Left ventricular diastolic function in mitral stenosis

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Abstract

The assessment of left ventricular (LV) function in the setting of mitral stenosis (MS) has been critically examined for decades. Accurate assessment of aberrations in diastolic function is important as these subjects often present with signs and symptoms of heart failure and pulmonary congestion that cannot be solely explained by the severity of mechanical obstruction. Echocardiographic evaluation of diastolic dysfunction includes an evaluation of reduced LV compliance, diminished restoring forces and enhanced stiffness, which are challenging in the setting of MS owing to altered hemodynamic loading. Conventional echocardiographic and Doppler measures offer limited information. Novel assessments employing speckle tracking echocardiography are relatively less studied. A more comprehensive assessment including clinical evaluation, identification of concomitant disorders and comorbidities is particularly warranted in older subjects with degenerative MS to suspect diastolic dysfunction and arrive at optimal medical therapy or intervention. This review provides an overview of etiological, pathophysiological, echocardiographic and invasive assessment of diastolic dysfunction in the setting of MS, with specific focus on strengths and limitations of available echocardiographic and Doppler techniques.

Introduction

The assessment of left ventricular (LV) function in the setting of mitral stenosis (MS) has been critically examined for decades. In the 1950s, studies by Harvey[1] and Fleming[2] explored mechanistic theories related to the presentation of depressed LV function in MS. Surgical commissurotomy was widely considered as an effective therapy to relieve symptoms at that time, and the ability to distinguish patients with mechanical obstruction that may benefit from surgery from those with primary myocardial insufficiency held clinical and prognostic relevance. Several studies have subsequently reported reduced pump performance in this setting[3-8] and have attributed this to variable mechanisms that include impaired LV filling secondary to mitral valvular obstruction[9-11], chronic myocardial inflammation[12-14], sub-valvular scarring resulting in regional abnormalities,[3 15 16] elevated systemic load[4 17-19] and right-left interactions[20]. (Table 1)

A more focused inspection of LV diastolic function in MS was first undertaken by Feigenbaum and colleagues, who measured mean compliance employing the ratio of mean mitral valve flow to temporal change in chamber pressure employing biventricular catheterization.[21] No differences in LV compliance was observed between controls and patients in this study. With wide utilization of invasive hemodynamic and subsequent advancement of echocardiographic techniques, multiple investigators have explored LV performance in this setting, paying specific attention to ventricular distensibility and the measurement of filling pressures.

The accurate identification of diastolic aberrations in MS is important as these subjects often present with signs and symptoms of heart failure and pulmonary congestion that cannot be solely explained by the severity of mechanical obstruction.[22] The evaluation of MS involves a stepwise process not limited to the assessment of mitral valve orifice area (MVOA), but also left atrial (LA) size, associated mitral regurgitation, LV dimensions and LV systolic function. LV diastolic function assessment (Table 2), while routinely done

as a part of a normal echocardiographic evaluation, remains challenging in the presence of MS and is most often not assessed in routine clinical practice.

LA pressure in significant MS is elevated owing to the inability of the stenotic valve to permit

complete passive atrial emptying during LV diastole, hence relying heavily on atrial kick. Consequently, LV end-diastolic volume is markedly reduced, which in turn lowers stroke volume. The expansibility of LV is impaired owing to a rigid, thickened mitral valve apparatus and its attachment to LV, leading to alterations in diastolic function.[6] Associated clinical conditions such as hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD) and advancing age may also contribute to impaired diastolic function, adding to the complexity of assessment.

Etiology

MS is usually a consequence of rheumatic fever in the context of developing nations, less often due to degenerative disease with annular calcification in the elderly in developed countries, and as a radiation therapy induced abnormality in cancer patients. Approximately one-fourth of all patients who have rheumatic fever develop MS.[23]Traditionally, it was believed that LV function was spared in patients with MS. However, LV dysfunction is frequently seen in this setting and the consequence of this is less known following mitral valve replacement.[24]

During the acute phase of the disease, inflammation encompasses the endocardium, myocardium and pericardium. While valvular scarring and subsequent deformation are most apparent long-term presentations, histological studies suggest that fibroid necrosis in the interstitial tissue of the myocardium, followed by histiocyte and giant cells during the granulomatous phase, and subsequent presentation of Aschoff nodules may contribute to myocardial disarray.[25]Ultrastructural alterations of LV muscle cells have supported the widely held concept of a myocardial factor as the basic pathogenetic mechanism behind impaired LV function in MS.[26] With increasing life expectancy, degenerative causes are more common in developed nations.[27] A fraction (6-8%) of subjects with severe mitral annular calcification (MAC), usually seen in elderly or in those patients who are dialysis-dependent, develop MS as a result of calcium encroaching the base of the valve leaflets.[28 29] Less common causes include systemic disorders like mucopolysaccharidosis, Whipple's disease and disorders associated with abnormal serotonin metabolism.

Prevalence

While studies have suggested that the rate of reduced ejection fraction (EF) in MS may be as high as 33%, [3-5] specific data concerning the prevalence of diastolic dysfunction in MS is sparse. This may be partially attributable to the declining occurrence of disease and inherent challenges related to diastolic function assessment in the setting of altered ventricular loading due to valvular obstruction. Indirect evidence, however, can be obtained from the Euro Heart Survey, where MS accounted for 12% of subjects and the prevalence of degenerative MS increased dramatically with aging.[27]In another study, close to 1 in 4 subjects with degenerative aortic stenosis were reported with hemodynamically significant MS secondary to MAC.[30] Additionally, comorbidities such as chronic renal disorders and DM are also associated with MAC[25 26] Taken together, this data suggests that diastolic aberrations in this population may not be uncommon.

Pathophysiology

Pathophysiological consequences of MS are primarily due to an increased transmitral pressure gradient across a stenosed valve, which in turn leads to both a reduction in forward flow across the valve and increased LA pressure that is retro-transmitted to elevate pulmonary pressures. Both myocardial and mechanical factors contribute to the pathogenesis of functional deterioration. Symptoms correlate with elevations in LA mean pressure and are often precipitated by tachycardia and onset of atrial fibrillation (AF).[31] Changes in LA and LV compliance also impact symptoms and exertion tolerance.[32 33]While reduced cardiac output in patients with MS is often attributed to mechanical obstruction across the mitral orifice, this frequently does not increase following mitral commissurotomy.[21]Tension created by a fibrosed mitral valve apparatus, altered

RV-LV interaction, passive elastic changes due to the chronic decrease in preload and myocardial fibrosis might be responsible for LV systolic and diastolic dysfunction.

In patients with LV diastolic dysfunction, symptoms of dyspnea exceed severity of MS and such patients may have persistent symptoms even after mitral valvotomy or valve replacement. Normally, negative LV intraventricular pressure generated in early diastole (diastolic suction) leads to lower reliance on LA filling during the cardiac cycle. Sabbah and colleagues observed that this mechanism was lost in MS patients having diastolic dysfunction.[34] Studies have suggested that over 30% of subjects with MS demonstrate elevated LVEDP based on invasive criteria. Recurrent symptoms and repeat intervention were more common in the group with elevated LVEDP as compared with those that did not present with marked diastolic dysfunction.[35]

Frequency of CAD in MS has also been studied. In 96 patients, angiographically significant coronary artery stenosis was found in 28% among patients above 40 years age and prognosis of these patients was compromised due to this added complication.[36] LV systolic and diastolic dysfunction can occur among MS patients irrespective of their basic rhythm. Systolic function is more affected in patients with AF and diastolic function is more affected in patients with sinus rhythm. Tissue doppler imaging and 2D speckle strain imaging are tools that are available to assess subclinical LV dysfunction in MS patients.

Invasive Evaluation

Direct estimation of LV diastolic performance can be obtained employing multiple invasive approaches, which include measuring LVEDP, rate of pressure decline during isovolumic relaxation or τ (tau), and passive chamber stiffness employing pressure-volume loops.[37]In an elegant study employing micromanometer techniques with concomitant transient occlusion of the inferior vena cava, Liu and colleagues demonstrated reduced diastolic compliance in MS and attributed this to tethering of an immobile mitral apparatus. In this study, increased LV chamber stiffness normalized after balloon intervention.[6] Other mechanisms proposed to explain reduced LV compliance in MS include restriction of regional myocardial segments[13] and the influence of a dilated, overloaded right heart on left-sided distensibility.[19] [38]Negative diastolic pressures have been demonstrated in MS which characterizes ventricular early diastolic suction.[34]With super-imposed diastolic aberrations, these early filling forces may be negated.[39]

In contrast, patients with normal LV diastolic function have low or normal LV diastolic pressures. To confirm whether LV diastolic dysfunction truly contributes to raised LA pressures, vasodilators can be used to reduce afterload and demonstrate significant decrease in diastolic pressures. In patients without diastolic dysfunction, the reduction in LA pressure is likely to be marginal.

Echocardiographic Evaluation

LV diastolic dysfunction is a consequence of dampened LV relaxation in the presence or absence of reduced restoring forces and elevated levels of ventricular stiffness, leading to elevated filling pressures.[40] Echocardiographic evaluation of diastolic dysfunction includes an evaluation of reduced LV compliance, diminished restoring forces and enhanced stiffness. An assessment of these three ventricular properties are particularly challenging in MS, where a significantly narrowed mitral valve obstructs flow into the LV, resulting in reduced filling and thereby, altered hemodynamic loading.

Transmitral Doppler indices

Key variables to be considered during echocardiographic evaluation of diastolic dysfunction include early diastolic transmitral velocity (E), early diastolic mitral annular velocity by tissue Doppler imaging (TDI) (e') and their corresponding relationship (E/e'), LA volume index (LAVi) and peak tricuspid regurgitation velocity.[40] In the setting of MS, however, these offer limited value to assess myocardial disease as they are often related to the degree of valvular stenosis. E-wave velocity reflects left-sided atrioventricular gradient during early diastole and is affected by alterations in LV relaxation and LA pressure. In the setting of significant LV diastolic dysfunction, transmitral gradient is low despite increased LA pressure owing to concomitant increase in LV diastolic pressure. Pressure half-time employing echocardiography, thereby, is decreased due to increase in LV diastolic pressure caused by increased LV chamber stiffness and hence,

may not provide an accurate estimation of valve area using this method.[40] (Figures – 1, 2). Further, elevated transmitral velocities secondary to valvular obstruction and lower myocardial velocities in the setting of reduced output result in abnormally high E/e' values that may not faithfully represent invasive filling pressures.[41] LA volumes are often increased as an adaptation response to elevated pressures secondary to valvular obstruction. This is further compounded by the frequent occurrence of AF, which further distorts LA geometry. In keeping with these observations, current guidelines have suggested that recommended echocardiographic measures to identify LV diastolic function may not be accurate to assess LV filling pressures in the setting of significant mitral valve disease.[40]

Pulmonary vein velocities

Pulmonary S-wave velocity (which includes S_1 and S_2 waves) is impacted by alterations in LA pressure, in addition to LA and LV contractility. D-wave velocity is influenced by early diastolic LV filling and maintains a strong relationship with mitral E velocity.[42] The resultant ratio (S/D) is related to changes in compliance of the LA but may have limited accuracy in mitral valve disease.[40] In addition, pulmonary vein flow is influenced by obstruction imposed by the valve[43] and is less likely to represent changes in LV compliance.

Mitral velocity propagation

Mitral flow propagation velocity (V_p) has been proposed as an indicator of LV relaxation and correlates with invasive time constants of relaxation.[44] Additionally, E/Vp ratio has been shown to correlate with LA pressure,[45] but may not be accurate in patients with normal EF.[40]Further, transmitral E wave velocity is governed by the severity of mitral obstruction, making this measurement unreliable in the setting of MS.

IVRT/$T_{E\text{-}e'}$ ratio

Time intervals are less prone to hemodynamic alterations and hold relevance in the load-altered MS milieu. Early clinical and auscultatory study suggest that IVRT, the time interval between aortic valve closure and mitral valve opening, is altered in MS.[46 47] More recent echocardiographic data suggests that IVRT demonstrates significant relationship with invasive filling pressures in the setting of mitral stenosis[41] and in degenerative mitral annular calcification.[48] Further, shorter IVRT and higher mitral A-wave velocity suggest elevated early diastolic LA pressures. However, IVRT is not routinely measured in clinical practice and is affected by heart rate and arterial pressure.[40]The time interval between E and e' ($T_{E\text{-}e'}$) has demonstrated good relation to τ in animal and human studies and is relatively load-independent.[49 50] Using pulse wave doppler, the E wave is recorded and the time interval between the onset of QRS complex and the E wave is taken note of. Similarly, using TDI, the time interval between the onset of QRS wave on the ECG and the e' wave is noted. The difference between the two is depicted as the $T_{E\text{-}e'}$ time interval. IVRT is then divided by this value. The normal value is <2. In normal LV diastolic function, E and e' occur at the same time or e' may precede it. With elevated LA pressure, the mitral E wave occurs earlier and annular e' velocity is delayed, lengthening $T_{E\text{-}e'}$. In keeping with these findings, Diwan et al. demonstrated that time-adjusted IVRT (IVRT/ $T_{E\text{-}e'}$) displayed the strongest correlation with capillary wedge pressure in MS and could track changes in capillary wedge pressure after valve surgery.[41] A value of < 4.2 indicates increased LV diastolic pressures in MS with reasonable accuracy. However, in the presence of atrial fibrillation, these values may be hard to ascertain.

Quantitative echocardiography

TDI as a quantitative tool is based on principles of lower velocity Doppler frequency shifts and has been extensively used to characterize both systolic and diastolic function. More specifically, mitral annular early diastolic recoil velocity (e') has been shown to be associated with invasively measured time constant of LV relaxation (τ), and has been validated in both animal models[51 52] and human studies.[53-55] Further, e' has been shown to be less load-dependent than conventional doppler-derived parameters. With this background, Ozdemir and colleagues first demonstrated reduced systolic and diastolic myocardial velocities in MS subjects with normal ejection fraction (EF). While systolic myocardial velocities demonstrated a positive correlation with mitral orifice area, no association was observed with e', suggesting that reduced LV performance in MS

could be attributed to both myocardial and functional factors.[56] Sengupta and colleagues also demonstrated decreased myocardial velocities in MS and subsequent elevation after balloon commissurotomy. In that study, increase in e' was associated with MVA. Serial measurements during follow-up showed progressive improvement in the annular velocities, prompting the authors to suggest that tissue velocity imaging can be used to monitor changes in LV function after PTMC.[57]

2D Speckle tracking echocardiography is another powerful parametric imaging tool now being increasingly employed in clinical practice. There is limited data studying diastolic function in MS employing speckle tracking echocardiography. Sengupta and colleagues showed decreased strain in patients with severe MS, with rapid improvement in LV deformation after PTMC, which correlated well with improved diastolic loading. The findings suggested that impaired LV mechanical function in MS can be attributed to decreased LV filling, instead of structural myocardial abnormalities.[58]

Balloon Mitral Commissurotomy

Percutaneous transvenous mitral commissurotomy (PTMC) is the treatment of choice for patients with symptomatic MS. Soon after PTMC, an improved LV filling and increased LV end diastolic volume is observed, with slight increase in LVEDP and subsequent normalization.[6 38] In the absence of LV diastolic dysfunction, no significant changes are seen in LV diastolic pressure, although a fall in LA pressure is observed. Limited data exists on the impact of PTMC on LV compliance and the effect of elevated baseline LVEDP on outcomes. Eleid et al reported LV diastolic dysfunction and elevated invasive LVEDP in one in three subjects undergoing PTMC and suggested that diastolic aberrations contribute to existing LA pressure and are associated with greater risk of failure to improve symptoms. In their study, both body mass index and DM were associated with diastolic dysfunction. While no significant differences in severity of pulmonary hypertension or post-interventional improvement in hemodynamic status was observed when comparing the group with elevated LV stiffness (LVEDP>15mmHg) with normal compliance (LVEDP[?]15mmHg), the group with elevated LVEDP had a higher risk of combined end-point, which included recurrent severe symptoms, repeat procedure or death (1-year estimate, 42% vs 81%; hazard ratio, 2.83; 95% CI, 1.62-4.96; P<.001). [35]Additionally, lower LVEDP has been proposed as an independent predictor for intermediate and long-term risk-free survival in multiple studies.[59 60]

Conclusion

The assessment of LV diastolic dysfunction in patients with MS is challenging. Identification of concomitant diastolic disorders is imperative in the management of older subjects with co-existent systemic disease, co-morbidities and mismatch between symptom class and MVOA, and to identify subgroups that may not benefit from balloon intervention. Such subjects may benefit from optimal medical therapy to decrease blood pressure, lower heart rate, improve LV diastolic filling and with diuretics to lower PH. Conventional echocardiographic methods are of limited value to assess LV diastolic dysfunction in MS. IVRT/$T_{E\text{-}e'}$ ratio is the recommended method to identify the presence of raised LV filling pressure. Newer diagnostic methods like speckle tracking echocardiography show promise, but widespread utility is currently limited owing to insufficient data.

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Table 1. Pathophysiology of left ventricular dysfunction in mitral stenosis

Proposed pathophysiology of left ventricular (LV) dysfunction in mitral stenosis include[4] Chronic inflammation leading to n

Table 2. Methods to assess left ventricular diastolic dysfunction

Invasive evaluation Echocardiographic evaluation Transmitral Doppler Pulmonary vein Doppler Flow propagation velocity T