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Diastolic Relaxation and Compliance Reserve during Dynamic Exercise in Heart Failure with Preserved Ejection Fraction

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Abstract

Background—Recent studies have examined hemodynamic changes with stressors such as isometric handgrip and rapid atrial pacing in heart failure with preserved ejection fraction (HFpEF), but little is known regarding left ventricular (LV) pressure-volume responses during dynamic exercise.

Objective—Assess LV hemodynamic responses to dynamic exercise in patients with HFpEF.

Methods and Results—Twenty subjects with normal EF and exertional dyspnea underwent invasive hemodynamic assessment during dynamic exercise to evaluate for suspected HFpEF. LV end-diastolic pressure (LVEDP) was elevated at rest (>15 mmHg, $n=18$) or with exercise (>20 mmHg, $n=20$) in all, consistent with HFpEF. Heart rate, blood pressure, arterial elastance and cardiac output increased with exercise (all $p<0.001$). Minimal and mean LV diastolic pressures increased by 43–56% with exercise (both $p<0.0001$), despite a trend toward reduction in LV end-diastolic volume ($p=0.08$). Diastolic filling time was abbreviated with increases in heart rate, and the proportion of diastole that elapsed prior to estimated complete relaxation increased ($p<0.0001$), suggesting inadequate relaxation reserve relative to the shortening of diastole. LV diastolic chamber elastance acutely increased 50% during exercise ($p=0.0003$). Exercise increases in LV filling pressures correlated with changes in diastolic relaxation rates, chamber stiffness and arterial afterload but were not related to alterations in preload volume, heart rate, or cardiac output.

Conclusion—In patients with newly-diagnosed HFpEF, LV filling pressures increase during dynamic exercise in association with inadequate enhancement of relaxation and acute increases in LV chamber stiffness. Therapies that enhance diastolic reserve function may improve symptoms of exertional intolerance in patients with hypertensive heart disease and early HFpEF.

Keywords

Heart Failure; Diastolic Dysfunction; Haemodynamics; Exercise; Old Age

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Competing Interests

None.

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INTRODUCTION

In the healthy human, cardiac output increases over 3-fold with exercise, through coordinated increases in heart rate, contractility, vasodilation and ventricular preload.[1] The latter, quantified by left ventricular (LV) end-diastolic volume, increases 20–40% during low-level exertion despite abbreviation of the time available for ventricular filling with tachycardia.[2] Enhanced chamber filling during exercise is accomplished with little change in ventricular filling pressures in the healthy heart, related principally to the greater “suction” of blood from atrium to a compliant LV chamber.[3] Indeed, the ability to enhance preload volume with exercise is a critical mechanism by which the aged heart maintains cardiac output responses during exercise, partially compensating for age-associated losses of systolic, chronotropic and vasodilator reserves.[4]

LV diastolic dysfunction is common with aging and is a hallmark finding among patients with heart failure with preserved ejection fraction (HFpEF),[5] leading to increases in LV filling pressures both at rest and with exertion.[6, 7, 8, 9, 10] Prior studies have investigated LV hemodynamic responses during stress in HFpEF, but were performed during stressors that are less typical of activities of daily living, such as rapid atrial pacing [11] or isometric handgrip [7, 9, 10], and little is known regarding the LV pressure-volume response to *dynamic* exercise. The current study examined hemodynamic changes with supine dynamic exercise in patients with newly-diagnosed HFpEF.

METHODS

Subjects

This was a prospective, single-center study conducted between February 2006 and April 2007 examining consecutive patients with normal LVEF (>50%) referred to the Mayo Clinic catheterization laboratory for the assessment of exertional dyspnea who were found to display invasive hemodynamic findings diagnostic of HFpEF. HFpEF was defined by invasive evidence of diastolic dysfunction: prolonged LV relaxation at rest (>48 ms) and/or elevated filling pressures: LV end diastolic pressure >15 mmHg at rest or >22 mmHg with exercise).[8, 10, 12] Patients with obstructive coronary artery disease (any stenosis $\geq 50\%$), significant valvular heart disease (any stenosis, $>$ mild left-sided regurgitation, severe tricuspid regurgitation, prior valve surgery), hypertrophic or infiltrative cardiomyopathy, pulmonary disease, atrial fibrillation, or acute pulmonary edema were excluded. Subjects were studied on chronic medications. All subjects provided informed consent, and the protocol was approved by the Mayo Clinic Institutional Review Board. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Cardiac catheterization

Left heart catheterization was performed through a 6 French sheath placed in the femoral or radial artery after minimal sedation. LV pressures were continuously measured using high fidelity micromanometer-tipped catheters (Millar Instruments, Houston, TX) and digitally saved (250 Hz). All pressures were measured at end-expiration and represent the mean of 3 beats.

Echocardiography

Transthoracic echocardiography was performed during catheterization by an experienced sonographer. High-fidelity pressure data was input directly to the echocardiography machine, projected simultaneously over Doppler spectra, and stored for off-line analysis. LV end systolic and end diastolic volumes were determined by the modified single plane

Simpson method from the apical 4-chamber view, with determination of LV mass.[13] Transmitral filling waves and E wave deceleration times were determined from pulse wave Doppler. Time-varying LV volume was derived by integrating the mitral inflow Doppler signal over time and using the end systolic and end diastolic LV volumes calculated from 2-D echocardiography.[5] Resting Tissue Doppler early diastolic velocity (e') was measured at the septal mitral annulus. Stroke volume (SV) was determined from pulse-wave Doppler of the LV outflow tract. Cardiac output was determined by the product of SV and heart rate (HR). Arterial afterload was assessed by effective arterial elastance (E_a =end systolic pressure/SV) a lumped measure of pulsatile and mean resistive arterial load.[14] Volumetric data were scaled to body surface area.

Assessment of Diastolic Function

The beginning and end of diastole were defined by peak negative pressure change and closure of the mitral valve, respectively.[15] Diastolic filling time was defined from opening to closure of the mitral valve. Minimal diastolic LV pressure (LV_{min}) was determined as a surrogate measure for early diastolic suction.[3] Mean LV diastolic pressure (mLVDP) was determined from opening to closure of the mitral valve and used as the primary index of LV filling pressures. LV end diastolic pressure (LVEDP) was determined after the atrial deflection and prior to isovolumic contraction. The time constant of isovolumic relaxation (τ) was calculated using the monoexponential zero asymptote method[16] as well as non-zero asymptote and hybrid logistic methods.[15] While the time to “complete relaxation” cannot be determined, we approximated this time after 3.5 monoexponential time constants, as shown by Weisfeldt et al.[17] The proportion of diastole which had elapsed at estimated complete relaxation was then calculated as $3.5 / \text{diastolic filling time}$ and examined as an index of relaxation reserve.[16, 17, 18]

LV volume was plotted against pressure to derive single-beat diastolic pressure-volume relationships. The linear slope of the single-beat diastolic pressure-volume relationship was designated as diastolic elastance (E_d), and was used as a measure of chamber stiffness.[15, 18] Pressure measured in this way does not accurately gauge passive ventricular stiffness properties, because relaxation is incomplete during early to mid diastole, making measured pressures higher than they would be from passive chamber filling alone.[19] In order to examine the “passive” compliance properties of the ventricle (independent of ongoing pressure relaxation), the theoretical “excess” pressure attributed to ongoing relaxation was determined from mono-exponential extrapolation of isovolumic pressure decay.[5] This excess LV pressure was then subtracted from the measured LV pressure to obtain corrected LV pressure (Figure 1).[20] Relaxation-corrected LV pressure was then plotted against the simultaneous LV volume to construct the relaxation-corrected diastolic pressure volume relationship. The linear slope of this relation (E_{dC}) was used to reflect passive diastolic chamber stiffness at rest and during exercise.

Study Protocol

Hemodynamic measurements were made at baseline and during supine exercise (cycle ergometer, $n=11$; arm weight adduction, $n=9$) performed to the level of patient exhaustion or systolic blood pressure >230 mmHg. Cycle ergometry was started at 20 Watts and increased by 20 Watts every 2 minutes, then maintained at maximally tolerated level to allow completion of echocardiographic measurements. For arm exercise, repetition frequency was gradually increased to subjective maximum tolerated effort.

Statistical analysis

Continuous variables are reported as median (interquartile range) and categorical variables as percentages. Changes in hemodynamics with exercise were assessed by Wilcoxon

Signed-Rank test. Bivariate (Pearson coefficient) linear regression was performed to test associations between changes in diastolic filling pressures and changes in hemodynamic responses during exercise.

RESULTS

Study population and Baseline hemodynamics

Subjects were predominantly older-aged men and women with chronic NYHA class II–III symptoms of exertional dyspnea (Table 1). Half were obese, 47% had left ventricular hypertrophy and 65% had left atrial enlargement. Systolic blood pressure and LV filling pressures were elevated at rest (Table 2). All subjects displayed objective evidence of diastolic dysfunction indicative of HFpEF as the etiology of chronic dyspnea: 85% displayed elevated resting LVEDP ($>15\text{mmHg}$), 50% had prolonged LV relaxation ($>48\text{msec}$), and one subject displayed diastolic dysfunction only during exercise (LVEDP $>22\text{mmHg}$).

Exercise Performance

Subjects performing cycle ergometry ($n=11$) exercised for 9.8 ± 4 minutes reaching peak workload of 60 ± 40 watts, while subjects performing arm weights ($n=9$) exercised for 5.8 ± 1 minutes. Hemodynamic responses were similar comparing cycle versus arm exercise and patients with or without chronic beta-blocker use ($p>0.1$ for all). Heart rate, blood pressure, cardiac output, and EF increased significantly with exercise (Table 2), while LV end systolic volume decreased, consistent with an increase in contractility.

LV Diastolic Reserve with exercise

While cardiac output increased with exercise, LV end diastolic volume tended to decrease ($p=0.08$), despite marked increase in LV diastolic filling pressures (Table 2). Minimum, mean and end diastolic pressures increased by 43–58% during exercise (all $p<0.0001$). The time constants of isovolumic pressure decay () tended to shorten as did the echo-Doppler isovolumic relaxation time ($p=0.003$). However, enhancement in relaxation with exercise was inadequate to compensate for rate-related shortening of the diastolic filling period, as the proportion of diastole elapsed prior to estimated complete relaxation lengthened from 32% to 50% ($p<0.0001$).

The increase in filling pressure without an increase in preload volume suggests an increase in the slope and/or position of the diastolic pressure-volume relationship. Single-beat diastolic pressure volume relationships demonstrate an acute change in position with exertion (Figure 2A), with an increase in the linear slopes of these relationships (Figure 2B), both prior to and after correcting for effects ongoing/incomplete relaxation (Table 2). E wave deceleration time, which varies inversely with chamber stiffness,[21] similarly declined with exercise.

The change in mean LVDP with exercise was correlated with acute changes in chamber stiffness ($r=0.76$, $p=0.0007$), the time constant of relaxation ($r=0.59$, $p=0.007$) and arterial elastance ($r=0.61$, $p=0.02$), but were unrelated to changes in end-diastolic volume, heart rate or cardiac output. In multivariate analysis, the combination of the changes in and Ed explained 74% of the variability in the change in mean LVDP ($p=0.0002$).

DISCUSSION

We examined left ventricular diastolic responses to dynamic exercise in stable outpatients with exertional dyspnea and normal ejection fraction who were found to have HFpEF based

upon invasive diagnostic criteria.[8, 10, 12] Marked elevations in LV filling pressure were noted during exercise, despite reductions in preload volume. Diastolic reserve with exertion was impaired: chamber elastance acutely increased, and enhancement in relaxation kinetics was insufficient to compensate for rate-related reduction in diastolic filling time. Exercise changes in relaxation and stiffness were each associated with the extent of elevation in filling pressures, as was the change in arterial afterload (Ea). These findings confirm and extend upon recent studies,[7, 8, 9, 10, 11] showing that abnormalities in diastolic reserve contribute to elevation of filling pressures with exercise in patients with hypertension and early-stage HFpEF and represent candidate therapeutic targets.

Diastolic Relaxation Reserve

Dynamic increases in cardiac output with physical exercise are achieved by augmentation in heart rate, contractility, vasodilation and diastolic ventricular chamber filling.[1, 2] The former three mechanisms become impaired with aging and in patients with chronic hypertension, making the aged, hypertensive heart more dependent upon diastolic reserve to increase cardiac output with exercise,[4] and thus more vulnerable to the deleterious effects of diastolic dysfunction. Enhanced diastolic filling is achieved via two principal mechanisms in the healthy heart: contraction to lower end systolic volumes (increasing elastic recoil), and enhanced relaxation related to β -adrenergic stimulation—promoting augmented diastolic “suction” during exercise.[3] These reserve mechanisms are lost in chronic heart failure with reduced EF, such that increased chamber filling occurs at the expense of left atrial (and ventricular) hypertension.[22]

Prior studies in healthy humans have shown that while preload volumes increase during exercise, LV filling pressures remain stable or increase only slightly.[18, 23] However, few studies have directly examined LV diastolic pressure-volume responses during dynamic exercise. Nonogi et al. showed in 9 healthy patients that isovolumic relaxation rates increase by greater than 50% with supine exercise, such that relaxation is more complete during early diastole and the ventricle can fill to greater preload volumes during a shorter interval, without increasing filling pressures.[18] In contrast, relaxation rates (assessed by τ) increased by half of this amount in the current study, and the extent of relaxation was consequently less complete in early diastole, promoting an increase in early diastolic LV minimal pressure. These findings observed during dynamic exercise are consistent with and extend upon recent studies in HFpEF patients showing blunted enhancement of diastolic relaxation during rapid atrial pacing,[11] and in response to isometric handgrip.[9]

Nonogi et al. showed in normal humans that while LV end diastolic pressures were not affected by exercise in healthy humans, viscoelastic diastolic chamber stiffness nonetheless increased, similar to increases noted in the current study.[18] However, in contrast to our data, this was due to a marked *decrease* in early diastolic LV minimal pressure in the latter study, with no change in end diastolic pressure, and this led to an increase in the slope of the pressure-volume relationship. In contrast, we found a marked *increase* in early diastolic minimal pressure in patients with early stage HFpEF, indicating insufficient ventriculoatrial suction with exercise.[22] Similar impairments in LV diastolic suction and untwist with exercise have recently been demonstrated noninvasively in elegant studies from the Sanderson laboratory in both HFpEF and hypertensives with exertional dyspnea.[24, 25] We observed an increase in the atrioventricular pressure gradient, as evidenced by an increase in the transmitral E wave velocity. This increase in the atrioventricular pressure gradient was achieved only at the expense of an increase in diastolic filling pressure, as would be expected to contribute symptoms of exertional dyspnea. The potential relevance of these findings to the pathophysiology of HFpEF are underscored by the observations that while the healthy human can increase cardiac output ~300% with little change in LV filling pressures,[1] the current study population were only able to achieve a 35% increase in

cardiac output at the cost of a 50% increase in LV filling pressures. This increase in diastolic pressures would be expected to contribute to pulmonary congestion, increase wall stress, myocardial oxygen demand and perhaps precipitate ischemia in vulnerable patients.

Comparison with Prior Studies in HFpEF

A number of recent studies have examined diastolic reserve responses to stress in hypertensive heart disease and HFpEF, both invasively and noninvasively, [6, 7, 8, 9, 10, 11, 24, 25, 26, 27, 28, 29] yet none have directly assessed LV pressure-volume responses during *dynamic* exercise. Kitzman and colleagues first showed that depressed cardiac output reserve with exercise in HFpEF was associated with a flat stroke volume response, which in turn was related to an inability to augment LV end diastolic volume.[6] This preload reserve deficit occurred despite marked increases in pulmonary capillary wedge pressure, similar to the findings noted in the current study, though LV pressures were not measured. In another seminal study examining LV pressure-volume relationships in HFpEF, Kawaguchi et al. found that while relaxation rate () was not different at rest in HFpEF compared with healthy controls, abnormalities in diastolic reserve could be precipitated during the stress of isometric handgrip.[9] Handgrip led to marked increases in blood pressure and cardiac afterload in HFpEF, and this was coupled with a prolongation of relaxation and increase in LVEDP. While we noted inadequate relaxation relative to the diastolic period, we did not detect prolongation of relaxation with stress and blood pressure elevation, as noted by Kawaguchi and colleagues.[9] This difference is likely due to fundamental differences in hemodynamic responses to isometric and dynamic exercise stressors.[30]

The current results are the first to our knowledge to describe acute increases in viscoelastic chamber stiffness during dynamic exercise in human HFpEF. Westermann and colleagues recently showed that both diastolic stiffness and relaxation are impaired in HFpEF compared to healthy controls at baseline, and that isometric handgrip leads to greater increases in LV filling pressures in HFpEF.[7] However, in contrast to the current study, they did not observe that chamber stiffness was acutely altered during exercise—it was similarly more abnormal at rest and during exercise compared with controls, with no stress-induced exacerbation.[7] The reason for these disparate findings in our study are not clear, but may relate to differences in the type of exercise performed (handgrip versus dynamic ergometry [30]), the duration of exercise (mean of 8 minutes in current vs 1.5 minutes in prior study), the methodology (single vs multi-beat technique) or the HFpEF populations enrolled. Penicka and colleagues reported an increase in the ratio of LVEDP to end diastolic volume with isometric handgrip in early HFpEF,[10] and Ha et al. observed an increase in Ed as estimated by the ratio of E/e to stroke volume [29] The current data shows that these changes in filling pressure are likely due to a shift up in slope *and* position of the diastolic pressure volume relationship (Figure 2). We noted a significant reduction in mitral E wave deceleration time, which varies inversely with chamber stiffness, providing further independent evidence for an acute increase in operant LV diastolic stiffness with exercise. [21]

Impact of Afterload

Elevated arterial elastance is characteristic of both hypertension alone and hypertensive HFpEF,[13] and the drop in arterial stiffness with low-level exercise is known to be attenuated in HFpEF.[28] There is important crosstalk between afterload and diastolic function, such that abnormal vascular loading may contribute to or exacerbate diastolic reserve in these diseases.[31] Indeed, both diastolic relaxation and chamber compliance are reduced with acute increases in afterload in animal models and some human studies,[14, 31, 32, 33] and recent data suggests that blood pressure reduction may enhance diastolic relaxation.[34] The significant correlation between the increases in arterial afterload (Ea)

and changes in LV filling pressures in the current study lends further support to the relationship between abnormal LV loading and diastolic reserve in HFpEF.

Limitations

This study did not include a control group; therefore we cannot determine how the observed changes in diastolic reserve in HFpEF would compare with hemodynamic responses to dynamic exercise in normal humans. However, prior studies have shown that filling pressures remain stable despite increases in LV preload during exercise in healthy humans, [23] in association with more dramatic enhancement of relaxation than observed here.[18] The theoretical time to “complete” relaxation was estimated as 3.5 time constants. This is an oversimplification that assumes the monoexponential model can be extrapolated beyond the points where the data is analyzed and that filling does not alter relaxation, and these assumptions were likely violated, though prior studies support this approach[17] and it is only intended as an approximation. The true diastolic pressure-volume relationship is curvilinear rather than linear (as estimated here), and is optimally measured from pressure-volume points obtained during diastasis at variable preload using caval occlusion.[15] This was not feasible to perform during dynamic exercise, thus we relied upon single-beat techniques. Approximately 40% of LV pressure is due to extrinsic restraint from right heart and pericardial interaction,[15] and these forces were not measured and likely contributed to rest and exercise pressures. Prior studies have found that the proportionate contribution of extrinsic forces to LV pressures remains fairly constant during exercise,[8, 15] though we cannot determine what effect pericardial restraint had on the shape, position or slope of the measured diastolic pressure-volume relationships at rest or with exercise in this study. The type of exercise (arm versus leg) was not standardized, though both were dynamic.

Conclusions

Patients with early HFpEF develop increased LV diastolic filling pressures during supine exercise in concert with acute increases in chamber stiffness and an inability to enhance relaxation to compensate for shortening of diastolic filling time. Dynamic increases in filling pressures correlate with the changes in relaxation, chamber stiffness and afterload during exercise, suggesting that these play important roles in limiting diastolic reserve function and contributing to symptoms of exertional intolerance. Therapies targeting diastolic reserve and abnormal vasodilation with exercise may mitigate symptoms of exertional dyspnea in patients with heart failure and preserved ejection fraction.

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Figure 1.

Estimation of left ventricular (LV) passive diastolic stiffness: “corrected” LV pressure (dotted red line) is obtained by subtracting the “relaxation pressure” (dashed blue line), obtained by mono-exponential extrapolation of the isovolumic relaxation period, from the measured LV pressure. This “corrected pressure” is then plotted against simultaneous LV volume, and the points (red dots) are fitted into a straight line.

Figure 2.

[A] Summary data for diastolic pressure-volume relationships of all patients at rest (black) and with exercise (gray), plotting both raw (solid lines) and relaxation-corrected data (dashed lines). With exercise, the position of the diastolic pressure-volume relationship curve shifts upward, with increasing pressure despite similar chamber volume. [B] Chamber stiffness, determined from the linear slopes of [A] similarly showed significant increases in chamber stiffness during exercise.

Table 1

Baseline characteristics

	Median (IQR) or %	Range
<i>Clinical Characteristics</i>		
Age (years)	67 (58–75)	44–82
Female (%)	55	
Body mass index (kg/m ²)	30.2 (27.6–32.2)	21.9–40
Obese (%)	50	
Diabetes Mellitus (%)	15	
Beta blockers (%)	50	
ACEI/ARB (%)	65	
Diuretics (%)	50	
Serum creatinine (mg/dl)	1.0 (1.0–1.1)	0.6–1.2
Hemoglobin (mg/dl)	13.0 (12.5–13.9)	10.6–17.4
<i>Echocardiography</i>		
LV mass index (g/m ^{2.7})	40.9 (35.4–54.2)	25.4–59.0
LV hypertrophy (%)	47	
Ejection Fraction (%)	62 (58–65)	50–70
Left Atrial volume index (ml/m ²)	35 (26–42)	17–64
Left Atrial Enlargement (%)	65	
E velocity (cm/s)	6.9 (5.8–7.5)	4.0–9.0
E/e ratio	12 (9–16)	8–20

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers

Table 2**Resting and Exercise Hemodynamics**

	Rest (n=20)	Exercise (n=20)	Exercise Change	P
<i>Integrated Responses</i>				
Heart rate (min ⁻¹)	66 (60–72)	92 (78–105)	+39%	<0.0001
Systolic blood pressure (mmHg)	144 (132–154)	200 (159–206)	+39%	<0.0001
Arterial Elastance (mmHg/ml)	1.62 (1.40–1.92)	2.26 (1.85–2.75)	+40%	0.0009
Cardiac index (L/min/m ²)	2.62 (2.34–3.35)	3.50 (3.00–4.50)	+34%	0.0001
<i>LV systolic function</i>				
Ejection fraction (%)	66 (62–71)	71 (67–72)	+8%	0.04
Stroke volume index (ml/m ²)	40 (34–47)	40 (35–48)	–	0.6
LV ESVI (ml/m ²)	18 (15–20)	15 (12–19)	–17%	0.008
<i>LV diastolic function</i>				
LV EDVI (ml/m ²)	53 (46–57)	50 (44–57)	–	0.08
LV _{min} pressure (mmHg)	9 (6–11)	14 (10–18)	+56%	<0.0001
Mean LVDP (mmHg)	14 (10–16)	20 (16–27)	+43%	<0.0001
LVEDP (mmHg)	19 (16–23)	30 (26–39)	+58%	<0.0001
ME (ms)	48 (45–54)	44 (35–51)	–8%	0.09
NZ (ms)	59 (54–86)	45 (36–64)	–24%	0.06
L (ms)	27 (23–34)	19 (16–26)	–30%	0.06
% Diastole to complete relax	32 (26–37)	50 (40–61)	+56%	<0.0001
Ed (mmHg/ml/m ²)	0.47 (0.37–0.67)	0.69 (0.46–0.90)	+47%	0.002
Ed _C (mmHg/ml/m ²)	0.54 (0.45–0.66)	0.82 (0.68–1.05)	+52%	0.0003
<i>Transmitral Flow</i>				
E wave (cm/s)	81 (72–94)	109 (88–114)	+35%	0.002
Deceleration time (msec)	196 (175–231)	129 (117–147)	–34%	0.003
IVRT (ms)	67 (50–98)	46 (39–61)	–31%	0.003
E/A ratio	1.28 (0.81–2.08)	1.31 (0.93–1.81)	–	0.6

LV: left ventricle; ESVI: end systolic volume index; EDVI: end diastolic volume index; LV_{min}: minimal diastolic LV pressure; LVDP: LV diastolic pressure; ME, NZ, HL: monoexponential, non-zero asymptote and hybrid logistic time constants of LV isovolumic relaxation; Ed: LV diastolic elastance; Ed_C: relaxation-corrected LV diastolic elastance; IVRT: isovolumic relaxation time.