JACC: CASE REPORTS VOL. 29, 2024

EDITORIAL COMMENT

Paroxysmal or "Eclipsed" Mitral Regurgitation

An Entity With Serious Consequences

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THE DEEPENING CONUNDRUM OF FUNCTIONAL MITRAL REGURGITATION

Functional (or secondary) mitral regurgitation (FMR) is the regurgitation occurring with structurally normal or near-normal mitral leaflets.[1] FMR has long been considered exclusively associated with global/regional left ventricular (LV) systolic dysfunction or remodeling, of ischemic or nonischemic origin, of uncertain mechanism and of uncertain prognostic significance.[2] With improved imaging, extensive cohorts, and clinical trials, understanding of mechanisms and outcome impact of FMR has been clarified. Mechanistically, although mitral annular flattening, dilation, and loss of contraction are all operative in generating FMR,[3] alterations of subvalvular support with displacement of papillary muscles and valvular tenting are major determinants of FMR severity.[4] FMR worsens the causal LV dysfunction outcome,[5,6] which is considerably improved by transcatheter mitral valve repair.[7] Thus, FMR is a crucial and treatable component of heart failure (HF) with reduced ejection fraction. However, the FMR conundrum has deepened further. Recently, identification of a new subtype of FMR different from the ventricular FMR and associated with predominant atrial remodeling while the left ventricle appears normal, has been emphasized,[8] often in association with longstanding atrial fibrillation[9] and/or LV diastolic dysfunction[10]; however, it remains a mystery in many aspects.[11]

A most striking conundrum of mitral regurgitation (MR) is related to its dynamic nature and to the possibility of paroxysmal variation of FMR severity. Dynamic changes of primary MR severity throughout systole in the setting of mitral valve prolapse are well known,[12] as are changes of FMR related to fluctuations of loading conditions,[13] HF medications,[14,15] or resynchronization therapy.[16] One special form of MR variation is the increase of effective regurgitant orifice of ventricular FMR reported during exercise, which indicates that the severity of the regurgitant lesion can acutely increase under certain circumstances, and can be associated with acute HF.[17] However, the sudden appearance and disappearance of FMR has been rarely reported as "eclipsed mitral regurgitation,"[18] a term intended to underscore the paroxysmal and complete nature of this appearance/disappearance. This type of MR is by nature functional because it is not just variable but is replaced by nearly complete restauration of leaflets' coaptation between acute phases and without significant primary mitral valve anomaly.[19] The demonstration of the existence of such paroxysmal, eclipsing FMR raises several important questions regarding its prevalence, mechanisms, and consequences.

Since its first mention,[18] only a small series[19] and few clinical cases[20-25] have been reported, suggesting either an extreme rarity of the condition or an underdiagnosis due to the paroxysmal nature of the leak and its prompt usual disappearance with acute HF treatment, and or changes in hemodynamics and loading conditions.[18,22] Only cases in which immediate echocardiography was performed during the acute phase of HF were detected, and it is possible that many cases are missed due to the lack of prompt imaging and auscultation. The mechanism of

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2024.102459

paroxysmal FMR is an acute lack of coaptation between mitral leaflets leading to acute HF,[18,19] but the reasons for such loss of coaptation remain uncertain. In the patients involved, the supposed final diagnosis of acute HF[18,19] is frequently that of HF with preserved ejection fraction (HFpEF), an entity that remains poorly understood. Whether eclipsed MR is a more frequent component of HFpEF than generally thought remains to be investigated.

THE PRESENT CASES: PAROXYSMAL FMR WITH HFpEF. In this issue of *JACC: Case Reports*, 2 reports emphasize the importance of eclipsed FMR. Kitamura et al[26] present the clinical case of a postmenopausal woman with past history and severe symptoms of recurrent episodes of acute pulmonary edema, which were ultimately attributed to paroxysmal acute massive restrictive FMR in the absence of preexisting significant mitral leak or LV systolic dysfunction remodeling, the so-called eclipsed MR. The acute FMR was reproduced by handgrip testing, and imaging showed that mechanistically the loss of mitral coaptation was related to systolic restriction of the mitral leaflets (type IIIb mechanism of Carpentier), with considerable separation of the tenting leaflets and FMR appearing massive in degree, providing an obvious explanation for the abrupt hemodynamic deterioration of the patient with pulmonary edema and hypotension. Prompt symptomatic recovery was associated with restoration of mitral coaptation. The authors concerned by the recurrent pulmonary edema under medical treatment decided to perform a transcatheter mitral edge-to-edge repair, with a result of no recurrence of paroxysmal FMR during a short follow-up. In the same issue, Knott et al[27] present the case of an 83-year-old woman with paroxysmal HF who developed positional severe FMR with acute exacerbation of the FMR and HF, with marked exacerbation of mitral tenting demonstrated by 3-dimensional echo. Here again, the patient was treated by transcatheter mitral edge-to-edge repair, which prevented the positional recurrence of eclipsed FMR and paroxysmal HF.

The Kitamura et al[26] case is not a case of isolated eclipsed MR due to the presence of known apical hypertrophic cardiomyopathy (HCM).[26] Although MR in HCM is usually associated with systolic anterior motion of mitral leaflets, such is not the case with apical HCM.[28] Whether paroxysmal FMR in this patient was related to LV diastolic dysfunction,[10] and/or abnormal mitral position due to the HCM, is putative.[29]

Coronary angiogram, as in previous cases, was normal (ie, nonobstructive), but provocative maneuvers with coronary imaging were not performed. Imaging during development of the paroxysmal FMR showed some mechanistic information with acute left atrial and LV dilatation during the episodes. Was it the mechanistic cause or consequence? Although the occurrence of paroxysmal MR may cause atrial and ventricular dilatation, the sudden tenting of mitral leaflets suggests acute papillary muscle displacement as directly responsible for the paroxysmal FMR. However, the primary cause of these changes is not understood. Is it an acute atrial remodeling with acute annular deformation,[20] secondary to sudden increase in preload,[24] to an acute widening of the papillary muscles separation such as in acute myocardial infarction,[22] or in Takatsubo-like ventricular alterations,[23] due to coronary spasm as suggested by methylergonovine MR triggering,[18] or due to an excess afterload-related LV dilation as hypothesized by the authors? Although the present cases cannot resolve these questions, the observation of paroxysmal tenting of mitral leaflet causing paroxysmal FMR is crucial.[26] Other important information regard the severity of the HFpEF caused by the paroxysmal FMR, with recurrent pulmonary edemas, already reported[30] but essential to underscore. This complication of paroxysmal FMR can indeed be life-threatening, requiring repeated admission in intensive care units, sometimes necessitating ventilatory support,[19] and resulting in cardiogenic shock[22] or cardiac arrest.[19] The diagnosis of paroxysmal FMR as the source of these complications is difficult, with reported erroneous diagnosis of precapillary pulmonary hypertension before the eclipsed FMR diagnosis was uncovered.[24] This profound diagnostic uncertainty prevents the investigation of the role of paroxysmal FMR in the advent of HFpEF and systematic prospective mechanistic and therapeutic evaluations.

PAROXYSMAL FMR AND HF: WHERE DO WE GO FROM HERE?

Over the years, little progress has been made in the concepts regarding eclipsed MR due to the lack of acute imaging of patients presenting with HF. If, as we suspect, paroxysmal FMR plays an underestimated role in HFpEF, prompt imaging of patients presenting with suspected acute HF in the emergency department is key to revealing this potential role,[17] and predefined Doppler echocardiographic protocols will be crucial in these emergency situations. Besides demonstration of acute FMR, secondary imaging protocols should also be devised. Although methylergonovine testing[18] appears ineffective in most cases,[19,21,23] preload or afterload stress testing may be considered by leg elevation,[24] exercise,[25] handgrip as in the present report, or possibly epinephrine

infusion.[23] Preadministration of nitrates may make these tests ineffective and should be avoided. Once identified, the treatment of paroxysmal FMR remains poorly defined and requires collaborative evaluation. Acutely, medical treatment, particularly nitrates,[18] may have a spectacular effect, even in the most serious presentations.[22] Counterintuitive beneficial effect of dobutamine and norepinephrine has been reported.[25] Long-term treatment by calcium channel blockers appears transiently effective.[18] Mitral valve replacement,[19,21,23,24] or transcatheter mitral valve repair,[25,29] has been used with good short-term outcomes, but uncertainty regarding long-term outcomes warrants well-designed multicenter trials. It is our plea that paroxysmal FMR be evaluated in collaborative multicenter series to elucidate the unresolved conundrum of eclipsed MR.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute heart failure, eclipsed, functional, mitral regurgitation