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ORIGINAL PAPER

Diastolic pressure–volume quotient (DPVQ) as a novel echocardiographic index for estimation of LV stiffness in HFpEF

Mario Kasner[1] · David Sinning[1] · Daniel Burkhoff[2] · Carsten Tschöpe[3,4,5]

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Abstract

Background End-diastolic pressure–volume relationship and LV stiffness, key parameter for diagnosing diastolic dysfunction within Heart failure with preserved ejection fraction (HFpEF) patients, can be directly obtained only by invasive pressure–volume (PV) measurements. Therefore, we aimed to establish diastolic pressure–volume quotient (DPVQ), as a new non-invasive parameter for estimation of LV stiffness in HFpEF obtained by 3D echocardiography (3DE) and tissue Doppler imaging.

Methods Twenty-three HFpEF patients with suspected diastolic dysfunction, scheduled for invasive pressure–volume loop analyses obtained by conductance catheterization were included. PV loop measurements were compared with simultaneous 3DE full-volume recordings of the LV and tissue Doppler measurements for LV diastolic function. LV filling index E/E' was used for estimation of diastolic pressure. Single-beat method was performed to calculate LV stiffness constant (β_{SB}).

Results Fourteen of twenty-three patients showed increased and 9/23 revealed normal LV stiffness β. End-diastolic, end-systolic and stroke volume obtained by 3DE correlated with those from PV loop analysis ($r = 0.63$, $r = 0.57$ and $r = 0.71$, respectively). Estimated diastolic pressure and DPVQ correlated with invasive measurements ($r = 0.81$ and $r = 0.91$, both $p < 0.001$). Accordingly, calculated stiffness constant β_{SB} revealed a significant correlation with invasive determined stiffness coefficient β ($r = 0.73$, $p < 0.001$). DPVQ and β_{SB} correlated with NT-proBNP plasma level ($r = 0.67$ and $r = 0.58$, both, $p < 0.001$).

Conclusion 3D echocardiography allows accurate non-invasive measurements of diastolic pressure–volume quotient which correlates with invasive determined LV stiffness in HFpEF.

Keywords Heart failure · Diastolic dysfunction · Echocardiography (three-dimensional) · Tissue Doppler · Pressure–volume relationship

✉ Mario Kasner
mario_kasner@yahoo.com; mario.kasner@charite.de

1 Department of Cardiology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany

2 Division of Cardiology, Columbia University, New York, USA

3 Department of Cardiology, Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany

4 Berlin-Brandenburg Center for Regenerative Therapies, Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany

5 German Centre for Cardiovascular Research (DZHK), Hamburg, Germany

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a common clinical syndrome with high morbidity and mortality, and one that is increasing in prevalence with the aging population. The heterogeneity of the disease also leads to difficulties in diagnostics. There is overall considerable variation in the degree of cardiac involvement in HFpEF patients. Although it is now well known that the pathophysiology of HFpEF is heterogeneous including changes in LV coupling, atria and right ventricular function and sizes, chronotropy, and pulmonary pressure, diastolic dysfunction is thought to be a prominent part of the HFpEF syndrome and can include insufficient diastolic suction, impaired relaxation, as well as disturbed compliance and stiffness properties of the LV [1–3]. The determination of invasive measured end-diastolic pressure–volume relationship (EDPVR) is hereby the best accepted index for LV stiffness in HFpEF. But in the clinical routine, EDPVR determination is not feasible and non-invasive echocardiographic based parameters need to be further developed [4–7]. The single use of Mitral Doppler indices are not anymore recommended due to their low sensitivity and specificity. Today, the LV filling index (E/E') is recommended for the estimation of LV diastolic pressure and E/E' mean >15 indicates severe diastolic dysfunction [13, 14]. However, E/E' shows in the clinical routine often non-conclusive results in the so called gray zone indicated by values between 8 and 15, most probably due to its volume dependency. Three-dimensional echocardiography (3DE) is a method which offers the non-invasive accurate measurements of LV volume changes [8–12]. Thus, we hypothesize that the calculation of the quotient of simultaneously determined E/E' to end-diastolic LV volume, the diastolic pressure–volume quotient (DPVQ) can overcome E/E' volume dependency and allow an improvement in the estimation of LV stiffness in HFpEF. To prove this hypothesis, we performed a clinical study to directly compare DPVQ with simultaneous pressure–volume (PV) analysis obtained by conductance catheterization in HFpEF [15].

Methods

Patient population

Twenty-three patients with heart failure symptoms (NYHA II–III) despite normal EF (HFpEF), and suggested diastolic dysfunction which underwent routine conductance catheterization procedure were investigated to further characterize their cardiac function. All patients had at least one episode of heart failure-related hospitalization within 1 year and were carefully screened for non-cardiac causes of heart failure symptoms, including lung function tests. All patients showed exercise dyspnea or exercise intolerance, quantified by 6-min walk test and by elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels (Elecsys 2010, Roche Diagnostics, Germany) [16]. Atrial fibrillation, valvular disease, significant coronary artery disease, and lung diseases had all been excluded in both groups. All patients gave written informed consent for invasive diagnostic procedures.

Simultaneous performance of echocardiography and pressure–volume measurement

Transthoracic echocardiography was performed by VIVID Seven Dimension (3 V and 3.5 MHz probe, GE Ultrasound) simultaneously with the conductance catheterization in supine position. Echocardiography acquisition included 3D full-volume measurement of the LV, mitral flow and tissue Doppler imaging from standard apical position and was obtained at the same time during PV loop registration in end- expiration. Echocardiographic loops were marked for the corresponding PV loop sequence. Cardiac cycles were recorded in a cine loop format. The studies were stored digitally for subsequent offline analysis at ECHOPAC PC Workstation. The exact analysis was performed by two independent investigators who were blinded for all information obtained from the invasive analysis.

Pressure–volume measurements by conductance catheter method

The conductance catheter was used to assess PV measurements in all patients as described recently [17, 18]. Systolic and diastolic LV function was obtained by LV end-diastolic pressure (LVEDP), isovolumetric relaxation (Tau), and minimal and maximal rate of LV pressure change (dP/dt_{min} and dP/dt_{max}) and LV maximal pressure (LVP), stroke volume (SV) and ejection fraction (EF). We calculated the average slope of the end-diastolic PV relationship during preload reduction by cavalballoon occlusion to determine functional LV chamber stiffness (LV stiffness, b) and the exponential curve fit to the end-diastolic LV pressure–volume points ($\text{LVEDP} = c \times \exp(\beta \times \text{LVEDV})$ to determine how rapidly stiffness increases with increasing pressure (LV stiffness β). Thus, the end-diastolic PV relationship was fitted with an exponential relation to obtain the chamber stiffness constant. Although not absolutely load-insensitive [19], this technique defines more precisely, the natural curvilinear relation of PV and still represents an established method for comparing LV stiffness among different subgroups. Diastolic dysfunction was considered to be present if a LV stiffness constant β ($\geq 0.015\ \text{ml}^{-1}$) and/or LV stiffness b (≥ 0.19 mmHg/ml) was increased in clinically symptomatic patients despite normal EF. These cut-off values were defined as values corresponding to the 90-th percentiles of our control patients from previous studies [17, 18].

Echocardiographic analysis

Chamber dimensions were evaluated using standard procedures, including LV mass index (LVMI) [20] and left atrial volume index (LAVI) [21]. The assessment of diastolic function included pulsed-wave Doppler measurements of the early (E) and late (A) mitral inflow velocities, deceleration time of early left ventricular filling, the peak early diastolic velocity (E') or the septal and lateral mitral annulus by tissue Doppler in the 4-chamber view over at least three cardiac cycles. Volume changes of the left ventricular are obtained by a three-dimensional acquisition using full-volume assessment over four cardiac cycles. A TomTec standard software integrated at ECHOPAC PC Workstation is used for post-acquisition volume analysis and measurement of left ventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), cardiac output (CO) and ejection fraction (EF). Accordingly, the ratio of early to late annular velocity (E'/A') and LV filling index as the transmitral flow velocity to annular velocity ratio (E/E') was determined for septal and lateral site. LV filling index E/E' has been used to estimate diastolic pressures [13, 14, 17]. Diastolic LV filling pressure (DP) was estimated by an equation, $0.85 \times E/E' + 4.4$ derived from a direct comparison between E/E' and LVEDP as previously revealed [17]. Simultaneously, assessment of a 3D volume acquisition allows an estimation of the diastolic pressure–volume quotient (DPVQ, ml^{-1}). In addition, using the single-beat method, the end-diastolic pressure–volume relationship (EDPVRSB) and LV stiffness constant β (β_{SB}) were calculated as described previously [22, 23]. Briefly, from a single measured end-diastolic pressure–volume point as obtained by TDI and 3DE (DP, LVEDV), the EDPVR can be predicted by calculating the volume at which pressure is 0 [$V_0 = \text{LVEDV} \times (0.6-0.006 \times \text{DP})$] and the volume at which pressure equals 30 mmHg [$V_{30} = V_0 + (\text{LVEDV}-V_0)/(\text{DP}/27.78)^{(1/2.76)}$]. The EDPVR is subsequently represented as $P = \alpha V^{\beta}$, where $\beta = \log(\text{DP}/30)/\log(\text{LVEDV}/V_{30})$ and $\alpha = 30/V^{\beta}$ [23].

Statistical analysis

SPSS software (version 15.0, SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Descriptive characteristics of continuous variables were expressed as mean values ± SD. Correlation analyses between echocardiographic and PV loop diastolic indices were provided using linear regression analyses. A p value below 0.05 was considered statistically significant in all analyses. The authors had full access to the data and take over the responsibility for its integrity. All authors have read and approved the manuscript as written.

Results

Patient characteristics

The study included 14 women and 9 men with a median age of 53 ± 10 years. The patients were suffering from arterial hypertension ($n = 11$) and/or diabetes mellitus ($n = 4$) and/or hyperlipoproteinemia ($n = 9$) and/or obesity ($n = 6$). They were characterized by NYHA II or III, increased plasma NT-proBNP levels or exercise intolerance as obtained by ergometry. LV was not dilated (LVEDVI <97 ml/m^2) but LA volume index and LV mass index were increased. All left atrial and ventricular dimensions are listed in Table 1.

LV systolic and diastolic function in HFpEF

According to the invasive PV loop analysis and echocardiography, all patients showed the indices of cardiac performance and LV systolic function within the normal range. Fourteen of twenty-three heart failure patients had impaired LV EDPVR as characterized by an increased LV stiffness constant β (increased stiffness group). They also showed an elevation of mean LV end-diastolic pressure (LVEDP), although at borderline absolute levels (Table 2) and showed only tendency towards prolonged isovolumic relaxation time index Tau. Nine of twenty-three patients showed normal LV compliance characteristics with normal LV stiffness (normal stiffness group). There were no differences regarding LV contractility and systolic function.

The patients with increased stiffness had increased LV filling index E/E' (Table 3). In general, left ventricular end-diastolic, end-systolic and stroke volume (LVEDV, LVESV and SV) obtained by 3DE showed up to 30 % lower values than those measured by conductance catheter (Tables 2, 3) whereas EF showed similar values among the two methods. There were no differences between the subgroups regarding LVEDV, LVESV, SV and EF, independently from method used, 3DE or conductance catheterization (Tables 2, 3).

Correlation of LV volume and derivate parameters between 3D echocardiography and pressure–volume analysis

EDV and ESV obtained by 3DE correlated significantly with those from conductance catheterization ($r = 0.87$ and $r = 0.78$, respectively, both $p < 0.001$). Measurements of stroke volume and ejection fraction showed a strong correlation between the two methods ($r = 0.62$ and $r = 0.71$, $p < 0.001$, respectively). DP correlated well with invasive measurements ($r = 0.84$, $p < 0.001$). DPVQ correlated significantly with LV chamber stiffness b ($\text{d}P/\text{d}V$) ($r = 0.57$,

Table 1 Patient characteristics (variable expressed as median [25–75 % quartile])

Demographics	All ($n = 23$)	Increased stiffness ($n = 14$)	Normal stiffness ($n = 9$)	p
Women n	14	8	6	0.221
Age (years)	53 [45–65]	54 [43–65]	46 [39–54]	0.091
NYHA II–III n (%)	23 (100 %)	14 (100 %)	9 (100 %)	–
NT-proBNP (pg/ml)	173 [98–224]	192 [134–529]	88 [55–138]	0.006
Exercise capacity (Watt)	100 [75–125]	100 [62.5–112.5]	125 [100–150]	0.046
BMI (kg/m^2)	25.5 [21.9–31.2]	27.1 [22.6–31.2]	22.5 [20.9–32.4]	0.397
BP systolic (mmHg)	125 [110–157]	139 [121–163]	113 [109–130]	0.054
BP diastolic (mmHg)	74 [67–82]	73 [63–87]	76 [69–82]	0.921
Heart dimensions				
LAVI (ml/m^2)	27 [14–31]	28 [22–37]	19 [14–25]	0.048
Septum (mm)	12 [10–13]	12 [11–13]	9 [8–10]	0.006
Posterior wall (mm)	11 [10–12]	11 [10–13]	9 [8–10]	0.026
LVEDD (mm)	45 [43–50]	45 [42–50]	46 [40–54]	0.942
LVMI (g/m^2)	121 [86–160]	122 [87–161]	97 [73–117]	0.398
LVEDVI (ml/m^2)	77 [68–83]	78 [69–83]	72 [67–89]	0.741
Concomitant disease n (%)				
Art. hypertension	12 (52 %)	10 (71 %)	2 (22 %)	0.01
Diabetes mellitus	4 (17 %)	4 (28 %)	0 (0 %)	–
Obesity	6 (26 %)	4 (28 %)	2 (22 %)	0.613
Hyperlipoproteinemia	9 (39 %)	7 (53 %)	2 (22 %)	0.084
Smoking	8 (34 %)	5 (36 %)	3 (33 %)	0.732

BMI body mass index, *NYHA* New York Heart Association class, *LA* left atrial diameter, *LAVI* left atrial volume index, *LVEDD* LV end-diastolic diameter, *LVMI* LV mass index, *LVEDVI* LV end-diastolic volume index

Table 2 LV systolic and diastolic parameters in patients with HFPEF compared with controls (variable expressed as median [25–75 % quartile])

	Increased stiffness ($n = 14$)	Normal stiffness ($n = 9$)	p
Cardiac performance			
HR (/min)	77 [66 to 88]	74 [66 to 78]	0.108
EF (%)	61 [58 to 68]	63 [61 to 71]	0.336
SV (ml)	89 [77 to 104]	100 [86 to 113]	0.071
CO (l/min)	7.5 [6.8 to 8.2]	7.0 [5.7 to 8.1]	0.734
Systolic indices			
ESP (mmHg)	139 [117 to 153]	110 [101 to 124]	0.014
LVESV (ml)	55 [45 to 59]	53 [40 to 68]	0.801
dP/d$t$max (mmHg/s)	1424 [1358 to 1723]	1403 [1336 to 1695]	0.962
Diastolic indices			
LVEDV (ml)	138 [127 to 151]	155 [132 to 178]	0.071
LVEDP (mmHg)	14.1 [10.6 to 18.0]	8.0 [7.0 to 10.9]	0.011
dP/d$t$min (mmHg/s)	−1870 [−1787 to −2156]	−1882 [−1442 to −2061]	0.369
Tau (ms)	51 [46 to 55]	45 [42 to 47]	0.549
Stiffness constant β (ml^{-1})	0.028 [0.024 to 0.035]	0.013 [0.011 to 0.014]	<0.001
LV stiffness b (mmHg/ml)	0.23 [0.17 to 0.43]	0.14 [0.06 to 0.16]	<0.001

HR heart rate, *EF* ejection fraction, *SV* stoke volume, *ESV* end-systolic volume, *EDV* end- diastolic volume, *CO* cardiac output, *ESP* end-systolic pressure, dP/dt_{max} maximum rate of pressure change, *EES* end-systolic elastance, *LVEDP* LV end-diastolic pressure, dP/dt_{min} minimal rate of LV pressure change, *Tau* isovolumetric relaxation time, *LV stiffness b* slope of end-diastolic PV relationship (dP/dV), *Stiffness constant* β exponential curve fit to end-diastolic PV relationship

Table 3 Measured and derived indices of conventional, TDI and 3D echocardiography (variable expressed as median [25–75 % quartile])

	Increased stiffness ($n = 14$)	Normal stiffness ($n = 9$)	p
E (m/s)	0.84 [0.75–0.91]	0.71 [0.62–0.79]	0.003
A (m/s)	0.88 [0.68–0.98]	0.64 [0.54–0.68]	0.014
E/A	1.05 [0.83–1.24]	1.07 [0.86–1.32]	0.747
DT (ms)	217 [185–248]	201 [173–208]	0.340
IVRT (ms)	97 [89–111]	91 [81–104]	0.328
$S'_{average}$ (m/s)	0.07 [0.06–0.09]	0.09 [0.07–0.10]	0.071
$E'_{average}$ (m/s)	0.08 [0.07–0.11]	0.13 [0.09–0.14]	0.050
$A'_{average}$ (m/s)	0.08 [0.07–0.10]	0.08 [0.07–0.11]	0.884
$E'/A'_{average}$	1.1 [0.72–1.45]	1.47 [1.22–1.78]	0.056
$E/E'_{average}$	11.0 [9.1–13.6]	6.5 [4.5–9.2]	0.003
LAVI (ml/m^2)	28 [22–37]	19 [14–25]	0.048
3D echocardiography			
LVEDV (ml)	101 [86–105]	121 [101–132]	0.062
LVESV (ml)	35 [33–43]	38 [34–61]	0.138
SV (ml)	60 [53–70]	71 [63–79]	0.141
EF (%)	62 [59–65]	64 [56–67]	0.701
Derived indices			
DP (mmHg)	13.7 [11.5–15.4]	8.3 [6.0–11.5]	0.001
E/E'/LVEDV (ml^{-1})	0.11 [0.10–0.14]	0.05 [0.04–0.07]	<0.001
DPVQ (ml^{-1})	0.14 [0.12–0.17]	0.07 [0.06–0.0.09]	<0.001
Stifness constant β_{SB}	5.96 [5.91–5.99]	5.86 [5.81–5.91]	0.004

E/A ratio of early (*E*) to late (*A*) mitral flow peak velocities, *DT* deceleration time of early mitral flow, *IVRT* isovolumetric relaxation time, S' systolic, E' early, A' late diastolic peak velocities of mitral annulus, E'/A' ratio, E/E' LV filling index

$p < 0.001$). The correlation to the exponential stiffness coefficient β was stronger ($r = 0.91$, $p < 0.001$) (Fig. 1) and Bland–Altman analysis showed low mean differences but wide limits of agreement. Using the cut-off value of DPVQ $\geq$0.10 ml^{-1}, 13/14 patients with increased LV stiffness were detected whereas none of them was false positive. All patients with normal LV stiffness were correctly selected (Fig. 1). DPVQ and calculated LV stiffness constant β using single-beat method (β_{SB}) were significantly increased in patients with increased LV stiffness.

Calculated stiffness constant β_{SB} revealed a significant correlation with stiffness coefficient β ($r = 0.73$, $p < 0.001$). DPVQ also correlated with NT-proBNP plasma level ($r = 0.67$, $p < 0.001$; Fig. 2) and exercise performance as obtained by bicycle exercise test ($r = 0.58$, $p < 0.01$).

Inter- and intraobserver variabilities of 3DE assessment of LV size and function

Full-volume analysis obtained by 3DE showed low interobserver variability of the measurements of EDV, ESV, SV and EF (1.7 ± 11.2; 2.2 ± 9.7; 0.6 ± 2.9; and -0.2 ± 1.91 ml, respectively) which is comparable with other studies. Volume analysis obtained by 3DE also showed low intraobserver variability (-1.3 ± 6.63; -1.1 ± 5.55; -0.2 ± 2.15 ml; and -0.3 ± 3.52 %, for EDV, ESV, SV and EF, respectively).

Discussion

The silent finding of our study is that the quotient of simultaneously measured E/E' and LV enddiastolic volume (DPVQ) by TDI and 3DE allows a simple LV stiffness determination in the clinical routine.

Direct measurement of EDPVR belongs to the gold standard to determine LV stiffness, a hallmark of diastolic dysfunction in HFPEF. It is usually determined by invasive PV loop recordings over multiple beats during transient preload reductions by vena cava occlusion maneuver. However, it was also shown that invasive single-beat recordings of pressure and volume are sufficient to estimate LV stiffness. Recently, non-invasive mathematic single-beat models using LV/RV catheter or echocardiographic parameters were introduced for the characterization of LV compliance. However, in the clinical routine, echocardiographic indices are recommended and predominantly used in RCTs. None of these parameters are generated to estimate LV stiffness, since none of them integrate LV

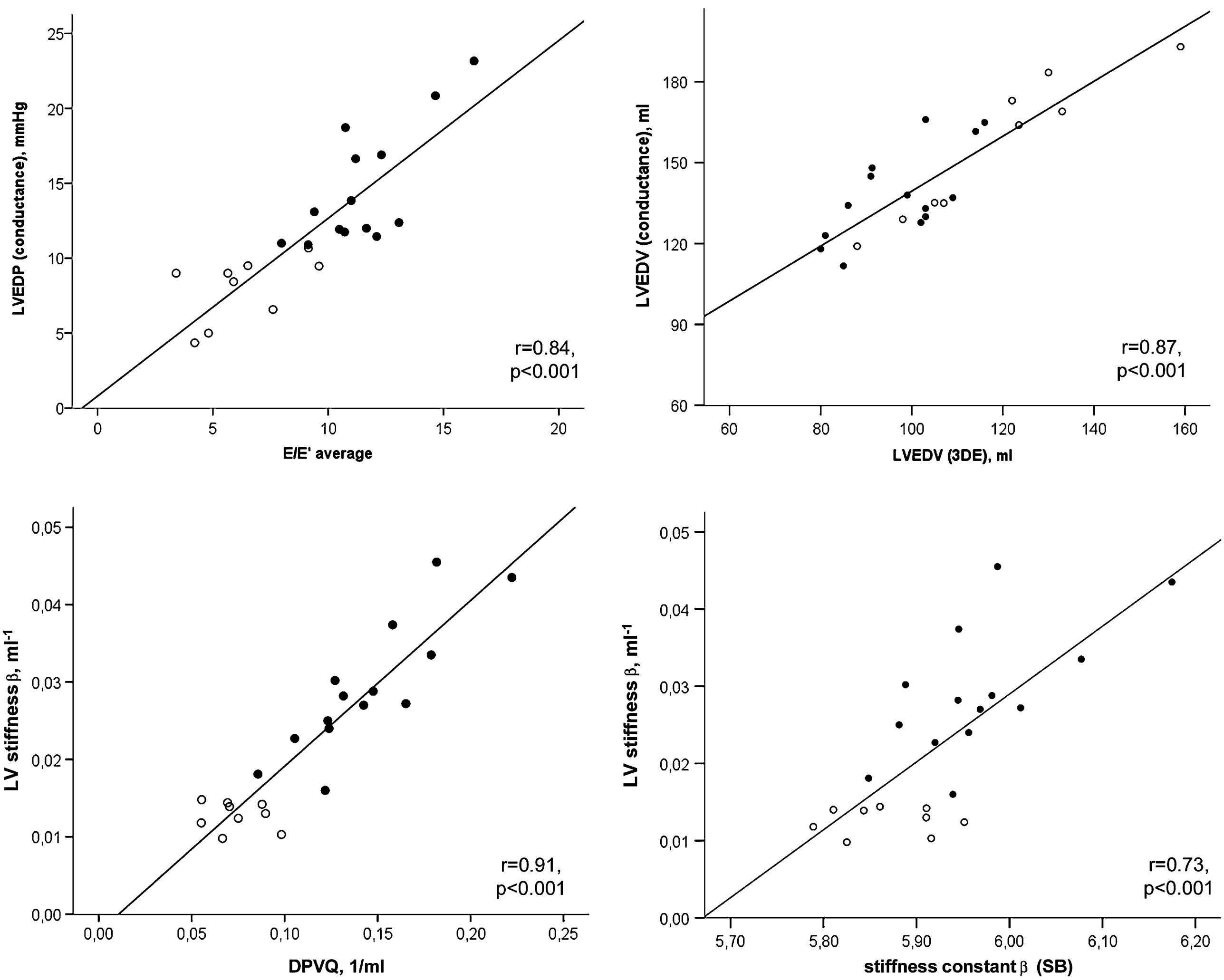

Fig. 1 Linear regression between PV loop and 3DE indices. LVEDV measured by 3D echocardiography (3DE) correlated with LVEDV obtained by conductance catheter (LVEDV = 1.07 × LVEDV(3DE) + 32.6; $r = 0.91$, $p < 0.001$); E/E' correlated with LVEDP (LVEDP = 1.17 × E/E' + 0.74; $r = 0.84$, $p < 0.001$); DPVQ and estimated stiffness constant β_{SB} correlated with LV stiffness β ($\beta = 0.214 \times$ DPVQ−0.002; $r = 0.91$, $p < 0.001$ and $\beta = 0.087 \times \beta_{SB}$−0.498; $r = 0.73$, $p = 0.004$). *Closed circles* indicate patients with increased LV stiffness and *open circles* indicate patients without increased LV stiffness

pressure with LV volume parameters. The recommended echo-parameter for the determination of diastolic impairment in HFpEF is E/E'. Nevertheless, E/E' is also a volume dependent parameter indicated by the clinical experience that diuretics can acutely reduce E/E' by the induction of a left shift of the LV-PV loop without changing LV stiffness. Therefore, interpretation of the E/E' values without knowing LV volume can lead to misinterpretations in the clinical routine. In addition, one of the failures of RCT in HFpEF could be argued by the heterogeneity of the investigated studies. It had been shown that, e.g., in CHARM-Preserved, I-Preserve or in TOP-CAT, echocardiographic analysis of subpopulations from these studies differs in the degree of diastolic dysfunction as well as in the forms of left ventricular hypertrophy. Therefore, a simple combination of E/E' and LV enddiastolic volume is abundant to investigate patient with suggested HFpEF as well as to homogenize HFpEF subpopulations.

The time and velocity measurements as well as estimated pressure data are already shown to be reliable if obtained by comprehensive and tissue Doppler echocardiography. In the clinical routine several echocardiographic approaches are used to investigate diastolic function in HFpEF, including comprehensive echocardiography and TDI [17, 24–28]. On the contrary, determination of LV volume obtained by 2D echocardiography has been shown to be observer variable [8, 12, 29] and therefore not reliable for precise calculation needed to reveal exact hemodynamic pressure/volume relation analysis in HFpEF. With this study, we compared three-dimensional echocardiography and TDI data with simultaneous pressure–volume analysis obtained by invasive conductance catheterization in patients with HFpEF. We

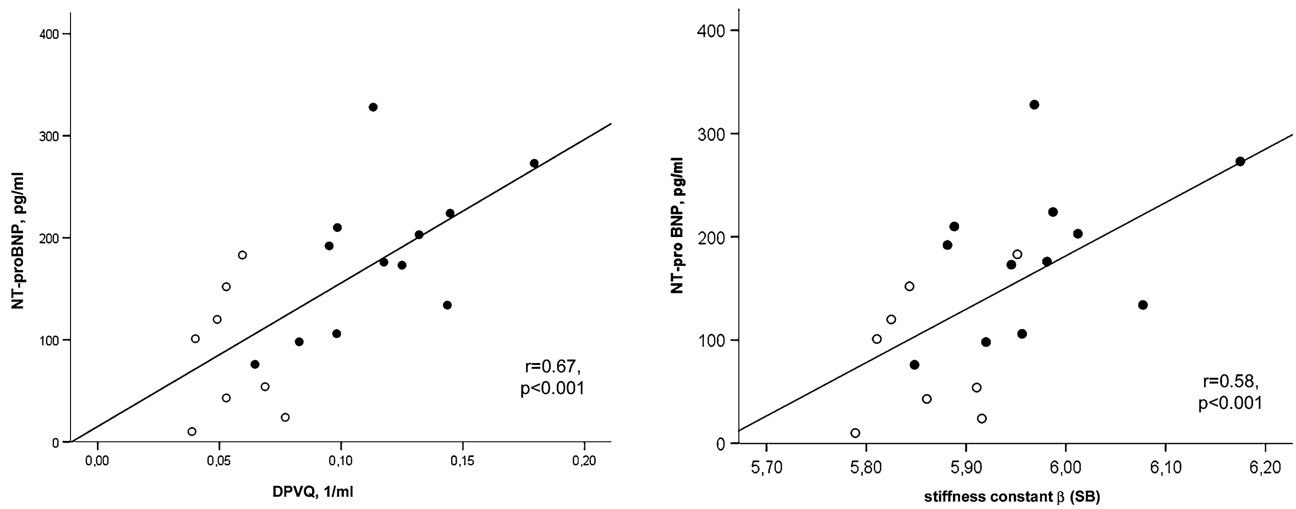

Fig. 2 Correlation of plasma NT-proBNP level with DPVQ and estimated stiffness constant *b* by single-beat analyzing ($r = 0.67$ and $r = 0.58$, $p < 0.001$, $N = 20$). *Closed circles* indicate patients with increased LV stiffness and *open circles* indicate patients without increased LV stiffness

could show that LV volumes obtained by 3DE are accurate and correlate with invasive measurements which are in agreement with comparison studies between 3DE and MRI [8, 9]. Comparable to our data, they also reported general volume underestimation by 3D echocardiography but relative parameter such as EF was found similar to invasive data. Furthermore, we proved that the quotient of simultaneously measured E/E' and 3D LV enddiastolic volume (DPVQ) correlated with EDPVR and LV stiffness, invasively measured by conductance catheter. Particularly, the pressure–volume relationship is crucial for understanding isolated diastolic dysfunction in HFpEF. The use of 3D echocardiography with full-volume modality and additional apply of TDI integrate all three qualities crucial for characterization of LV diastolic function: timing, flow/tissue velocity and volume changes. These are important findings with a clinical relevance since it may have an impact on more specific non-invasive diagnostic of diastolic function including crucial pressure–volume relations in everyday clinic not only at steady state but also during physiological exercise (e.g. bicycle exercise). However, further prospective clinical studies with larger population size have to show the significance of the method in providing prognosis-relevant results in HFpEF.

Reproducibility

Previous studies on real time three-dimensional echocardiography have shown that this technique has higher reproducibility than 2DE, underlining that the most important aspect of minimizing variation is the use of a three-dimensional dataset [8, 11, 30–32]. Similarly, we could also show low inter- and intraobserver variabilities of LV volumes taking into account the limitation that the small sample size of the study and the selection of patients with good image quality could explain these results.

Conclusion

Three-dimensional echocardiography is helpful in diagnosing diastolic dysfunction and contributes to better understand myocardial pathomechanisms in HFpEF, particularly in patients with borderline results in TDI analysis. 3DE allows an accurate measurement of diastolic pressure–volume relationship which correlates with invasive determined LV stiffness. Further studies have to prove whether DPVQ allows to identify subpopulations of HFpEF with severe LV stiffness, whether it correlates with the degree of the disease and whether it is a reliable parameter useful for risk stratification of HFpEF individuals. In addition, it is important to prove whether DPVQ allows to identify homogeneous subpopulations of HFEPF which might benefit from more specific treatments targeting LV stiffness in the future. Thus, DPVQ could be a helpful clinical tool to develop personalized treatment options in HFpEF.

Limitations

A small study population is one of the limiting factors in interpreting the results. However, the aim of the study was to evaluate a new non-invasive echocardiographic method to estimate LV stiffness in HFpEF. Since this was evaluated and compared with a highly invasive catheter procedure, from an ethical point of view, no age matched healthy control group was available. Furthermore, an absolute LVEDP level of some patient with increased LV stiffness were below the cut-off defined by ESC recommendations, since LVEDP is preload dependent and was not an obligatory criterion. Also, LV filling pressures are influenced by intrapericardial pressure and RV–LV interaction, which was not performed by the current study. However, the study was conducted to investigate new techniques independent from the underlying disease mechanism. Therefore, further studies in different and larger cohorts are necessary to investigate the accuracy of the method in other patients groups.

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Conflict of interest None declared.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 355:251–259
2. Zile MR, Baicu CF, Gaasch WH (2004) Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 350:1953–1959
3. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP (2002) Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 288:2144–2150
4. Goto K, Mikami T, Onozuka H, Kaga S, Inoue M, Komatsu H, Komuro K, Yamada S, Tsutsui H, Kitabatake A (2006) Role of left ventricular regional diastolic abnormalities for global diastolic dysfunction in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr 19:857–864
5. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP (2006) Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 355:260–269
6. Sanderson JE (2007) Heart failure with a normal ejection fraction. Heart Br CardiacSoc 93:155–158
7. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ (2006) Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 113:1966–1973
8. Nucifora G, Badano LP, Dall'Armellina E, Gianfagna P, Allocca G, Fioretti PM (2009) Fast data acquisition and analysis with real time triplane echocardiography for the assessment of left ventricular size and function: a validation study. Echocardiography Mt Kisco NY 26:66–75
9. Pouleur AC, le Polain de Waroux JB, Pasquet A, Gerber BL, Gerard O, Allain P, Vanoverschelde JL (2008) Assessment of left ventricular mass and volumes by three-dimensional echocardiography in patients with or without wall motion abnormalities: comparison against cine magnetic resonance imaging. Heart Br Cardiac Soc 94:1050–1057
10. Hoole SP, Boyd J, Ninios V, Parameshwar J, Rusk RA (2008) Measurement of cardiac output by real-time 3D echocardiography in patients undergoing assessment for cardiac transplantation. Eur J Echocardiogr 9:334–337
11. Hare JL, Jenkins C, Nakatani S, Ogawa A, Yu CM, Marwick TH (2008) Feasibility and clinical decision-making with 3D echocardiography in routine practice. Heart Br Cardiac Soc 94:440–445
12. Jenkins C, Leano R, Chan J, Marwick TH (2007) Reconstructed versus real-time 3-dimensional echocardiography: comparison with magnetic resonance imaging. J Am Soc Echocardiogr 20:862–868
13. Burgess MI, Jenkins C, Sharman JE, Marwick TH (2006) Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 47:1891–1900
14. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE (2009) The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 54:36–46
15. Burkhoff D, Mirsky I, Suga H (2005) Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol 289:H501–H512
16. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP (2005) The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J 26:2277–2284
17. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschope C (2007) 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. Circulation 116:637–647
18. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschope C (2008) Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation 117:2051–2060
19. Gaasch WH, Little WC (2007) Assessment of left ventricular diastolic function and recognition of diastolic heart failure. Circulation 116:591–593
20. Devereux RB, Reichek N (1977) Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 55:613–618
21. Murray JA, Kennedy JW, Figley MM (1968) Quantitative angiocardiography. II. The normal left atrial volume in man. Circulation 37:800–804
22. Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, Kass DA, Burkhoff D (2006) Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. Am J Physiol 291:H403–H412
23. Ten Brinke EA, Burkhoff D, Klautz RJ, Tschope C, Schalij MJ, Bax JJ, van der Wall EE, Dion RA, Steendijk P Single-beat estimation of the left ventricular end-diastolic pressure-volume relationship in patients with heart failure. Heart Br Cardiac Soc 96:213–219
24. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ (2000) Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 102:1788–1794
25. Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK (2004) Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of

survival after acute myocardial infarction. J Am Coll Cardiol 43:360–367
26. Dokainish H, Zoghbi WA, Lakkis NM, Al-Bakshy F, Dhir M, Quinones MA, Nagueh SF (2004) Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation 109:2432–2439
27. Hummel YM, Klip IT, de Jong RM, Pieper PG, van Veldhuisen DJ, Voors AA (2010) Diastolic function measurements and diagnostic consequences: a comparison of pulsed wave- and color-coded tissue Doppler imaging. Clin Res Cardiol 99(7):453–458
28. Tschope C, Westermann D (2009) Heart failure with normal ejection fraction. Pathophysiology, diagnosis, and treatment. Herz 34:89–96
29. Mor-Avi V, Sugeng L, Weinert L, MacEneaney P, Caiani EG, Koch R, Salgo IS, Lang RM (2004) Fast measurement of left ventricular mass with real-time three- dimensional echocardiography: comparison with magnetic resonance imaging. Circulation 110: 1814–1818
30. Herberg U, Gatzweiler E, Breuer T, Breuer J (2013) Ventricular pressure-volume loops obtained by 3D real-time echocardiography and mini pressure wire—a feasibility study. Clin Res Cardiol 102(6):427–438
31. Nikitin NP, Constantin C, Loh PH, Ghosh J, Lukaschuk EI, Bennett A, Hurren S, Alamgir F, Clark AL, Cleland JG (2006) New generation 3-dimensional echocardiography for left ventricular volumetric and functional measurements: comparison with cardiac magnetic resonance. Eur J Echocardiogr 7:365–372
32. Jacobs LD, Salgo IS, Goonewardena S, Weinert L, Coon P, Bardo D, Gerard O, Allain P, Zamorano JL, de Isla LP, Mor-Avi V, Lang RM (2006) Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data. Eur Heart J 27:460–468