Prognostic Value of Diastolic Dysfunction: State of the Art Review

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Abstract: Left ventricular diastolic dysfunction (DD) is recognized as an important contributor to diastolic heart failure and is associated with increased morbidity and mortality. The evaluation of diastolic function has become an integral part of a full echocardiographic study and is recommended by the current guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Recent data show that diastolic function is not static, but rather a dynamic phenomenon; worsening of diastolic function is associated with worse outcomes, whereas its improvement is associated with better survival. The purpose of this article is to review the echocardiographic assessment of diastolic function with an integrative clinical practical approach, discuss plausible mechanistic links between DD and clinical outcomes, summarize the prognostic value of left ventricular and right ventricular DD in various patient cohorts, the strengths and limitations of the data, and finally, give insight into future directions.

Key Words: diastolic dysfunction, prognostic value

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Diastolic dysfunction (DD) reflects impaired ability of the myocardium to relax and the left ventricle (LV) to fill appropriately without increasing filling pressures.[1] It may relate to altered LV geometry, myocardial stiffness and fibrosis, molecular mechanisms underlying delayed myocardial relaxation and tone, and disturbed ventricular–arterial coupling. DD may manifest as altered diastolic suction and filling, mitral annular movements, myocardial strain patterns, torsional movements, LV synchrony, and left atrial (LA) size and function. DD is associated with aging among other comorbidities[2] and recognized as a contributor to clinical heart failure[3] with increased morbidity and mortality similar to systolic heart failure.[4] The evaluation of LV diastolic function as part of routine echocardiographic testing is recommended by the current guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[2] Echocardiography, and to a lesser extent, cardiac magnetic resonance imaging, are currently the most widely used tools in day-to-day assessment of diastolic function. Recent data confirmed that diastolic function is dynamic with corresponding prognostic value.[5–7] This article will review the echocardiographic assessment of diastolic function with an integrative clinical practical approach, discuss plausible mechanistic links between DD and clinical outcomes, summarize the prognostic value of LV and right ventricular (RV) DD in various patient cohorts, the strengths and limitations of the data, and finally, give insight into future directions.

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Using PubMed search, we identified original articles evaluating DD and clinical outcomes in general and in specific cohorts of patients; nonrelevant studies, those of small sample size or with poor methodology, were excluded. Given that most of the published data were collected from echocardiographic studies, the focus of this review will be on echocardiographically derived parameters and measurements.

ECHOCARDIOGRAPHIC ASSESSMENT OF DIASTOLIC FUNCTION

Echocardiography is the noninvasive method of choice for evaluation of LV diastolic function.[8] Commonly measured parameters include: mitral inflow velocities, isovolumic relaxation time (IVRT), deceleration time, pulmonary vein flow patterns, mitral A duration–pulmonary vein A reversal, flow propagation velocity, and tissue annular velocities. These measurements are obtained using pulse-wave Doppler from the apical 4-chamber views. A 2- to 3-mm sample volume is placed at the region of interest with adjustment of spectral gain, wall filter, and sweep speed for best tracings. Although most waveforms such as pulsed Doppler E and A wave and tissue Doppler e' and a' are easily obtainable and reproducible, adequate tracings of the pulmonary venous flow and timing measurements are more challenging.[2,9] All these parameters are prone to angulation errors, affected by filling conditions (although annular tissue velocities are less preload-dependent), and altered by systolic pressures[10] or arterial properties determining time-varying systolic wall stress.[11] The interrelationship between LV relaxation, stiffness, and mitral valve filling patterns has been described.[12] In addition, accurate evaluation of diastolic function is challenging in patients with tachycardia, heart block, arrhythmia, mitral annular calcification, valvular disease, constriction, and most commonly, poor acoustic windows. Indeed, in view of the U-shape relation between LV filling patterns and diastolic function,[13] interpretation of diastolic function becomes difficult particularly with preserved LV ejection fraction (EF). In such condition, the deceleration time correlates poorly with filling pressures, and Valsalva maneuver, pulmonary venous flow, and flow propagation velocity become unreliable. However, E/e' and mitral A duration–pulmonary vein A reversal are more robust in this scenario.[14] E/e' has been proposed as a surrogate for LA pressure and plays a prominent role in the guidelines. However, it has been shown to be less reliable in normal subjects,[15] in those with hypertrophic cardiomyopathy (HCM)[16] and acutely decompensated heart failure.[17] In general, E/e' seems to be most reliable in ambulatory patients with established heart disease. Finally, LA volume index (VI) reflects long-term LA pressure and is incorporated in the evaluation and grading of DD.[2]

Additional promising parameters include deformation measures, LV torsion, and untwisting; these are angle independent and less prone to tethering with speckle-tracking, but require high frame-rate image acquisition with potential measurement error.[18] Also, circumferential and longitudinal early strain rates are associated with DD and are helpful in patients with preserved EF in whom assessment of LV filling pressure with traditional parameters is challenging; the ratios of E to longitudinal diastolic strain and strain rate may better predict LV filling pressure than E/e'.[19] Significant work has also shown

that ventricular torsion and untwisting are independent predictors of tau and intraventricular pressure gradients and likely a manifestation of elastic recoil, which plays an important role in LV suction.[20]

Based on the updated guidelines, DD is graded as: grade I (mild), grade II (moderate/pseudonormal), or grade III (severe/restrictive).[2] Grade I is characterized by impaired relaxation, E/A ratio less than 0.8, prolonged deceleration time and IVRT (>200 ms and >100 ms, respectively), predominant pulmonary vein systolic flow, and reduced tissue annular velocities. In long-standing grade I DD, the LA filling pressures might be elevated with an increased LAVI. Grade II DD is characterized by E/A 0.8–1.5 that decreases with Valsalva by 50%, reduced tissue annular velocities, high filling-pressures, and dilated LAVI (Fig. 1). Finally, grade III DD is characterized by short deceleration time and IVRT (<160 ms and <60 ms, respectively), E/A ratio of 2 or more, elevated filling pressures with reduced tissue annular velocities, mitral A flow duration–pulmonary vein A reversal less than 30 milliseconds, predominant pulmonary vein diastolic flow, and dilated LAVI. With Valsalva maneuver, the LV filling pattern may revert to impaired relaxation (grade IIIa, reversible) or remain unchanged (grade IIIb, irreversible, also known as grade IV).[2]

THE PRACTICAL APPROACH TO EVALUATING DIASTOLIC DYSFUNCTION

A comprehensive assessment of DD should include echocardiographic parameters in addition to clinical variables such as age, symptoms, exercise capacity, hypertension, LV hypertrophy, diabetes,

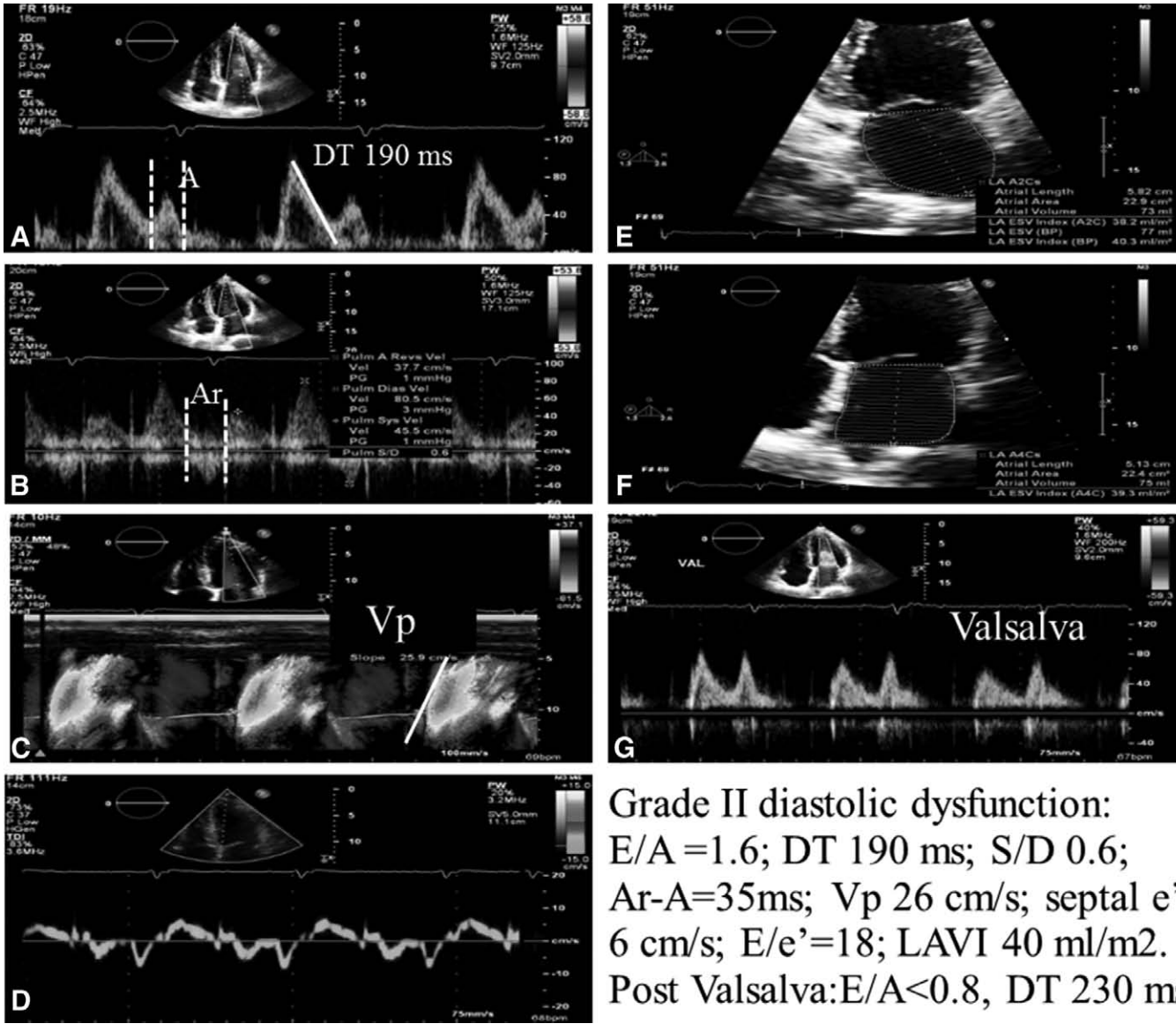

FIGURE 1. Echocardiographic parameters of diastolic function. The figure illustrates pulse-wave Doppler across the mitral valve showing a "pseudonormal pattern" (A); across the right upper pulmonary vein showing blunted systolic flow and prolonged Ar time (B); impaired velocity propagation speed (C); reduced septal tissue annular velocity (D) with elevated E/e'; dilated left a trial volume index (LAVI) (E and F); and with Valsalva reduction of E/A (mitral early to late inflow ratio) by 50% to <0.8 (G). DT indicates deceleration time.

coronary artery disease, EF, and brain-natriuretic peptide.[14] Although the guidelines are helpful in assessing DD, often several parameters yield discordant results. In such situations, clinical variables and the presenting case scenario become useful, particularly when differentiating normal from pseudonormal patterns. Indeed, elderly patients and those with significant comorbidities are more likely to have DD. In patients with systolic dysfunction and EF less than 40%, the question is not whether there is DD, but rather the grade and estimation of the LV filling pressures. Also, in symptomatic patients with preserved EF, brain-natriuretic peptide of more than 100 pg/mL is likely associated with diastolic heart failure (HF), whereas a level less than 50 pg/mL is unlikely. Functional capacity and response of LV filling with exercise are also important in unmasking DD.[14] Hence, an integrative approach is often needed to assess diastolic function and filling pressures.

MECHANISTIC LINKS BETWEEN DIASTOLIC DYSFUNCTION AND CLINICAL EVENTS

DD is associated with increased all-cause mortality, cardiovascular death, sudden cardiac death, and hospitalization for heart failure. However, no definitive pathophysiologic mechanism linking DD to clinical events has been identified yet. A plausible explanation is that DD may lead to diastolic heart failure (although the terms are not interchangeable), a leading cause of morbidity and mortality. In addition, DD is associated with new-onset atrial fibrillation,[21] which could be a link to worse cardiovascular outcomes. Stress perfusion defect size and valvulo-arterial impedance are independent predictors of DD and may represent other mechanisms for worse outcomes, at least in diabetic patients.[22] Furthermore, fibrosis is commonly seen in DD due to intrinsic myocardial disease;[23] it is a substrate for reentry arrhythmia, and could be the pathophysiologic milieu that links DD to poor clinical outcomes such as sudden cardiac death (Fig. 2). The fact that aldosterone receptor antagonists improve diastolic function and impact LV remodeling, including fibrosis, sheds light on the possible interaction between fibrosis, DD, and adverse events.[24] Finally, DD may represent a marker of subclinical ischemic heart disease (as such, correlation with coronary artery calcium score and/or inflammatory markers might prove useful) and a convergence point of deconditioning, physical inactivity, and serological risk factors.

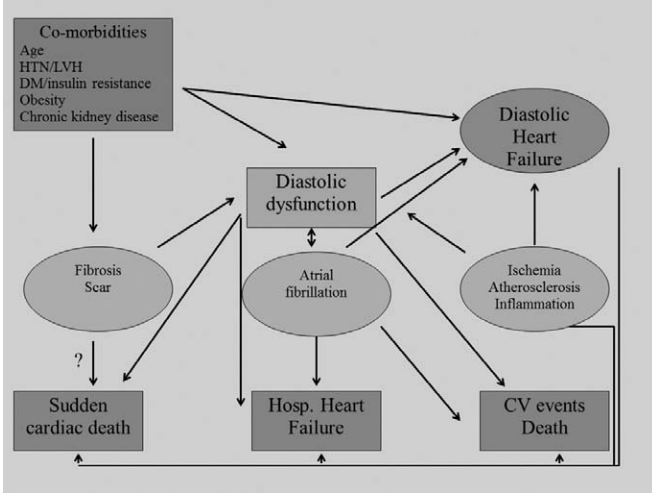

FIGURE 2. Speculative mechanistic links between diastolic dysfunction and clinical events. CV indicates cardiovascular; DM, diabetes mellitus; Hosp, hospitalization; HTN, hypertension; LVH, left ventricular hypertrophy.

Despite the lack of a clear biologic link between DD and outcomes, data showing the independent predictive value of DD are numerous and are summarized in the following sections.

PROGNOSTIC VALUE OF DIASTOLIC DYSFUNCTION

Cardiomyopathy

DD is commonly seen in different cardiomyopathies, including ischemic, nonischemic, hypertrophic, and infiltrative/restrictive, and has significant prognostic value (Table 1).[25–51]

Ischemic and Nonischemic Cardiomyopathy

In acute myocardial infarction, impairment of regional myocardial contractility, scar formation, and changes in filling pressures result in DD. Data from 1992 were the first to show that deceleration time and restrictive filling were independent predictors of heart failure.[25] A meta-analysis in 2008 (N = approximately 3400) confirmed that restrictive filling pattern was an independent predictor of death and was the strongest diastolic parameter.[33] More recently, strain and deformation indices have been used.[32] The difference in measured outcomes among studies, however, preclude comparing which diastolic parameter carries more prognostic weight (Table 1). It is clear, however, that grade III DD, restrictive filling pattern, and elevated E/e' are the most powerful parameters. However, the optimal cut offs for E/e' varied in each study, and in many others E/e' was used as a continuous variable without setting or identifying cut offs. DD, which is characterized by elevated filling pressure (at least in the more advanced stages), could be in part due to decreased LV contractility which impacts the restoring forces. The latter contribute along with LV relaxation to the untwisting rate, an important marker of diastolic function.[52]

Although patients with depressed systolic function may have traveled different clinical routes to arrive at this echocardiographic phenotype, DD is prevalent in this cohort (Table 1). In the largest and most up-to-date study, Gardin et al[41] showed that E/e' and E/A were independent predictors of all-cause mortality, cardiac death, and hospitalization, and added incremental value to baseline demographics and peak oxygen consumption. This is one of the few studies that assessed for incremental value of DD. Throughout the studies, DD was consistently associated with worse outcomes, although different parameters or "surrogates" of DD were used, such as elevated E/e'[37,39] and E/A ratio,[34,36,40] restrictive filling pattern,[33,35] and dilated LAVI.[36]

Although different endpoints were used, the message is clear: the assessment of diastolic function in ischemic and nonischemic cardiomyopathy provides independent and incremental prognostic information. The presence of restrictive filling pattern and elevated filling pressures were most predictive of clinical events.

Hypertrophic Cardiomyopathy

HCM (often genetic) is characterized by increased LV wall thickness, interstitial fibrosis, which is implicated with myocardial stiffness[23] and decreased global longitudinal strain,[42] and DD. The prognostic value of DD has been evaluated in children[43,44] and adults[45,46] (Table 1). Elevated E/e' ratio, restrictive filling, and dilated LAVI are independent predictors of clinical outcomes; however, E/e', which is traditionally a marker of LV filling pressure, does not optimally perform in HCM, whereas dilated LAVI could be a manifestation of mitral regurgitation rather than DD. Restrictive filling or grade III DD is the most powerful predictor of outcomes and is associated with 4- to 9-fold increase in death, sudden cardiac death, or heart transplantation.[44,46] Peak negative myocardial velocity gradient is an alternative index of DD in HCM[53] but has not been adopted in routine practice and is without prognostic data.

TABLE 1. Prognostic Value of Diastolic Dysfunction in Patients with Cardiomyopathy

Reference	N	Cohort	Diastology Parameter	Outcome	Results
Patients with CAD, ICM, and NICM					
Oh et al[25]	62	AMI	Deceleration time (continuous)	Heart failure	Deceleration time was an independent predictor of heart failure
Poulsen et al[26]	58	AMI	Deceleration time <140 ms	In-hospital heart failure or cardiac death	Independent predictor
Poulsen et al[29]	183	AMI	Grades I–III	Cardiac death	Diastolic dysfunction: independent predictor; $P = 0.0001$
Hillis et al[27]	250	AMI	E/e' >15	All-cause death	HR 4.8; $P = 0.0002$
Beinart et al[28]	395	AMI	Restrictive	All-cause death	OR 1.89 [1.09–3.31]
Quintana et al[31]	520	AMI	Grades I–III	Nonfatal AMI/cardiac death	P = NS
Moller et al[33]	3396	AMI meta-analysis	Restrictive filling	All-cause death	HR 2.67; $P < 0.0001$
Shanks et al[32]	371	AMI	Strain rate-isovolumic relaxation <0.24/s	All-cause death, heart failure hospitalization, repeat MI, repeat revascularization	HR 2.74; $P < 0.001$*
Jons et al[30]	62	AMI	Grades I–III	Repeat MI, stroke, or cardiac death	HR 4.70, $P = 0.002$
Hansen et al[35]	311	ICM, NICM	Restrictive filling	All-cause death or heart transplant	2-yr survival 80% vs. 95%; $P < 0.05$
Acil et al[37]	132	ICM, NICM	E/e' >12.5	Cardiac death/transplant/ heart failure hospitalization	AUC 0.85; $P < 0.05$; HR 1.13 [1.07–1.20]
Seo et al[40]	58	ICM, NICM	E/A >1.05. Brain-natriuretic peptide >255 pg/mL	Readmission for heart failure/cardiac death	E/A: AUC 0.836; $P = 0.02$. Brain natriuretic peptide: AUC 0.768; $P = 0.002$
Gardin et al[41]	2331	ICM, NICM	E/A, E/e'(continuous)	All-cause death, hospitalization	Increased C-index; $P < 0.0001$
Shen et al[34]	62	NICM	E/A >2	Cardiac events	Independent predictor; $P < 0.01$
Rossi et al[36]	337	NICM	LAVI >68 mL/m^2. E/A (continuous)	All-cause death	E/A: HR 1.6; $P < 0.0001$. LAVI >68 mL/m^2: RR 3.8; $P < 0.05$
Galrinho et al[39]	33	NICM	E/e' >15	Heart failure hospitalization/ transplant/all-cause death	AUC 0.73; $P < 0.05$
Patients with HCM					
McMahon et al[43]	80	HCM (children)	Septal E/e' (continuous)	Cardiac death/arrest/ ventricular tachycardia	$R^2 = 0.18$; $P < 0.001$
Yang et al[45]	81	HCM	E/e', LAVI (continuous)	Hospitalization for heart failure, stroke, and cardiac death	LAVI: HR 1.28; $P < 0.01$ per 5 mL/m^2↑
Pinamonti et al[46]	101	HCM	Restrictive filling	All-cause death/transplant	HR 8.9 [2.5–32]
Maskatia et al[44]	119	HCM (children)	Restrictive filling	Death/sudden cardiac death. Death/transplant	HR 3.5, $P = 0.01$. HR 5.7; $P = 0.04$
Patients with storage, infiltrative, and restrictive cardiomyopathy					
Hou et al[47]	45	Thalassemia	Total diastolic period, deceleration time	New-onset heart failure. All-cause death	90% of patients with diastolic dysfunction had new-onset heart failure and 40% died after 2 yr
Klein et al[48]	63	Amyloidosis	Deceleration time <150 ms, E/A >2.1	All-cause death/cardiac death	Independent predictors; $P < 0.01$
Mohty et al[49]	111	Amyloidosis	LA >23 mm/m^2	All-cause death	HR 2.47; $P = 0.02$
Whalley et al[50]	3024	Idiopathic and mixed restrictive cardiomyopathy	Restrictive filling	All-cause death	Death: OR 4.4 [3.6, 5.0]

*, Delete; ↑, increase. AMI indicates acute myocardial infarction; AUC, area under curve; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; ICM, ischemic cardiomyopathy; LAVI, left atrial volume index; NICM, nonischemic cardiomyopathy; NS, non-significant; OR, odds ratio; RR, relative risk.

Storage, Infiltrative, and Restrictive Cardiomyopathy

Cardiac siderosis and amyloidosis are the most common causes of storage or infiltrative cardiomyopathy and are associated with increased morbidity and mortality. Deposition of iron into the interstitial space leads to impaired LV diastolic function and eventually end-stage nonischemic cardiomyopathy; similarly, the deposition of amyloid proteins leads to increased wall thickness, stiffness, impaired relaxation, and elevated filling pressures. Although there are limited prognostic data of DD in cardiac siderosis,[47] recent advances in speckle-tracking strain imaging have provided sensitive and specific tools to identify cardiac amyloidosis based on "apical sparing" pattern on longitudinal strain imaging[54] with prognostic value.[55] Early on, Klein et al[48,56] showed that there is a spectrum of DD with restrictive filling pattern occurring late in the disease process and with worse prognosis (Table 1). More recently, LA size was shown to be an independent predictor of death,[49] although unidimensional M-mode measurement of the LA was performed which is suboptimal and correlates poorly with 3-dimensional LAVI. Newer methods of evaluating DD in cardiac amyloidosis, such as strain and speckle-tracking, are being evaluated.[57] Although restrictive filling pattern is strongly associated with worse outcome irrespective of the primary etiology,[58] idiopathic restrictive cardiomyopathy is commonly described in pediatrics and in young adults and associated with poor outcomes in the absence of transplantation.[59]

Normal Left Ventricular Ejection Fraction

Although DD is commonly seen with depressed LVEF, it may also be prevalent among patients with preserved systolic function. Indeed, Redfield et al[60] showed in 2003 that in such a cohort, DD (grades I and ≥II) was associated with increased all-cause death. Also, Halley et al[4] evaluated approximately 3,6000 patients with normal systolic function and showed that grades II and III DD (but not grade I) were associated with increased mortality after propensity matching of more than 30 risk factors and covariates (Table 2). However, one of the limitations is that the definition and grading of DD have evolved over the course of the study (1996–2005). DD was graded in most studies before 2001 without the use of tissue Doppler imaging or LAVI, which are now an integral part of the guidelines, and were retrieved retrospectively from chart review without

TABLE 2. Prognostic Value of Diastolic Dysfunction in Different Cohorts

Reference	N	Cohort	Diastology Parameter	Outcome	Results
Patients with preserved systolic function or LVEF					
Redfield et al[60]	502	EF ≥55%	Grades I–IV	All-cause death	Grade I: HR 8.3; $P < 0.001$. Grade ≥II: HR 10.2; $P < 0.001$
Halley et al[4]	3,6261	EF ≥55%	Grades I–III	All-cause death	Grade II: HR 1.6; $P < 0.001$. Grade III: HR 1.8; $P < 0.001$
Patients with cardiovascular risk factors					
Bella et al[62]	3008	Middle-aged and elderly	E/A >1.5	Cardiac death	HR 2.8; $P < 0.05$
Tsang et al[21]	840	Elderly	Grades I–III	New-onset atrial fibrillation	HR 3.3 [1.5, 7.4]; 4.8 [2.1, 11]; 5.3 [2.3, 12] for grades I, II, and III, respectively
Andersson et al[65]	388	Diabetes	a': 1 cm/s ↓	Heart failure hospitalization/all-cause death	HR 1.2 [1.05–1.37]
Shah et al[66]	820	Diabetics post-MI	E/e' (continuous)	Heart failure hospitalization/ all-cause death/ recurrent MI/stroke/ sudden cardiac death	Diabetics had worse outcomes; adjusted HR 1.63 [1.01; 2.6]
Patients without cardiovascular risk factors or from the general community					
Mogelvang et al[72]	1036	Low risk	a' (continuous)	All-cause death	Adjusted HR 1.20/1 cm/s decrease; $P = 0.001$
AlJaroudi et al[61]	1039	Low risk	Grades I–III	All-cause death	Diastolic dysfunction: HR 2.73; $P < 0.001$; NRI 15%
Patients with systemic disease					
Sharma et al[74]	125	ESRD	E/e' ≥15	All-cause death	OR 8.1; $P = 0.003$
Siqueira et al[75]	60	ESRD	Grades I–III	Fatal, nonfatal cardiac events	Grades II and III: HR 3.76; $P = 0.04$
Alexopoulou et al[77]	76	ESLD	E/A (continuous)	All-cause death	Trend; $P = 0.09$
Josefsson et al[76]	234	ESLD	Grade I	Transplant-free mortality	HR 4.8 [1.8, 13]
Dowsley et al[78]	107	ESLD	E/e' >10. LAVI >40 mL/m^2	Heart failure posttransplant	E/e' >10: OR 3.4 [1.2, 9.4]. LAVI >40 mL/m^2: OR 2.9 [1.1, 7.5]
Movers et al[80]	2860	HIV	Grade ≥II	Sudden cardiac death	Sudden cardiac death was associated with diastolic dysfunction, OR 32 [2.3, 423]

↓ EF indicates ejection fraction; ESLD, end-stage liver disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HR, hazard ratio; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NRI, net reclassification index; OR, odds ratio.

an independent blinded adjudication and reviewing. Nevertheless, these findings might explain the observation that heart failure with preserved EF is associated with morbidity and mortality and suggests DD as a potential determinant of symptomatology. Although patients might be asymptomatic, aggressive risk factor modification is needed in the hope of reversing DD and preventing progression to symptoms and poor outcomes.

Cardiovascular Risk Factors

Age, hypertension, diabetes, and obesity are among the most common cardiovascular risk factors that have been associated or implicated in the pathogenesis of DD. The prognostic value of DD in patients with such comorbidities has been evaluated, with age being the strongest determinant of DD (odds ratio, 3.2 per 10-year increase[61]; Fig. 3). In one of the largest studies of middle-aged and elderly American Indians, E/A greater than 1.5 was still associated with increased relative risk of cardiac death and all-cause death.[62]

Diabetes mellitus is often thought to be a risk factor for DD, myocardial impairment, and stiffness, and with a synergistic effect in the presence of hypertension.[63] It is prevalent in almost half of asymptomatic patients.[64] Decreased late diastolic tissue Doppler velocity and E/e' are associated with an increased risk of composite endpoints in this cohort.[65,66]

Obesity, which is a major public health epidemic that is associated with heart failure[67] and cardiac death,[68] has been linked to increased odds of DD in the elderly,[69] in a general community cohort in Europe,[70] and more recently a study from our group that included a significant number of young patients (aged younger than 35 years[71]; Table 3). The high association of DD with obesity might explain the high incidence of diastolic heart failure in the obese population. The prognostic value of DD in morbidly obese patients and the possible change in diastolic function after significant weight loss, beyond changes in blood pressure, diabetes, and other risk factors, warrant further investigation.

The prognostic value of DD in the absence of such cardiovascular risk factors or any others, however, has also been recently investigated in low-risk patients.[61,72] In one of the studies, even after adjusting for Framingham risk score, DD was still associated with increased all-cause death (hazard ratio 2.73), and added incremental prognostic value (Table 4).[61] However, in that study, less than 5% of the cohort were analyzed (after excluding all those patients with risk factors or comorbidities), and therefore the results cannot be extrapolated to the general community. Also, patients were presenting to a tertiary center for another reason and many must have had symptoms or suspected disease that led the physician to request an echocardiogram.

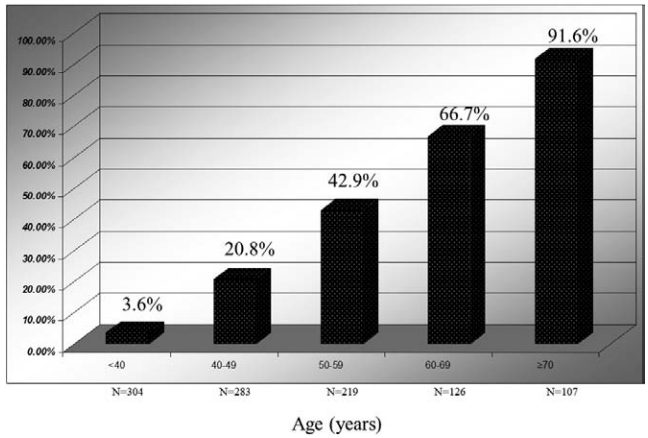

FIGURE 3. Prevalence of diastolic dysfunction in low-risk adults. The prevalence of diastolic dysfunction (grade ≥I) was assessed in 1039 outpatients with normal left ventricular ejection fraction, and in the absence of cardiovascular risk factors or comorbidities (Data from AlJaroudi et al[61]).

TABLE 3. Incremental Prognostic Value of Diastolic Dysfunction in Low-Risk Adults

Model Based on Framingham Risk Score	Model Based on Framingham Risk Score and Diastolic Dysfunction		
	Low Risk (<0.35%/yr)	Intermediate Risk (0.35–1.0%/yr)	High Risk (>1.0%/yr)
Participants dead at 7-yr follow-up (n = 61)			
Low risk (<0.35%/yr)	3	1	0
Intermediate risk (0.35–1.0%/yr)	1	5	9
High risk (>1.0%/yr)	0	5	37
Participants alive at 7-yr follow-up (n = 852)			
Low risk (<0.35%/yr)	245	25	0
Intermediate risk (0.35–1.0%/yr)	83	145	71
High risk (>1.0%/yr)	0	84	199

Net reclassification index = [(1 + 9) − (1 + 5)]/61 − [(25 + 71) − (83 + 84)]/852 = 15%; $P = 0.029$.

Systemic Disease

Patients with systemic disease, such as end-stage renal and liver disease, HIV, and those undergoing chemotherapy, suffer high morbidity and mortality. Recent data have shown a high prevalence of DD in such cohorts with prognostic value. Indeed, patients with end-stage renal disease often suffer from LV hypertrophy, fibrosis, and DD.[73] Increased LV filling pattern and advanced DD (≥ grade II) independently predict all-cause death[74] and fatal or nonfatal cardiac events[75] (Table 2). The LV filling pattern, however, is dependent on timing of dialysis and volume status at the time of diastolic function evaluation.

TABLE 4. Diastolic Dysfunction and Obesity

	Odds Ratio	95% CI	*P*
All patients (N = 2,1666)			
Body mass index <25 kg/m² (N = 6703)	1.0 (reference)		
Body mass index 25–29.9 kg/m² (N = 7352)	1.30	1.20–1.42	<0.0001
Body mass index 30–39.9 kg/m² (N = 5995)	1.88	1.71–2.06	<0.0001
Body mass index ≥40 kg/m² (N = 1616)	2.16	1.87–2.49	<0.0001
Patients <35 yr (N = 1733)			
Body mass index <25 kg/m² (N = 866)	1.0 (reference)		
Body mass index 25–29.9 kg/m² (N = 460)	1.04	0.60–1.81	0.89
Body mass index 30–39.9 kg/m² (N = 300)	2.95	1.81–4.83	<0.0001
Body mass index ≥40 kg/m² (N = 107)	1.76	0.80–3.90	0.16

Adjusted odds ratio of having diastolic dysfunction based on body mass index.
CI indicates confidence interval.

DD is prevalent in end-stage liver disease[76,77] and associated with new incidence of heart failure postliver transplant.[76] This is relevant when screening patients because even grade I DD has prognostic value. Indeed, heart failure posttransplant is associated with a longer intensive care unit stay, more cardiac events, and long-term increased mortality.[76] Also, E/e' and LAVI are independent predictors of heart failure posttransplant. However, these parameters might reflect a state of high cardiac output and volume shifts rather than intrinsic myocardial stiffness and DD,[78] which make the assessment and grading of DD less reliable.

In patients with HIV, DD is prevalent in up-to half of them[79] and is associated with sudden cardiac death[80] without clear or plausible biologic explanation. In the study of 2860 patients,[80] however, there were only 30 sudden cardiac deaths, which prevented adequately powered adjustment beyond 3 covariates in the multivariate analysis.

The prognostic value of DD among patients undergoing chemotherapy is under investigation. There is increased awareness of subclinical and clinical cardiomyopathy postchemotherapy, and several centers including ours established a Cardio-Oncology Program to enable early recognition of LV dysfunction before a visual drop in LVEF after chemotherapy. Although there is an increasing role for global longitudinal strain,[81] recent data showed that DD may develop immediately after the administration of cardio-toxic agents and remain present for years; such changes are closely linked to new systolic dysfunction.[82] The prognostic value of new-onset or persistent DD postchemotherapy, however, needs further evaluation.

Valvular Heart Disease

In most studies evaluating the prognostic value of DD, patients with significant valvular disease are often excluded, in part because of the confounding effect, particularly in severe valvular regurgitation. Nevertheless, there have been many studies with prognostic data of DD in valvular heart disease.

DD is often seen in aortic stenosis and is likely a consequence of aging, chronic pressure overload, LV hypertrophy, and fibrosis, with clinical outcomes (Table 5 and Fig. 4).[83–88] Advanced DD and restrictive filling are the most predictive of death. Although most of these studies evaluated high-gradient aortic stenosis, the role and prognostic value of DD in low-gradient severe aortic stenosis but with normal EF remain to be defined. Although DD often improves after aortic valve replacement (AVR) (discussed later), its persistence is associated with increased death.[86] Research is currently underway regarding the prognostic value of improvement in DD posttranscatheter aortic valve replacement (TAVR).

However, patients with chronic volume overload states such as aortic regurgitation have elevated filling pressures and DD.[89] Data by Cayli et al[90] showed that elevated mitral E/A and short deceleration time (ie, restrictive filling pattern) are predictive of worsening LV systolic function post-AVR (Table 5). Evaluation of diastolic function with standard load-dependent parameters, however, could be problematic. Other parameters such as early diastolic strain rate are promising.[91]

The evaluation of diastolic function in mitral stenosis using traditional parameters is often unreliable. Although the LV is

TABLE 5. Prognostic Value of Diastolic Dysfunction in Patients with Valvular Disease

Reference	N	Cohort	Diastology Parameter	Outcome	Results
Patients with aortic stenosis					
Gjertsson et al[83]	399	Severe aortic stenosis	Grades I–III	All-cause death	Grades II and III: HR 1.72; $P = 0.004$
Poh et al[84]	53	Aortic stenosis	Septal a' <9.6 cm/s	Cardiac death or AVR	AUC 0.89; $P < 0.001$
Ding et al[85]	86	Severe aortic stenosis	Restrictive filling	All-cause death	HR 1.77; $P = 0.003$
Brown et al[86]	156	Status post-AVR	Grades I–III	All-cause death	Diastolic dysfunction, HR 1.76; $P = 0.04$
Stewart et al[87]	183	Moderate–severe aortic stenosis	e' (continuous)	Symptomatic deterioration	P = NS
Rassi et al[88]	1267	Aortic stenosis	Grades I–III	All-cause death or AVR	Grade ≥II: HR 1.75; $P = 0.01$
Patients with aortic regurgitation					
Cayli et al[90]	41	Aortic regurgitation	E/A, deceleration time (continuous)	Worsening of LVEF	E/A: R^2 −0.62; $P < 0.001$. Deceleration time: R^2 0.75; $P < 0.001$
Olsen et al[91]	64	Aortic regurgitation	Early diastolic strain rate	Persistent symptoms or LV dilatation	Diastolic strain rate cut off 1.0/s: AUC 0.77
Patients with mitral stenosis					
Eleid et al[92]	104	Mitral stenosis undergoing balloon valvuloplasty	LV end-diastolic pressure ≥16	All-cause death or recurrent symptoms	1-yr freedom of events: 54% vs. 83%; $P = 0.002$
Patients with mitral regurgitation					
Ereminiene et al[93]	53	Ischemic mitral regurgitation	Restrictive filling	Perioperative mortality, postoperative mitral regurgitation	Wald 4.4; $P = 0.03$
Gelsomino et al[94]	234	Premitral valve repair	Deceleration time <140 ms; pulmonary vein S/D <0.8	All-cause death	$P < 0.01$ for both
Le Tourneau et al[95]	492	Organic mitral regurgitation	LAVI ≥60 mL/m^2	Cardiac and all-cause death	HR 5.2; $P < 0.0001$ and HR 2.8; $P = 0.016$

AUC indicates area under curve; AVR, aortic valve replacement; E/A, mitral early to late inflow ratio; HR, hazard ratio; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction.

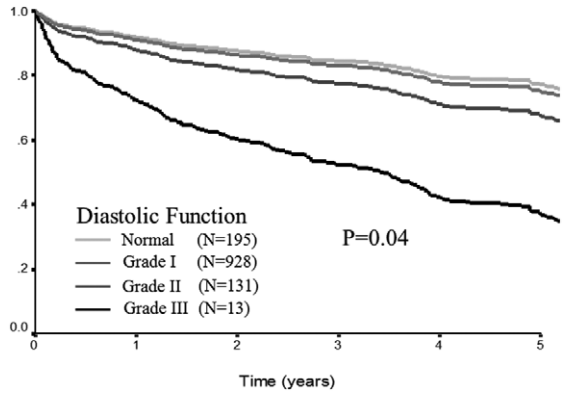

FIGURE 4. Adjusted freedom from aortic valve replacement (AVR) or all-cause death in patients with aortic stenosis. After adjusting for demographics, comorbidities, and echocardiographic parameters, baseline diastolic dysfunction was independently associated with increased risk of aortic valve replacement or all-cause death in patients with aortic stenosis (Data from Rassi et al[88]).

unloaded, DD can still develop due to underlying comorbidities. In a recent study from the Mayo Clinic, LV end-diastolic pressure of 16 mm Hg or more was considered a marker of DD and predicted worse combined outcomes in patients undergoing balloon valvuloplasty[92] (Table 5). However, this requires invasive assessment in the catheterization laboratory.

Finally, significant mitral regurgitation is associated with increased filling pressures mimicking restrictive pattern. The latter is associated with failure of surgical repair,[93] all-cause mortality,[94] and cardiac death[95] (Table 2). Other less commonly used parameters such as A reversal greater than 30 milliseconds, IVRT less than 60 milliseconds, and IVRT/$T_{E\text{-}e'}$ less than 3 have been proposed as better predictors of LV filling pressure even in patients with normal LVEF,[96] however, prognostic data are lacking.

DIASTOLIC DYSFUNCTION IN ATHLETES

On the whole, athletes have normal systolic and diastolic functions irrespective of type of training.[97] Although some exhibit impaired early diastolic filling pattern thought to be due to an intrinsic aging phenomenon,[98] other data have shown that dynamic exercise training improves cardiac performance by improving diastolic filling.[99] Hence, the association of physical activity, age, and diastolic function is important as it might clarify the interaction between sedentary lifestyle, obesity, and DD, and offer a way to reverse or halt the process.[100] This line of thinking, however, is speculative and needs prospective testing.

DIASTOLIC FUNCTION: DYNAMIC OR STATIC?

Although most studies evaluated diastolic function at one time point, diastolic function is dynamic and influenced by loading conditions, heart rate, and peripheral vascular tone. Data have shown improvements in diastolic function and myocardial stiffness[101] and diastolic strain post-AVR,[102] and post-TAVR[103] (Fig. 5). Long-term improvement in diastolic function has been in part attributed to regression of fibrosis with AVR[104] and TAVR.[105] Furthermore, in HCM, diastolic function improves after alcohol septal ablations.[106] However, in cardiac amyloidosis, there is rapid progression of DD in 29% of patients within 1 year, that is associated with new heart failure symptoms.[107] Conversely, treatment of cardiac amyloidosis with chemotherapy is associated with improvement of diastolic function and likely represents an improvement in myocardial disease/mechanics.[108]

In patients with preserved systolic function without significant valvular disease or other cardiomyopathy, there is increasing evidence showing that diastolic function is dynamic[5–7] (Fig. 6). This is clinically relevant because worsening of diastolic function is an independent prognostic marker of heart failure (hazard ratio 1.81)[6] and all-cause mortality (hazard ratio 1.78).[5]

Additionally, change in diastolic function and filling pressures during exercise testing may unmask subclinical DD and could be a more sensitive marker for outcomes.[109] For example, patients with resting grade I DD might exhibit grade II DD after a short time of exercise stress testing, unmasking the cause of cardiac dyspnea and closing the loop. The assessment of E/e' at peak exercise is feasible, correlates with the invasive measurements of LV filling pressures,[110] predicts exercise capacity,[111] and cardiovascular hospitalization independent and incremental to inducible ischemia.[112] The assessment of peak exercise diastolic parameters has become standard at our laboratory.

RIGHT VENTRICULAR DIASTOLIC DYSFUNCTION

Although most studies looked at LV DD, one must not forget the RV. Indeed, recent updates of the echocardiographic guidelines have highlighted the feasibility and importance of RV diastolic function.[113] The prognostic value of RV diastolic function is summarized in Table 6.[38,51,114–117]

STRENGTHS, LIMITATIONS, AND FUTURE DIRECTIONS

Herewith, we have reviewed the prognosis of DD in patients with normal LVEF, various cardiomyopathies, and valvular disease, as well as other cohorts, showing consistently that DD predicts adverse long-term outcomes and might serve as an important noninvasive risk-stratifying tool. Furthermore, we have shown that diastolic function is dynamic and is affected by loading conditions, potentially explained by regression or worsening of fibrosis and other unknown factors. DD can also be unmasked by exercise and other hemodynamic maneuvers. Importantly, worsening of DD is a powerful prognostic marker of all-cause mortality (as strong as worsening systolic dysfunction)[5] and should alert physicians to aggressively modify risk factors.

The assessment of DD by echocardiography can be frustrating, with key indices sometimes yielding discrepant information. In part, this reflects the complex pathophysiology of diastole, with some indices sensitive to delayed LV relaxation (e', mitral propagation velocity, untwisting rate), whereas others reflect compliance of the ventricle in early (E-wave deceleration time) and late (pulmonary vein A-wave reversal) diastole. What is clear from these studies is that an abnormality in any diastolic parameter confers an adverse prognosis, at least in population-based studies, although some parameters carry different weight, particularly restrictive filling pattern. Although translating this to the individual is imprecise, any sign of DD in ostensibly normal individuals should prompt the clinician to seek out modifiable risk factors such as hypertension, diabetes, and ischemia. Screening for DD in the clinical practice setting can help risk stratify patients and should be evaluated prospectively; a cost-effectiveness evaluation is warranted given the potential high cost and limited economic resources.

We acknowledge several limitations. The review and integration of the literature is challenging given the changes in DD

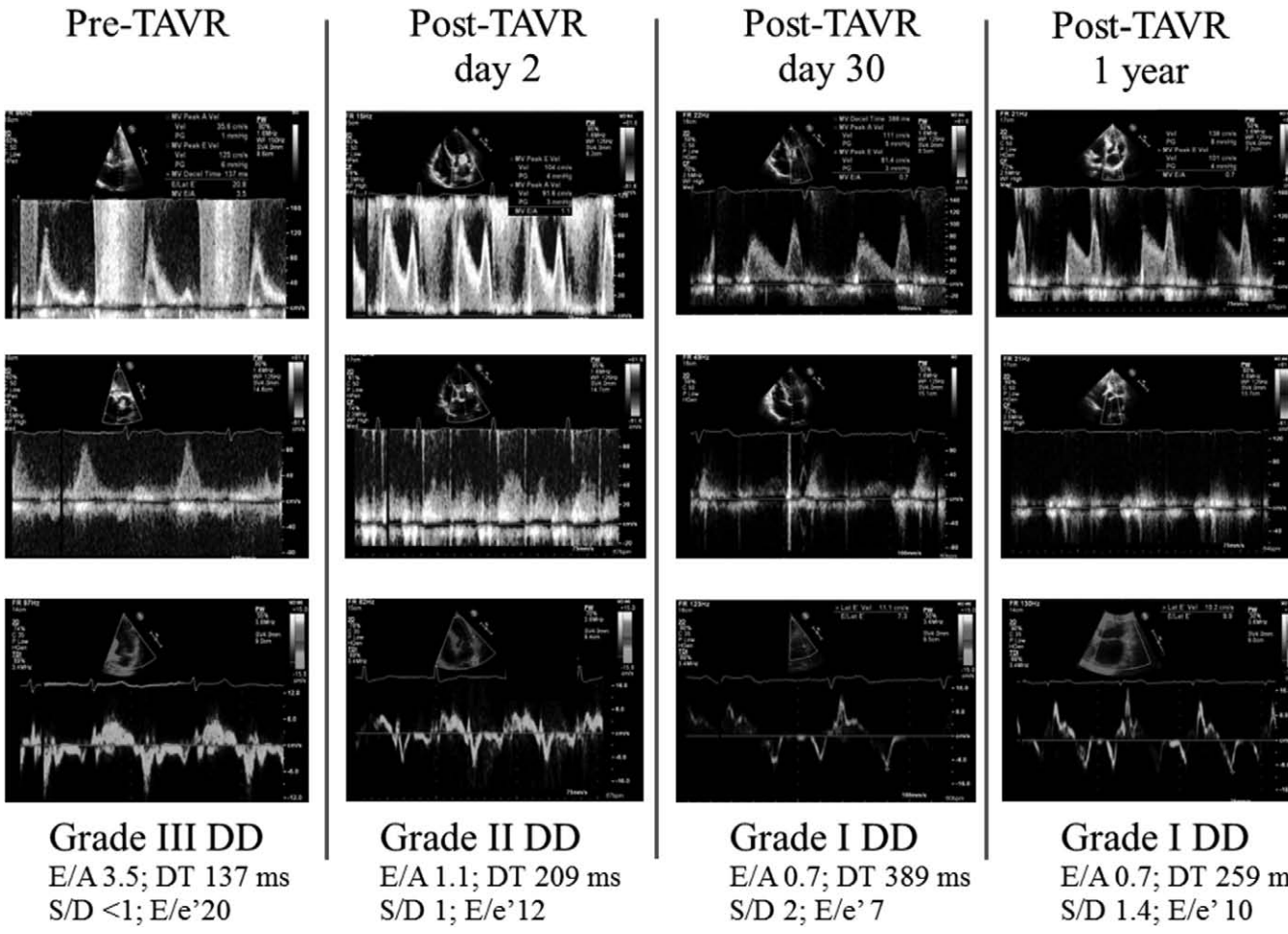

FIGURE 5. Change in diastolic function posttranscatheter aortic valve replacement (TAVR). An 82-year-old patient with grade III diastolic dysfunction (DD) at baseline echocardiography who underwent TAVR. Post-TAVR echocardiogram showed improvement of DD (grade II, day 2), then grade I at 30 days post-TAVR that persisted at 1-year follow-up. The upper, middle, and lower rows illustrate pulse Doppler tracing of mitral inflow, pulmonary vein, and tissue annular velocities, respectively. DT indicates deceleration time

definition and guidelines over the past few decades. Another limitation is that most data were from retrospective or observational studies, with various outcomes and diastolic function markers (some less reliable than others). Also, diastolic function may be ambiguous in a large percentage of patients (approximately 25% in some cohorts).[1,5,6] LV indices of deformation and untwisting are promising, but not yet integrated into DD guidelines. Similarly, advances in cardiac magnetic resonance techniques, such as 4D flow,[58] quantification of blood flow and tissue velocity, diastolic strain, strain rate, twisting, and detection of interstitial fibrosis,[118] may provide new insight into DD.[1] Although cardiac magnetic resonance for DD is feasible,[119] its applicability in daily clinical practice is limited by low temporal resolution, prolonged study times, scarce availability, and high cost.

Information on the myocardial substrate (biopsy or autopsy material) in patients with DD, and genetic and proteomic profiling that might identify those at risk, should be the focus of future research. Besides risk factor modification and addressing comorbidities, there is no tailored therapy for DD, except for potentially promising early results with aldosterone receptor antagonists.[24] Moving forward, we support a uniform integrative multiparametric grading of diastolic function as recommended

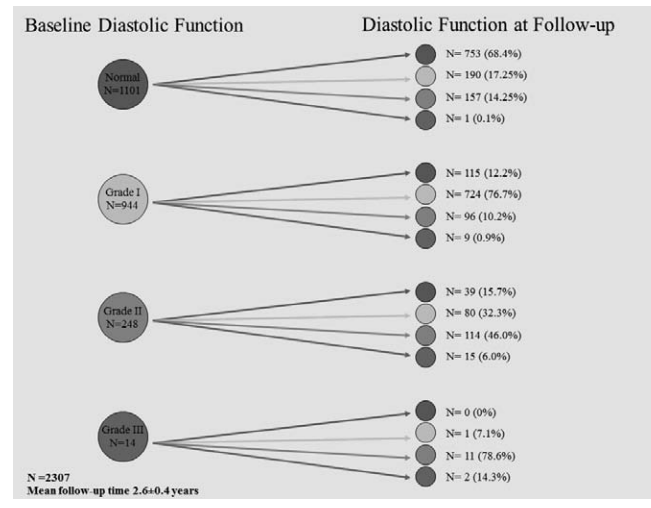

FIGURE 6. Diastolic function: a dynamic process. The figure illustrates the results of three prior studies[5–7] evaluating the change of baseline diastolic function on follow-up echocardiography.

TABLE 6. Prognostic Value of Right Ventricular Diastolic Dysfunction

Reference	N	Cohort	Diastology Parameter	Outcome	Results
Meluzin et al[38]	177	ICM, NICM	Tricuspid e': 8.9 cm/s	Cardiac death or nonfatal events	HR 0.78; $P = 0.005$
Yu et al[114]	105	LVEF <50%	Restrictive filling	All-cause death. Heart failure hospitalization/ unstable angina	All-cause death: P = NS. Hospitalization/unstable angina: $P = 0.016$
Pagourelias et al[115]	386	HCM	Right ventricle E/e' 6.9	Cardiac death	Area under curve 0.85; $P = 0.02$
Tallaj et al[117]	250	Heart transplant	Right atrial pressure/ stroke volume	Cardiac death	Relative risk 2.7; $P = 0.02$ (6 weeks). Relative risk 3.6; $P = 0.002$ (1 yr)
Efthimiadis et al[51]	45	Thalassemia	Restrictive filling	All-cause death	Unadjusted 15-yr survival: 34% vs. 82%; $P = 0.0013$

HCM indicates hypertrophic cardiomyopathy; HR, hazard ratio; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; LVEF, left ventricular ejection fraction.

by the guidelines, but suggest recording the individual indices as well, because they are not interchangeable. Furthermore, the echocardiography laboratory accreditation require standardized measurement and reporting of diastolic function with minimal inter- and intraobserver variability. Finally, core laboratories should advise researchers to look at DD as a primary or surrogate endpoint when evaluating new cardiovascular medications or devices.

CONCLUSION

In conclusion, the evaluation of diastolic function has become an integral part of a full echocardiographic study and is recommended by the current guidelines. Baseline LV and RV diastolic functions are independent predictors of outcomes in different cohorts. Diastolic function, however, is not static, and worsening of DD is also a predictor of heart failure and death. The evaluation and integration of baseline and follow-up diastolic function should become part of routine clinical practice.

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