevalence of functional MR varies depending on a diagnostic method (angiography, color Doppler echocardiography) and heart failure etiology (ischemic, non-ischemic) [1–5]. The incidence of functional MR after myocardial infarction varies from 20 to 50% but exceeds 50% in patients with non-ischemic dilated cardiomyopathy [4–6]. According to general estimates, nearly a half of heart failure patients may have a functional MR of some degree, and approximately one-third of them may suffer from moderate or severe functional MR [1, 3, 7]. Functional MR is an independent predictor of worse prognosis in patients with either ischemic or non-ischemic etiology of heart failure [3]. In patients with non-ischemic LV dysfunction, functional MR is associated with a two- to three-fold increased risk of heart failure episodes and cardiac mortality [4]. After myocardial infarction the presence of at least moderate functional MR is associated with a 3-fold increased risk of heart failure and a 1.6-fold increased risk of death at the 5-year follow-up [2]. Assessment of mitral valve function is included in routine risk stratification after myocardial infarction.

Functional MR is present in a large proportion of patients eligible for cardiac resynchronization therapy, with the incidence varying slightly from population to population and depending
on the evaluation method. Significant—that is, at least moderate—functional MR is present in about 40% of patients qualified to CRT [8–10]. Nowadays, functional MR no longer disqualifies patients from resynchronization therapy if such treatment is indicated. Furthermore, a decrease in functional MR severity is a determinant of response to CRT [10–12].

3. Difficulties in echocardiographic quantification of functional mitral regurgitation

Adequate evaluation of functional MR requires detailed clinical information (including functional NYHA class), physical examination, electrocardiography, and imaging studies. Echocardiography is essential for the evaluation of mitral valve anatomy and quantification of MR severity [13]. Transthoracic and transesophageal echocardiography may provide complementary clinically useful information, especially in the context of surgical or transcatheter repair feasibility. Usually, transesophageal echocardiography is more suitable for the evaluation of underlying anatomical conditions and identification of functional MR mechanism. However, due to changes in LV loading conditions during transesophageal evaluation (vasodilatory effect of sedation, hypovolemia, or anesthesia), the severity of functional MR may be underestimated; this favors transthoracic echocardiography as a method to quantify mitral regurgitation. Moreover, transthoracic examination is more suitable for the evaluation of other important parameters, such as LV volume, function and sphericity, left atrial size, pulmonary artery pressure, and function of the right ventricle and tricuspid valve. Three-dimensional (3D) echocardiography (either transesophageal or transthoracic) may provide additional information about MR severity, especially with regard to noncircular orifice geometry in functional MR [14]. 3D echocardiography overcomes some limitations of two-dimensional (2D) imaging; for example, it can be used for direct planimetric measurement of vena contracta area, a parameter which corresponds directly to the effective regurgitant orifice area (EROA) irrespective of the orifice shape or number of jets. However, both 3D and 2D color Doppler flows tend to overestimate the jet area (volume) due to their known bias in correct assessment of a turbulent stream. Considering all the difficulties previously mentioned, it needs to be stressed that no single parameter (also “quantitative”) is sufficient to adequately assess the severity of functional MR and thus, this condition should be evaluated with multiple methods [14].

In practical terms, echocardiographic severity of MR can be graded as mild, moderate or severe. Since available evidence suggests that functional MR of lesser severity may have similar or greater impact on mortality than primary MR [2], distinguishing between moderate and severe MR becomes of vital importance [15]. While severe primary MR is defined as EROA $\geq 40 \text{ mm}^2$ and regurgitant volume $\geq 60 \text{ mL}$, in line with current guidelines, severe secondary MR should be diagnosed whenever EROA $\geq 20 \text{ mm}^2$ and regurgitant volume $\geq 30 \text{ mL}$ [13, 15] (Table 1) [16]. However, adequate evaluation of functional MR severity in a clinical setting is far more challenging. In functional MR, both regurgitant orifice and jet area depend strongly on the mechanism of mitral regurgitation. Functional MR severity may be overestimated if determined based on the jet size on color Doppler imaging, or underestimated if
assessed using other traditional measures of mitral regurgitation such as proximal isovelocity surface area (PISA) and vena contracta width \[\text{[14]}\]. Also the limitations of the volumetric method in the assessment of regurgitant volume and fraction are well-known issues \[\text{[14]}\]. Furthermore, low inter- and intra-observer agreement between cardiologists reviewing the same dataset was documented \[\text{[17]}\]. It is now known that due to the limitations inherent to each available method, no single parameter is accurate enough to quantify the degree of MR. Therefore, current guidelines recommend an integrative approach including multiple qualitative and quantitative parameters, along with certain signs and measures of MR severity, such as left ventricular size and function, left atrial size, mitral valve leaflet morphology and motion, mitral filling pattern, pulmonary venous flow pattern and others \[\text{[13, 16]}\].

If during the first attempt MR is not unequivocally defined as mild or severe, the integrative approach should be used to exclude the severe character of mitral regurgitation.

Functional MR is an evidently dynamic phenomenon. A typical phasic variation in regurgitant volume and orifice, with the maximum values observed in early and late systole and minimum ones in mid-systole (at peak transmural pressure gradient generated by LV), is documented \[\text{[18]}\]. This intra-beat variability (referred to as the “loitering pattern”) hinders functional MR assessment, which is traditionally carried out in mid-systole. The severity of functional MR may also show a beat-to-beat variability depending on changes in loading conditions and hemodynamic parameters (e.g., during arrhythmia). The dynamic nature of functional MR has particular practical meanings in two situations: during physical exertion and intraoperative assessment. Induction of anesthesia and inotropic agents may significantly reduce MR and thus, may directly affect intraoperative decisions regarding its repair. Owing the dynamic nature of functional MR, in patients whose symptoms at rest are inadequate to assess the severity of mitral regurgitation, more accurate information may be obtained during exercise echocardiography. Exercises contribute to a greater cardiac load and thus, may also trigger dynamic geometric changes in the LV and mitral valve apparatus (even despite the lack of provoked ischemia), which may eventually result in acute “flash pulmonary edema” \[\text{[19]}\]. This may be a reason behind worse prognosis associated with even a mild functional MR. An exercise-induced increase in EROA by at least 13 mm$^2$ was shown to correlate with higher morbidity and mortality \[\text{[20]}\]. Exercise echocardiography may also unmask increasing pulmonary artery pressure and the lack of LV contractile reserve, both being important predictors of the outcome \[\text{[19, 20]}\]. Finally, exercises may reveal or trigger greater LV dyssynchrony with increased functional MR \[\text{[21]}\]. Despite some caveats of this approach, current guidelines recommend echocardiographic quantification of secondary MR during exercises, as this may

<table>
<thead>
<tr>
<th>Primary (organic) MR</th>
<th>Secondary (functional) MR</th>
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<tr>
<td>EROA ≥0.4 cm$^2$</td>
<td>≥0.2 cm$^2$</td>
</tr>
<tr>
<td>Regurgitant volume ≥60 mL</td>
<td>≥30 mL</td>
</tr>
<tr>
<td>Regurgitant fraction ≥50%</td>
<td>≥50%</td>
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<tr>
<td>Vena contracta ≥0.7 cm</td>
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<tr>
<td>Jet area Central jet &gt;40% LA or holosystolic eccentric jet</td>
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Table 1. Quantitative echocardiographic criteria for severe MR in primary and secondary disease of the mitral valve \[\text{[16]}\].
provide prognostically important information about dynamic characteristics of this condition [13]. Owing to documented limitations of echocardiography in this setting, newer imaging techniques, such as cardiac magnetic resonance and multidetector-row computed tomography, play an increasing role in the evaluation of patients with heart failure and functional MR. Both these techniques provide complementary data, such as true volumetric measures of cardiac chamber size and function, and can be used to assess myocardial viability and scars.

4. Pathophysiology of functional mitral regurgitation

The term “functional mitral regurgitation” refers to a dysfunction of the valve without its primary organic damage. Optimal function of the mitral valve provides nonrestrictive blood flow during diastole and leak tightness during systole. This diastolic and systolic competence is possible due to a synchronous coordination of all components of the mitral valve apparatus, acting under a balanced influence of closing and opening forces. Mitral valve apparatus is an integrated unit consisting of mitral valve itself (formed by two leaflets and mitral annulus) and subvalvular components (chordae tendineae, two papillary muscles, left ventricle and posterior left atrial wall). An effective function of the mitral valve is determined not only by the compatible cooperation between its components but also by their appropriate structural and spatial relations.

4.1. Left ventricular remodeling and dysfunction as a mechanism of functional mitral regurgitation

All changes in LV function and geometry affect functioning of mitral valve through opposing strength vectors: the tethering force (created by displacement of papillary muscles) and the LV-generated leaflet closing force (created by effective contraction causing transmitial pressure gradient) (Figure 1) [22]. Global LV dilation results in incomplete mitral leaflet closure and mitral regurgitation, which correlates with LV dysfunction. Local or global dilation of the LV is a prerequisite for incomplete mitral leaflet closure [22]. However, functional MR does not result from LV dilatation per se but from an increase in LV sphericity and resultant posterolateral displacement of the papillary muscles [23, 24]. If functional MR has an ischemic etiology, it does not necessarily need to be preceded by global systolic dysfunction [25]. Regional abnormalities in cardiac wall motion after inferior myocardial infarction may contribute to mitral valve tethering (with systolic tenting of the leaflets), which is strong enough to cause severe mitral regurgitation despite preserved LV ejection fraction (LVEF) [25].

Two main patterns of leaflet tethering can be distinguished in functional mitral regurgitation (Figure 2) [26, 27]. The symmetric pattern is characterized by global LV dilation with increased sphericity and predominant apical displacement of both leaflets with central regurgitant jet direction. Also the mitral valve annulus dilates symmetrically, primarily in the septal-lateral direction [26, 27]. This configuration is typical for non-ischemic functional MR (Carpentier type III B symmetric) [27, 28]. The asymmetric pattern is typically resulted from local remodeling of the posterior papillary muscle-bearing wall segment, with posterior tenting of both leaflets and a posteriorly directed asymmetric regurgitant jet (Carpentier type III B asymmetric) [25–28]. While the displacement of posterior papillary muscle is similar regardless of the leaflet tethering pattern, symmetric tethering is characterized by greater posterior and lateral displacement of
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[74] Delgado V, van Bommel RJ, Bertni M, et al. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation. 2011;123:70-78. DOI: 10.1161/CIRCULATIONAHA.110.945345


