

Pre- and Post-Operative Diastolic Dysfunction in Patients With Valvular Heart Disease

Diagnosis and Therapeutic Implications

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Patients with valvular heart disease often have left ventricular diastolic dysfunction. This review summarizes the underlying mechanisms for diastolic dysfunction in patients with mitral and aortic valve disease. In addition to load, intrinsic myocardial abnormalities occur related to changes in sarcomeric proteins, abnormal calcium handling, and fibrosis. Echocardiography is the initial modality for the diagnosis of left ventricular diastolic function. Although there are challenges to conventional Doppler parameters of diastolic function, it is often possible to arrive at a clinically useful assessment of left ventricular filling pressures using a comprehensive approach. When needed, cardiac magnetic resonance and cardiac catheterization can be obtained. Medical therapy can be of value for the treatment of diastolic dysfunction, but there is a paucity of data evaluating its clinical utility. More importantly, diastolic dysfunction usually improves with timely surgical intervention, although surgery does not always lead to normalization of function. (J Am Coll Cardiol 2013;62:1922–30) © 2013 by the American College of Cardiology Foundation

The diagnosis of diastolic heart failure is entertained in the absence of hemodynamically significant valvular heart disease. However, patients with valvular heart disease frequently have symptoms of pulmonary and/or systemic congestion due to increased left ventricular (LV) filling pressures and/or diastolic dysfunction. In this review, we discuss the mechanisms behind pre-operative and post-operative diastolic dysfunction in patients with aortic and mitral valve disease, the diagnostic aspects of diastolic dysfunction in these patients, and the implications for treatment.

Aortic Stenosis

Aortic stenosis (AS) is the most common reason for valve replacement in the United States. Calcific AS is present in 2% to 4% of the population over age 65 years and in as many as 8% of the elderly population by age 85 years (1).

Mechanisms of diastolic dysfunction in AS. Patients with moderate to severe AS usually have concentric LV hypertrophy, which is associated with myocardial dysfunction due to abnormal calcium handling, disruption of cellular

organization, loss of contractile elements, apoptosis, vascular rarefaction, titin isoenzyme shifts, and fibrosis. The LV hypertrophy allows for a lower end-systolic wall stress, and normal ejection fraction (EF), albeit systolic abnormalities can be detected by myocardial strain (2). At this stage, diastolic dysfunction is quite common and is related to impaired and delayed relaxation and increased LV chamber stiffness.

Increased chamber stiffness is in turn related to increased LV mass/end-diastolic volume (EDV) ratio and increased myocardial stiffness. For myocardial stiffness, increased interstitial fibrosis is an important contributing factor (3,4). Other mechanisms include decreased titin N2BA/N2B isoform ratio and its hypophosphorylation (5,6). Both changes result in a higher tension for a given sarcomere length. Secondary pulmonary hypertension is one of the consequences of diastolic dysfunction, and the link between them can be evaluated by noninvasive studies at rest and during exercise (7,8). Secondary mitral regurgitation (MR) can occur with LV systolic dysfunction and annular dilation, and when MR is hemodynamically significant, it can contribute to elevated left atrial (LA) pressure and pulmonary artery (PA) pressures. Finally, subendocardial ischemia can occur because of lower coronary perfusion and exacerbates myocardial abnormalities.

Diagnosis of diastolic dysfunction. **ECHOCARDIOGRAPHY.** The American Society of Echocardiography/European Association of Echocardiography diastolic function guidelines can be applied to AS patients on the basis of LV EF and taking into consideration the limitations of

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the different indices (Table 1). Impaired myocardial relaxation can be inferred in the presence of reduced e' velocity as well myocardial diastolic strain rate. In the presence of normal or reduced LV EDV along with Doppler findings of increased filling pressures, one can conclude that LV chamber stiffness is increased. Doppler predictors of elevated LV end-diastolic pressure (EDP) are particularly useful in identifying myocardial abnormalities independent of MR and LA dysfunction. These include mitral A-wave duration and its deceleration time (DT [both shortened]), pulmonary vein atrial reversal velocity (Ar) and duration (both increased), and mitral annulus a' velocity (decreased). Clinical management can be influenced by knowing the status of LV filling pressures as this would confirm or refute the presence of a cardiac etiology for dyspnea in patients with coexisting pulmonary disorders. With depressed EF, mitral inflow parameters can be applied for assessment of LV filling pressures (9). When LV EF is $>50\%$, mitral E/e' ratio is the starting point (9). Of note, some elderly patients with AS have severe mitral annular calcification, which is a limitation to the application of E/e' ratio (Fig. 1).

Stress echocardiography using a supine bike protocol can provide useful data on LV systolic reserve (changes in stroke volume, EF, and global longitudinal strain) and diastolic reserve (changes in e' velocity, E/e' ratio, and PA pressures). It is often difficult to distinguish the effects of the valve lesion itself, systolic dysfunction, and diastolic dysfunction on abnormal resting or exercise echocardiographic and hemodynamic recordings. Notwithstanding, recent studies support the clinical promise of using exercise PA pressure estimation for the management of patients with asymptomatic severe AS (8).

CARDIAC MAGNETIC RESONANCE. In patients with suboptimal echocardiographic images, cardiac magnetic resonance (CMR) can provide an accurate assessment of LV and aortic valve morphology and function. In addition, CMR can be used to quantify the presence and extent of replacement fibrosis due to myocyte loss as well as interstitial fibrosis (10,11). Fibrosis measurements are of interest because they

can help explain the mechanisms behind diastolic dysfunction as well as predict outcome after surgery (3,4).

CARDIAC CATHETERIZATION. Aside from the assessment of aortic valve hemodynamics, it is possible to measure LV diastolic pressures, PA pressures, and the time constant of LV relaxation (Tau) using high-fidelity pressure transducers. LV volumes, operating chamber stiffness, and modulus of chamber stiffness (k) can be obtained using conductance catheters.

Diastolic dysfunction and clinical outcomes before and after aortic valve replacement.

There are few studies that evaluated the relation between diastolic dysfunction and clinical outcomes in AS. In a recent study of 125 AS

patients who have not undergone valve surgery, E/e' ratio was the most predictive parameter of clinical events among clinical and imaging measurements (12). Likewise, LV diastolic dysfunction (inferred using E/e' ratio) was an important independent predictor of early, midterm, and late mortality after aortic valve replacement (AVR) (13,14).

LV diastolic dysfunction after AVR in patients with AS.

After surgery, LV filling usually improves, with an increase in LV EDV and regression of LV hypertrophy. Early improvement in LV filling appears related to the decrease in LV mass/EDV ratio (15,16). Likewise, an increase in coronary flow reserve can be seen early on concomitant with the decrease in LV EDP (17).

Notwithstanding the above observations, there are carefully performed clinical studies that have shown an increase in LV chamber stiffness early after AVR. This was associated with an increase in interstitial fibrosis and occurred

Abbreviations and Acronyms

AR = aortic regurgitation
Ar = atrial reversal velocity
AS = aortic stenosis
AVR = aortic valve replacement
CMR = cardiac magnetic resonance
DT = deceleration time
EDP = end-diastolic pressure
EDV = end-diastolic volume
EF = ejection fraction
IVRT = isovolumic relaxation time
LA = left atrial
LV = left ventricular
MR = mitral regurgitation
MS = mitral stenosis
PA = pulmonary artery

Table 1 Summary of Applications and Limitations of Doppler Parameters in Patients With Valvular Heart Disease

Doppler Parameter	Values Indicating Increased LV Filling Pressures	Limitations
Mitral E/A ratio*	>1.2 with depressed EF	Severe AR and MR with normal EF
DT of mitral E	<160 ms with depressed EF	Severe AR
Pulmonary vein S/D*	<1 with depressed EF	Severe MR
Peak Ar velocity*†	>30 cm/s	Suboptimal signals, LA dysfunction
Ar – A duration*†	≥ 35 ms	Suboptimal signals, LA dysfunction
E/e' ratio	Septal >15 , lateral >12 , avg >13	Severe MR or MS, severe MAC
IVRT/ $T_{E-a'}$ ‡	<3 for MR, <4.2 for MS	Challenging in atrial fibrillation
PA systolic pressure	>35 mm Hg	Coexisting pulmonary disease

*Parameter cannot be obtained with atrial fibrillation. †Signal detects increased left ventricular (LV) end-diastolic pressure. ‡While challenging in atrial fibrillation, it can still be applied if matched RR intervals are available.

Ar = aortic reversal velocity; AR = aortic regurgitation; Avg = average of septal and lateral E/e' ratios; DT = deceleration time; EF = ejection fraction; IVRT = isovolumic relaxation time; LA = left atrial; MAC = mitral annular calcification; MR = mitral regurgitation; MS = mitral stenosis; PA = pulmonary artery; S/D = systolic/diastolic; $T_{E-a'}$ = time between onset of mitral E velocity and annular e' velocity.

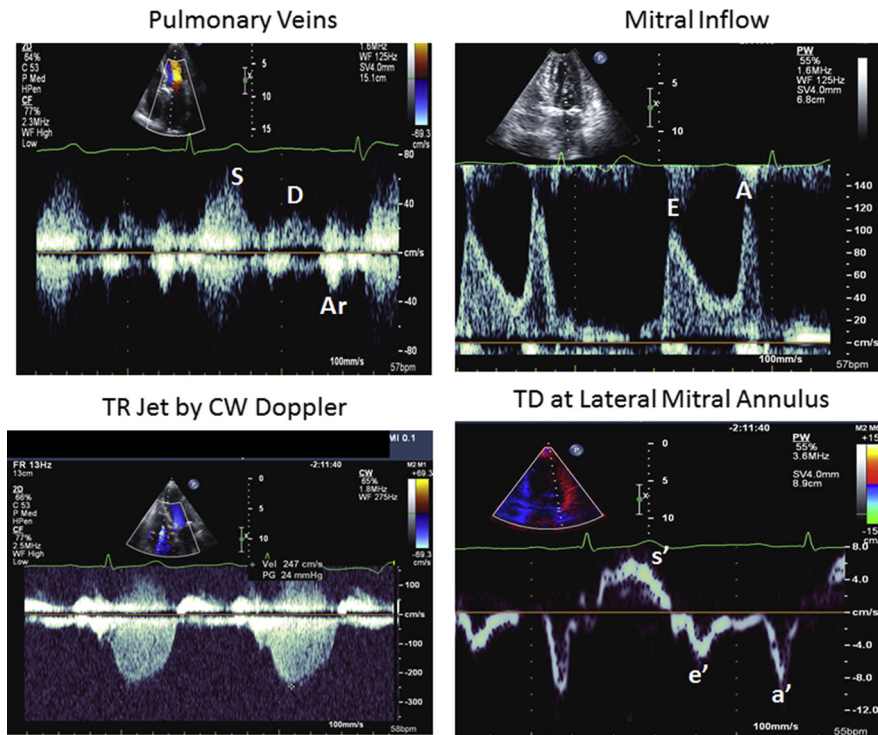


Figure 1 Doppler Signals From a Patient With AS and Severe Mitral Annulus Calcification

Pulmonary venous flow (**upper left**), mitral inflow (**upper right**), tricuspid regurgitation (TR) jet by continuous wave (CW) Doppler (**lower left**), and mitral annulus velocities at lateral annulus (**lower right**) from a patient with severe mitral annular calcification and severe aortic stenosis (AS). Mitral peak E velocity is increased and lateral annular e' velocity is decreased because of heavy annular calcification, and thus E/e' erroneously suggests increased left ventricular (LV) filling pressures. Pulmonary veins systolic/diastolic ratio, pulmonary veins atrial reversal velocity (Ar) minus mitral A-wave velocity duration, and pulmonary artery systolic pressure (estimated at 29 mm Hg assuming right atrial pressure of 5 mm Hg; inferior vena cava diameter <2 cm with spontaneous collapse) are all indicative of normal LV filling pressures. This patient had LV diastolic pressure before left atrial contraction of 8 mm Hg and LV end-diastolic pressure of 9 mm Hg by left heart catheterization. a' = late diastolic velocity; S' = systolic velocity; TD = tissue Doppler.

despite a reduction in LV mass. Late after surgery, myocardial stiffness constant decreases in parallel with the decrease in myocyte diameter and fibrosis (18).

Patient-prosthesis mismatch can contribute to persistent diastolic dysfunction due to elevated LV systolic pressure and limited regression of LV hypertrophy. It appears that diastolic dysfunction is one of the major mechanisms by which mismatch contributes to clinical events of death and hospitalizations in this setting (19).

Diagnosis of LV diastolic dysfunction after AVR. The diagnostic evaluation of these patients is geared toward identifying and grading the diastolic dysfunction as well as determining the potential underlying reasons. The latter include LV systolic dysfunction, post-operative valve problems including patient-prosthesis mismatch, and pericardial diseases. Doppler methodology as described earlier can be applied to provide important insights explaining the persistent symptoms of pulmonary congestion (Fig. 2).

Implications for treatment before and after AVR. Aside from the temporary use of diuretics, AVR (surgery or percutaneous) is the treatment for diastolic dysfunction in AS patients. Several reports have shown that AVR leads to an

improvement in LV filling pressures (20). Post-operatively, adequate control of hypertension and the careful use of diuretic therapy can help achieve better symptomatic control in patients with pulmonary congestion. In that regard, the use of selective antihypertensive therapy may have unique advantages of improving diastolic dysfunction and clinical outcomes.

Angiotensin-receptor blockers have been examined as potential therapy after AVR because of their ability to accelerate LV mass regression and thus improve diastolic function. Candesartan was administered after AVR in 114 patients, who were randomly assigned to the drug at 32 mg per day or to conventional treatment. Although there were no significant differences between the 2 groups in blood pressure, candesartan was effective in accelerating LV and LA remodeling at 12 months, compared to conventional treatment, but had no effects on E/e' ratio and B-type natriuretic peptide levels (21). In another randomized study with 91 patients, the administration of the drug at 32 mg per day was associated with a significantly lower incidence of post-operative new-onset atrial fibrillation at 3 to 12 months after AVR (22). This is likely related to the improvement in

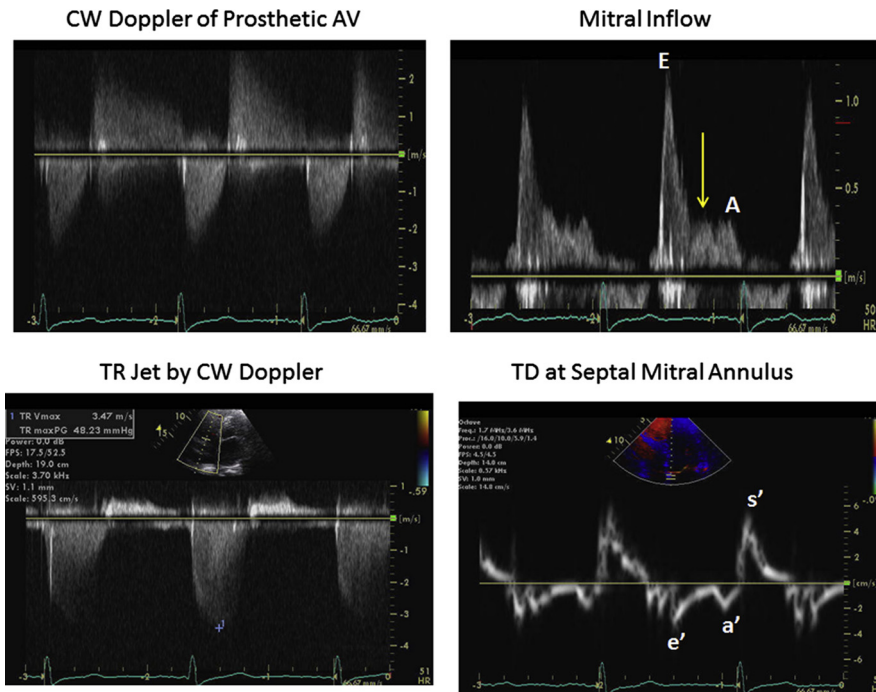


Figure 2 Doppler Signals From a Patient With Persistent Dyspnea After AVR

Doppler data from a patient with prosthetic aortic valve (AV) who presented with persistent dyspnea 8 months after aortic valve replacement (AVR). The left ventricle (LV) was normal in size with ejection fraction at 58%. Continuous wave (CW) Doppler of the AV is shown (**upper left**) with normal peak velocity and mean gradient of 12 mm Hg consistent with normal prosthetic valve function. Mitral inflow at tips level is shown (**upper right**) with restrictive LV filling (peak E velocity at 115 cm/s). There is an L-wave (**arrow**), which is consistent with impaired LV relaxation and increased LV filling pressures. Peak velocity of tricuspid regurgitation (TR) jet (3.5 m/s) corresponds to a pulmonary artery systolic pressure of at least 48 mm Hg (**lower left**). Septal annular velocities are shown (**lower right**); septal E/e' ratio is 38.3, consistent with markedly elevated LV filling pressures (>25 mm Hg). TD = tissue Doppler.

LV filling and the decrease in LA volumes as a consequence of accelerated LV mass regression. The use of these drugs was further explored in patients with prosthesis mismatch in a randomized trial that included 72 patients in which a dual renin-angiotensin inhibition regimen was associated with a larger decrement in LV mass and a lower incidence of residual LV hypertrophy (23). In comparison with these studies, there is no evidence that statin therapy alters valvular or ventricular function after AVR.

Aortic Regurgitation

Mechanisms of diastolic dysfunction. In patients with chronic aortic regurgitation (AR), the left ventricle undergoes remodeling such that its dimensions/volumes and mass increase with eccentric hypertrophy. In the compensated state, the LV is more compliant and accommodates the increased LV EDV with normal diastolic pressures. Later on, LV stiffness and filling pressures increase marking the presence of the decompensated state. This stage can be accompanied by symptoms and signs related to the increase in LV filling pressures and pulmonary congestion.

Diastolic dysfunction in chronic AR occurs because of impaired LV relaxation and increased myocardial stiffness (24). Myocardial samples from chronic AR patients exhibit

increased cell diameter and fibrous content (25). In 1 study, c-Myc protein expression was related to pathological changes (26), whereas in another study, upregulation of the fibronectin gene along with increased fibronectin deposition were implicated (27).

Diagnosis of diastolic dysfunction. In the presence with severe AR and normal LV diastolic function, mitral inflow is characterized by predominant early filling and the annular e' velocity is normal or increased due to increased LV stroke volume. Accordingly, E/e' ratio is usually not increased, and PA pressures are normal (Fig. 3). With LV diastolic dysfunction, LV filling pressures and PA pressures are elevated at first with exercise, and later on, at rest. Of note, severe AR in and of itself can influence Doppler parameters if the AR jet contributes to the rapid rise in LV diastolic pressures (9). This can be manifested by a short DT of mitral E velocity (Table 1).

Diastolic dysfunction and clinical outcomes after AVR. There is a paucity of data on the relationship between LV diastolic function and clinical events in patients with chronic AR undergoing AVR. In 1 study of 41 patients with chronic severe AR and LV systolic dysfunction, LV diastolic function was useful in predicting outcome after AVR (28). The EF increased in patients with grade I

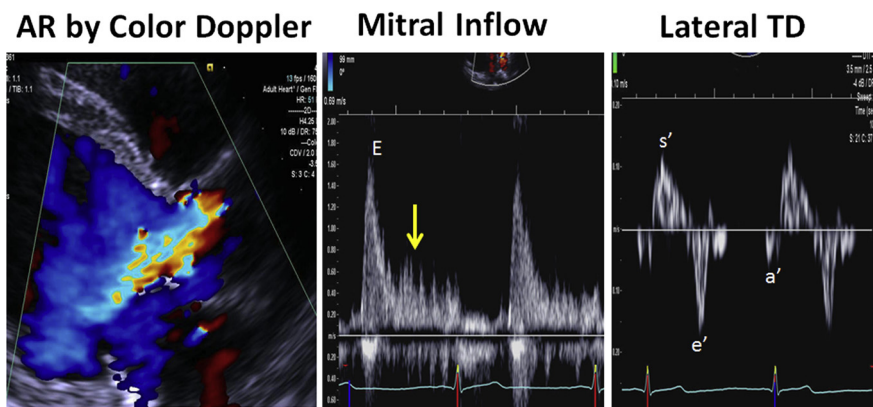


Figure 3 Doppler Findings From a Patient With Severe AR

Color Doppler of the atrial regurgitation (AR) jet in the parasternal long axis view (**left**), mitral inflow (**middle**), and lateral mitral annulus TD velocities (**right**). The patient has severe chronic AR with a severely enlarged left ventricle. The AR regurgitant volume was 70 ml, with regurgitant fraction of 50%. Mitral peak E velocity and annular e' velocity are increased, with E/e' ratio of 9.3. The AR jet (**arrow**) is impinging on mitral inflow and is precluding clear delineation of mitral A-wave velocity. TD = tissue Doppler.

diastolic dysfunction whereas it decreased in patients with grade III dysfunction. On multivariable regression analysis, DT was an independent predictor of changes in EF after AVR.

Diastolic dysfunction after AVR. After AVR, LV volume and mass decrease with improvement in LV filling, although this can be delayed (15). In that regard, the type of the prosthetic valve used can affect post-operative LV function as stentless valves—in comparison with stented valves—are usually associated with earlier and larger decrements in LV dimensions and mass as well as better LV function (29).

Overall diastolic dysfunction appears to have a higher prevalence and worse severity late after surgery after AVR for AR as opposed to surgery for AS. In 1 study, LV structure and function were evaluated serially in 11 patients before AVR and 21 and 89 months after AVR. Post-operatively, LV mass decreased but EF did not change. LV relaxation was significantly prolonged before surgery and was normalized at 87 months after AVR. LV diastolic stiffness constant was increased not only before surgery, but also remained elevated early and late after AVR. That occurred despite significant decrease in muscle fiber diameter, which nevertheless remained increased at late follow-up. Interstitial fibrosis likely played a major role in the persistently elevated diastolic stiffness constant as it was increased pre-operatively and increased even further early after surgery, although it decreased late after AVR, albeit still higher than that seen in control subjects. Importantly, fibrosis was positively correlated to myocardial stiffness (30).

Diagnosis of diastolic dysfunction after AVR. In the presence of persistent findings of pulmonary or systemic congestion, it is reasonable to obtain an echocardiogram for the evaluation of LV diastolic function. The already mentioned guidelines (9) can be applied in this setting. It is important to look at potential contributing factors for

diastolic dysfunction such as patient-prosthesis mismatch, and significant residual AR.

Implications for treatment before and after AVR. AVR can lead to an improvement in LV diastolic dysfunction, but not necessarily normalization in patients with severe chronic AR. Aside from surgery, there are few investigations that explored the effects of medical therapy on LV diastolic function. In 1 study, spironolactone was administered to adult Wistar rats with severe AR for 6 months. Treatment led to a decrease in cardiac mass, decreased expression of atrial natriuretic peptide messenger ribonucleic acid, collagen I, and LOX1 messenger ribonucleic acids, and total fibrosis (31). Given the detrimental effects of fibrosis on LV diastolic function, this drug can be of potential value, although this awaits clinical studies.

Beta-blockers are another class of drugs that can improve LV diastolic function. Data from an animal model of severe AR showed favorable effects of carvedilol on LV remodeling and filling pressures (32). This was accompanied by an increase in β 1-receptor expression and an improvement in myocardial capillary density. In addition, there is an observational study showing survival advantage for AR patients treated with beta-blockers (33).

The presence of diastolic dysfunction after AVR can be treated with adequate control of hypertension and careful use of diuretics. In particular, spironolactone and torsemide may offer additional benefits through their additional effects on decreasing interstitial fibrosis. Unlike for AS, there are no studies that specifically examined medical treatment after AVR for patients with severe AR.

Mitral Stenosis

Mechanisms of diastolic dysfunction. Patients with mitral stenosis (MS) often have an elevated LA pressure at rest and/or with exercise. That is primarily due to the

stenotic mitral valve. The LV stroke volume is often reduced with severe stenosis as a result of decreased LV filling and EDV. In most patients, LV systolic and diastolic functions are normal. However, there are reports of abnormal LV function (34,35). In 1 study with conductance catheters, LV chamber stiffness was increased in severe MS and improved acutely with valvuloplasty. The exact mechanism behind the altered LV chamber stiffness is not clear, although restriction of LV expansion by its attachment to a thickened and immobile mitral valve has been postulated (34). In addition, older patients with MS can have myocardial abnormalities related to coronary artery disease, AS, or hypertension.

Diagnosis of diastolic dysfunction. ECHOCARDIOGRAPHY. There are challenges to the accuracy of Doppler indices of MS in the setting of LV diastolic dysfunction. These include a lower transmitral pressure gradient despite an elevated LA pressure due to the concomitant increase in LV diastolic pressures. Likewise, pressure half time of mitral E velocity can be short due to the increase in LV chamber stiffness leading to a faster rise in LV diastolic pressure despite MS. Ultimately, the true severity of valvular stenosis can be most reliably assessed in these patients by using 3-dimensional planimetry of the mitral valve area (Fig. 4, Online Video 1).

Regarding the assessment of LV diastolic function in patients with MS, conventional Doppler indices are not reliable (Table 1). The E/e' ratio is usually elevated, as peak E velocity is increased and e' velocity is reduced (36). Nevertheless, it is still advantageous to estimate LA pressure as it relates to MS severity. When LA pressure is increased, LV isovolumic relaxation time (IVRT) is short (<70 ms),

and peak E velocity is increased in the range of 1.5 m/s to 2 m/s (9). Furthermore, patients with elevated LA pressure often have an increased late diastolic A velocity >1.5 m/s along with pulmonary hypertension. More recently, the time interval delay between onset of mitral E velocity and annular e' velocity has been examined. With normal LV relaxation, e' occurs at the same time as mitral E or precedes it. Conversely, with impaired LV relaxation, onset of e' is delayed after onset of mitral E velocity (37,38). This time interval when combined with IVRT as the ratio of IVRT/T_{E-e'} has been shown to relate well to mean pulmonary capillary wedge pressure and LA pressure in MS patients (decreasing ratio as LA pressure increases) (36).

CARDIAC CATHETERIZATION. Cardiac catheterization directly assesses MS severity (transmitral pressure gradient and mitral valve area) and its consequences of pulmonary hypertension. With severe LV diastolic dysfunction, the transmitral pressure gradient can underestimate MS severity as LV diastolic pressures are elevated because of associated cardiac disease. That is observed more frequently in older patients with MS. In these patients, it is important to measure not only the gradient but also isolated LA and LV diastolic pressures, as both will be elevated. In comparison, patients with MS and normal diastolic function usually have low to normal LV diastolic pressures due to reduced LV filling.

When both conditions of MS and diastolic dysfunction coexist, it is possible to distinguish the contribution of diastolic dysfunction to the elevated LA pressure by lowering LV afterload using a vasodilator agent (such as sodium nitroprusside). When LV diastolic dysfunction is the main reason for dyspnea, the decrease in LV systolic and

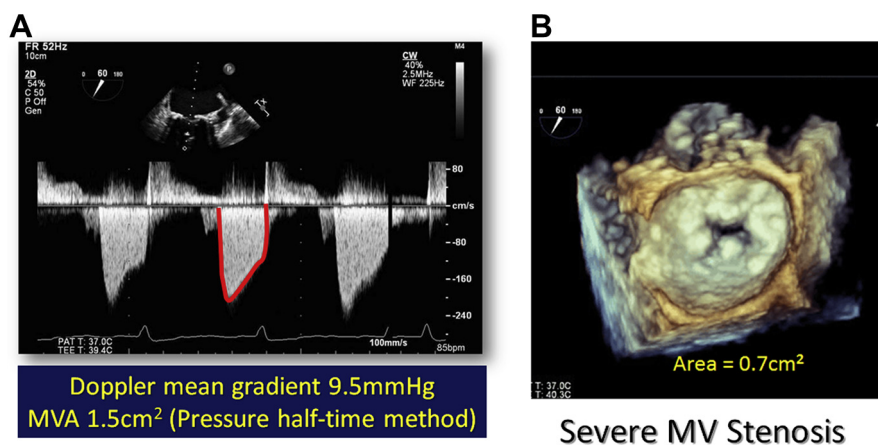


Figure 4 Echocardiographic Assessment of Mitral Stenosis in Patient With Coexisting Diastolic Dysfunction

(A) Continuous wave (CW) Doppler of mitral inflow obtained by transesophageal echocardiogram from a patient with New York Heart Association functional class IV. The patient had hypertension and concentric left ventricular (LV) hypertrophy. Mitral valve area (MVA) by pressure half time was 1.5 cm² with a mean gradient of 9.5 mm Hg. The area by pressure half time is suggestive of moderate mitral stenosis. That was largely due to increased LV stiffness leading to shorter pressure half time. (B) Mitral valve (MV) area by 3-dimensional echocardiography in the same patient. Valve area by 3-dimensional echocardiography was 0.7 cm², consistent with severe mitral stenosis. See accompanying Online Video 1.

diastolic pressures with lower afterload can be accompanied by a decrease in LA pressure (39). Conversely, with severe MS and minor abnormalities of LV diastolic function, one would expect only small decrease, if any, in LA pressure. Finally, it is possible to measure the time constant of LV pressure decay and LV chamber stiffness using conductance catheters to document the presence and severity of diastolic abnormalities, although this is not routinely performed.

Implications for treatment. The presence of diastolic dysfunction and its contribution to symptoms is important to recognize as isolated treatment of MS may not result in complete relief of symptoms, particularly in cases with severe diastolic dysfunction. Furthermore, when MS plays only a minor role in causing cardiac symptoms, invasive procedures aimed at its treatment expose the patient to risks (such as bleeding and perforation), while offering little, if any benefit. For these patients, good control of blood pressure and adequate doses of diuretic therapy can result in symptomatic improvement and lower PA pressures. In particular, beta-blockers and rate-slowing calcium-channel blockers can be helpful as they prolong the diastolic filling interval, which is beneficial for MS as well as LV diastolic dysfunction (although there are situations where the negative lusitropic properties of these drugs can lead to slower LV relaxation).

Effects of balloon valvuloplasty on LV diastolic function. After percutaneous mitral valve commissurotomy, LV filling improves with an increase in LV EDV, EF, stroke volume, and a decrease in systemic vascular resistance. That is accompanied by a small increase in LV EDP immediately after the procedure, but with normalization of EDP at 12 months of follow-up (40). It is likely that the increase in LV filling accounts for the early increase in LV EDP, but in the absence of intrinsic myocardial disease, the procedure in and of itself does not result in long-term changes in LV diastolic pressures, although LA pressure decreases.

Mitral Regurgitation

Mechanisms of diastolic dysfunction. Isolated severe chronic MR leads to LV and LA dilation in an attempt to accommodate the MR volume without an increase in LV and LA pressures. Accordingly, in patients with chronic MR and normal LV function, LV chamber stiffness is usually reduced (41). However with LV contractile dysfunction, LV filling pressures and myocardial stiffness constant are elevated. In addition, patients with MR can have LV diastolic dysfunction due to coexisting hypertension, diabetes mellitus, and coronary artery disease.

After surgical correction, LV volumes, early filling rate, and compliance all decrease (42). Interestingly, in isolated cardiomyocytes from animals with chronic severe MR, the lengthening rate was reduced only in myocytes with reduced shortening (43), and isolated problems with myocyte lengthening have not been reported.

Diagnosis of diastolic dysfunction. ECHOCARDIOGRAPHY. There are challenges to the echocardiographic assessment of diastolic function with severe MR. With severe MR and normal EF, mitral peak E velocity is often increased (usually >1.2 m/s) and E/A ratio is >1 . That is due to severe MR and not to diastolic dysfunction (9). Likewise, systolic blunting can be observed in pulmonary venous flow in the absence of increased LA pressure (9). Likewise, e' velocity is increased and E/ e' ratio is not predictive of LV filling pressures (9,36). Conversely, the Ar velocity in pulmonary venous flow can be helpful as it relates to LV late diastolic pressures that are not affected by severe MR (36,44).

It is also possible to use the time interval between onset of E velocity and onset of e' velocity to assess LV diastolic function in MR. Similar to MS, this time interval is prolonged with impaired LV relaxation, and the ratio of IVRT to $T_{E-e'}$ can be used to predict LV filling pressures, irrespective of LV systolic function and MR severity (36).

CARDIAC CATHETERIZATION. Cardiac catheterization directly assesses the severity of MR and its consequences of pulmonary hypertension. Importantly, one can measure LV pre-A pressure and LV EDP. In patients with severe MR and normal LV function, both pressures are normal. Pulmonary hypertension when present is due to the increase in mean LA pressure that occurs when LA stiffness is increased. The increased LA stiffness can be manifested by a prominent "v" wave signal in the LA pressure recording. Although it is important to determine the contribution of LV diastolic dysfunction to the symptomatic status in hypertensive patients with significant MR, that can be challenging because a decrease in LA pressure with arterial vasodilators can be due to lower LV diastolic pressures as well as to a decrease in MR severity.

Diastolic dysfunction and prediction of outcome. Diastolic function is an important determinant of exercise tolerance in patients with MR. In 1 report, baseline LV EDV, time to peak systolic mitral annular velocity, and E/ e' ratio were the determinants of exercise PA systolic pressure in asymptomatic patients with at least moderate MR (45). In another study, mitral e' velocity and pulmonary venous Ar velocity were the only parameters that determined exercise duration in MR patients (46). Interestingly, rest and stress PA systolic pressure, LV EF, and MR regurgitant fraction showed no significant correlation with exercise duration.

A recent study reported the impact of LV diastolic function on outcome after restrictive mitral ring annuloplasty in chronic ischemic MR. Early mortality rate was highest among patients with restrictive LV filling. A DT <140 ms and pulmonary vein systolic/diastolic velocity ratio <0.80 were the independent predictors of early and late mortality. Importantly, DT <140 ms was the only independent predictor of MR recurrence (47).

MR treatment and LV diastolic function. Early surgery preceding the development of the decompensated stage can

prevent the occurrence of myocardial dysfunction in patients with MR, and late surgery may have a minor impact on myocardial abnormalities. More recently, there has been growing interest in the treatment of patients with functional MR. The surgical approach often includes the use of restrictive annuloplasty. Invasive studies using pressure-volume loops in patients with dilated cardiomyopathy and functional MR have reported a modest decrease in LV EDV and end-systolic volume, accompanied by a small increment in LV EF (on average 4%, although statistically significant). Conversely, both tau and stiffness constant increased significantly, indicating deterioration in LV diastolic function after surgery (48).

For percutaneous treatment for MR, there is a paucity of data on the effects of the MitraClip procedure on LV function. In a recent study of 33 patients with functional and degenerative MR, the procedure was associated with an increase in end-systolic wall stress and a decrease in end-diastolic wall stress and mean wedge pressure, but without a significant change in LV end-systolic pressure volume relation (49). Additional studies are needed with adequate numbers in the different subsets as the effects of percutaneous repair on LV function are likely variable based on MR etiology.

Diagnosis of diastolic dysfunction after surgery. The diagnosis of diastolic dysfunction by echocardiography after surgery can be challenging as many Doppler parameters are affected by the surgery itself. After implantation of a surgical ring or a prosthetic valve, mitral E velocity increases and e' velocity decreases. Accordingly, E/e' ratio can be increased even though LA pressure may not be elevated. Other signals should be evaluated in this setting, including pulmonary veins, tricuspid regurgitation peak velocity, and the ratio of IVRT to T_{E-e'}. The latter ratio was able to track changes in filling pressures after mitral valve surgery with reasonable accuracy (36). Of note, it is important to exclude other reasons (aside from diastolic dysfunction) that can lead to increased LA pressure in the post-operative setting, such as a restrictive annular ring leading to MS, prosthetic valve dysfunction, and paravalvular MR.

Treatment of diastolic dysfunction after surgery. Isolated diastolic dysfunction in the post-operative setting does not occur. However, it usually occurs with coexisting systolic dysfunction. Accordingly, patients can be treated with beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, and spironolactone with loop diuretics as needed. Although it is not known whether medical treatment in the pre-operative setting can affect post-operative LV diastolic function, beta-blockers can be of potential value; a recent randomized study in 38 asymptomatic patients with moderate to severe MR using metoprolol for 2 years showed favorable effects not only on LV EF but also on LV early diastolic filling rate as assessed by CMR. The drug had no significant effects on LV mass, wall thickness, or longitudinal strain rate (50).

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Key Words: aortic ■ diastolic ■ surgery ■ valvular.

APPENDIX

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