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REVIEW ARTICLE

CME

Perioperative Assessment of Diastolic Dysfunction

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Assessment of diastolic function should be a component of a comprehensive perioperative transesophageal echocardiographic examination. Abnormal diastolic function exists in >50% of patients presenting for cardiac and high-risk noncardiac surgery, and has been shown to be an independent predictor of adverse postoperative outcome. Normalcy of systolic function in 50% of patients with congestive heart failure implicates diastolic dysfunction as the probable etiology. Comprehensive evaluation of diastolic function requires the use of various, load-dependent Doppler techniques This is further complicated by the additional effects of dehydration and anesthetic drugs on myocardial relaxation and compliance as assessed by these Doppler measures. The availability of more sophisticated Doppler techniques, e.g., Doppler tissue imaging and flow propagation velocity, makes it possible to interrogate left ventricular diastolic function with greater precision, analyze specific stages of diastole, and to differentiate abnormalities of relaxation from compliance. Additionally, various Doppler-derived ratios can be used to estimate left ventricular filling pressures. The varying hemodynamic environment of the operating room mandates modification of the diagnostic algorithms used for ambulatory cardiac patients when left ventricular diastolic function is evaluated with transesophageal echocardiography in anesthetized surgical patients. (Anesth Analg 2011;113:449–72)

The echocardiographic assessment of diastolic function has increasingly gained relevance as a predictor of adverse perioperative outcome.[1–3] Before the widespread use of Doppler echocardiography, the presence of different symptoms in 2 patients with a similar degree of systolic dysfunction could not be explained,[4] and invasive measurement of left ventricular (LV) end-diastolic pressure (LVEDP) was the only means to conclusively diagnose the presence of diastolic dysfunction. The use of pulse wave Doppler (PWD) to estimate LV relaxation made such an assessment clinically feasible. PWD has furthered our understanding of diastolic function and solved the mystery of discordance between symptoms and ventricular systolic function.[4]

Echocardiographic assessment of diastolic function has been extensively reviewed in recent American Society of Echocardiography (ASE) guidelines.[5] Although not explicitly stated, these guidelines pertain to spontaneously breathing patients undergoing transthoracic echocardiography (TTE).[a] In this review, we provide a synopsis of the physiology of diastolic function and definitions of diastolic dysfunction, present the various Doppler modalities and how they are potentially affected by the intraoperative environment, and finally, consider how the aforementioned guidelines[5] may be applicable in the perioperative setting when using transesophageal echocardiography (TEE).

IMPORTANCE OF PERIOPERATIVE ASSESSMENT OF DIASTOLIC FUNCTION

It is now established that 50% of patients with congestive heart failure (CHF) have normal systolic function,[6,7] and the same percentage of patients undergoing cardiac or noncardiac procedures have echocardiographically demonstrable diastolic function abnormalities.[8] This may be important, because the presence of preoperative asymptomatic ventricular dysfunction (systolic and diastolic) has been associated with increased 30-day and long-term morbidity and mortality.[1] The assessment of diastolic function provides incremental prognostic value over systolic function assessment[5,9] and the presence of diastolic dysfunction is highly predictive of adverse events after myocardial infarction.[5,10] Echocardiography

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[a]Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. Available at: http://www.asecho.org/files/DF.pdf. Accessed May 12, 2011.

Table 1. Studies Reporting Diastolic Dysfunction in Patients Undergoing Surgery

Study	Type of study	Doppler modality	Patient populations and study design	Findings
Swaminathan et al.,[3] 2011	Prospective	Mitral inflow PWD, mitral lateral DTI, PVF	905 patients undergoing CABG; 2 grading algorithms used and compared for association with adverse cardiac events and ability to categorize DD	Simplified algorithm categorized more patients (99% vs 62%) and was also associated with long-term major adverse cardiac events ($P = 0.013$)
Flu et al.,[1] 2010	Prospective	Mitral inflow PWD, PVF	1005 consecutive open vascular patients enrolled	Asymptomatic DD is independently related to increased 30-day and long-term cardiovascular mortality (OR, 1.8 [95% CI, 1.1–2.9])
Matyal et al.,[2] 2009	Prospective	Vp	313 consecutive vascular surgery patients	Vp (<45 cm/s) independent predictor of postoperative congestive heart failure, prolonged length of stay ($P < 0.01$) (OR, 2.5 [95% CI, 1.3–4.6])
Diller et al.,[13] 2008	Prospective	Mitral inflow PWD, mitral lateral and medial annulus DTI, tricuspid inflow PWD	32 consecutive patients with preserved ejection fraction undergoing CABG	DTI (E′) improved at septal and mitral lateral positions 5 d and 6 wk after CABG ($P < 0.05$); tricuspid lateral DTI (E′) decreased after CABG ($P = 0.005$)
Mahmood et al.,[153] 2008	Prospective	MPI, Vp	51 consecutive patients undergoing elective abdominal aortic aneurysm repair	MPI >0.36 had greater postoperative congestive heart failure/prolonged intubation ($P < 0.001$); MPI higher in patients with complications (0.50 vs 0.30, $P < 0.001$)
Xu-Cai et al.,[16] 2008	Retrospective chart review	Ejection fraction, clinical signs of heart failure	557 consecutive patients with heart failure and 10,583 controls undergoing noncardiac surgery evaluated preoperatively by hospitalists	Patients with DD (heart failure with ejection fraction >40%) had higher readmission rates and hospital stays compared with matched controls; patients in systolic failure had no significant differences from matched controls
Mahmood et al.,[90] 2007	Prospective	Mitral inflow PWD, PVF, Vp, CCG	45 consecutive patients undergoing elective abdominal aortic aneurysm repair	DD worsened with application of aortic cross-clamp using Vp and CCG ($P < 0.05$); Vp identified 93% of DD; $r^2 > 0.5$ for all 3 methods of DD assessment ($P < 0.05$)
Denault et al.,[12] 2006	Prospective	Mitral inflow PWD, PVF, mitral lateral DTI, tricuspid inflow PWD, HVF, tricuspid lateral DTI	Cardiac surgery patients; algorithm reproducibility group ($n = 74$); validation group ($n = 179$)	Moderate and severe left ventricular ($P = 0.019$) and right ventricular ($P = 0.049$) DD associated with difficult separation from cardiopulmonary bypass
Salem et al.,[15] 2006	Retrospective	LVEDP	3024 consecutive cardiac surgery patients	LVEDP independent risk factor for in-hospital mortality in cardiac surgical patients (area under ROC curve: 0.85)
Fayad et al.,[154] 2006	Prospective	Mitral inflow PWD	9 patients undergoing thoracoabdominal aortic aneurysm repair	6 of 9 patients developed DD during aortic cross-clamp (E/A <1 [0.75 ± 0.05])
Meierhenrich et al.,[152] 2005	Prospective	Mitral inflow PWD, PVF	45 consecutive patients undergoing open abdominal aneurysm repair	DD present in 20 of 39 patients; DD manifest in 3 of 20 patients with aortic cross-clamp; laparo to my improved DD in 9 of 20 patients
Djaiani et al.,[14] 2002	Prospective	Mitral inflow PWD, PVF, Vp, IVRT	63 consecutive patients undergoing CABG	Vp <50 cm/s reflective of DD; unaffected by Valsalva maneuver
Bernard et al.,[11] 2001	Prospective	Mitral inflow PWD, PVF, Ar	92 consecutive cardiac surgery patients	DD is associated with higher preoperative myocardial infarction ($P = 0.02$), weight ($P = 0.046$), CABG alone ($P = 0.0004$), wall motion abnormalities ($P = 0.0002$), cardiopulmonary bypass ($P = 0.004$) and ischemic time ($P = 0.007$), and postoperative inotropes ($P = 0.006$)
De Hert et al.,[146] 2001	Prospective	LVEDP, dP/dt	10 coronary artery surgery patients underwent invasive measurements of left ventricular pressures and volumes	Stroke work, stroke volume, and end-diastolic volumes increased in open-chest, open-pericardium procedures after leg elevation, not in closed-pericardium and closed-chest procedures

(Continued)

Table 1. (Continued)

Study	Type of study	Doppler modality	Patient populations and study design	Findings
De Hert et al.,[147] 2000	Prospective	LVEDP, dP/dt, mitral inflow PWD	50 coronary artery surgery patients underwent invasive measurements of left ventricular pressures and volumes	Changes in dP/dt and end-diastolic pressures were associated with changes in E-wave and deceleration time changes with leg elevation; impairment of left ventricular function with leg elevation was associated with restrictive DD pattern
De Hert et al.,[144] 1999	Prospective	LVEDP, dP/dt	120 coronary artery surgery patients underwent invasive measurements of left ventricular pressures and volumes and 40 underwent transgastric TEE evaluation	LVEDP increased from 93 ± 9 to 107 ± 11 after leg elevation; changes were correlated to changes in dP/dt and stroke area; leg elevation identified patients who developed load-dependent left ventricular impairment
De Hert et al.,[145] 1999	Prospective	LVEDP, dP/dt	25 coronary artery surgery patients underwent invasive measurements of left ventricular pressures and 10 underwent left ventricular conductance measurement	Leg elevation homogeneously increased LVEDP, and variably affected stroke volume/work and dP/dt; phenylephrine increased stroke work and dP/dt with no change in stroke volume
Gillespie et al.,[151] 1994	Prospective	LVEDP, dP/dt, PAOP, LVEDA	22 patients undergoing abdominal aortic aneurysm repair underwent invasive monitoring of PAOP and LVEDA assessed using TEE	Weak correlation demonstrated between PAOP and LVEDA; correlation worsened with aortic cross-clamping
Aroesty et al.,[161] 1985	Prospective	LVEDV	22 patients undergoing cardiac catheterization were paced at increasing heart rates; underwent hemodynamic and electrocardiographic monitoring and radionuclide ventriculography	Ischemic response to pacing induced systolic and diastolic dysfunction; DD changes preceded systolic dysfunction

Ar = atrial reversal wave; CABG = coronary artery bypass graft; CCG = Canadian consensus guidelines; CI = confidence interval; DD = diastolic dysfunction; dP/dt = rate of ventricular contraction; DTI = Doppler tissue imaging; HVF = hepatic venous flow; IVRT = isovolumetric relaxation time; LVEDA = left ventricular end-diastolic area; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; MPI = myocardial performance index; OR = odds ratio; PAOP = pulmonary artery occlusive pressure; PVF = pulmonary vein flow; PWD = pulse wave Doppler; TEE = transesophageal echocardiography; Vp = flow propagation velocity.

has been used to diagnose perioperative diastolic dysfunction during cardiac surgery.[11–15] However, other than being a predictor of difficult weaning from cardiopulmonary bypass,[11,12] the impact of perioperative diastolic dysfunction on short- and long-term postoperative morbidity and mortality in cardiac surgery patients is not conclusively established. Alternatively, in a retrospective review of vascular surgical patients with normal systolic function, patients with a history of CHF were found to have a longer hospital length of stay and a higher readmission rate and postoperative mortality than those without this history (Table 1).[16] Although TEE has been used extensively during noncardiac surgery, its use for assessment of perioperative diastolic function is limited.[17] In a prospective observational study of patients undergoing vascular surgery,[2] the presence of diastolic dysfunction in hospitalized patients was a predictor of increased all-cause morbidity and mortality.[18–20] The presence of perioperative diastolic dysfunction, diagnosed with TEE, had a significant association with postoperative CHF and postoperative length of stay after vascular surgery (Table 1).[2] Although not conclusively established, it seems that pre- and perioperative diagnosis of diastolic dysfunction may have implications for perioperative anesthetic management and, potentially, postoperative outcome.

PHYSIOLOGY OF DIASTOLIC FUNCTION

Diastole refers to the period of ventricular filling after a contraction (Fig. 1). Diastole is divided into 4 discrete parts: isovolumetric relaxation, rapid filling phase, diastasis, and atrial contraction.[4] LV filling during diastole is a complex interplay regulated primarily by the pressure differences between volume and compliance of the left atrium (LA) and LV, and energy-dependent LV relaxation (Fig. 1).[21] In addition to LV relaxation, extrinsic factors such as pericardial restraint, ventricular interaction, and intrinsic factors including myocardial stiffness, myocardial tone, chamber geometry, and wall thickness also have a role in LV filling.[5,22] The diastolic phase of the cardiac cycle is also dependent on events that occur at the cellular, physiological, and organ level. At the cellular level, diastole begins with the hydrolyzation of adenosine triphosphate and unlinking of actin and myosin cross-linkages,[23] followed by a reduction in sarcoplasmic calcium concentration and its separation from troponin (Fig. 2). Physiologically, ventricular relaxation at the onset of diastole as defined by the rate of decline

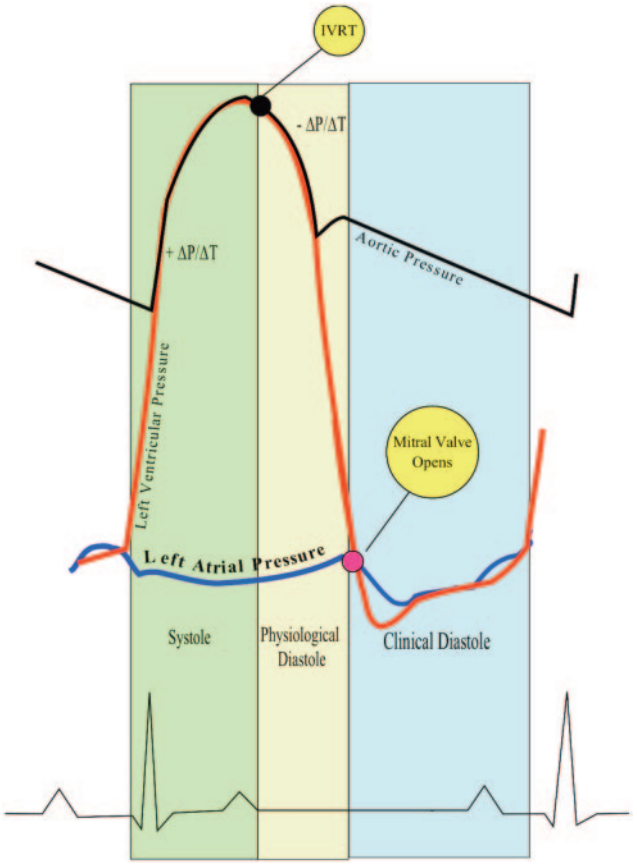

Figure 1. Simultaneous display of left atrial, aortic, and left ventricular pressures during the cardiac cycle. Physiological diastole, as defined by the $-\Delta p/\Delta t$ begins in the later part of systole with the onset of isovolumetric relaxation time (IVRT). Clinical diastole as defined by the opening of the mitral valve starts after opening of the mitral valve. (Adapted from Nishimura and Tajik.[4])

of intracavitary pressure ($-dP/dt$) actually begins in the later portion of clinical systole, while the mitral valve is still closed (Fig. 1).[4] Ventricular relaxation is an energy-dependent process, physiologically commencing during systole, continuing after mitral valve opening (clinical diastole) during rapid LV filling, lasting for the first third of this early filling phase and normally accounts for almost 70% of LV filling (Fig. 1). Hence, during the early LV diastole, in addition to the LA-LV gradient, the effectiveness of LV suction also determines the adequacy of filling. The LV continues to fill until closure of the mitral valve. The last part of the filling phase is associated with atrial contraction which normally contributes almost 30% of the LV filling. Factors that delay calcium removal impair actin-myosin cross-bridge detachment and therefore slow myocardial relaxation.[22] Multiple energy-dependent enzymatic pathways maintain calcium homeostasis in the cytosol.[23–28]

DIASTOLIC DYSFUNCTION AND HEART FAILURE

In the natural course of myocardial dysfunction caused by ischemia or hypertension, relaxation (early diastolic) abnormalities often precede systolic dysfunction. This results in impairment of early/rapid LV filling and a compensatory increase in late LV filling.[4] The LA contribution is determined by LA preload and contractility as well as the "effective LV compliance."[4,29–32] With disease progression, abnormalities of relaxation eventually progress to reduced compliance and increase of filling pressures in both the LA and LV, i.e., mean pulmonary capillary wedge pressure >12 mm Hg and LVEDP >16 mm Hg.[33] The invasively measured peak negative change in LV pressure during diastole ($-dP/dt$) and the time constant of relaxation (τ) are considered the "gold standard" measures of LV relaxation,[34,35] against which the accuracy of Doppler-derived variables of diastolic function should be established.

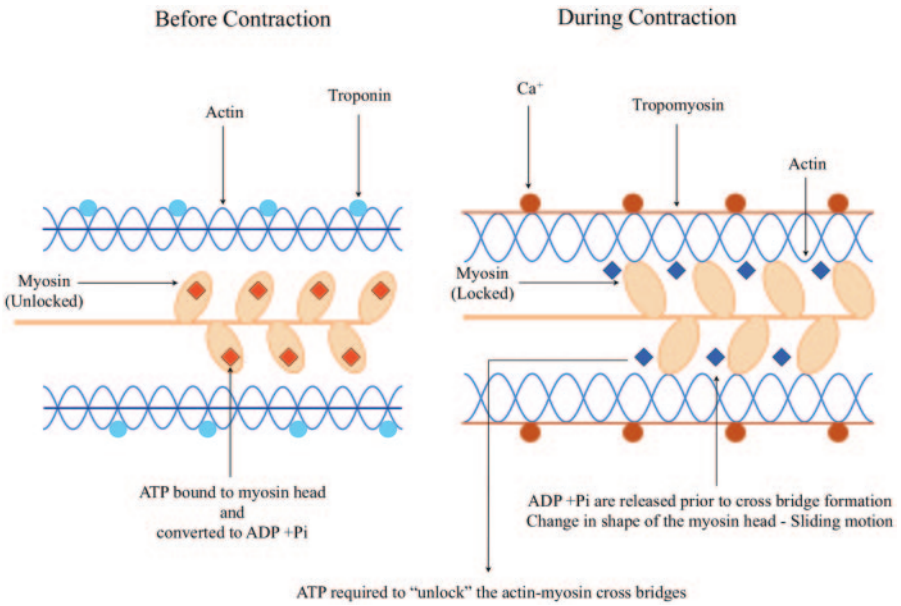

Figure 2. Calcium ions (Ca^{+}) bind to sites on the actin filament. Ca^{+} binds to the troponin molecule causing tropomyosin to expose positions on the actin filaments for attachment of myosin heads. As a result, cross-bridges between actin filaments and myosin heads are formed. ADP = adenosine diphosphate; ATP = adenosine triphosphate; Pi = inorganic phosphate.

Table 2. Normal Values of Doppler-Derived Diastolic Function Parameters

	Age group (y)			
Measurement	**16–20**	**21–40**	**41–60**	**>60**
IVRT (ms)	50 ± 9 (32–68)	67 ± 8 (51–83)	74 ± 7 (60–88)	87 ± 7 (73–101)
E/A ratio	1.88 ± 0.45 (0.98–2.78)	1.53 ± 0.40 (0.73–2.33)	1.28 ± 0.25 (0.78–1.78)	0.96 ± 0.18 (0.6–1.32)
DT (ms)	142 ± 19 (104–180)	166 ± 14 (138–194)	181 ± 19 (143–219)	200 ± 29 (142–258)
A duration (ms)	113 ± 17 (79–147)	127 ± 13 (101–153)	133 ± 13 (107–159)	138 ± 19 (100–176)
PV S/D ratio	0.82 ± 0.18 (0.46–1.18)	0.98 ± 0.32 (0.34–1.62)	1.21 ± 0.2 (0.81–1.61)	1.39 ± 0.47 (0.45–2.33)
PV Ar (cm/s)	16 ± 10 (1–36)	21 ± 8 (5–37)	23 ± 3 (17–29)	25 ± 9 (11–39)
PV Ar duration (ms)	66 ± 39 (1–144)	96 ± 33 (30–162)	112 ± 15 (82–142)	113 ± 30 (53–173)
Septal e′ (cm/s)	14.9 ± 2.4 (10.1–19.7)	15.5 ± 2.7 (10.1–20.9)	12.2 ± 2.3 (7.6–16.8)	10.4 ± 2.1 (6.2–14.6)
Septal e′/a′ ratio	2.4[a]	1.6 ± 0.5 (0.6–2.6)	1.1 ± 0.3 (0.5–1.7)	0.85 ± 0.2 (0.45–1.25)
Lateral e′ (cm/s)	20.6 ± 3.8 (13–28.2)	19.8 ± 2.9 (14–25.6)	16.1 ± 2.3 (11.5–20.7)	12.9 ± 3.5 (5.9–19.9)
Lateral e′/a′ ratio	3.1[a]	1.9 ± 0.6 (0.7–3.1)	1.5 ± 0.5 (0.5–2.5)	0.9 ± 0.4 (0.1–1.7)

Data are expressed as mean ± SD (95% confidence interval). Note that for e′ velocity in subjects aged 16 to 20 years, values overlap with those for subjects aged 21 to 40 years. This is because e′ increases progressively with age in children and adolescents. Therefore, the e′ velocity is higher in a normal 20 year old than in a normal 16 year old, which results in a somewhat lower average e′ value when subjects aged 16 to 20 years are considered.

DT = deceleration time; IVRT = isovolumetric relaxation time; PV Ar = pulmonary venous atrial reversal wave; PV S/D = pulmonary venous systolic/diastolic wave ratio.

[a] Standard deviations are not included because these data were computed, not directly provided in the original articles from which they were derived.

Reproduced with permission from Nagueh et al.[5]

Although used interchangeably, diastolic dysfunction and diastolic heart failure are actually 2 different pathophysiological conditions. The use of the term "diastolic dysfunction" implies an echocardiographically demonstrated abnormality of LV filling, i.e., impaired relaxation and/or reduced compliance, which results in increased LVEDP, whereas diastolic heart failure is a clinical term, which is the symptomatic manifestation (shortness of breath and exercise intolerance) of the underlying filling abnormality, i.e., an increased LVEDP, in the presence of normal LV systolic function.[36] The time course of progression from diastolic dysfunction to diastolic heart failure can be variable. For example, in patients with hypertension and LV hypertrophy, impaired relaxation may remain the predominant abnormality for a long time without any increase in LVEDP.[37]

ECHOCARDIOGRAPHIC ASSESSMENT OF DIASTOLIC FUNCTION: CHALLENGES AND PITFALLS

Assessment of diastolic function based on Doppler findings acquired with TTE may not be entirely applicable to TEE techniques. Because of its noninvasive nature, TTE has been extensively used over the decades in epidemiological studies in subjects with normal and abnormal filling patterns. Hence, the reference values for Doppler indices of LV diastolic function are well established with this technique (Table 2).[5] The invasive nature of TEE and variable intraoperative hemodynamic state has precluded similar efforts. The majority of echocardiographic studies of the assessment of diastolic function have been conducted in outpatient cardiology clinics in patients breathing spontaneously in the lateral decubitus position.[30] However, the filling variables of LA and LV significantly change with alterations in posture from supine to upright and left to right lateral decubitus position.[38–40] In contrast, echocardiographic studies under general anesthesia (GA) are performed with TEE under varying hemodynamic states and in patients in the supine position who are receiving positive pressure ventilation and are under the effects of anesthetic drugs.

CLASSIFICATION OF PERIOPERATIVE DIASTOLIC FUNCTION

The classification of diastolic dysfunction has evolved from the initial, transmitral flow (TMF) examination with a PWD-based explanation of LA and LV filling and its abnormalities, to the most current guidelines, which have incorporated PWD and more sophisticated techniques (Fig. 3).[4,5,29,30,41–46] However, such classification schemes[4,29,30,44,47] for the assessment of diastolic dysfunction are suited for categorization of larger patient populations and assess response to therapy (epidemiological studies).[5] For the individual patient, it is recommended to use a customized approach to answer specific mechanistic questions, e.g., diagnosis of impaired relaxation and/or a coexistent reduced compliance abnormality.[5]

The clinical application of these guidelines has also demonstrated the limitations of such classification schemes. In one study, one of the Doppler criteria, pulmonary venous PWD profile, could not be obtained in 28% of patients undergoing elective TTE examinations,[48] and in the study by Redfield et al.[44] (n = >2000), in which only 2 of the 4 Doppler criteria were required for classification, 12% of patients could not be accurately classified and were termed "indeterminate patterns." Intraoperative rigid application of the most recent ASE guidelines has also demonstrated their limitation in classifying perioperative diastolic dysfunction.[3]

Factors such as ventricular interdependence,[49] effects of positive pressure ventilation,[50,51] and even acute alterations in coronary blood flow by altering the vascular turgor (i.e., the "erectile effect"),[52] are not accounted for in these classifications, but affect ventricular compliance.[4,29,30,44,47] Changes in LV filling variables with induction of GA are also associated with significant changes in LA and LV diameters implying contribution of the loading conditions to these observed effects.[53]

The intraoperative hemodynamic state is very variable. Consequently, an isolated Doppler measurement should be considered only a "snapshot" of a continuous process. Even minor alterations in the Doppler measurements can lead to a patient being classified into a different grade/stage of

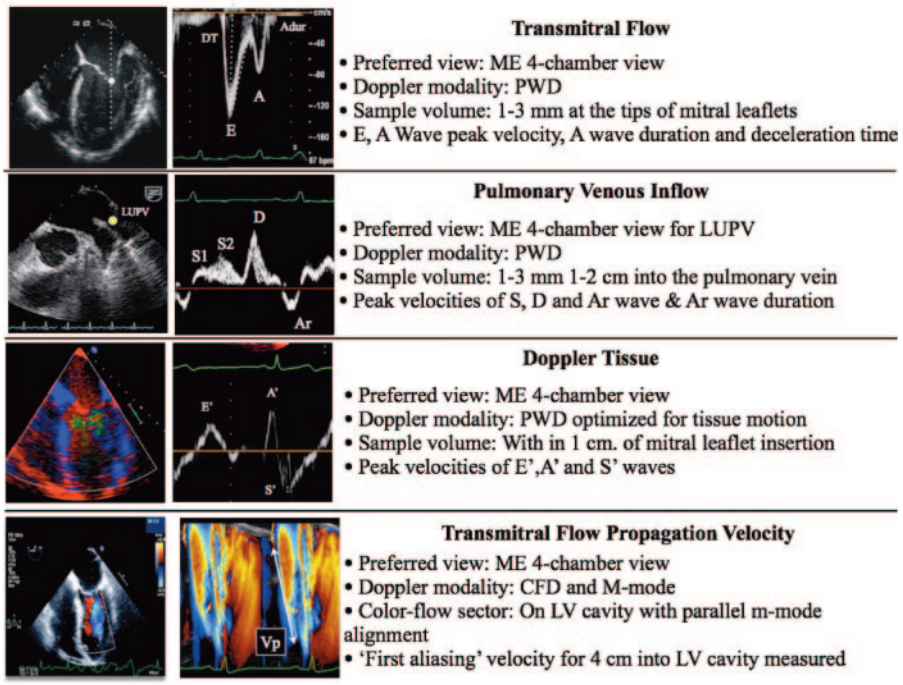

Figure 3. Doppler modalities for assessment of myocardial diastolic function. PWD = pulse wave Doppler; DT = deceleration time; Adur = A-wave duration; ME = midesophageal; LAA = left atrial appendage; LUPV = left upper pulmonary vein; CMM = color M-mode; DTI = Doppler tissue imaging; Ar = atrial reversal wave; RV = right ventricle.

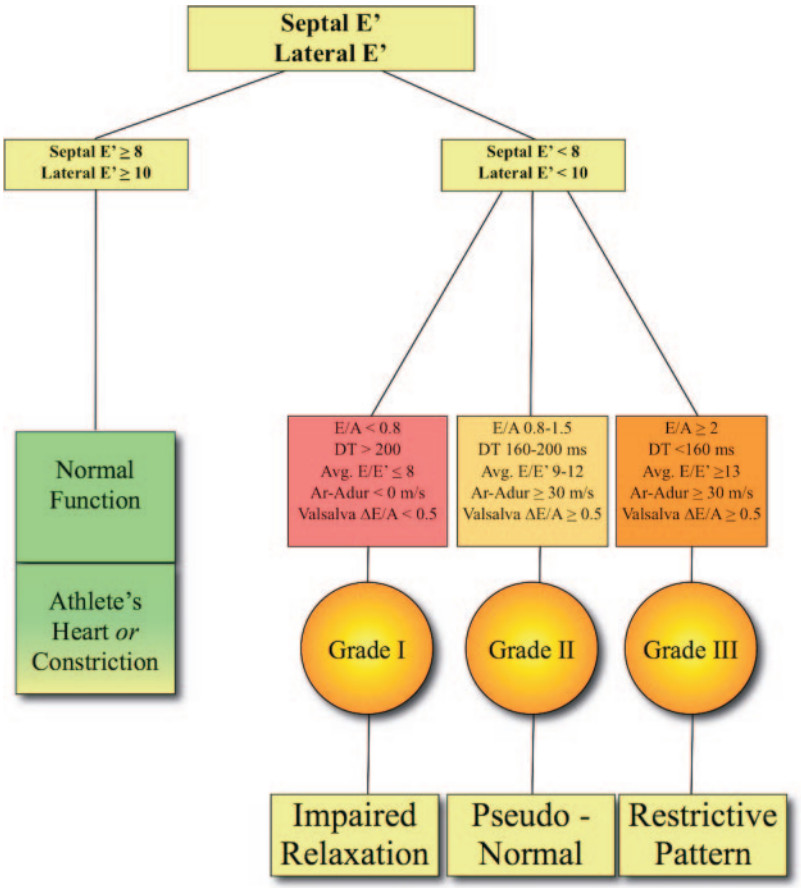

Figure 4. Practical approach to diastolic function. DT = deceleration time; Avg. = average; Ar = pulmonary venous A-wave reversal wave; Adur = transmitral A-wave duration. (Adapted from Nagueh et al.[5])

diastolic dysfunction in the same clinical setting. Unlike the previous recommendations,[4,29,30,44] the current ASE guidelines for echocardiographic assessment of diastolic function have acknowledged the limitations of rigid application of the conventional Doppler indices.[4,30,54–60] Therefore, the most recent guidelines no longer recommend the acquisition of E and A waves of the TMF with PWD as the initial step in the decision tree of grading diastolic dysfunction (Fig. 4).[5]

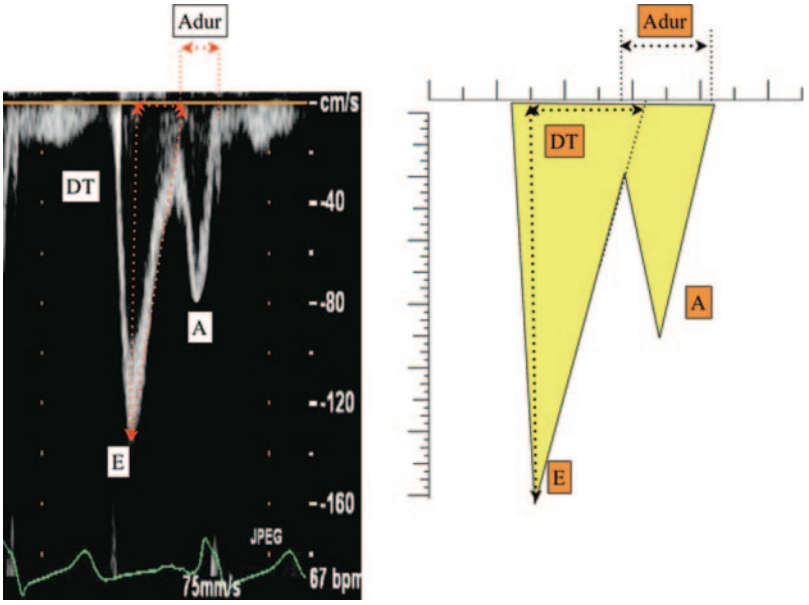

Figure 5. Typical transmitral pulse wave Doppler pattern. Left panel, Actual pulse wave Doppler pattern. Right panel, Graphic description of measurement of peak velocities and gradients. E wave = rapid filling phase; A wave = atrial "kick"; DT = deceleration time; Adur = duration of transmitral A wave.

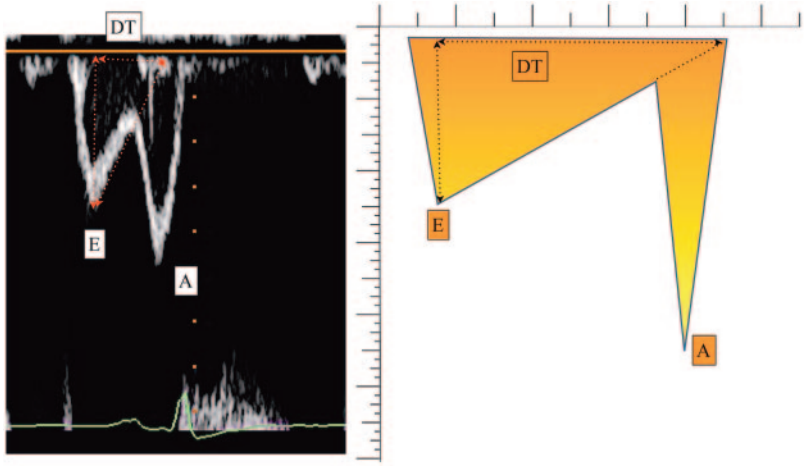

Figure 6. Transmitral pulse wave Doppler: impaired relaxation pattern. Left panel, Actual pulse wave Doppler pattern. Right panel, Graphic description of measurement of peak velocities and gradients. E/A <1 = prolonged deceleration time; DT = deceleration time.

TECHNICAL CONSIDERATIONS

The techniques for acquisition and interpretation of specific Doppler abnormalities have already been extensively reviewed.[5,54] In the following section, the specific steps of obtaining satisfactory Doppler profiles for diastolic function evaluation using TEE are discussed. Echocardiographic evaluation of diastolic function is best accomplished when it is incorporated within a standardized echocardiographic examination, which should also include a comprehensive evaluation of LV systolic function.[56,61] Before starting the Doppler examination, it is essential to ensure the most optimal parallel Doppler alignment during interrogation to minimize the degree of underestimation of peak velocities and gradients. Alignment is usually most optimal when using the midesophageal (ME) 4-chamber and ME long-axis views for the majority of the Doppler indices. Echocardiographic evaluation of perioperative diastolic dysfunction with TEE should include a focused and precise examination using a combination of PWD (transmitral and pulmonary venous flows), transmitral color M-mode, and Doppler tissue imaging (DTI) (Fig. 3).

LV Inflow

The traditional assessment of LV filling has been based on assessment of the pattern of diastolic blood flow through the mitral valve (LV inflow) using PWD.[43] Flow across the mitral valve during the relaxation phase is determined by the LA-LV pressure gradient and the effectiveness of the suction properties of the LV (Fig. 5).[60,62] Kitabatake et al.,[43] in 1982, described Doppler interrogation of mitral inflow during diastole as a reflection of the global LV relaxation properties.[57,58,60,63,64] Abnormalities of the "active relaxation phase" of diastole are generally the earliest manifestations of diastolic dysfunction. The relaxation abnormalities present echocardiographically as changes in E wave peak velocity and deceleration time (DT) initially, and then further changes with disease progression. Based on this progression of abnormalities (impaired relaxation to reduced compliance), distinct echocardiographic patterns, including normal, impaired relaxation, pseudonormal, and restrictive patterns (Figs. 5–8) of LV filling, were described.[41,65–71] Mathematical modeling has demonstrated that LA stiffness remains constant during early LV relaxation and DT is proportional

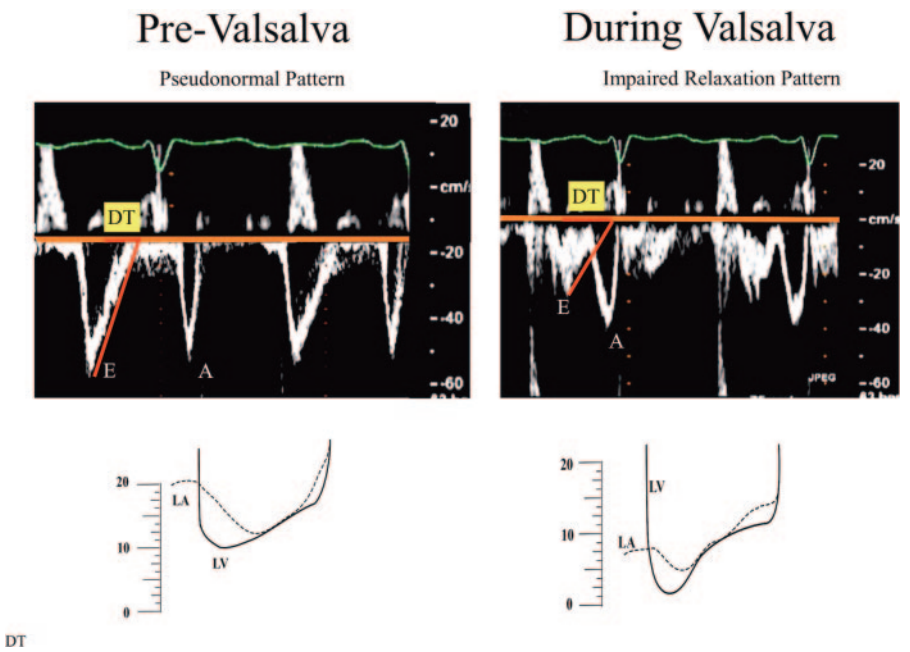

Figure 7. Pseudonormal pattern and Valsalva maneuver. Left panel, Typical transmitral pulse wave Doppler pseudonormal pattern. Right panel, Transmitral pulse wave Doppler during a Valsalva maneuver. Left atrial (LA) pressure reduction maneuvers to "unmask" the underlying relaxation abnormality. In a typical LA pressure reduction maneuver, a pseudonormal transmitral flow (TMF) pattern changes to an impaired relaxation pattern, with a reduction in the amplitude of the rapid filling phase (E wave) and increased amplitude and duration of the atrial "kick" (A wave) with a prolongation of the deceleration time (DT). LV = left ventricle.

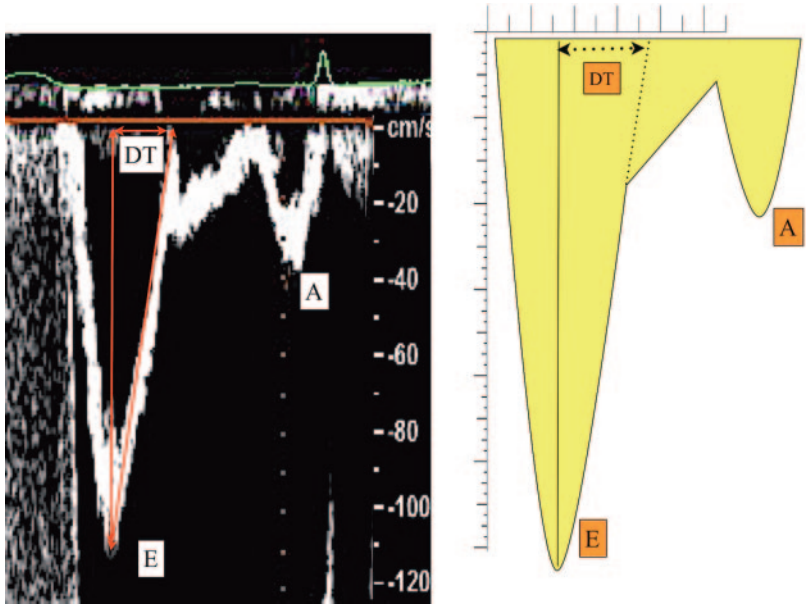

Figure 8. Transmitral pulse wave Doppler: restrictive pattern elevated left atrial pressure. Left panel, Actual pulse wave Doppler pattern. Right panel, Graphic description of measurement of peak velocities and gradients. E/A >1.5 = shortened deceleration time (DT).

to the inverse square root of LV stiffness.[31,72–74] Consequently, when there is advanced diastolic dysfunction with reduced compliance, DT is shortened again in the more advanced stage of diastolic dysfunction (Fig. 8). Therefore, in addition to being prolonged during the impaired relaxation phase, DT is an important variable that reliably predicts LV compliance in the more advanced stages of diastolic dysfunction.[75]

Intraoperative Measurement

Placement of a color flow Doppler (CFD) sector on the LV inflow can be helpful in aligning the Doppler beam with the direction of the blood flow, which is generally directed toward the lateral wall.[61] All measurements should be made during apnea to minimize the hemodynamic changes and movement of the PWD sample volume during controlled mechanical ventilation. For LV inflow assessment, a sample volume of 1 to 3 mm is placed between the mitral tips during diastole with the sweep speed set at 50 to 100 mm/s (Fig. 5). Measurements should include peak E and A velocity, the E/A ratio, DT, and A-wave duration (Adur). For measurement of Adur, it is best to move the cursor to the mitral annular plane with a simultaneous reduction in wall filters (Fig. 5).[61] The actual measurement of volumetric flow (continuity equation) does not add any further information.[30]

Intraoperative Application

Transmitral PWD has been the cornerstone of classification schemes for diastolic dysfunction. Because of its load

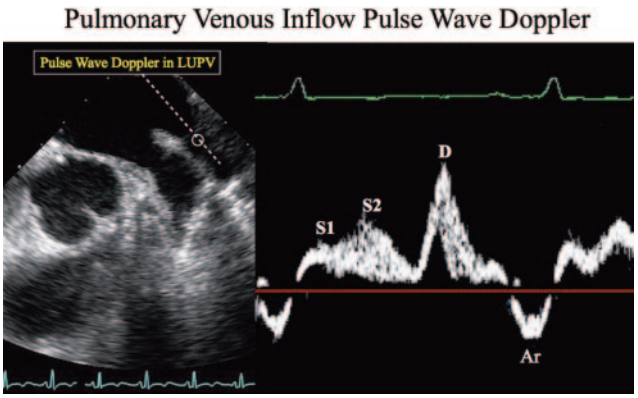

Figure 9. Pulse wave Doppler of the left upper pulmonary vein (LUPV). S1 = systolic 1 wave caused by left atrial relaxation; S2 = systolic 2 wave caused by right ventricular systole; D = diastolic wave; Ar = atrial reversal wave caused by atrial systole.

dependence, TMF is of value only when considered in combination with other Doppler variables, such as the pulmonary venous inflow (PVF), TMF propagation velocity (Vp), and DTI, which are discussed in later sections.

Pulmonary Venous Inflow

The LA acts as a conduit during early diastole, as a contractile chamber during late diastole, and as a reservoir during systole when the mitral valve is closed. During diastole, the LV, LA, and pulmonary veins remain in continuity with a shared pressure gradient.[76–83] Hence, the assessment of diastolic function by transmitral PWD can be further refined with incorporation of measurements from the pulmonary venous PWD spectral recording.[79,80,84–87] The PVF pattern has shown good correlation with LV filling pressures (LVFPs) in patients with sinus rhythm as well as heart block, but is generally less reliable in patients with significant mitral regurgitation, stenosis, or prosthetic mitral valves and annuloplasty rings.[82,88]

Intraoperative Measurement

To acquire a PVF PWD spectral display, a 2- to 3-mm sample volume is placed at 1 cm depth usually in the left upper pulmonary vein visualized in an ME view (Fig. 9). Wall filters must be low to optimize the acquisition of the atrial reversal (Ar) wave. Although satisfactory acquisition of the Ar wave has been reported in almost 80% of ambulatory patients, it is more difficult in critical care settings.[89,90]

Intraoperative Application

During a PWD examination of the PVF, peak S and D waves, the S/D ratio, and Ar peak velocity and duration should be measured (Fig. 10). Technical difficulties in obtaining the PVF wave profiles, their load dependence, presence of LA wall artifacts, and the effects of arrhythmias on atrial contraction are the major limiting factors.[30,91] Further extrapolation of the PVF profile includes S/D ratio calculation and comparison of the duration of the Ar wave with transmitral Adur for LVEDP estimation (Ar duration will be longer than Adur because of decreased antegrade flow caused by reduced LA compliance with LA contraction) (Fig. 10).

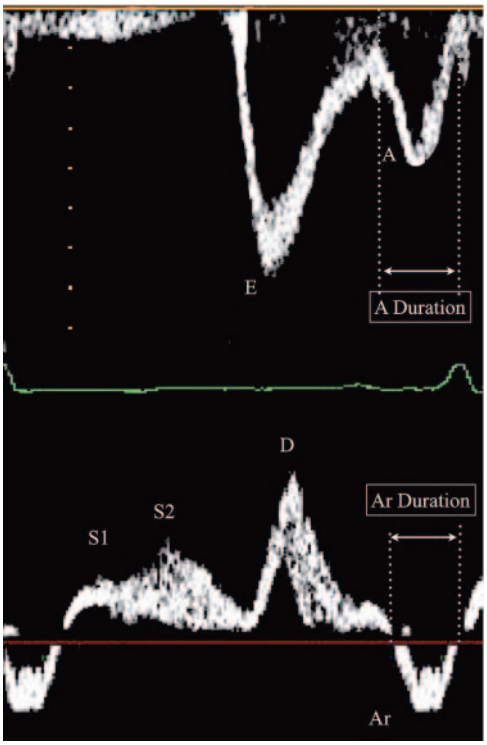

Figure 10. A comparison of the transmitral A-wave duration, i.e., the "antegrade flow," with the duration of the pulmonary venous inflow atrial reversal (Ar) wave, i.e., the "retrograde flow," which occur simultaneously because of atrial contraction. Greater retrograde flow implies increased left ventricular end-diastolic pressure.

Transmitral Color M-Mode–Derived Early Propagation Velocity

Early diastolic LV filling is dependent on the development of progressively negative intraventricular pressure gradients, which create a wavefront of propagation from the LV base to the apex.[92–96] This wavefront can be visually appreciated with CFD interrogation of the LV cavity during diastole, when blood is seen entering along the lateral LV walls (Fig. 11). Transmitral Vp is a velocity profile derived by simultaneous use of CFD and M-mode (Fig. 11). Similar to the transmitral E wave, Vp reflects the effectiveness of the LV "suction" during early diastole. Vp is a more valid assessment of the LV relaxation properties compared with TMF, which is a point measurement at the tips of the mitral leaflets.

Intraoperative Measurement

A CFD sector using a Nyquist limit <40 cm/s is placed on the LV cavity, directed toward the lateral wall, to develop a flow profile. An M-mode cursor is then positioned through the center of the flow profile (Fig. 11). Multiple methods of measuring Vp have been described with varying degrees of intra- and interobserver variability.[92,97,98] The method described by Garcia et al., in which the slope of the first aliasing velocity (the outermost velocity) is measured, is considered the most reliable and reproducible method.[97,99] A Vp value of <0.50 m/s is consistent with impaired relaxation.[5]

Intraoperative Application

The feasibility of the intraoperative use of Vp for assessment of diastolic function has been demonstrated.[2,12,14,90]

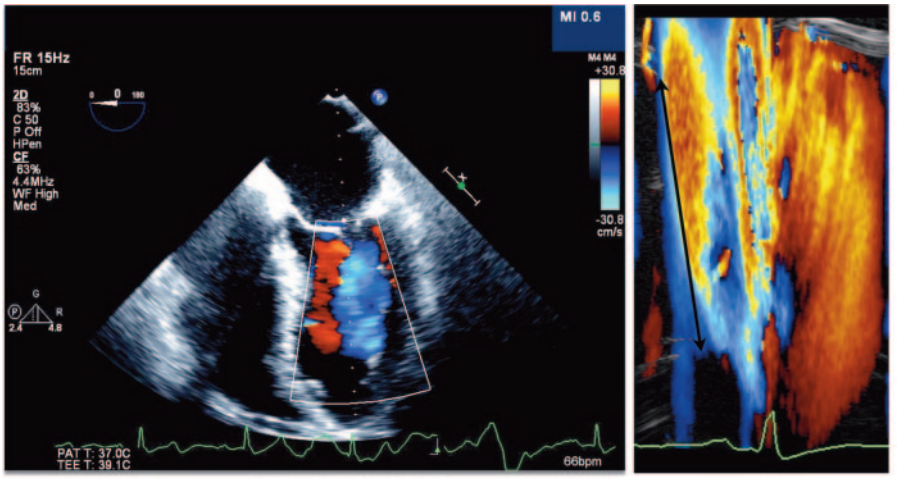

Figure 11. Transmitral flow propagation velocity. Left panel, Midesophageal 4-chamber view with color flow Doppler sector and M-mode cursor aligned with the left ventricular (LV) inflow. Right panel, Measurement of the transmitral flow propagation velocity.

Because Vp can be easily measured in a single step, it is an attractive option for intraoperative assessment of LV relaxation. However, sometimes in addition to the diastolic suction force, multiple other factors, e.g., changes in LV geometry, contractile dyssynchrony, and tissue viscoelastic forces also have a role in creating these LV inflow vortices.[100–102] However, it may not be possible to measure Vp because the slope of flow propagation is sometimes curvilinear and does not "travel" a sufficient distance (<4 cm) into the LV cavity or is difficult to appreciate.[99] Additionally, an abnormal Vp merely diagnoses the presence of abnormal relaxation, and not necessarily its severity. Therefore, an abnormal Vp may not differentiate among the various stages of abnormal diastolic function, and a decreasing Vp value has not been associated with progressive worsening of diastolic function. Despite these limitations, Vp remains a valuable tool in the determination of development of intraventricular pressure gradients. However, Vp has been shown to increase with increasing preload and can be normal despite increased filling pressures in patients with a normal ejection fraction (EF) and LV volume.[99]

Doppler Tissue Imaging

Recent advancements in echocardiographic equipment, including the ability to record "high amplitude and low velocity" signals, have made it possible to measure tissue velocities and motion. In ultrasound systems with installed DTI presets, a 5- to 10-mm sample volume is placed in the lateral or medial mitral annulus to obtain a PWD spectral pattern (Fig. 3). A typical DTI signal consists of the following 3 main waves: early (E′) and late (A′) diastolic, and a systolic (S′) (Fig. 12).[61] Similar to the TMF E wave, the E′ wave peak velocity has been associated with the relaxation constant (τ). Although both TMF E and the DTI E′ waves represent early diastolic filling, under normal conditions, the DTI E′ wave precedes the TMF E wave because myocardial relaxation precedes opening of the mitral valve and LV inflow. Similarly, the DTI A′ wave is associated with late LV inflow and atrial contraction. Myocardial motion at the atrioventricular (AV) interface has also been shown to correlate with LVFP.[103–106]

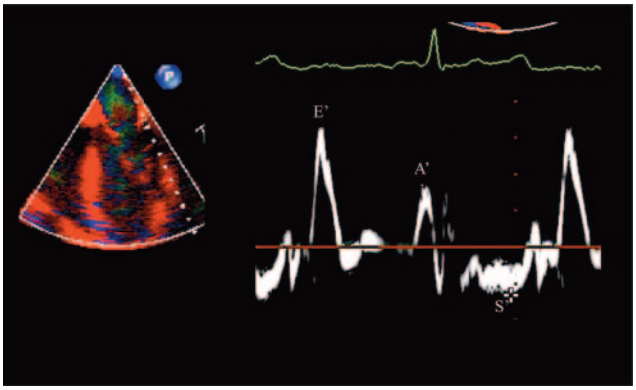

Figure 12. Spectral tissue Doppler display. E′ = rapid relaxation wave; A′ = atrial systolic wave; S′ = ventricular systolic wave.

Intraoperative Measurement

DTI should be performed in the ME 4-chamber view to obtain a parallel Doppler alignment. Most modern echocardiographic systems have manufacturer-installed presets to obtain DTI signals. During acquisition, the velocity scale should be set to <20 cm/s. Acquisition should be performed at end-expiration, and at a sweep speed of 50 to 100 mm/s. An average of >3 beats of the lateral mitral annular DTI should be measured. Because systolic function also has a role in mitral annular excursion, it is recommended that different E′ cutoff values be used for patients with a depressed EF. In cases of regional LV dysfunction and wall motion abnormalities, it is important to average velocity measurements from both septal and lateral mitral annuli.[5,107]

Intraoperative Application

The normal value of the E′ wave is age dependent and determined by the site of measurement (i.e., lateral versus medial mitral annulus) (Table 2).[5] For diastolic function interrogation, a reduced E′ velocity for age is considered diagnostic of abnormal LV relaxation. Further measurements of the E′ wave (acceleration/deceleration rate) do not add any incremental information.[108] However, calculation of the time interval between the QRS wave and

onset of the E′ wave can possibly provide incremental information about diastolic function generally and relaxation abnormalities in particular.[107,109] An E′/A′ ratio of >1 during a Valsalva maneuver has also been used to establish normalcy of diastolic function.[105,110] As opposed to pseudonormalization of TMF, an abnormal E′/A′ ratio (<1) does not revert to normal (>1) when the LA pressure is increased.[105] In addition, the average E′ velocity may not accurately represent global LV diastolic function in the presence of basal lateral and septal wall motion abnormalities, after mitral valve replacement and surgical septal myectomy.[61] Furthermore, similar to Vp, the E′ wave represents only the relaxation (early) phase of diastole and does not provide any information about LV compliance.

INTEGRATED APPROACH

With a primary relaxation abnormality, there is a delayed equilibration of pressure between LA and LV, which results in less filling in early diastole and more filling during atrial contraction. Therefore, in a typical impaired relaxation pattern, which is considered the initial stage of diastolic dysfunction, there is a decrease in E wave velocity, prolongation of DT, and a compensatory increase in A wave velocity, resulting in an E/A ratio <1 (DT >220 milliseconds) (Fig. 6). A typical impaired relaxation pattern is also characterized by a PVF pattern in which the S/D ratio remains <1 expressing decreased early diastolic flow, and a Vp <50 cm/s, while E′/A′ will be <1 and the onset of E′ will be delayed compared with the E wave. Persistence of relaxation abnormalities due to continued myocardial dysfunction causes LV remodeling and leads to reduced LV compliance, which manifests itself as an increase of LVEDP and an increase in LA pressure. The increased LA pressure overcomes the resistance to LV early filling because of impaired relaxation, and results in increased filling during early diastole and rapid equalization of pressure between the LA and LV because of reduced compliance characterized by an increased E velocity and shortened DT. As a result, there is limited filling during atrial contraction because of decreased LV compliance (Fig. 8). Also, PVF will show an S/D ratio >1, implying increased LA pressure and decreased flow from the pulmonary veins into an incompletely emptied LA during diastole. Vp will be <50 cm/s and DTI will reveal an E′/A′ <1 (Ar duration will be longer than Adur because of decreased antegrade flow due to reduced LA compliance with LA contraction). This is described as a restrictive filling pattern, the final stage of diastolic dysfunction (Fig. 8). An intermediate pattern can sometimes be appreciated during progression from impaired relaxation to the restrictive phase. Because it resembles the normal pattern, it is called a "pseudonormal" pattern and is difficult to appreciate, mostly because of load dependence of the Doppler variables. Because of impaired filling during early diastole, blood backs up in the LA and leads to an increase of the LA pressure. In this intermediate stage, the LA pressure, not ventricular relaxation, is the driving force for early LV filling, and compliance can be normal in this stage (Fig. 13). This indeterminate pattern often precedes the appearance of the restrictive phase. Echocardiographic representation of this stage is seen as a "recovered" E/A ratio (E/A >1) and a shortened DT (Fig. 13), which approaches a normal value. Therefore, in pseudonormalization, despite the underlying impaired relaxation, the transmitral PWD velocities change to a "normal-appearing" profile (Fig. 7).

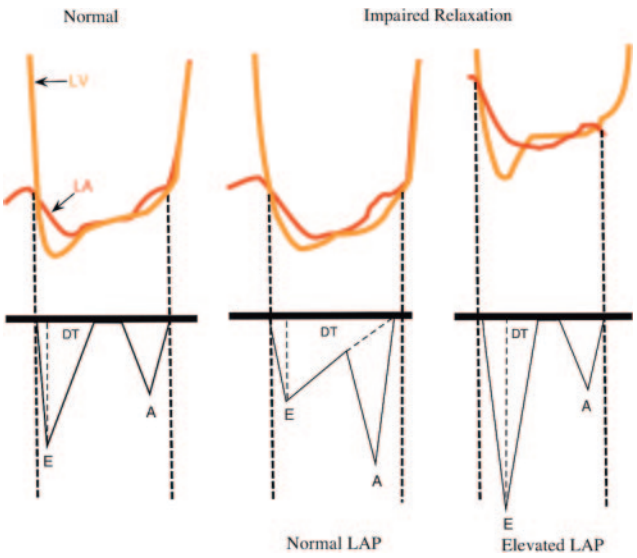

Figure 13. Effect of elevated left atrial (LA) pressure (LAP) on the transmitral filling patterns. Normal relaxation and normal LAP (E/A >1, normal deceleration time [DT]). Impaired relaxation and normal LAP (E/A <1, prolonged DT). Impaired relaxation and elevated LAP (E/A >1, normalization of DT). LV = left ventricle.

Hence, the challenge during echocardiographic evaluation is to differentiate pseudonormal (volume compensation with impaired relaxation) from a true normal filling pattern. Because the underlying relaxation abnormality coexists with a compensatory increase of LA pressure to preserve early LV filling, maneuvers that reduce LA pressure including the Valsalva maneuver have been advocated to unmask this compensation and uncover the underlying impaired relaxation. A reduction in LA pressure results in a decreased LA-LV gradient during early diastole, thus negating the effect of increased LA pressure as the main driving force for LV filling. Typically, during such a maneuver, a normal-appearing pattern reverses to an impaired relaxation pattern (E/A <1) and a prolongation of DT (Fig. 7).[42,45,46] Performance of the Valsalva maneuver in a "true" normal TMF pattern would result in an equal reduction in the E and A wave magnitude with the E/A ratio remaining >1. Although frequently used, there is no standardized method of performing the Valsalva maneuver. An increase of intrathoracic pressure to 40 mm Hg for at least 10 seconds with simultaneous recording of transmitral PWD has been used in various studies.[111,112] During controlled mechanical ventilation, the Valsalva maneuver can be performed by discontinuing the controlled mode and using the "pop-off" valve of the anesthesia machine to generate the required peak inspiratory pressure. The accuracy of Valsalva as well as other preload reduction maneuvers (nitroglycerin administration, which acts by reducing cardiac preload) in conclusively differentiating a normal from pseudonormal pattern of LV filling has been questioned.[112] Particularly during an intraoperative TEE examination, the inability to maintain parallel

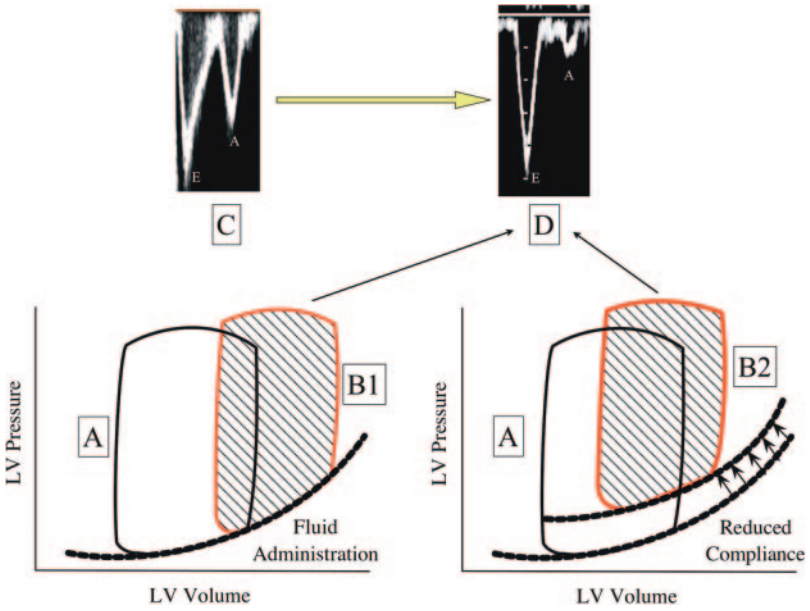

Figure 14. Pressure-volume relationship in 2 different clinical conditions and their effect on pulse wave Doppler–derived transmitral flow patterns. A, A normal pressure volume. C, The pulse wave Doppler–derived transmitral flow pattern from a normal pressure-volume relationship. B1, Pressure-volume relationship of the left ventricle (LV) after preload augmentation. B2, Pressure-volume relationship of the LV after reduced compliance. D, Transmitral pulse wave Doppler resulting from situations B1 and B2, demonstrating identical effects of the 2 situations on the transmitral filling patterns. Both situations give rise to indistinguishable E and A waves on the pulse wave Doppler interrogation of the transmitral flow, i.e., increased E-wave peak velocity and reduced A-wave velocity.

Doppler alignment during the Valsalva maneuver, the associated hemodynamic instability (hypotension) and availability of Doppler indices, which are less likely to demonstrate pseudonormalization, e.g., Vp and DTI, limit the utility of information gained from routine performance of the Valsalva maneuver.

INFLUENCE OF HEMODYNAMICS ON DOPPLER ASSESSMENT OF DIASTOLIC FUNCTION

The dependence of PWD variables on loading conditions was established early on.[54,57,113] Different LV filling patterns could be observed in the same patient, because of varying loading conditions, only hours apart.[4,57,58,60,114–116] For example, because of the curvilinear relationship of the pressure-volume relationship, sudden preload augmentation without alteration in compliance results in a higher pressure (Fig. 14). A similar and indistinguishable effect can also be observed with increased pericardial restraint associated with pericardial effusion or constrictive pericarditis (Fig. 14).[4] Both of the aforementioned scenarios would lead to an increased LA pressure resulting in an increase in the peak E velocity and shortened DT,[4] causing a pseudonormal pattern.

Preload

It has been demonstrated in animal experiments that a moderate increase in preload does not affect relaxation.[117] Although the exact mechanism is unknown, changes in sarcolemmal calcium ion metabolism with preload alterations have been demonstrated on a cellular level.[118] Clinically, TMF (E and A waves and DT), PVF (S and D), and DTI E′ waves show changes with alteration of the loading conditions.[4,5,29] Because patients undergoing hemodialysis undergo acute reduction in preload with dialysis, they are a unique cohort for such an assessment.[119–124] Such studies have, however, generated conflicting results, with some showing independence,[119–125] and others demonstrating dependence on preload changes.[126–129] It is quite possible that the conflicting results are attributable to the differences in the duration of dialysis and volume of fluid removed during dialysis in these patients.

Whether Vp is load independent has not been conclusively established.[5,29,96,98,99,130–133] Even though the E′ peak velocity has also shown to be preload dependent when diastolic function is normal, in the presence of diastolic dysfunction, both Vp and E′ become preload independent and remain reduced despite increasing preload.[105] However, in a study in which preload was reduced during hemodialysis, DTI values consistently varied with the magnitude of preload reduction.[126,134,135] However, these findings were dependent on the site of DTI measurement with the lateral mitral annular E′ velocity being more resistant to acute reduction in preload than the medial annulus E′ peak velocity.[134,136] It is important to consider that a single DTI E′ value is a regional value only, and unless averaged from as many basal sites as possible, it should not be used independently in the diagnosis of diastolic dysfunction.

Afterload

The response of myocardial relaxation to increasing afterload depends on the LV contractile reserve.[137–141] The magnitude, duration, and timing of increased afterload also affect diastolic function.[21,142] If LV systolic function is normal, an afterload increase shortens DT, implying improved relaxation and a more rapid, compensatory pressure equilibration between the LA and LV.[21] Alternatively, if systolic function is depressed, severe afterload increase in the latter third of diastole prolongs DT, implying impairment in active relaxation[143] and is a decompensatory response.[142] "Afterload reserve" determines the ability of the LV to respond to increases in afterload without changes in end-systolic volume. Reduced afterload reserve has been shown in the LV with systolic dysfunction[143–147] and increases of afterload in such a situation can cause marked deterioration of diastolic function.[137,148] A decrease in the rate of LV pressure decline and incomplete relaxation during diastole eventually lead to an increase of pressure in the LA and pulmonary vasculature.[149,150]

Clinically, the echocardiographic changes in LV diastolic function have been investigated in patients undergoing open abdominal aortic aneurysm surgery.[90,151–153] In a study using intraoperative TEE and a pulmonary artery catheter, it was demonstrated that application of an aortic cross-clamp in the infrarenal position led to increased pulmonary artery occlusion pressure without a concomitant change in LV end-diastolic area. Because of the lack of Doppler availability, the authors attributed this observation to reduced compliance of the LV after cross-clamp application with a higher intracavitary pressure for the same volume and, thus, a change in diastolic filling without a concomitant change in systolic function.[151] Minor changes in diastolic function with abdominal and thoracoabdominal aortic cross-clamp application were reported in TMF with PWD, probably reflecting changes with loading conditions.[152,154] However, when Vp with a cutoff value of <0.45 m/s was used for a similar assessment, an abdominal aortic cross-clamp application was associated with a worsening of LV relaxation, which returned to baseline value after unclamping of the aorta.[90] In this study,[90] traditional PWD measures (including TMF and PVF) of diastolic function were also used for comparison with Vp but were not as conclusive.

Heart Rate

TMF variables are affected by heart rate and rhythm.[5,155] Sinus tachycardia and first-degree AV block can result in fusion of E and A waves,[5] making it difficult to distinguish E from A and measure DT. Similarly, in atrial flutter, there are usually no A waves.[5,155] Different AV blocks (3:1, 4:1) may show multiple atrial filling waves and occasionally diastolic mitral regurgitation during the nonconducted beats.[156] During atrial fibrillation, there are no A waves on the spectral PWD, but the DT correlates with the LVFP if systolic function is impaired.[155,157] Similarly, peak E′ velocity can be reliably used for assessment of relaxation abnormalities in patients with atrial fibrillation using the same cutoff values as for patients with sinus rhythm.[155,157]

Heart rate alterations have not been shown to affect the Vp slope.[100] Because direct atrial pacing does not seem to change the Vp slope, the positive correlation between Vp and heart rate observed in animal studies is attributed to the pharmacological β-adrenergic stimulation used in these studies.[98,130]

Myocardial Ischemia

The effects of acute ischemia on diastolic function depend on the specific mechanism.[158] Myocardial ischemia due to acute or chronic reduction of blood supply leads to the onset of systolic dysfunction with diastolic function remaining relatively preserved.[159,160] Alternatively, myocardial ischemia due to increased demand causes diastolic dysfunction with little or no effect on systolic function.[160–164] The exact cause of these different responses is unknown.[160] Perioperatively, myocardial ischemia occurs because of increased demand, and hence changes of diastolic function associated with impaired relaxation are more likely to occur during such an episode. More recently, DTI has been investigated as a sensitive marker of myocardial ischemia, with E′ velocities decreasing acutely with the onset of ischemia.[165,166] In an animal model of myocardial ischemia, reduction of E′ peak velocity and E′/A′ ratio occurred before the appearance of wall motion abnormalities,[167,168] in proportion to the reduction in blood supply,[167,168] making it a promising early echocardiographic marker of ischemia. The reduction in E′/A′ ratio is easy to appreciate visually, and does not require an absolute parallel Doppler alignment. An E′/A′ ratio <1 is usually measured in a majority of hypokinetic and akinetic segments.[105]

PERIOPERATIVE APPLICATION

When evaluating diastolic function, measurements should be performed multiple times during periods of apnea and relative hemodynamic stability to minimize the effects of hemodynamic alterations (preload, afterload, heart rate, and contractility). In light of the recent ASE guidelines, the Doppler variables used to interrogate LV diastolic function should be used to assign a severity grade and define and diagnose the specific abnormality, e.g., abnormal relaxation and/or decreased compliance. It is important to remember that the diastolic function assessment must be performed within the context of the recommendations of the current ASE guidelines.

The changes in appearance of Doppler modalities in an impaired relaxation abnormality are determined by the rapidity of equilibration of LA and LV pressures. When this is delayed, it manifests itself as a reduced E velocity, prolonged DT, decreased E′, and reduced Vp. These changes can be masked with increased filling pressures, particularly if systolic function is intact. Because the exact effect of alterations in loading conditions on Doppler assessment of LV filling is unknown, preferably a single Doppler variable should not be used to interrogate diastolic function. The ASE guidelines recommend the assessment of relaxation abnormalities using Doppler modalities, which assess LV relaxation directly or indirectly. Of the "direct" measures of relaxation, isovolumetric relaxation time (IVRT) can be easily measured in the operating room (Fig. 15); however, as an independent measure, it has limited accuracy as a result of multiple factors. For practical application in the operating room, the modalities that assess LV relaxation indirectly are easier to measure and compute (Fig. 16). Particularly, Vp has been shown to be a more reliable index of LV relaxation in patients with depressed EF and those with dilated cardiomyopathy. Similarly, most patients with lateral E′ velocity <8.5 cm/s have impaired relaxation abnormalities.

Assessment of Compliance

Invasive calculation of the LV chamber stiffness constant (i.e., pressure-volume relationship) is considered the gold standard of LV compliance. The compliance constant can be estimated indirectly using echocardiography, but is of limited accuracy, particularly in patients with advanced diastolic dysfunction. Reduced LV compliance is associated with a faster pressure equilibration between the LA and LV, which leads to a shortened DT, an important surrogate measure of reduced compliance (Fig. 18). The transmitral A wave represents the LA-LV pressure gradient during late diastole, and is affected by the LA contractile function as well as LV compliance. Similarly, A-wave transit time, which is the time it takes for the atrial contraction wave to propagate to the LV apex, can be considered a surrogate

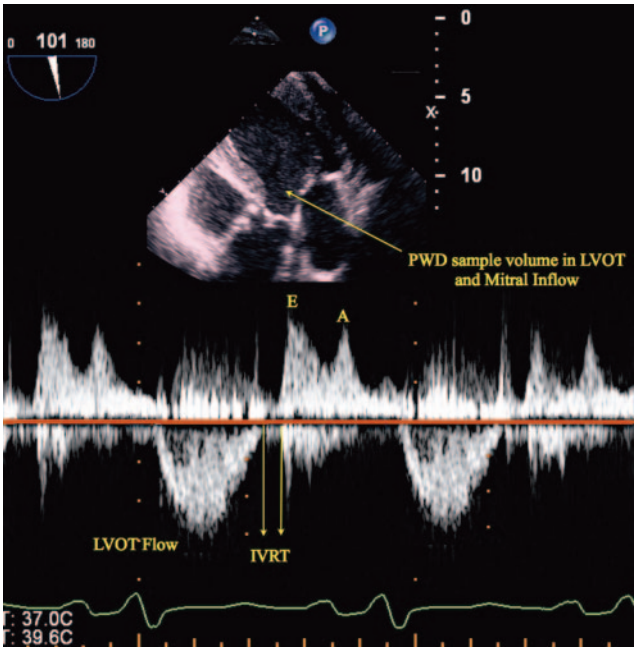

Figure 15. Measurement of isovolumetric relaxation time (IVRT). The transesophageal echocardiography probe is advanced to the deep transgastric position, and with omniplane rotation and probe manipulation, a parallel Doppler alignment is achieved and a sample volume of pulse wave Doppler (PWD) is placed between the left ventricular outflow tract (LVOT) and mitral inflow to obtain a spectral display that simultaneously displays the left ventricular outflow and mitral inflow profile. IVRT is measured as the time interval between the LVOT velocity time integral to the start of the transmitral flow. AV = aortic valve; MV = mitral valve.

measure of LV stiffness and has shown good correlation with simultaneously measured invasive LV pressures.[169,170] However, the applicability of this particular Doppler modality for use in the operating room as a sole measure of LV compliance remains to be established.

Echocardiographic assessment of diastolic function is performed to specifically assess relaxation or compliance,

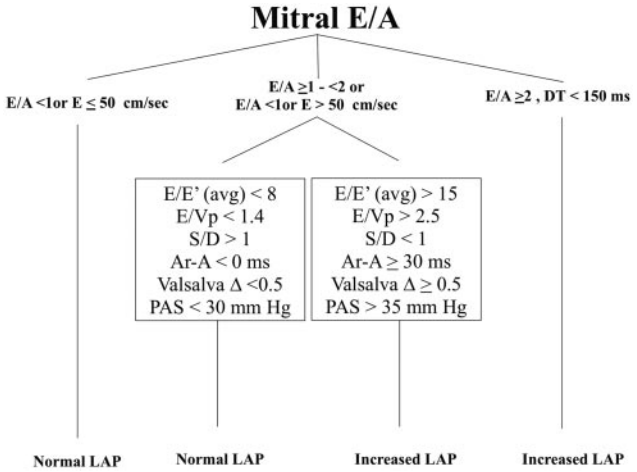

Figure 17. Estimation of filling pressures in patients with a depressed ejection fraction. LAP = left atrial pressure; Ar = pulmonary venous A wave; A = transmitral A wave; E = transmitral pulse wave Doppler E wave; E′ = Doppler tissue mitral annular wave; avg = average; PAS = pulmonary artery systolic pressure. (Adapted from Nagueh et al.[5])

but has to be performed in the context of assigning a severity grade based on the recommended guidelines (Fig. 4). According to the recommendations, it should start with DTI of the mitral annulus and then progress in a stepwise logical approach incorporating information obtained from the TMF, PVF, and, if required, subsequent performance of a Valsalva maneuver (Fig. 7). Using the ratios of various peak velocities obtained with Doppler, LVFP can be estimated and hence help in further refining the assessment of diastolic function.

Estimation of LVFP

The ASE guidelines suggest that Doppler variables can also be used for estimation of LVFP. However, the degree of systolic function should be taken into consideration when making such estimations (Figs. 17 and 18). For patients with

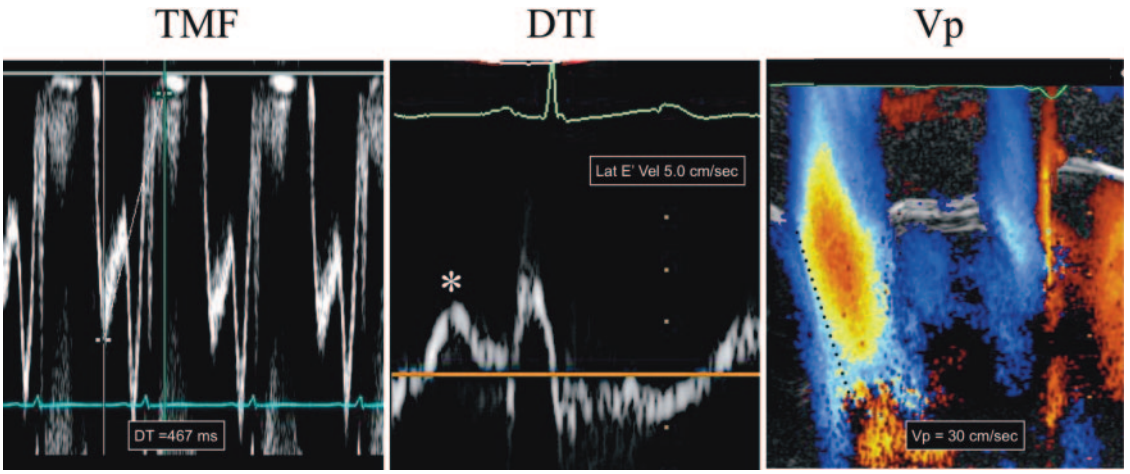

Figure 16. Indirect measures of left ventricular (LV) relaxation. Transmitral flow (TMF) demonstrating a typical impaired relaxation pattern E/A <1 and deceleration time (DT) >220 milliseconds. Impaired relaxation is the earliest abnormality and present in most patients with diastolic dysfunction. E′ velocity <8 cm/s is consistent with the diagnosis of diastolic dysfunction and is more sensitive than the pulse wave Doppler–derived TMF. Flow propagation velocity (Vp) correlates with the rate of myocardial relaxation. It can be normal despite impaired relaxation, particularly in patients with normal ejection fractions and LV volumes. DTI = Doppler tissue imaging.

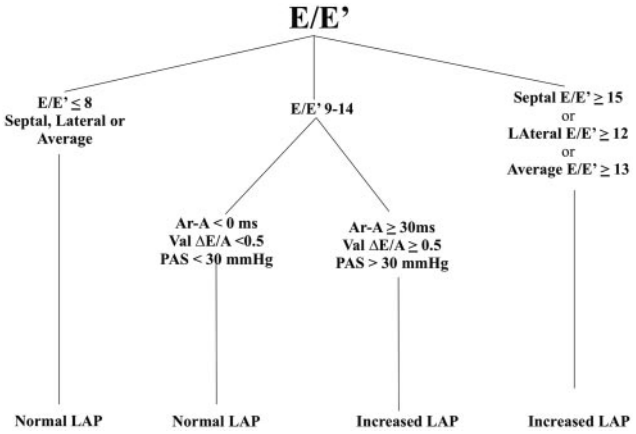

Figure 18. Estimation of filling pressures in patients with a normal ejection fraction. LAP = left atrial pressure; Ar = pulmonary venous A wave; A = transmitral A wave; E = transmitral pulse wave Doppler E wave; E′ = Doppler tissue mitral annular wave; PAS = pulmonary artery systolic pressure; Val = Valsalva. (Adapted from Nagueh et al.[5])

a depressed EF, such an assessment should start with a PWD of the TMF. A peak E velocity <50 cm/s or E/A ratio <1 implies a normal LA pressure. An E/A ratio >2 or a DT <160 milliseconds is considered diagnostic of increased LA pressure (Fig. 17). For TMF, E/A patterns between the 2 extremes need further assessment using DTI (E′), PVF (S/D ratio, Adur, and Ar duration comparison), Vp, and sometimes changes in E/A ratio with the Valsalva maneuver. In the presence of systolic dysfunction, preload does not affect E′ velocity; hence, in patients with impaired relaxation, the ratio of E/E′ can be used to correct for the effect of increased preload on the E wave and prediction of filling pressures. Similarly, E/Vp ratio has also been shown to correlate with increased LA pressure, and a longer Ar duration than the Adur implies increased filling pressure. Although recommended by the ASE guidelines, LA volume cannot be calculated or measured reliably using intraoperative TEE.

Specifically, in patients with depressed systolic function (EF <50%), E/Vp >2.5,[97,107] E/E′ >15,[171] and Ar-Adur >30 milliseconds (Figs. 17 and 18) are indicative of increased filling pressures.[5] When LA pressure is elevated, the transmitral E wave occurs before the mitral annular E′ wave, and the time interval between the onset of E and E′ wave ($T_{E-E'}$) is prolonged. An IVRT/$T_{E-E'}$ ratio of <2 is dependent on τ and is a sensitive indicator of increased LV pressures.[172]

Estimation of LVFPs in patients with preserved systolic function is approached differently. It should be initiated with calculation of an E/E′ ratio. An E/E′ ratio >13 indicates increased LVFP (Fig. 18).[103,104,107,171,173–176] An E/E′ ratio of <8 implies normal LVFPs and when the ratio is between 9 and 13, other Doppler variables may be used to estimate LVFP.[103] It is recommended to use the averaged mitral annulus–derived E/E′ ratio calculation for LVFPs.[107,173] An Ar-Adur >30 milliseconds and an IVRT/$T_{E-E'}$ ratio of <2 are also indicative of increased LVFPs.[5]

Because an E/E′ ratio of 9 to 13 can be associated with a normal or an increased LA pressure, it is important to integrate information from multiple Doppler modalities and clinical information. For example, pulmonary artery catheter–derived systolic pressure can be used to diagnose increased LA pressure when E/E′ is 9 to 13 in the presence of depressed or normal systolic function. The ratio E/Vp can be more reliably used to predict LVFP in patients with depressed systolic function.[5]

LA Size and Diastolic Dysfunction

Recently, LA size/volume measured with TTE has been found to be an indicator for the severity/chronicity of diastolic dysfunction, because during diastole the LA gets exposed to the elevated LVEDP. Clinically, LA size can be considered the "barometer" of the severity of diastolic dysfunction.[177] It is recommended that the size of the LA should be measured by Simpson's biplane method and indexed to the body surface area.[177–179] The graded LA volume is a simple measure and can be clinically used as a predictor of adverse cardiovascular complications including myocardial infarction and stroke.[180–184] However, it is important to know that LA size cannot be accurately measured with TEE because of atrial foreshortening. Hence, the relevance of LA size in the perioperative assessment of diastolic dysfunction is limited to the knowledge of its preoperative size and interpretation of perioperative Doppler indices in the context of this information.

ANESTHETIC DRUGS AND DIASTOLIC FUNCTION

Since the early pioneering work performed by Pagel et al.[49,160,185–191] to assess the effects of anesthetic drugs on LV diastolic function, there has been little or no effort by anesthesiologists to use Doppler to investigate the same effects (Table 3). Incorporation of Doppler interrogation of ventricular filling characteristics has the potential to transform the currently performed "anatomical" intraoperative TEE examination to an "anatomical and physiological" examination. In the following section, a synopsis of the available literature on the effects of anesthetic drugs on LV diastolic characteristics (echocardiographic and invasively measured) is presented.

Inhaled Anesthetics

The effect of anesthetic drugs on LV relaxation is not well known. Animal studies with invasive manometric catheters in the 1990s have demonstrated that halothane, isoflurane, enflurane, and desflurane prolong the IVRT,[187,192,193] leading to impaired early LV filling.[188,190] Echocardiographic studies in rats have demonstrated significant changes in TMF of LV filling during induction of GA with inhaled drugs.[194] Among the inhaled anesthetics, only halothane has been shown to reduce LV compliance in an animal model.[187,195] Impaired LV relaxation caused by inhaled anesthetics is possibly mediated by altered sarcoplasmic calcium metabolism because it is possible to reverse it with exogenous calcium administration in animal experiments.[186,188] In the aforementioned studies, LV and aortic pressures were measured invasively with micromanometric catheters.[187,192,193,196–198] Whether inhaled drugs have similar effects on patients with preexisting diastolic dysfunction is unknown. Interestingly, desflurane and isoflurane have been shown to preserve regional systolic function and improve diastolic function in ischemic dogs, an effect possibly mediated by a reduced LV preload.[185]

Table 3. Studies Assessing the Effects of Anesthetic Drugs on Left Ventricular Diastolic Function

Study	Anesthetic drug	Cardiac function modality	Study design	Findings
Doyle et al.,[192] 1989	Halothane	Coronary blood flow, dP/dt, time constant of relaxation	6 dogs undergoing open chest surgery with invasive monitoring	Halothane caused dose-related reductions in coronary blood flow; inverse relation to time constant of relaxation
Pagel et al.,[187] 1991	Desflurane, isoflurane, and halothane	Isovolumetric relaxation time, passive chamber compliance	23 experiments on 11 dogs with autonomous blockade with invasive monitoring	All 3 caused dose-dependent increase in isovolumetric relaxation; halothane increased passive chamber resistance
Pagel et al.,[191] 1992	Propofol and ketamine	Aortic and left ventricular pressure, dP/dt, cardiac output, subendocardial segment length	14 experiments on 7 dogs with autonomous blockade with invasive hemodynamic monitoring	Unlike propofol, ketamine increased passive chamber stiffness and isovolumetric relaxation time in a dose-dependent manner; both produced similar hemodynamic profile
Pagel et al.,[186] 1993	Amrinone	Aortic and left ventricular pressure, dP/dt, cardiac output, subendocardial segment length	27 experiments on 9 dogs with autonomous blockade with invasive hemodynamic monitoring	Amrinone increased myocardial contractility, shortened isovolumetric relaxation, and enhanced rapid ventricular filling in a dose-dependent response; systolic and diastolic improvement with concurrent isoflurane or halothane
Pagel et al.,[188] 1993	$CaCl_2$	Aortic and left ventricular pressure, dP/dt, cardiac output, subendocardial segment length	27 experiments on 9 dogs with autonomous blockade with invasive hemodynamic monitoring	$CaCl_2$ increased contractility; in the presence of halothane or isoflurane, $CaCl_2$ increased myocardial contractility, shortened isovolumetric relaxation, enhanced rapid ventricular filling, and reduced chamber stiffness in a dose-dependent response
Pagel et al.,[185] 1995	Desflurane and isoflurane	Coronary blood flow, dP/dt, aortic and left ventricular pressure, cardiac output, subendocardial segment length	18 experiments on 9 dogs with invasive hemodynamic monitoring before and during LAD occlusion	Increase in myocardial contractility after LAD occlusion was preserved with desflurane or isoflurane, which also reduced isovolumetric relaxation time and chamber stiffness

dP/dt = rate of increase of left ventricular pressure; LAD = left anterior descending.

More recently, investigators using Doppler echocardiography and a standardized GA protocol in patients without any preexisting cardiac disease demonstrated that halothane and sevoflurane did not cause prolongation of the IVRT[199] and the impairment of relaxation was not considered of significant magnitude to be clinically relevant.[199] In patients with preexisting diastolic dysfunction, however, administration of sevoflurane caused a slight improvement in early LV relaxation assessed with E′ velocity.[200] The results seem to contradict the earlier reported adverse effects of inhaled anesthetics on LV relaxation.[187,192,193,196–198] Differences in study population (animals versus humans), medication doses, and methodology (Doppler versus invasive pressure measurements) could possibly explain these contradictory results.[199,200] Similar effects were also observed in one human study in which isoflurane did not exacerbate preexistent diastolic dysfunction[201] and had no lusitropic effects, i.e., improving relaxation in an animal study using invasive means.[202] In 2 separate animal studies, the addition of nitrous oxide and desflurane was shown to increase chamber and myocardial stiffness.[203,204] Inhaled anesthetic drugs also exert profound effects on the contractile, reservoir, and conduit function of the LA and also significantly impact LV filling as assessed by TMF with E and A waves.[189,205] This loss of LA contractile function was also observed in human atrial tissue in an in vitro study.[206]

IV Drugs

There are only a few studies that have investigated the effects of IV drugs on perioperative diastolic function.

Barbiturates and ketamine exert similar effects by inhibition of sarcolemmal transport of calcium ions, and ketamine has also been additionally shown to reduce chamber compliance.[191,207–212] In animal studies, propofol does not seem to affect myocardial relaxation or compliance.[191] One study in humans using echocardiography has demonstrated that propofol prolongs the IVRT in patients with no history of cardiac disease,[199] but does not cause worsening of preexisting diastolic dysfunction.[200,213] The impact of etomidate on LV diastolic function has not been studied, but in vitro experiments have shown that it has minimal effects on intracellular calcium metabolism; therefore, it is unlikely that it would affect LV diastolic function.[214]

SUGGESTED PERIOPERATIVE STRATEGY

The ASE guidelines for assessment of diastolic function recommend a very comprehensive grading algorithm.[5] However, the guidelines also recommend a simplified and reproducible approach for individual patients. In the perioperative arena during variable hemodynamics, an approach that rigorously requires the presence of all of the measured variables may be particularly difficult to apply. In one such study, the rigorous application of ASE guidelines for grading diastolic dysfunction during cardiac surgery led to only 20% of the 905 patients being graded as having diastolic dysfunction with no association with postoperative outcome.[3] Conversely, when a simplified algorithm (lateral annulus E′ velocity) was used in the same patient group, almost 99% of patients were diagnosed with diastolic dysfunction and demonstrated a significant association with postoperative outcome.[3] However, this study is limited by its retrospective nature, the possibility of selection bias, and lack of availability of any hemodynamic data. Validation of such an approach would require prospective application of simplified algorithms, which are modifications of the ASE guidelines.

In anesthetized patients, the ranges of normal values of the Doppler indices of LV filling have not yet been established. Currently, perioperative assessment of diastolic function is based on extrapolation of data obtained during awake-state hemodynamics. According to the ASE guidelines,[5] An E′ velocity >8 cm/s essentially excludes the presence of diastolic dysfunction. However, because of the aforementioned factors, TMF and PVF should also be recorded for a comprehensive assessment and interrogation and severity grade assignment (Fig. 4). It is usually not difficult to distinguish an impaired relaxation abnormality (E/A <1, prolonged DT, and S/D >1) from a typical restrictive pattern (E/A >2, short DT, and S/D <1). These findings should be considered in the context of the underlying systolic function and E′ velocity to assign a grade of severity. Systolic function is often within normal limits in most patients with impaired relaxation compared with those with a restrictive pattern. The following caveats should be kept in mind: rhythm other than sinus makes interpretation of E/A and S/D difficult or impossible, "accessory" LV filling with aortic insufficiency, for example, will affect both E/A and S/D, and impaired relaxation will revert to a pseudonormal pattern with increased preload and vice versa. A brief "Valsalva" should be executed; reverse Trendelenburg or a lung recruitment maneuver with a prolonged inspiratory hold will probably unmask preload compensation because increased intrathoracic pressure will decrease blood return to the chest and eventually decrease LA preload. If a normal E/A ratio changes to impaired relaxation, the true underlying diastolic abnormality is most likely a pseudonormal state. A DTI E′/A′ <1 or a Vp <45 cm/s suggests the presence of diastolic impairment; however, the ratio will be decreased once relaxation is impaired.

Regarding estimation of LVFPs, systolic function should be evaluated as the first step. If normal, longer forward flow during atrial systole (A-Ar >0) generally means that the LVFP is normal. The same holds true if the change in E/A ratio with a Valsalva maneuver is <0.5. Retrograde flow for a longer duration during atrial contraction (A-Ar <30 milliseconds) or E/A change >0.5 with Valsalva is associated with increased LVFP. Interestingly, echocardiographic assessment of diastolic function is more reliable if there is concomitant systolic dysfunction because there is less preload effect on E′, Vp and it is easier to apply indices such as E/E′, E/Vp to estimate LVFP. In depressed LVEF, the S/D and E/Vp ratios also provide a clear separation between normal or elevated LVFP, in addition to the aforementioned E/A and A-Ar cutoffs mentioned above. Irrespective of the underlying LVEF, E/E′ <8 and >13 to 15 distinguish normal from elevated LVFP.

CONCLUSION

The established cutoff values for the various Doppler indices have been derived from TTE studies in awake patients, and may not be entirely applicable to patients examined with TEE under GA. However, in the absence of such normal values, a modified strategy based on the TTE-derived standards should be attempted. Hence, the perioperative approach described in this review, although different, is based on the same principles, avoiding cutoff values of any single Doppler variable. There is no single Doppler index that can diagnose with absolute certainty the presence or absence of diastolic dysfunction. A comprehensive approach should use multiple Doppler modalities with realization of their strengths and weaknesses. Future studies will be needed to establish the standards of LV filling characteristics of patients under GA.

Assessment of systolic function is based on a 2-dimensional examination, whereas diastolic function assessment is performed with Doppler, creating the impression that somehow these 2 exist separately.[177] The use of Doppler has allowed us to define events during the cardiac cycle with precision, and to appreciate global myocardial function or performance (combined systolic and diastolic function).[154] Newer techniques such as strain, speckle tracking, and velocity vector imaging may allow us to better define the LV filling dynamics and more accurately classify diastolic function. It is now important for anesthesiologists to incorporate Doppler examination of LV filling as part of a "comprehensive" intraoperative echocardiographic examination. In the absence of a specific therapy to improve diastolic function, the impact of routine intraoperative echocardiographic assessment of diastolic function on postoperative outcome is unclear. However, recent

evidence suggests that the presence of preoperative asymptomatic LV systolic and diastolic dysfunction is associated with adverse outcome. Anesthesiologists involved in the perioperative care of patients with cardiovascular disorders routinely manage these patients appropriately, perhaps without realizing the stages of diastolic dysfunction. The appreciation of the severity stage of diastolic dysfunction can possibly be used to modify/refine clinical care. For example, during the impaired relaxation phase, augmentation of LA pressure and heart rate control can optimize LV filling by increasing the LA-LV pressure gradient and increasing filling time. However, in the more advanced stage of diastolic dysfunction, fluid restriction and judicious use of diuretics would be the logical therapeutic choices. Future studies will be needed to accurately assess the therapeutic impact of such a strategy.

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