Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 21, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.08.1619

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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Manuscript received May 30, 2013; revised manuscript received August 19, 2013, accepted August 20, 2013.

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/ $T_{E\text{-}e'}$‡	<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; $T_{E\text{-}e'}$ = time between onset of mitral E velocity and annular e' velocity.