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Clinical Study

Increased Left Ventricular Stiffness Impairs Exercise Capacity in Patients with Heart Failure Symptoms Despite Normal Left Ventricular Ejection Fraction

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Aims. Several mechanisms can be involved in the development of exercise intolerance in patients with heart failure despite normal left ventricular ejection fraction (HFNEF) and may include impairment of left ventricular (LV) stiffness. We therefore investigated the influence of LV stiffness, determined by pressure-volume loop analysis obtained by conductance catheterization, on exercise capacity in HFNEF. *Methods and results*. 27 HFNEF patients who showed LV diastolic dysfunction in pressure-volume (PV) loop analysis performed symptom-limited cardiopulmonary exercise testing (CPET) and were compared with 12 patients who did not show diastolic dysfunction in PV loop analysis. HFNEF patients revealed a lower peak performance ($P = .046$), breathing reserve ($P = .006$), and ventilation equivalent for carbon dioxide production at rest ($P = .002$). LV stiffness correlated with peak oxygen uptake ($r = -0.636$, $P < .001$), peak oxygen uptake at ventilatory threshold ($r = -0.500$, $P = .009$), and ventilation equivalent for carbon dioxide production at ventilatory threshold ($r = 0.529$, $P = .005$). *Conclusions*. CPET parameters such as peak oxygen uptake, peak oxygen uptake at ventilatory threshold, and ventilation equivalent for carbon dioxide production at ventilatory threshold correlate with LV stiffness. Increased LV stiffness impairs exercise capacity in HFNEF.

1. Introduction

Recent epidemiological studies have provided evidence that heart failure despite normal ejection fraction (HFNEF) accounts for more than 50% of all heart failure patients [1, 2]. Their prognosis compares to those of patients suffering from heart failure with reduced ejection fraction [3]. Impaired exercise tolerance is a main clinical feature of patients presenting with HFNEF. Several pathophysiological mechanisms have been suggested to be involved in the development of the clinical scenario that limits physical performance in HFNEF patients [4]. They include an inadequate increase of ventricular diastolic filling and cardiac output during exercise, consequently leading to pulmonary congestion [5]. Echocardiographic studies have shown that, in HFNEF patients undergoing exercise, an increasing proportion of late diastolic filling can lead to a drop of the early proportion of diastolic filling. A pseudonormalization of the echocardiographic transmitral flow pattern at aerobic exercise was observed indicating a rise in atrial pressure induced by exercise [6]. Similarly, elevated levels of NT-proBNP, a biomarker of heart failure, were verified in patients who showed normal ventricular function at rest but elevated filling pressures at exercise [7]. Diastolic dysfunction is also associated with an increased pulmonary blood volume at exercise [8], a reduced coronary flow reserve at peak-dose dobutamine [9], an altered breathing pattern characterized by rapid shallow breaths [10], and a reduced cardiac energetic reserve [11]. Tan et al. [12] found that symptoms are related to an increased left ventricular (LV) stiffness at rest, and in an invasive, pressure-volume (PV) loop analysis [13] it was shown that, apart from dyssynchrony and dynamic mitral

regurgitation, increased LV stiffness is a major mechanism underlying development of HFNEF.

Still, the question whether increased LV stiffness accounts for the development of exercise intolerance in HFNEF patients remains unanswered, since LV stiffness has not yet been measured directly (invasively) when correlating it with parameters of cardiopulmonary exercise capacity. Therefore, we aimed to investigate the influence of LV stiffness, determined by the gold standard method in evaluating diastolic function, pressure-volume loop analysis obtained directly by conductance catheterization [14], on cardiac performance and exercise capacity in HFNEF obtained by cardiopulmonary exercise testing- (CPET-) derived parameters, commonly used as precise predictors of survival in heart failure [15, 16].

2. Methods

2.1. Patient Population. We investigated 39 patients admitted to our department with symptoms of heart failure despite normal LVEF and suggested diastolic dysfunction. Reasons for admission were dyspnea, orthopnea or paroxysmal nocturnal dyspnea, exertional dyspnea, and/or exercise intolerance. Atrial fibrillation, heart valve disease, significant coronary artery disease, and lung diseases had been excluded by means of electrocardiogram, laboratory values, angiography, echocardiography, chest X-ray, and lung function test. All patients gave written consent for invasive diagnostic procedures. The research protocol was approved by the local institutional review committee.

2.2. Cardiopulmonary Exercise Testing. Symptom-limited CPET was performed in all patients. β-blockers, ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics were withdrawn from the patient's medication 24 hours before CPET examination. Heart rate was measured continuously. Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least three minutes during the recovery phase. Blood pressure was measured using a standard cuff sphygmomanometer. Ventilation equivalent for oxygen uptake (VEO_2) and carbon dioxide output ($VECO_2$) at rest and at ventilatory threshold (VEO_2 at VT and $VECO_2$ at VT), peak oxygen uptake at ventilatory threshold (VO_2 at VT) and at peak exercise, peak oxygen uptake per exercise level, breathing reserve, and breathing frequency were acquired. Peak VO_2 was defined as the highest continuous 30-second average VO_2 occurring within the final minute of exercise. Peak oxygen consumption (VO_2 (mL/min/kg)) was acquired by dividing peak oxygen uptake by the patient's body weight. In this study, the ventilatory threshold, a point during exercise after which ventilation abruptly increases despite gradual increase in work rate and VO_2, was identified using the ventilation equivalent of oxygen [17]. All tests were performed with physician supervision. All results were interpreted by a cardiologist and/or a pneumologist.

2.3. PV Measurements by Conductance Catheter Method. Three to five days after the CPET investigations, PV measurements were performed, as previously described in [14]. β-blockers, ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics were withdrawn from the patient's medication 24 hours before the examination.

The conductance catheter allows continuous online measurements of LV pressure and volume [18]. 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, pressure, and ECG. Total LV volume was calibrated with thermodilution and hypertonic saline dilution [19]. Hemodynamic indexes were obtained from steady-state PV loops at sinus rhythm. PV relationships were then derived from PV loops recorded during preload reduction through temporary balloon occlusion (NuMED, Hopkinton, NY, USA) of the inferior vena cava. 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 EF, end-systolic pressure, and maximum rate of pressure change (dP/dt_{max}). Diastolic load-dependent LV function was assessed by 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 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). Increased LV stiffness was considered present if β ($\geq 0.015\,mL^{-1}$) was increased in clinically symptomatic patients despite normal EF, as described previously in [14].

2.4. Echocardiography. Three to five hours before the PV-loop measurement was performed, echocardiography studies had been performed by 2 independent investigators who were blinded to all information derived from CPET analyses.

Mitral flow velocities were recorded in the apical 4-chamber view with a VingMed System FiVe (GE Healthcare, Chalfont St. Giles, UK). The LVEF was calculated from two-dimensional apical images according to the Simpson method. The LV mass was calculated according to the formula proposed by Devereux and divided by body surface area for LV mass index calculation [20]. 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). Data were adjusted for age and heart rate according to guidelines [21]. Chamber dimensions were evaluated using standard procedures, including LV mass index [20] and left atrial (LA) diameter.

The tissue Doppler 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. The analysis was performed for systolic (S'), early diastolic (E'), and late diastolic (A') peak tissue

velocities. As a noninvasive parameter for LV stiffness, the LV filling index (E/E'), calculated by the ratio of transmitral flow velocity to annular velocity, was determined [22]. Adequate mitral and TDI signals were recorded in all patients.

2.5. Statistical Analysis. SPSS software for Macintosh OS (Version 18, SPSS Inc., Chicago, Ill, USA) was used for statistical analysis. Descriptive characteristics of continuous variables were expressed as median values with the first and third quartiles. Correlation analyses between CPET, echocardiographic, and PV-loop indexes were provided using linear regression model. Comparisons between groups were performed with ANOVA if variables were normally distributed the Mann-Whitney U test if the data were not normally distributed, and Pearson's χ^2 test was used to analyze categorical variables. A value of $P < .05$ was considered statistically significant in all analyses. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

3. Results

3.1. Patient Characteristics. Population characteristics, heart dimensions, and concomitant diseases are presented in Table 1. According to the results from the end-diastolic pressure volume relationship patients were divided into 2 groups: those with impaired EDPVR as characterized by increased LV stiffness indicating diastolic heart failure (DHF, $n = 27$) and those with normal EDPVR (noDHF, $n = 12$).

With respect to gender, age, race, and body mass index there were no significant differences between the subgroups. There was a tendency towards higher prevalences of arterial hypertension (48% versus 17%), diabetes mellitus (19% versus 8%), obesity (37% versus 17%), hyperlipoproteinemia (26% versus 17%), and nicotine abuse (19% versus 17%) in the DHF group, but statistically significant differences were not found.

3.2. Heart Dimensions and LV Diastolic Properties. As presented in Table 1, all investigated patients showed normal heart dimensions. There were no significant differences between the groups regarding LV mass, LA diameter, and LV end-diastolic diameter. LV mass index tended to be higher in HFNEF patients with increased LV stiffness. LA diameter correlated with τ ($r = 0.473$, $P = .005$).

3.3. Cardiac Performance, Systolic Function, and LV Contractility. According to PV loop analysis and echocardiographic parameters, both conventional and TDI derived, there were no significant differences in heart rate, end-systolic pressure, end-systolic volume, stroke volume, stroke work, cardiac output, LVEF, and myocardial systolic velocities (S' sep, S' lat), as presented in Tables 2 and 3. LV contractility (dP/dt_{max}) was lower in patients with an increased LV stiffness ($P = .026$, Table 2).

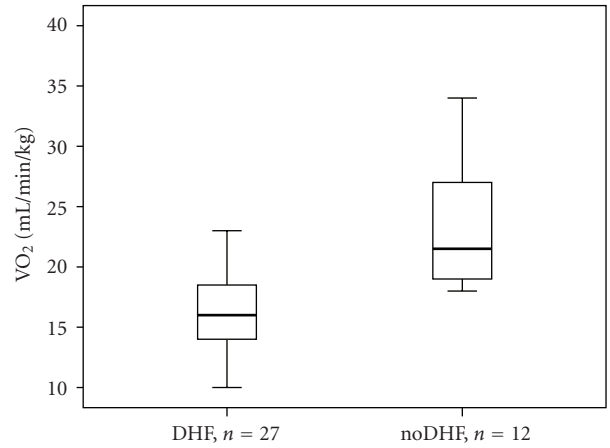

Figure 1: Relationship between peak oxygen consumption and groups defined by LV stiffness. Thick vertical lines represent mean and thin vertical lines represent standard deviation, $P < .001$.

3.4. LV Diastolic Function. Table 2 presents diastolic indexes provided by conductance catheter-derived PV loop analysis. Patients with increased LV stiffness showed a prolonged τ ($P = .001$) and a lower dP/dt_{min} ($P = .007$). Their LVEDP was significantly increased ($P < .001$), whereas EDV did not differ significantly.

Conventional echocardiographic and TDI diastolic parameters are shown in Table 3. Peak late mitral inflow (A) was significantly higher in patients with increased LV stiffness ($P = .013$). The septal and lateral LV filling index (E/E') was significantly higher in the DHF group ($P < .001$, and $P = .007$, resp.). DHF patients showed a significantly decreased early diastolic peak velocity (E'). No patient showed a pseudonormal or restrictive filling pattern. The E/A ratio tended to be lower in HFNEF patients with increased LV stiffness, but the difference did not reach statistical significance. Echocardiographic findings showed mild diastolic dysfunction in patients with increased LV stiffness, indicated by a slightly elevated LV filling index (E/E' sep 10.83 (8.40–16.05), E/E' lat 8.69 (6.62–13.46)) and a normal E/A ratio (1.21 (1.01–1.51)).

3.5. CPET and LV Stiffness, Ejection Fraction, and Systolic Indexes. CPET findings are presented in Table 4. With normal LV stiffness with respect to heart rate at peak exercise, breathing frequency, VEO_2 at rest, VEO_2 at ventilatory threshold, and $VECO_2$ at ventilatory threshold there were no significant differences between patients with increased LV stiffness and subjects. HFNEF patients, in whom LV stiffness was increased according to PV loop analysis, showed significantly decreased exercise tolerance indicated by a decreased peak performance, as well as significantly decreased breathing reserve, significantly lower peak oxygen consumption (16 mL/min/kg (14 mL/min/kg–19 mL/min/kg) versus 21.5 mL/min/kg (18.5 mL/min/kg–27 mL/min/kg), $P < .001$, Figure 1), and significantly higher ventilation equivalent values for carbon dioxide output at rest and at ventilatory threshold (Table 4). As shown in

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

	Patient population ($n = 39$)	DHF ($n = 27$)	noDHF ($n = 12$)	P
Demographics:				
Men, n (%)	16 (41)	11 (41)	5 (42)	.957
Age, y	50 [38–60]	54 [41–60]	41 [36–52]	.113
BMI, kg/m^2	24 [22–32]	25 [22–33]	23 [21–28]	.083
NYHA class II/III, n (%)	21/18	10 (36)/17 (63)	11 (92)/1 (8)	
Concomitant disease				
Art. hypertension, n (%)	15 (38)	13 (48)	2 (17)	.062
Diabetes mellitus, n (%)	6 (15)	5 (19)	1 (8)	.416
Obesity, n (%)	12 (31)	10 (37)	2 (17)	.203
Hyperlipoproteinemia, n (%)	9 (23)	7 (26)	2 (17)	.526
Smoker, n (%)	7 (18)	5 (19)	2 (17)	.889
Heart dimensions				
LA, mm	34 [31–38]	34 [30–40]	35 [32–36]	.882
LVEDD, mm	48 [45–52]	48 [45–52]	48 [46–51]	.708
Septum, mm	10 [10-11]	10 [10–13]	10 [9–11]	.155
Posterior wall, mm	10 [9–11]	11 [9–13]	10 [9–11]	.076
LV mass, g	173 [140–225]	173 [125–225]	172 [145–200]	.503
LVMI, g/m^2	96 [76–105]	96 [74–117]	91 [75–97]	.281

BMI indicates body mass index, NYHA New York Heart Association class, LA left atrial parasternal diameter, LVEDD LV end-diastolic diameter, and LVMI LV mass index.

Figure 2, exercise capacity, indicated by peak performance, correlated with the degree of LV stiffness not only in all patients ($r = -0.487$, $P = .002$) but also within the groups of patients who had been diagnosed with increased LV stiffness ($r = -0.518$, $P = .006$). As presented in Figure 3, CPET parameters of cardiopulmonary function peak VO_2 ((mL/min/kg), $r = -0.427$, $P = .007$), O_2 pulse ($r = -0.366$, $P = .022$), peak VO_2 at ventilatory threshold ($r = -0.489$, $P = .002$), VEO_2 at rest ($r = 0.380$, $P = .017$), VEO_2 at ventilatory threshold ($r = 0.452$, $P = .005$), as well as $VECO_2$ at rest ($r = 0.521$, $P = .001$), $VECO_2$ at ventilatory threshold ($r = 0.569$, $P < .001$), and breathing reserve ($r = -0.353$, $P = .028$) correlated with LV stiffness in all patients, whereas breathing frequency did not show a significant correlation with LV stiffness ($r = -0.073$, $P = .658$). Also, heart rate at peak exercise ($r = -0.309$, $P = .056$), breathing frequency ($r = -0.073$, $P = .658$), and peak oxygen uptake per exercise level ($r = -0.047$, $P = .778$) did not correlate significantly with the degree of LV stiffness determined by PV loop analysis obtained directly by conductance catheterization. Ejection fraction ($r = -0.023$, $P = .889$), ESP ($r = -0.101$, $P = .541$), and myocardial contractility (dP/dt_{max}, $r = 0.206$, $P = .209$) did not show a significant correlation with exercise capacity indicated by CPET-derived peak performance.

4. Discussion

This study is the first to date to investigate the direct influence of LV stiffness, determined by PV loop analysis [13, 14], on exercise capacity, determined by CPET, in patients with HFNEF. We show that exercise capacity correlates with the degree of LV stiffness.

CPET represents a widespread method for evaluation of exercise capacity in patients with heart failure symptoms despite normal ejection fraction (HFNEF). Disturbed LV stiffness is considered a cardinal mechanism of diastolic dysfunction [23] and therefore may contribute to exercise intolerance in health and HF patients [24]. In healthy subjects, the strong and independent association between exercise capacity and resting LV filling pressures assessed by echocardiography has been demonstrated [25]. In hypertrophic cardiomyopathy, a significant correlation between LA fractional shortening, an index of passive diastolic filling, and both the ventilatory threshold and peak VO_2 has been found [26]. These findings reported LA fractional shortening and pulmonary systolic filling fraction to be the only independent predictors of exercise capacity, suggesting that, in the setting of hypertrophic cardiomyopathy, exercise tolerance is determined rather by diastolic than by systolic function.

In our study, HFNEF patients with increased LV stiffness showed a significantly impaired exercise tolerance and breathing reserve, as well as significantly increased ventilation equivalents for carbon dioxide output at rest and at ventilatory threshold. In this comparably young DHF population, there were no appearances of hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, and/or pseudonormalization. We were still able to show that exercise intolerance is linked to an increased LV stiffness in this population.

Table 2: PV measurements by Conductance Catheter Method (variable expressed as median [25%–75% quartile]).

	Patient population ($n = 39$)	DHF ($n = 27$)	noDHF ($n = 12$)	P
Heart rate, bpm	79 [68–88]	75 [68–88]	81 [70–87]	.648
Systolic indexes				
ESP, mmHg	121 [112–138]	130 [112–144]	117 [113–121]	.094
ESV, mL	56 [31–85]	57 [30–84]	53 [34–88]	.903
SV, mL	100 [79–121]	95 [68–122]	105 [81–120]	.584
SW, mmHg $*$ mL	9813 [7434–12542]	9614 [7120–12542]	11323 [7526–14136]	.411
CO, mL/min	7183 [5956–9423]	7183 [5224–9414]	7365 [6276–10125]	.338
dP/dt_{max}, mmHg/s	1447 [1337–1695]	1429 [1275–1590]	1584 [1425–1777]	.026
LVEF, %	65 [55–70]	65 [60–70]	69 [60–77]	.353
Diastolic indexes				
EDV, mL	141 [107–190]	141 [99–194]	149 [110–178]	.927
LVEDP, mmHg	10 [8–14]	12 [11–18]	7 [6–10]	<.001
dP/dt_{min}, mmHg/s	−1827 [(−2037)–(−1589)]	−1715 [(−1937)–(−1486)]	−1979 [(−2170)–(−1883)]	.007
τ, ms	50 [43–60]	54 [47–62]	45 [40–48]	.001
Stiffness β, 1/mL	0.018 [0.011–0.028]	0.027 [0.016–0.036]	0.011 [0.009–0.012]	.001

ESP indicates end-systolic pressure, ESV end-systolic volume, SV stoke volume, SW stroke work, CO cardiac output, dP/dt_{max} maximum rate of pressure change, LVEF left ventricular ejection fraction, EDV end-diastolic volume, LVEDP LV end-diastolic pressure, dP/dt_{min} minimal rate of LV pressure change, τ isovolumetric relaxation time, Stiffness constant β exponential curve fit to end-diastolic PV relationship, and Stiffness b slope of end-diastolic PV relationship (dP/dV).

Table 3: Indices of conventional and TDI echocardiography (variable expressed as median [25–75% quartile]).

	Patient population ($n = 39$)	DHF ($n = 27$)	noDHF ($n = 12$)	P
LVEF, %	62 [55–70]	61 [53–69]	63 [55–73]	.512
Mitral flow				
E, m/s	0.81 [0.69–0.96]	0.87 [0.73–1.02]	0.7 [0.6–0.85]	.036
A, m/s	0.66 [0.51–0.76]	0.7 [0.6–0.8]	0.56 [0.42–0.7]	.013
E/A	1.25 [1.05–1.51]	1.21 [1.01–1.51]	1.29 [1.17–1.52]	.424
DT, ms	179 [139–211]	185 [142–224]	180 [156–190]	.412
IVRT, ms	91 [85–103]	92 [85–110]	91 [88–97]	.591
TDI				
S' sep, m/s	0.05 [0.04–0.08]	0.06 [0.04–0.08]	0.05 [0.04–0.07]	.752
E' sep, m/s	0.09 [0.08–0.12]	0.09 [0.05–0.09]	0.12 [0.11–0.13]	.001
A' sep, m/s	0.06 [0.05–0.07]	0.06 [0.04–0.07]	0.06 [0.05–0.07]	.712
E/E' sep	8.46 [6.55–13.08]	10.83 [8.40–16.05]	5.98 [4.76–6.88]	<.001
S' lat, m/s	0.05 [0.04–0.07]	0.05 [0.04–0.07]	0.05 [0.04–0.08]	.958
E' lat, m/s	0.11 [0.08–0.13]	0.1 [0.06–0.12]	0.12 [0.08–0.14]	.139
A' lat, m/s	0.04 [0.03–0.07]	0.05 [0.03–0.07]	0.04 [0.03–0.07]	.792
E/E' lat	7.6 [6.26–9.8]	8.69 [6.62–13.46]	6.26 [5.39–7.56]	.007

LVEF indicates left ventricular ejection fraction; 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; and A', late diastolic peak velocities of mitral annulus at lateral site; E'/A', ratio of E' to A'; E/E', LV filling index; sep, septal; lat, lateral.

4.1. LV Diastolic Function and Heart Dimensions. Our DHF patients, who were characterized by an almost 3-fold increase in LV stiffness (median: 0.027 mL^{-1}), showed an only moderately increased LVEDP at rest (median: 12 mmHg, Table 2). In addition, LA diameters in the DHF group were almost the same as those in the noDHF group, ranging within normal limits. This finding is in agreement with the short duration of heart failure symptoms in our relatively young population (median age: 54 versus 41 years, $P = .113$), where structural LV remodeling on myocardial structure, as proposed by

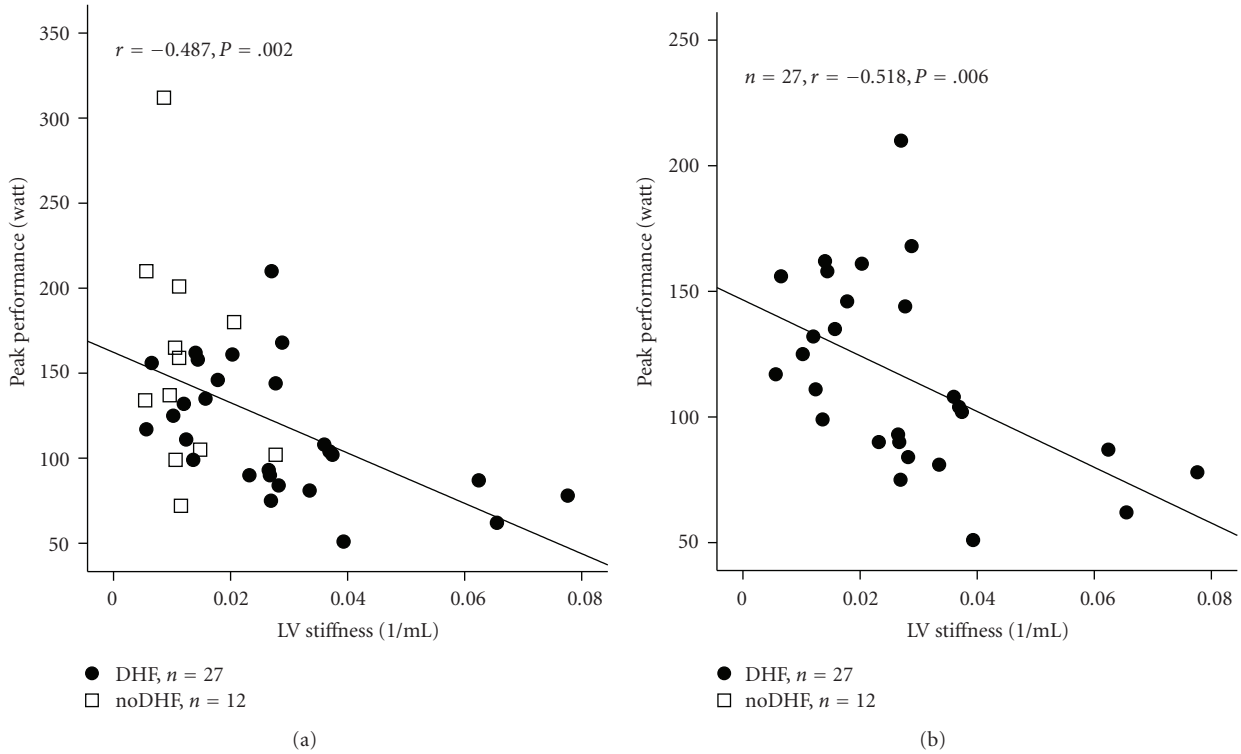

Figure 2: Linear regression between peak performance and LV stiffness in all patients (above, $n = 39$) and in HFNEF patients with increased LV stiffness (below, $n = 27$). Stiffness beta indicates exponential curve fit to end-diastolic PV relationship, r correlation coefficient, and P significance level.

Table 4: Indices of cardiopulmonary exercise testing (variable expressed as median [25–75% quartile]).

	Patient population ($n = 39$)	DHF ($n = 27$)	noDHF ($n = 12$)	P
Performance, watt	117 [90–159]	108 [87–146]	148 [103–196]	.046
Heart rate, 1/min	138 [119–162]	133 [112–148]	150 [128–166]	.110
VO_2, mL/min/kg	18 [16–20]	16 [14–19]	21.5 [18.5–27]	<.001
O_2 pulse, mL/beat	11.6 [9.2–13.2]	11.6 [9.2–13]	11.5 [9–13.5]	.715
VO_2/exercise level, mL/min/Watt	9.6 [8.4–10.8]	9.7 [8.3–11.5]	9.2 [8.4–9.8]	.161
Breathing reserve, L	64 [42–83]	57 [37–72]	81 [74–98]	.006
Breathing frequency, 1/min	32 [29–37]	32 [29–37]	31 [25–40]	.502
VO_2 at VT, L/min	0.96 [0.75–1.25]	0.94 [0.72–1.13]	1.03 [0.82–1.39]	.172
Ventilation equivalents				
$VECO_2$ at rest	40 [37–46]	43 [39–49]	37 [34–39]	.002
$VECO_2$ at VT	31 [30–33]	33 [30–36]	31 [24–33]	.023
VEO_2 at rest	34 [32–37]	35 [32–39]	34 [29–36]	.138
VEO_2 at VT	31 [29–35]	31 [29–35]	31 [23–34]	.423

VO_2 indicates peak oxygen uptake, VT ventilatory threshold, $VECO_2$ ventilation equivalent for carbon dioxide output, VEO_2 ventilation equivalent for oxygen uptake.

Van Heerebeek et al. [27], is still moderate. Moreover, catheter measurements were performed in clinical stable patients after recompensation using diuretics, which may have altered LVEDP. According to our previous findings [22], DHF patients were characterized by an elevated and significantly higher echocardiographic LV filling index compared with the noDHF group, who showed a normal LV filling index.

4.2. CPET and LV Stiffness. Several studies have already discussed the association of reduced exercise capacity and diastolic function, as suggested by echocardiographic analysis

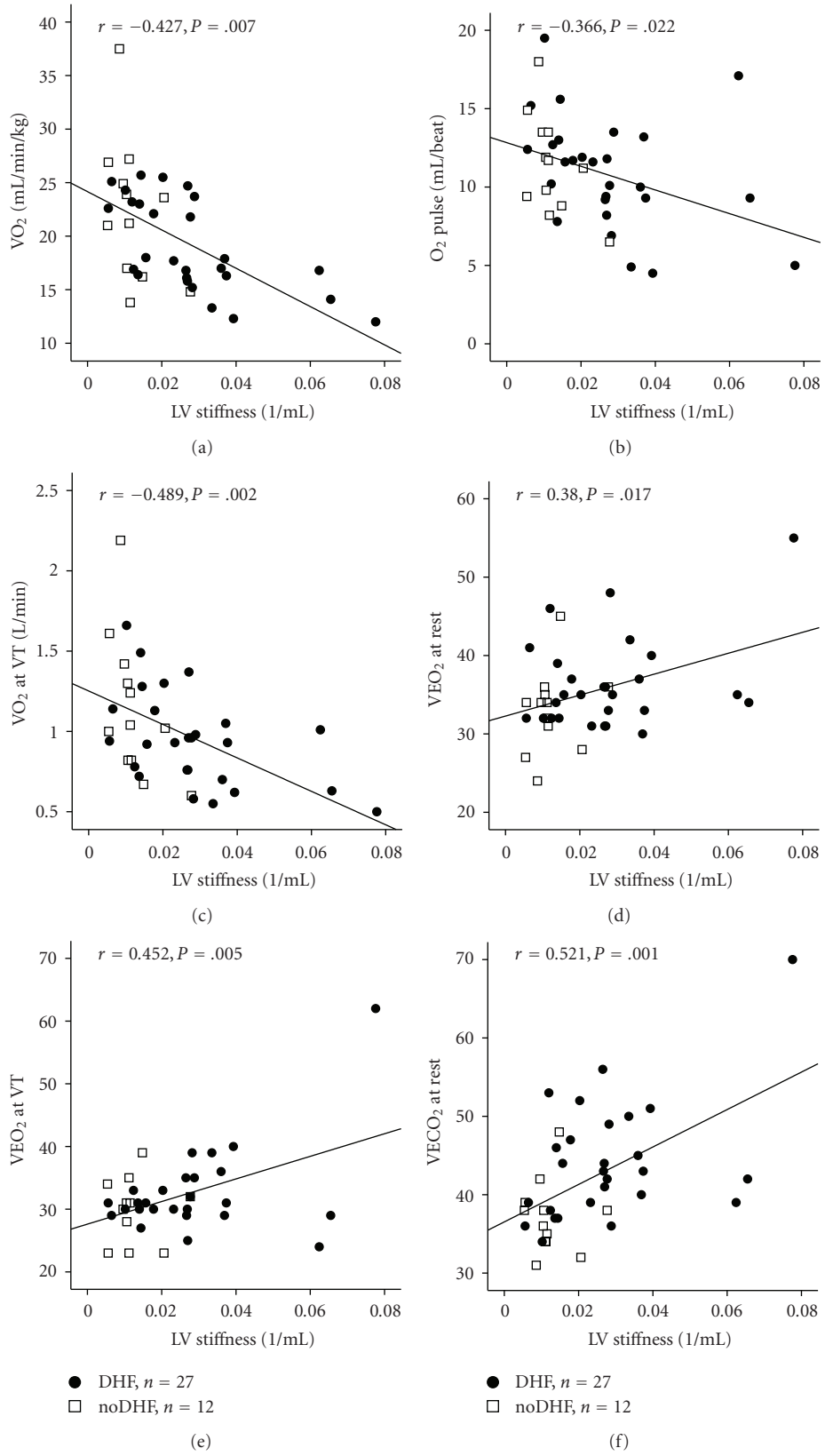

Figure 3: Continued.

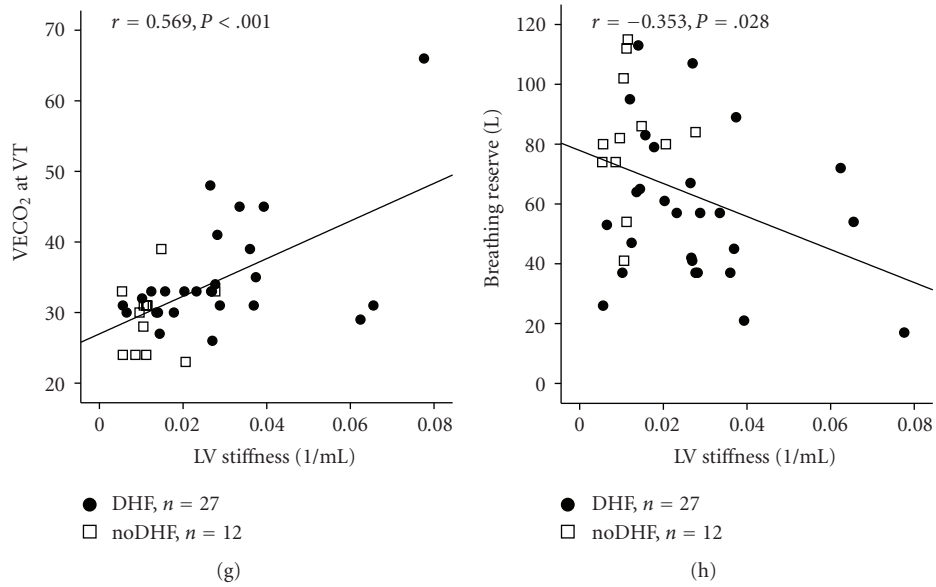

Figure 3: Linear regression between CPET indices and LV stiffness in all patients. VO_2 indicates peak oxygen uptake, VT ventilatory threshold, $VECO_2$ ventilation equivalent for carbon dioxide output, VEO_2 ventilation equivalent for oxygen uptake, stiffness beta exponential curve fit to end-diastolic PV relationship, r correlation coefficient, and P significance level.

[24, 28, 29]. However, the pathomechanism responsible for the main clinic limitation of those patients—exercise intolerance—remains unclear. It is particularly difficult to divide pulmonary limitations or training deficiency from cardiac dysfunction.

In a recent heart failure study, Arruda et al. [28] reported that, among 40 patients with diastolic dysfunction and 46 patients with systolic dysfunction, LA volume highly correlated with exercise capacity, breathing pattern, and gas exchange during exercise in the diastolic dysfunction patient group. In the same study no significant differences between the diastolic dysfunction and the systolic dysfunction group regarding breathing pattern and gas exchange parameters were described, which is in agreement with the findings of Kitzman et al. [24], who reported a similar peak exercise VE/VCO_2 ratio in patients suffering from diastolic heart failure and in patients suffering from systolic heart failure. We now extend this knowledge by correlating parameters of exercise capacity and gas exchange with invasively measured parameters of diastolic dysfunction in a relatively young HFNEF population, which was stable at rest. We found correlations between LV stiffness and VO_2 at VT, VEO_2 at rest, VEO_2 at VT, VCO_2 at rest, $VECO_2$ at VT, breathing reserve, and peak performance on CPET (Figures 2 and 3). This validates the concept of impaired diastolic cardiac function, characterized by increased LV stiffness, accounting for exercise intolerance in HFNEF patients. Our data suggest that increased LV stiffness, leading to pulmonary congestion and, consecutively, an impaired breathing reserve, represents the main pathomechanism underlying the development of dyspnea on exertion in HFNEF patients.

It has been suggested that impaired diastolic filling may lead to restrictive pulmonary changes, which contribute to a limited increase of the tidal volume during exercise and, because of fix dead space ventilation taking up greater percentage of the tidal breath, higher $VECO_2$ values [28]. Of all investigated CPET parameters the highest correlation was found between LV stiffness and $VECO_2$ at VT ($r = 0.569$, $P < .001$). CPET-derived $VECO_2$ at VT may therefore be a helpful parameter in the noninvasive estimation of LV stiffness and diastolic dysfunction at an early stage, given the relatively young age and comparably mild changes of diastolic echocardiographic parameters in our patient population.

In a recent noninvasive study [12], Tan et al. examined the pathophysiological mechanisms of HFNEF by exercise echocardiography. They elegantly show that a combination of reduced myocardial strain, rotation, LV suction, longitudinal function, and delayed LV untwisting rather than elevated LV stiffness alone causes symptoms in HFNEF. However, the correlation of invasively measured LV stiffness and CPET parameters in this study underlines the importance of LV stiffness as a predictor of exercise intolerance in HFNEF.

Increased LV stiffness correlates with alterations in exercise performance, gas exchange, and breathing pattern during exercise. In this study population, HFNEF patients, in whom increased LV stiffness indicating DHF is present, show significantly lower cardiopulmonary performances at CPET. Several CPET parameters of cardiac capacity, such as oxygen consumption and $VECO_2$ at VT, correlate significantly with left ventricular stiffness obtained by conductance catheter-derived PV loop analysis. Impaired diastolic cardiac function, characterized by impairment in LV stiffness, plays an important role in determining exercise capacity in HFNEF patients with diastolic dysfunction.

Abbreviations and Acronyms

A:	Late peak mitral flow velocity
A':	Late velocity of mitral annulus
ACE:	Angiotensin-converting enzyme
b:	LV stiffness b, slope of EDPVR (dP/dV)
β:	Constant of LV stiffness, exponential curve fit to EDPVR
c:	Curve fitting constant
CO:	Cardiac output
CPET:	Cardiopulmonary exercise testing
DHF:	Diastolic heart failure
dP/dt_{max}:	Maximum rate of LV pressure change
dP/dt_{min}:	Minimum rate of LV pressure change
E:	Early peak mitral flow velocity
E':	Early diastolic velocity of mitral annulus
E/A:	Ratio of early peak (E) to late peak (A) mitral flow velocities
E/E':	LV filling index
E'/A':	Early (E') to late (A') diastolic velocity ratio of mitral annulus
EDV:	End-diastolic volume
EDPVR:	End-diastolic pressure-volume relationship
EF:	Ejection fraction
ESP:	End-systolic pressure
ESPVR:	End-systolic pressure-volume relationship
ESV:	End-systolic volume
HFNEF:	Heart failure with preserved ejection fraction
IVRT:	Isovolumetric relaxation time
LA:	Left atrial
LAVI:	Left atrial volume index
LV:	Left ventricular
LVEDP:	LV end-diastolic pressure
LVMI:	LV mass index
LVP_{min}:	LV minimal pressure
PV:	Pressure volume
S':	Systolic velocity of mitral annulus
SW:	Stroke work
τ:	Isovolumetric relaxation time constant
TDI:	Tissue Doppler imaging
VCO_2:	Peak carbon dioxide output
VE:	Ventilation equivalent
VO_2:	Peak oxygen uptake
VT:	Ventilatory threshold.

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