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Utility of Doppler Echocardiography and Tissue Doppler Imaging in the Estimation of Diastolic Function in Heart Failure With Normal Ejection Fraction
A Comparative Doppler-Conductance Catheterization Study

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Background—Various conventional and tissue Doppler echocardiographic indexes were compared with pressure–volume loop analysis to assess their accuracy in detecting left ventricular (LV) diastolic dysfunction in patients with heart failure with normal ejection fraction (HFNEF).

Methods and Results—Diastolic dysfunction was confirmed by pressure–volume loop analysis obtained by conductance catheter in 43 patients (19 men) with HFNEF. Their Doppler indexes were compared with those of 12 control patients without heart failure symptoms and with normal ejection fraction. Invasively measured indexes for diastolic relaxation (τ, dP/dt_{min}), LV end-diastolic pressure, and LV end-diastolic pressure–volume relationship (stiffness, b [dP/dV], and stiffness constant, β) were correlated with several conventional mitral flow and tissue Doppler imaging indexes. Conventional Doppler indexes correlated moderately with the degree of LV relaxation index, τ (E/A: $r=-0.36$, $P=0.013$; isovolumic relaxation time: $r=0.31$, $P=0.040$) and b (deceleration time: $r=0.39$, $P=0.012$) but not with β, in contrast to the tissue Doppler imaging indexes E'/A'$_{lateral}$ ($r=-0.37$, $P=0.008$) and E/E'$_{lateral}$ ($r=0.53$, $P<0.001$). Diastolic dysfunction was detected in 70% of the HFNEF patients by mitral flow Doppler but in 81% and 86% by E'/A'$_{lateral}$, and E/E'$_{lateral}$, respectively.

Conclusions—Of all echocardiographic parameters investigated, the LV filling index E/E'$_{lateral}$ was identified as the best index to detect diastolic dysfunction in HFNEF in which the diagnosis of diastolic dysfunction was confirmed by conductance catheter analysis. We recommend its use as an essential tool for noninvasive diagnostics of diastolic function in patients with HFNEF. (***Circulation***. 2007;116:&NA;-.)

Key Words: diastole ■ heart failure ■ hemodynamics ■ echocardiography ■ hypertension ■ diagnosis

Heart failure is a common cardiovascular syndrome that may occur in conjunction with either normal or abnormal left ventricular (LV) ejection fraction (EF). Patients with reduced EF have predominantly systolic dysfunction, whereas those with heart failure symptoms despite normal EF (HFNEF) are thought to have predominantly anomalies of active relaxation and passive stiffness that lead to impaired diastolic filling.[1] Diastolic dysfunction in patients with HFNEF is increasingly recognized,[2–8] but its clinical diagnosis remains challenging.[9,10] HFNEF cannot be diagnosed from history, physical examination, ECG, or chest radiography.[11] The need for objective evidence of diastolic dysfunction in HFNEF has been emphasized,[3,5,7,12–14] but debate continues on the definition and diagnostic approach. It has been pointed out that mitral flow Doppler alone, with its 40% to 70%

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Clinical Perspective p ●●●

specificity, cannot reliably detect diastolic dysfunction in HFNEF.[15–17] Tissue Doppler imaging (TDI), including the transmitral flow velocity to annular velocity ratio (E/E' index),[16,18] which measures myocardial velocities during the cardiac cycle, is considered more reliable for diagnosing diastolic dysfunction. Oh et al[19] proposed comprehensive Doppler echocardiography with color flow or TDI as the most practical and reliable method for either confirming or excluding diastolic dysfunction in HFNEF. In contrast, Maurer et al[20] recently argued that Doppler-derived diastolic parameters do not provide specific information on intrinsic passive diastolic properties and thus that diastolic dysfunction

cannot be diagnosed by Doppler echocardiography. Invasive measurement of pressure–volume (PV) relationships with a conductance catheter system is generally considered most accurate for characterizing diastolic cardiac function.[21] It allows direct detection of LV relaxation abnormalities and passive LV stiffness characterized by a change in diastolic LV pressure relative to diastolic LV volume. Because it has not yet been clarified which echocardiographic method is the most accurate for diagnosing diastolic dysfunction in patients with HFNEF, we performed a clinical study to evaluate conventional and TDI echocardiographic diastolic indexes in HFNEF in which diastolic dysfunction was directly proven by conductance catheter analysis.

Methods

Patient Population

Conventional Doppler and TDI echocardiographic indexes were correlated with invasively determined indexes for diastolic function in 43 patients admitted to our unit between 2003 and 2006 with HFNEF in whom diastolic dysfunction had been confirmed by PV analysis obtained by a conductance catheter system. They suffered from dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and/or exercise intolerance, which was quantified by the 6-minute walk test,[22] bicycle ergometry, and N-terminal probrain natriuretic peptide plasma levels (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). These patients were compared with 12 control patients who had been admitted for evaluation of chest discomfort with no symptoms of heart failure and with normal EF. Atrial fibrillation, heart valve disease, significant coronary artery disease, and lung diseases had been excluded in both groups. All patients investigated gave written informed consent for invasive diagnostic procedures. The research protocol was approved by the local institutional review committee.

Echocardiography

Three to 5 hours after the PV-loop measurement, echocardiography studies were performed by 2 independent investigators who were blinded to all information derived by the invasive analysis.

Conventional Doppler Measurements

Mitral and pulmonary venous Doppler flow velocities were recorded in the apical 4-chamber view with a VingMed System FiVe (GE Healthcare, Chalfont St Giles, UK) as previously described.[23] Mitral inflow measurements included peak early (E) and peak late (A) flow velocities, the E/A ratio, the deceleration time of early mitral flow velocity (DT), and the isovolumic relaxation time (IVRT) at rest and during the Valsalva maneuver. Pulmonary venous flow was characterized by peak systolic (S), diastolic (D), and atrial reversal (Ar) velocities; the systolic filling fraction (S/D); and the time difference between A and the duration of atrial reverse flow (A−Ar). The LV Doppler chamber stiffness (K) was calculated as previously described[24,25]: $K=[70/(DT-20)^2]$. Data were adjusted for age and heart rate according to guidelines.[9,10]

Chamber dimensions were evaluated using standard procedures, including LV mass index[26] and left atrial (LA) volume index.[27] End-diastolic wall stress was calculated from hemodynamic and echocardiographic data as previously described.[28]

Tissue Doppler Measurements and LV Filling Index

The TDI of the mitral annulus movement was obtained from the apical 4-chamber view. A 1.5-mm sample volume was placed sequentially at the lateral and septal annular sites.[29] Analysis was performed for the systolic (S') and the early (E') and late (A') diastolic peak velocities. The ratio of early to late annular velocity (E'/A') was determined as a parameter of diastolic function, as well as the LV filling index, by the ratio of transmitral flow velocity to annular velocity (E/E') and the time interval between the onset of mitral inflow and early diastolic velocity ($T_{E'-E}$).[30] Adequate mitral and TDI signals were recorded in all patients, whereas pulmonary venous flow signals were suitable for analysis in only 60% of the cases.

PV Measurements by Conductance Catheter Method

The conductance catheter allows continuous online measurements of LV pressure and volume.[31] A 7F combined pressure-conductance catheter (CD Leycom, Zoetermeer, the Netherlands) was introduced retrogradely into the LV by standard methods and connected to a cardiac function laboratory (CD Leycom) for acquisition of the LV volume and pressure and ECG. Total LV volume was calibrated with thermodilution and hypertonic saline dilution.[32] Hemodynamic indexes were obtained from steady-state PV loops at sinus rhythm. PV relationships were derived from PV loops recorded during preload reduction by temporary balloon occlusion (NuMED, Hopkinton, NY) of the inferior vena cava.[31] Although it has to be mentioned that transient vena cava occlusion can result in short-term alterations in sympathetic tone and LV constraint, which can influence the PV relationship, this technique belongs to an established method comparing LV stiffness in control patients with that in heart failure patients. Cardiac performance was assessed by heart rate, stroke volume, end-diastolic volume, end-systolic volume, cardiac output, and stroke work. Systolic load-dependent LV function was determined by the EF, end-systolic pressure, maximum rate of pressure change (dP/dt_{max}), and load-independent LV function by the linear slope of the end-systolic PV relationship, defined as end-systolic elastance (E_{ES}). Diastolic load-dependent LV function was assessed by the LV end-diastolic pressure (LVEDP), LV minimal pressure (LVP_{min}), isovolumetric relaxation time constant (τ), minimal rate of LV pressure change (dP/dt_{min}), and maximum rate of LV filling (dV/dt_{max}). We calculated the average slope of the end-diastolic PV relationship (dP/dV) to determine functional LV chamber stiffness (LV stiffness, b) and the exponential curve fit to the diastolic LV PV points to determine how rapidly stiffness (dP/dV) increases with increasing pressure (LV stiffness constant, β). Thus, the end-diastolic PV relationship was fitted with an exponential relation, $LVEDP=c \exp(\beta LVEDV)$, to obtain the chamber stiffness constant, β, and the curve-fitting constant, c, as load-independent indexes of diastolic function.

Diastolic dysfunction was considered present if τ was prolonged ($\tau \geq 48$ ms), LVEDP was elevated (≥ 12 mm Hg), and/or β (≥ 0.015 mL^{-1}) and/or b (≥ 0.19 mm Hg/mL) were increased in clinically symptomatic patients despite normal EF. These cutoff values were defined as values corresponding to the 90th percentiles of our control patients.

Statistical Analysis

SPSS software (version 13.0, SPSS Inc, Chicago, Ill) was used for statistical analysis. Descriptive characteristics of continuous variables were expressed as median values with the first and third quartiles.

In the first step, the patients were classified according to the filling pattern measured with mitral flow Doppler. Furthermore, patient subgroups with abnormal[9] single Doppler parameters were defined and compared with control subjects (Figure 1). The proportion of detected diastolic dysfunction was calculated for single Doppler parameters or their combinations. Two-sample comparison between subgroups was performed by ANOVA if variables were normally distributed and by the Mann-Whitney U test if the data were not normally distributed. Categorical data were compared by use of the χ^2 test. In the second step, correlation analyses between echocardiographic and PV-loop diastolic indexes were provided using Pearson correlation coefficients. In addition, comparisons between HFNEF patients and control subjects were performed with ANOVA if variables were normally distributed, the Mann-Whitney U test if the data were not normally distributed, and the χ^2 test for categorical
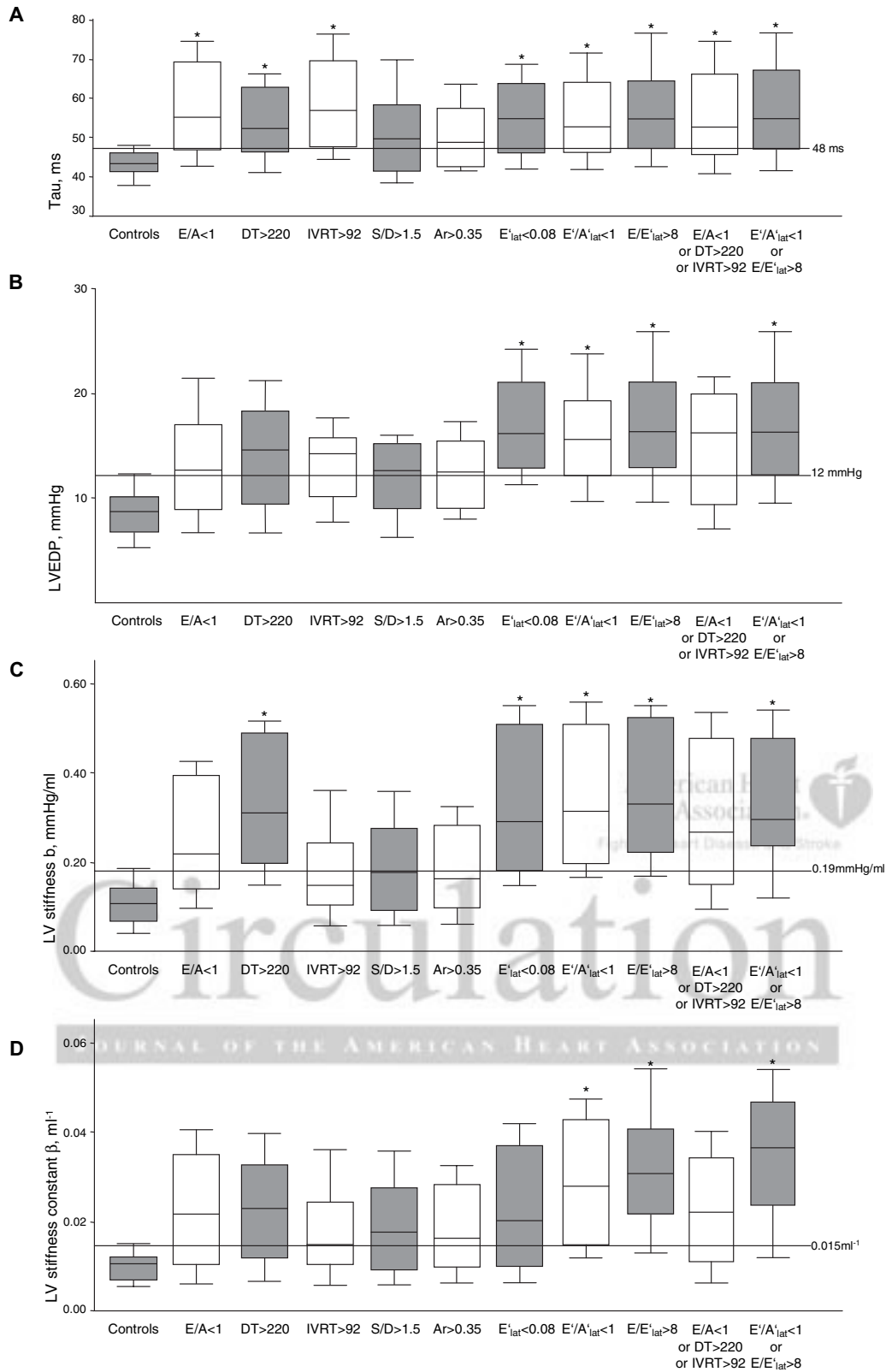
Figure 1. Comparison of subgroups with pathological conventional Doppler and TDI age-adjusted parameters related to diastolic dysfunction: E/A <1, DT >220/280 ms, IVRT >92/100 ms, S/D >1.5/2.5, Ar >0.35 m/s, E'<0.08 m/s, E'/A'$_{lat}$ <1, E/E'$_{lat}$ >8, and the combinations E/AorDTorIVRT and E'/A'$_{lat}$orE/E'$_{lat}$, with regard to the indexes determined by PV-loop analysis. A, τ, indicating that E/A, DT, IVRT, E'$_{lat}$, E'/A'$_{lat}$, E/E'$_{lat}$, E/AorDTorIVRT and E'/A'$_{lat}$orE/E'$_{lat}$ are significantly impaired in patients with prolonged τ. B, LVEDP, indicating that E'$_{lat}$, E'/A'$_{lat}$, and E/E'$_{lat}$ are significantly impaired in patients with elevated LVEDP. C, LV stiffness, b, indicating that DT, E'$_{lat}$, E'/A'$_{lat}$, E/E'$_{lat}$, and E'/A'$_{lat}$orE/E'$_{lat}$ are significantly impaired in patients with increased b. D, LV stiffness constant β, indicating that only TDI (E'/A'$_{lat}$), E/E'$_{lat}$ and E'/A'$_{lat}$ or E/E'$_{lat}$ are significantly impaired in patients with increased LV stiffness. The lines represent cutoff values: τ, 48 ms; LVEDP, 12 mm Hg; b, 0.19 mm Hg/mL; and β, 0.015 mL^{-1}. *$P<0.05$.

TABLE 1.   Patient Characteristics

Demographics:	Controls (n=12)	HFNEF (n=43)	P
Women/men, n (%)	4 (33)/8 (67)	24 (56)/19 (44)	0.205*
Age, y	50 (41–54)	54 (43–60)	0.181
NYHA class II/III, n (%)	0 (0)/0 (0)	29 (67)/14 (33)	…
Six-min walk test, m	503 (431–551)	326 (260–394)	<0.001
Bicycle exercise level, W	175 (150–200)	111 (75–125)	<0.001
NT-proBNP, pg/mL	40 (12–70)	156 (87–231)	<0.001†
BMI, kg/m^2	23.9 (21.7–27.3)	27.3 (23.3–32.7)	0.073†
Heart dimensions			
LA parasternal, mm	35 (31–37)	39 (33–44)	0.123
LAVI, mL/m^2	17.7 (14.5–22.9)	27.1 (20.2–33.1)	0.009
LVEDD, mm	50 (45–51)	49 (45–54)	0.553
Septum, mm	9.0 (8.0–10.5)	12.0 (11.0–13.5)	<0.001
Posterior wall, mm	9.0 (8.0–10.0)	11.5 (10.5–12.5)	<0.001
LVMI, g/m^2	89 (78–98)	127 (105–139)	<0.001
LVEDVI, mL/m^2	86 (65–95)	78 (63–94)	0.466
LVMV, g/mL	0.94 (0.82–1.38)	1.52 (1.17–2.02)	<0.001
EDWS, kdyne/cm^2	15.6 (11.7–21.5)	25.8 (20.3–34.7)	<0.001
Concomitant disease, n (%)			
Art. Hypertension	0 (0)	34 (79)	…
Diabetes mellitus	0 (0)	5 (12)	…
Obesity	0 (0)	7 (16)	…
Hyperlipoproteinemia	5 (42)	19 (44)	0.488*
Angina pectoris, atypical	6 (50)	16 (37)	0.134*
Smoker	3 (25)	12 (27)	0.193*

NYHA indicates New York Heart Association class; NT-BNP, N-terminal probrain natriuretic peptide; BMI, body mass index; PCWP, pulmonary capillary wedge pressure; LAVI, LA volume index; LVEDD, LV end-diastolic diameter; LVMI, LV mass index; LVEDVI, LV end-diastolic volume index; LVMV, ratio of left ventricular mass to volume; and EDWS, end-diastolic wall stress. Values are median (25%–75% quartile).

*χ^2 test.

†Mann-Whitney *U* test.

data. On the basis of the results of step 2, candidate diagnostic TDI variables were selected. Linear regression analyses were performed to determine the exact relations between each of these potentially clinically relevant TDI candidate indexes and LV stiffness. Furthermore, to compare the sensitivity and specificity of these selected indexes, receiver-operating characteristics (ROC) curve analysis was used.

A value of $P<0.05$ was considered statistically significant in all analyses. In the intergroup comparisons, probability values should be regarded as descriptive.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Population characteristics, heart dimensions, and concomitant diseases are presented in Table 1. The study included 28 women and 27 men with a median age of 51 years (range, 43 to 59 years). HFNEF patients had arterial hypertension (n=34) and/or diabetes mellitus (n=5) and/or were obese (n=7). All HFNEF patients showed increased New York Heart Association classifications, increased N-terminal pro-brain natriuretic peptide, a reduction in the 6-minute walk test, and reduced bicycle ergometry levels. No difference existed between groups with respect to age, and BMI tended to be higher in patients with HFNEF (Table 1).

Heart Dimensions and LV Diastolic Properties

All investigated patients showed normal LV end-diastolic volume index. LV mass index and ratio of LV mass to volume correlated with τ ($r=0.45$, $P=0.004$; $r=0.42$, $P=0.001$), LVEDP ($r=0.48$, $P<0.001$; $r=0.49$, $P<0.001$), b ($r=0.37$, $P=0.009$; $r=0.48$, $P=0.001$), and β ($r=0.35$, $P=0.012$; $r=0.49$, $P<0.001$). Compared with control subjects, HFNEF patients had a significantly increased wall thickness (septum, 33%; posterior wall, 27%; both $P<0.001$), LV mass index (43%), and ratio of LV mass to volume (60%; both $P<0.001$). In HFNEF patients, wall stress was increased by 65% and correlated with b ($r=0.43$, $P=0.002$), β, E/E'$_{lat}$, and τ ($r=0.63$, $r=0.45$ and $r=0.61$, respectively; $P<0.001$). The LA diameter was higher and likewise LA volume index was significantly increased in HFNEF patients compared with our control subjects (53%; $P=0.009$) (Table 1). LA volume index correlated with LVEDP, b, and β ($r=0.40$,

TABLE 2.   LV Systolic and Diastolic Parameters in Patients With HFNEF Compared With Control Subjects

	Control Subjects (n=12)	HFNEF Patients (n=43)	P*
Cardiac performance			
HR, bpm	75 (68–82)	71 (63–81)	0.392
EF, %	65 (60–71)	64 (58–74)	0.724
SV, mL	108 (88–119)	94 (80–114)	0.096
ESV, mL	59 (43–83)	58 (37–83)	0.739
EDV, mL	165 (123–198)	152 (115–182)	0.236
CO, L/min	7.9 (6.7–9.6)	7.0 (5.4–9.1)	0.083
SW, mm Hg · mL	11.16 (8.30–13.69)	9.54 (7.62–10.94)	0.076
Systolic indexes			
ESP, mm Hg	115 (110–118)	140 (116–154)	0.008
dP/dt$_{max}$, mm Hg/s	1491 (1368–1726)	1436 (1235–1691)	0.096
E$_{ES}$, mm Hg/mL	1.2 (1.0–1.4)	1.3 (1.2–1.6)	0.053
Diastolic indexes			
LVEDP,* mm Hg	7.5 (5.8–9.7)	15.4 (12.0–18.9)	<0.001
LVP$_{min}$, mm Hg	2.0 (0.9–3.2)	6.5 (4.3–9.4)	<0.001
dP/dt$_{min}$, mm Hg/s	−1869 (−1961−−1674)	−1678 (−1969−−1466)	0.289
τ†, ms	43 (42–46)	54 (48–65)	<0.001‡
dV/dt$_{max}$, mL/s	1124 (1023–1397)	751 (645–1071)	0.043
β*, mL^{-1}/mL	0.010 (0.008–0.012)	0.029 (0.016–0.037)	<0.001
b*, mm Hg/ml	0.15 (0.12–0.17)	0.30 (0.21–0.44)	<0.001
c, mm Hg	2.7 (2.1–3.1)	1.2 (0.9–1.7)	0.004

HR indicates heart rate; SV, stoke volume; ESV, end-systolic volume; EDV, end-diastolic volume; CO, cardiac output; SW, stroke volume; ESP, end-systolic pressure; LVP$_{min}$, minimal LV pressure; dV/dt$_{max}$, maximal LV filling rate; dPdV, slope of end-diastolic pressure–volume relationship; β, stiffness constant; b, LV stiffness; and c, curve-fitting constant. Values are median (25%–75% quartile).

*Descriptive probability values.

†Variables defined as diagnostic criteria.

‡Mann-Whitney U test.

$P=0.003$; $r=0.29$, $P=0.043$; $r=0.26$, $P=0.049$, respectively).

Cardiac Performance, Systolic Function, and Left Ventricular Contractility

According to PV-loop analysis, no significant difference existed between HFNEF patients and control subjects in heart rate, end-diastolic volume, end-systolic volume, stroke volume, cardiac output, stroke work, EF, and LV contractility (E$_{ES}$, dP/dt$_{max}$) (Table 2).

Diastolic Function of the Left Ventricle

Table 2 presents diastolic indexes provided by conductance catheter-derived PV-loop analysis. HFNEF patients showed a prolonged τ (25%; $P<0.001$) compared with control patients, whereas dP/dt$_{min}$ did not differ significantly (10%; $P=0.289$). Their LVEDP, b, and β were all significantly increased by 105%, 100%, and 190%, respectively. The curve-fitting constant (c) and the maximum rate of LV filling (dV/dt$_{max}$) were decreased by 66% ($P=0.004$) and 33% ($P=0.043$), respectively (Table 2).

Conventional Doppler Echocardiography Versus PV-Loop Analysis

We classified HFNEF patients according to the filling pattern of mitral flow Doppler as normal or indicating progressively increased diastolic dysfunction if one of the mitral flow indexes was abnormal[9] (E/A, DT, IVRT) at rest and during the Valsalva maneuver. Analysis of diastolic filling pattern indicated diastolic dysfunction in 30 of 43 HFNEF patients (70%). These patients showed significantly increased τ compared with control subjects (50 ms [46 to 63 ms] versus 43 ms [42 to 46 ms]; $P=0.003$), but LVEDP (12 mm Hg [8.8 to 18.6 mm Hg] versus 7.5 mm Hg [5.8 to 9.7 mm Hg]; $P=0.069$), b (0.22 mm Hg/mL [0.15 to 0.35 mm Hg/mL] versus 0.15 mm Hg/mL [0.12 to 0.17 mm Hg/mL]; $P=0.057$), and β (0.019 mL^{-1} [0.011 to 0.034 mL^{-1}] versus 0.010 mL^{-1} [0.008 to 0.012 mL^{-1}]; $P=0.089$) did not reach statistical significance (Figure 1).

Further subgroup analyses were performed to compare single mitral flow with PV-loop parameters in HFNEF patients with impaired relaxation (n=38) and pseudonormal filling pattern (n=5) separately. Flow Doppler indexes of the

TABLE 3. Diastolic Indices of Conventional and TDI Echocardiography

	Control Subjects (n=12)	HFNEF Patients (n=43)	P
Mitral flow*			
E, m/s	0.75 (0.62–0.83)	0.81 (0.70–0.93)	0.162
A, m/s	0.61 (0.46–0.69)	0.83 (0.73–0.99)	<0.001†
E/A	1.23 (1.04–1.43)	0.98 (0.82–1.19)	0.012
DT, ms	205 (181–217)	242 (206–256)	0.026
IVRT, ms	88 (84–90)	98 (87–109)	0.094
K	0.14 (0.11–0.17)	0.16(0.10–0.19)	0.241†
Pulmonary vein			
S, m/s	0.54 (0.37–0.71)	0.64 (0.53–0.77)	0.414†
D, m/s	0.64 (0.57–0.76)	0.55 (0.45–0.68)	0.110
S/D	0.86 (0.59–1.03)	1.21 (0.89–1.58)	0.030
Ar, m/s	0.36 (0.30–0.38)	0.38 (0.32–0.40)	0.274†
Ar duration, ms	95 (67–122)	128 (116–158)	0.064
Ar−A duration, ms	−31 (−38−−22)	−10 (−30–10)	0.080
Tissue Doppler			
S'$_{lateral}$, m/s	0.09 (0.07–0.12)	0.08 (0.06–0.11)	0.721
E'$_{lateral}$, m/s	0.12 (0.09–0.14)	0.07 (0.05–0.10)	<0.001
A'$_{lateral}$, m/s	0.07 (0.06–0.12)	0.09 (0.06–0.11)	0.521
E'/A'$_{lateral}$	1.44 (1.10–2.12)	0.92 (0.65–1.30)	0.008
E/E'$_{lateral}$	6.40 (4.83–7.76)	11.47 (8.56–14.10)	<0.001
$T_{E-E'\ lateral}$, ms	30 (26–37)	32 (28–38)	0.673†
S'$_{septal}$, m/s	0.07 (0.05–0.09)	0.07 (0.04–0.08)	0.584
E'$_{septal}$, m/s	0.09 (0.06–0.11)	0.07 (0.05–0.10)	0.209
A'$_{septal}$, m/s	0.07 (0.05–0.08)	0.07 (0.06–0.09)	0.855
E'/A'$_{septal}$	1.13 (0.80–1.40)	0.90 (0.67–1.25)	0.188†
E/E'$_{septal}$	9.55 (7.06–12.14)	12.35 (8.33–16.33)	0.099†
$T_{E-E'\ septal}$, ms	28 (25–33)	29 (25–35)	0.883

See text for an explanation of symbols. Values are expressed as median (25%–75% quartile).
*Pseudonormal filling pattern excluded.
†Mann-Whitney U test.

former are summarized in Table 3, showing decreased E/A ratio and increased A wave, DT, and S/D ratio.

Figure 1 demonstrates the comparison of patient subgroups with abnormal Doppler diastolic parameters with regard to the indexes determined by PV-loop analysis. All patients with abnormal E/A ratio (n=22, 50%) showed a prolonged τ (54 ms [47 to 70 ms]; $P<0.001$; Figure 1A) compared with control subjects, whereas the increases in b, β, and LVEDP did not reach statistical significance (Figure 1B through 1D). Patients with abnormal IVRT (n=19, 44%) or DT (n=21, 49%) showed significant prolongation of τ (IVRT, 57 ms [48 to 71 ms], $P<0.001$; DT, 52 ms [47 to 63 ms]; $P=0.003$) compared with control subjects (Figure 1A). Although patients with a prolonged DT (n=21, 49%) had an increase in b (0.30 mm Hg/mL [0.20 to 0.55 mm Hg/mL]; $P<0.01$; Figure 1C), they did not show an increase in β compared with control subjects (Figure 1D). In conclusion, the single mitral flow parameter alone diagnosed diastolic dysfunction in only about half of HFNEF patients.

However, mitral flow analysis correctly diagnosed all 5 pseudonormal patients. HFNEF patients with pseudonormal filling pattern showed elevated LVEDP (18.7 mm Hg [14 to 25 mm Hg]; $P<0.001$), prolonged τ (48 ms [43 to 52 ms]; $P<0.05$); increased b (0.29 mm Hg/mL [0.21 to 0.30 mm Hg/mL]; $P<0.001$), and increased β (0.027 mL^{-1} [0.017 to 0.037 mL^{-1}]; $P<0.001$) compared with control subjects.

The pulmonary venous flow examination yielded similar findings, taking into account that only 31 patients (23 HFNEF patients, 8 control subjects) had a signal adequate for analysis. Twelve of 23 HFNEF patients (52%) showed a pathological S/D, Ar, or A−Ar. When E/A criteria were additionally met, 17 of 23 HFNEF patients (73%) with diastolic dysfunction were detected. HFNEF patients with LV diastolic dysfunction determined by PV-loop analysis did not show an elevated Doppler chamber stiffness constant, K (Table 3).

TDI Versus PV-Loop Analysis

TDI measurements are listed in Table 3. The peak systolic velocity S' in HFNEF patients did not differ from that in control subjects. The E' and the E'/A' ratio measured at the lateral mitral annulus were significantly decreased in HFNEF

patients, in contrast to the septal side. Of 43 HFNEF patients, 35 (81%) had at least 1 abnormal TDI value (E'/A'$_{lat}$ <1 or E'$_{lat}$ <0.08 m/s). Patients with an E'/A'$_{lat}$ <1 evidenced significant elevation of b (0.30 mm Hg/mL [0.20 to 0.50 mm Hg/mL]; P<0.001) and β (0.028 mL^{-1} [0.015 to 0.043 mL^{-1}]; P<0.001), whereas E'$_{lat}$ <0.08 m/s alone showed increased b (0.27 mm Hg/mL [0.19 to 0.50 mm Hg/mL]; P<0.001) but not β (Figure 1C and 1D). Furthermore, these patients had an elevated LVEDP (E'/A'$_{lat}$ <1, 15 mm Hg [12 to 19 mm Hg]; E'$_{lat}$ <0.08 m/s, 16 mm Hg [13 to 21 mm Hg]) and a prolonged τ (E'/A'$_{lat}$ <1, 52 m/s [47 to 65 ms]; E'$_{lat}$ <0.08 m/s, 55 ms [47 to 58 ms]; Figure 1A and 1B).

LV Filling Index E/E' and Relaxation Index T$_{E'-E}$ Versus PV-Loop Analysis

Patients with HFNEF showed a significantly increased filling index E/E'$_{lat}$ (79%; P<0.001) compared with control subjects (Table 3). An E/E' >8 was found in 37 of HFNEF patients (86%), which showed a significant increase in all diastolic indexes compared with control subjects (Figure 1A through 1D): b (0.31 [0.22 to 0.51]; P<0.001), β (0.030 mL^{-1}; [0.020 to 0.041 mL^{-1}]; P<0.001), an elevated LVEDP (16 mm Hg [13 to 21 mm Hg]; P<0.001), and prolonged τ (55 [48 to 65]; P<0.001). No differences existed between the 2 groups with regard to T$_{E'-E}$. Patients with an impaired LV relaxation tended to have a prolonged T$_{E'-E}$, but the difference did not reach statistical significance.

Correlations Between Echocardiographic and PV-Loop Diastolic Parameters: ROC Curve Analysis

The clinic relevant correlation coefficients are summarized in Table 4. In all investigated patients, the flow Doppler parameters E/A, IVRT, and DT correlated with τ, whereas only DT and its derivate Doppler chamber stiffness, K, were related to LVEDP and b. dP/dt$_{min}$ correlated only with IVRT and E/A. However, neither E/A nor any other of the mitral or pulmonary flow parameters, including ln(K), correlated significantly with β. In contrast, TDI indexes (E'$_{lat}$, E'/A'$_{lat}$, E/E'$_{lat}$) correlated not only with LVEDP but with both b and β, whereas E'$_{lat}$ and E/E'$_{lat}$ also were related to τ, and neither of those correlated with dP/dt$_{min}$. Thus, the best correlation with LVEDP, b, and β showed E/E'$_{lat}$. Linear regression analysis revealed a positive trend of E/E'$_{lat}$ with b (b=0.016×E'/E'$_{lat}$+0.10) and β (β=0.002×E/E'$_{lat}$+0.008) (Figure 2). Furthermore, the same analysis conducted in the group of HFNEF patients which showed similar relations.

A ROC curve analysis revealed a higher area under the curve for E/E'$_{lat}$ (0.907) compared with E'/A'$_{lat}$ (0.778; Figure 3). A statistical comparison of the ROC curves based on the method suggested by Hanley and McNeil[33] yields a value of P=0.073. Hence, the differences between the ROC curves for E'/A'$_{lat}$ and E/E'$_{lat}$ are not statistically significant in our study. The optimum cut points suggested by the ROC curves (E/E'$_{lat}$ ≥8.0 versus <8.0; E'/A'$_{lat}$, <1.0 versus ≥1.0) correspond to a sensitivity of 83% (E'/A'$_{lat}$, 67%; P=0.290) and a specificity of 92% (E'/A'$_{lat}$, 84%; P=0.030). Hence, the ROC curves

TABLE 4. Correlation of Mitral Flow and Tissue Doppler Indexes With PV-loop Indexes of Diastolic Function

	τ	LVEDP	b	β
Mitral flow Doppler				
E/A*				
r	−0.36	−0.04	−0.24	−0.22
P	0.013	0.750	0.092	0.123
IVRT*				
r	0.31	−0.11	−0.11	−0.14
P	0.040	0.479	0.086	0.370
DT*				
r	0.28	0.30	0.39	0.09
P	0.051	0.034	0.012	0.558
ln(K)*				
r	−0.27	−0.28	−0.36	−0.18
P	0.050	0.071	0.010	0.220
Tissue Doppler				
E'$_{lateral}$				
r	−0.33	−0.50	−0.39	−0.41
P	0.014	0.001	0.005	0.002
E'/A'$_{lateral}$				
r	−0.24	−0.42	−0.31	−0.37
P	0.082	0.004	0.026	0.008
E/E'$_{lateral}$				
r	0.34	0.71	0.46	0.53
P	0.013	0.001	0.001	0.001

See text for an explanation of symbols.
*Pseudonormal filling pattern excluded.

provide some indication that E/E'$_{lat}$ could be superior with respect to specificity for detecting diastolic dysfunction. This finding, however, should be verified in future analyses with larger sample size.

Discussion

Despite widespread use of echocardiography to evaluate diastolic function, the present study is the first to investigate the accuracy of several echocardiographic Doppler techniques in detecting diastolic dysfunction in HFNEF by direct comparison with invasive PV-loop data. In our study population, no diastolic index of conventional Doppler echocardiography alone was sufficient to make the correct diagnosis. These indexes correlated only weakly with diastolic relaxation anomalies and not at all with the degree of LV stiffness. On the other hand, TDI investigations and the LV filling index E/E'$_{lat}$ were well suited for detecting invasively proven diastolic dysfunction in HFNEF patients.

PV-Loop Analysis and Heart Dimensions

Disturbed LV stiffness is considered a cardinal mechanism of diastolic dysfunction, although 80% of patients with diastolic dysfunction also show signs of impaired LV relaxation.[1] Similarly, although our HFNEF patients, all of whom were stable at rest, showed an only moderately increased LVEDP
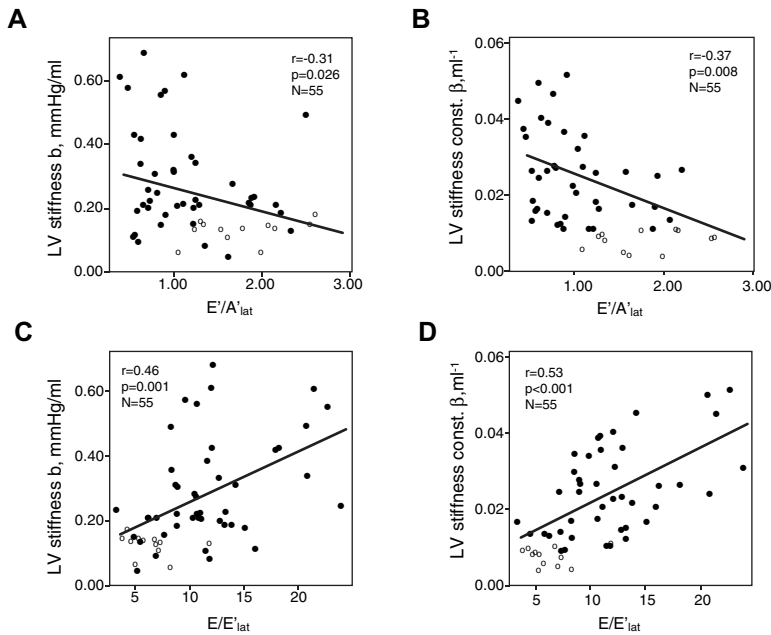
Figure 2. Linear regression between the LV stiffness (b and β) and tissue Doppler indexes. Blank spots represent controls. Linear regression lines, E'/A'_{lat}: b$=-0.08$ (95% confidence interval, -0.15 to -0.02)$\times E'/A'_{lat}+0.37$, $r=-0.31$, $P=0.026$; and $\beta=-0.008$ (95% confidence interval, -0.014 to -0.002)$\times E'/A'_{lat}+0.032$, $r=-0.37$, $P=0.008$; E/E'_{lat}: b$=0.016$ (95% confidence interval, 0.008 to 0.023)$\times E/E'_{lat}+0.10$, $r=0.46$, $P<0.001$; and $\beta=0.0014$ (95% confidence interval, 0.001 to 0.002)$\times E/E'_{lat}+0.008$, $r=0.53$, $P<0.001$. E'/A'_{lat} indicates ratio of early to late diastolic velocity of mitral annulus at lateral site; E/E'_{lat}, LV filling index at lateral site; and P, descriptive significance level).

(median, 15 mm Hg), they were characterized by a 2- to 3-fold increase in b and β, increased wall stress, and/or an impaired relaxation despite preserved LV contractility and EF (Table 2). This was associated with a higher prevalence of concomitant diseases, arterial hypertension, and diabetes mellitus, known to be linked to diastolic dysfunction, and is in agreement with findings on their LV and LA dimensions.[34] HFNEF patients were characterized by a larger LA volume index, confirming that impaired LV filling impairs mitral inflow and gives rise to LA enlargement. Their LA dimensions were still within the normal range, however, probably because of the shorter duration of heart failure in our relatively young population (median age, 54 years) compared with other studies of older HFNEF patients. Furthermore, an increased LV mass index and ratio of LV mass to volume as signs of LV hypertrophy correlated not only with the LV relaxation impairment characterized by prolonged τ but also with LVEDP and LV stiffness. A higher ratio of LV mass to

volume suggests that structural remodeling was present in HFNEF patients, confirming recent findings of Paulus et al[14] on myocardial structure in diastolic heart failure.

Conventional Echocardiography

It is generally accepted that Doppler echocardiography cannot provide unequivocal evidence of diastolic dysfunction in HFNEF. The E/A ratio, IVRT, DT, and pulmonary vein Doppler[16] characterizing flow across the mitral valve do not allow direct measurement of LV relaxation, stiffness, or filling pressure.[15,17] Several authors have demonstrated that conventional Doppler is accurate in patients with a reduced EF but not in those with normal EF.[16,35] We also found only a weak correlation between IVRT and τ in our study population, in agreement with others.[36,17] Furthermore, a short DT indicates increased LA pressure in patients with systolic[37] or pseudonormal and restrictive diastolic heart failure.[15] In contrast, patients with a mild diastolic dysfunc-
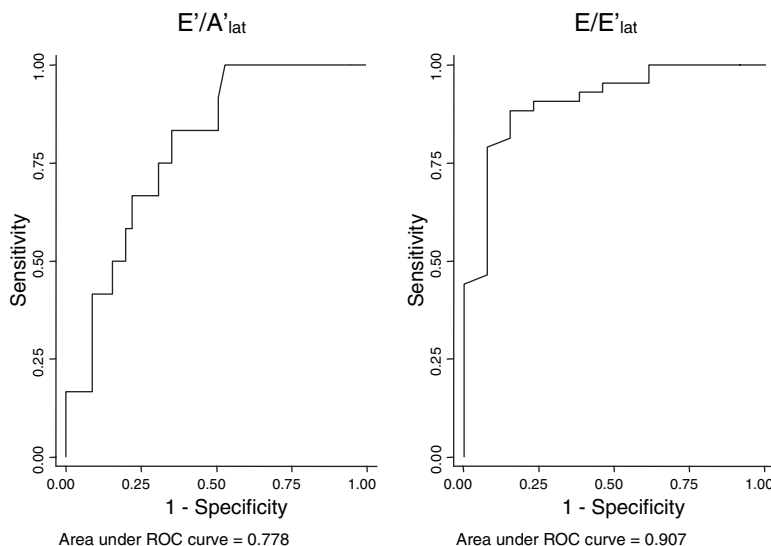
Figure 3. ROC-analysis for TDI indexes E'/A'_{lat} and E/E'_{lat}. The sensitivity/specificity ratio for E'/A'_{lat} (<1) is 67%/84% and for E/E'_{lat} (≥ 8) is 83%/92%. E'/A'_{lat} indicates early to late diastolic velocity ratio of mitral annulus at lateral site; E/E'_{lat}, LV filling index at lateral site.

tion have a prolonged DT and therefore reduced K. Thus, with regard to their biphasic response to increasing diastolic dysfunction, the interpretation of E/A or DT in diagnosing diastolic dysfunction is rather complicated. Although the mitral inflow parameters DT and K correlated with b (dP/dV), simple analysis of E/A or DT was limited in at least our study population, which was patients with impaired mitral flow. This limitation is further underscored by our finding that these parameters were not significantly related to β, known to be a relatively load-independent parameter. If we had used the mitral flow Doppler as the only technique for detecting diastolic dysfunction in HFNEF, $\approx$70% of patients would have been correctly identified. Although all 5 patients with pseudonormal mitral flow pattern had been identified correctly in our study, indicating that the mitral Doppler is a helpful diagnostic tool in cases of more severe diastolic dysfunction, we conclude that it is of only limited value in the diagnosis of early diastolic dysfunction in HFNEF. We observed that the duration of atrial reverse flow was significantly prolonged, an early sign of disturbed mitral inflow resulting from increased LV stiffness. However, the limited diagnostic accuracy and signal quality limited the practical use of pulmonary vein Doppler in our study. A combined analysis based on E/A and IVRT, DT, or Ar−A duration improved the accuracy of the mitral flow Doppler method, but only to a moderate degree. In summary, filling pattern analysis from mitral flow Doppler measurement alone is found to be more complicated and limited to detecting early diastolic dysfunction in patients with HFNEF.

Tissue Doppler Imaging

TDI proved to be more accurate than conventional Doppler for detecting impaired diastolic function in patients with HFNEF.[29,36] In general, we found that the lateral annular velocities were more closely related to the LV relaxation and compliance indexes as determined by PV-loop analysis than the septal annular velocities (Table 3). Thus, only the lateral velocities are taken into consideration in the following discussion. With regard to impaired LV relaxation, we confirmed its relation to the early diastolic mitral annular velocity (E')[18] and $T_{E-E'}$.[30] However, the latter did not correlate with the filling pressure, as previously suggested.[30] We found that the TDI indexes E'_{lat} and E'/A'_{lat} correlated more closely with LV stiffness than any conventional echocardiography index. Similarly, the dimensionless E/E' index, introduced recently as an echocardiographic measure of LA pressure and LV filling,[2,16,35,38,39] showed the best correlation with indexes of diastolic parameters obtained by PV-loop measurements. In our study, patients with HFNEF and E/E'_{lat} >8 had a significantly increased LV stiffness (Figure 1). Both E/E'_{lat} >8 and E'/A'_{lat} <1 detected HFNEF patients with diastolic abnormalities equally well, but E'/A'_{lat} showed lower sensitivity, yielding more false-negative results than E/E'_{lat}. Because we did not perform PV-loop and echocardiographic investigations simultaneously, however, we found only rather moderate correlations in our small study population. Nevertheless, from a clinical point of view, the key question is whether the echocardiographic method used allows reliable detection of the correct diagnosis. In contrast

to Doppler echocardiography, TDI detected diastolic dysfunction in 81% (35 of 43) and the E/E'_{lat} index in 86% (37 of 43) of our patients with HFNEF. Three additional patients with HFNEF were identified by adding E'/A' to E/E'_{lat}, raising the detection rate to 93% (40 of 43). In contrast, the additional application of conventional Doppler indexes did not considerably improve the diagnostic accuracy.

Some recent studies[40–42] reported reduced regional systolic peak velocities in patients with HFNEF and impaired systolic reserve,[43] suggesting that systolic function also is impaired. Our study has not confirmed this finding. In addition, our invasive catheter measurements showed that global systolic function and contractility of the patients with HFNEF were not impaired under basal condition, in agreement with others.[1,19,44,45] Compensatory capacities and/or systolic reserve in our relatively young study population may have contributed to a limited difference in systolic parameters. However, further studies under stress conditions are needed to further clarify the role of systolic function in patients with HFNEF.

In summary, in clinically stable patients at rest presenting with reduced exercise capacity in whom the diagnosis of diastolic dysfunction was proven by conductance catheter analysis, single indexes of conventional Doppler echocardiography were insufficient or inferior compared with TDI parameters in detecting the correct diagnosis. Although the diagnostic accuracy improved after several indexes of the mitral and pulmonary venous flow analysis were added, we do not recommend their use as isolated method for investigating diastolic function, which is in agreement with the latest consensus statement of the Heart failure and Echocardiography Association of the European Society of Cardiology.[46] In contrast to flow Doppler, TDI parameter showed better linear correlation with diastolic parameters and provided a simple means of diagnosing diastolic dysfunction. Accordingly, TDI was a more reliable technique to identify early disturbances of both LV relaxation and stiffness. However, although the LV filling index E/E'_{lat} showed a similar sensitivity but higher specificity than E'/A'_{lat} in detecting diastolic dysfunction, we recommend the use of E/E'_{lat} in both clinical diagnostic routine and scientific studies to investigate diastolic function in patients with HFNEF.

Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure with normal ejection fraction is present in >50% of all heart failure patients. The mortality and morbidity of these patients may be quite elevated, and making the diagnosis accurately is important. The gold standard for assessing diastolic function remains the pressure–volume relationship, but it requires an invasive approach, ideally with a conductance catheter system. Doppler echocardiography and tissue Doppler imaging have been studied and validated in patients with systolic dysfunction and congestive heart failure and have been shown to be reliable in assessing filling pressures. The utility of these techniques in patients with heart failure with normal ejection fraction has not previously been clearly established. This is the first study to compare flow Doppler and tissue Doppler imaging with the pressure–volume loop analysis obtained by conductance catheterization in patients with mild diastolic dysfunction. Although the use of traditional pulsed-wave spectral Doppler might be adequate in patients with severe diastolic dysfunction (pseudonormal and restrictive filling patterns), according to our results, its single use in early or mild forms of diastolic dysfunction cannot be recommended. Tissue Doppler imaging was significantly superior in detecting diastolic dysfunction in this patient population. The combination of mitral flow Doppler and tissue Doppler imaging index, known as the left ventricular filling index (E/E'), was the most accurate echocardiographic method (area under the curve, 90%) for diagnosing diastolic dysfunction in heart failure with normal ejection fraction and identified early disturbances of left ventricular relaxation and stiffness. These findings provide evidence that the E/E', similar to that used in patients with systolic dysfunction, is an accurate, noninvasive diagnostic tool in patients with diastolic dysfunction. This study supports the use of this index for clinical evaluation and in future clinical trials investigating treatment options for heart failure with normal ejection fraction.