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SHORT COMMUNICATION

Impaired myocardial relaxation with exercise determines peak aerobic exercise capacity in heart failure with preserved ejection fraction

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Abstract

Background Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by impaired exercise capacity due to shortness of breath and/or fatigue. Assessment of diastolic dysfunction at rest and with exercise may provide insight into the pathophysiology of exercise intolerance in HFpEF.

Aims To measure echocardio-Doppler-derived parameters of diastolic function as they relate to various indices of aerobic exercise capacity in HFpEF.

Methods We selected 16 subjects with clinically stable HFpEF, no evidence of volume overload, but impaired functional capacity by cardiopulmonary exercise testing [peak oxygen consumption (VO_2)]. We measured the transmitral E and A flow velocities, E/A ratio, and E deceleration time (DT) and tissue Doppler E′ velocity. We also indexed the E′ to the DT, as additional measure of impaired relaxation (E'_{DT}), and calculated the diastolic functional reserve index (DFRI), as the product of E′ at rest and change in E′ with exercise.

Results E′ velocity, at rest and peak exercise, as well as the DFRI positively correlated with peak VO_2, whereas DT, E'_{DT}, and E/E′ with exercise inversely correlated with peak VO_2. Of note, the E'_{DT} at rest also significantly predicted E′ velocity at peak exercise (R = +0.81, $P < 0.001$). Exercise E′ was the only independent predictor of peak VO_2 at multivariable analysis (R = +0.67, P = 0.005).

Conclusions The E′ velocity at peak exercise is a strong and independent predictor of aerobic exercise capacity as measured by peak VO_2 in patients with HFpEF, providing the link between abnormal myocardial relaxation with exercise and impaired aerobic exercise capacity in HFpEF.

Keywords Diastole; Heart failure; Doppler; Exercise

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Background

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome characterized by impaired cardiac function, mainly diastolic, that induces exertion-limiting shortness of breath and fatigue.[1] Abnormalities in the echocardio-Doppler derived parameters of diastolic function are present in patients with HFpEF and are part of the European Society of Cardiology recommended diagnostic criteria.[2] One such parameter, the early diastolic mitral annular velocity (E′), reflects the elastic recoil and the early active phase of relaxation during diastole.[3] Assessment of myocardial relaxation, however, is limited if completed only at rest, as the initiation or significant worsening in symptoms occurs primarily with physical exertion.

Aims

The aim of this study was to measure myocardial relaxation using the E′ velocity at rest and peak exercise in patients with symptomatic HFpEF limited by shortness of breath and/or fatigue, as it relates to various indices of aerobic exercise capacity, and to other echocardio-Doppler derived parameters of systolic and diastolic function.

Methods

We selected 16 subjects with symptomatic HFpEF [New York Heart Association (NYHA) functional class II–III] who showed impaired functional capacity due to shortness of breath or fatigue. Heart failure with preserved ejection fraction was diagnosed on the basis of clinical, Doppler echocardiography, laboratory, and/or hemodynamic data according to the European Society of Cardiology recommendations.[2] Patients with moderate–severe valvular heart disease, pericardial disease, restrictive cardiomyopathy, pulmonary artery hypertension (group I), atrial fibrillation, obstructive pulmonary disease, anaemia (haemoglobin <11 g/dL or ferritin <100 μg/L), or mechanical limitation to exertion due to musculoskeletal or neurologic disease were excluded.

We measured Doppler echocardiography parameters of systolic and diastolic function, including left ventricular end-diastolic and end-systolic volumes, stroke volume, ejection fraction (LVEF), transmitral flow velocities [E, A, E/A ratio, and E wave deceleration time (DT)], tissue Doppler-derived early diastolic mitral annular velocity (E′), and longitudinal systolic strain (S′) measured at tissue Doppler averaged between lateral and septal according to the American Society of Echocardiography recommendations.[4] We also indexed the E′ velocity by the DT to obtain a measure (E'_{DT}) that reflected both the delay in relaxation (DT) and the peak velocity in diastolic filling (E′). A higher E′ and shorter DT would reflect better myocardial relaxation, whereas reduced E′ or prolonged DT would each reflect impaired relaxation with an additive value. E, E′ and E/E′ ratio were also measured at peak exercise by having the patient sit down immediately after interruption of the exertion and obtaining an apical view within 1 min. The interval change in E′ and E/E′ were calculated ($\Delta E'_{exercise}$ and $\Delta E/E'_{exercise}$, respectively), as was the diastolic functional reserve index (DFRI), defined as the product of $E'_{rest} \bullet \Delta E'_{exercise}$.[5] Subjects were also asked to complete the Duke Activity Status Index (DASI) and the Minnesota Living With Heart Failure (MLWHF) questionnaires to estimate functional capacity.

Cardiopulmonary exercise testing (CPX) was performed using a metabolic cart that interfaced with a treadmill using a conservative ramping protocol according to the American Heart Association recommendations,[6] as previously described by our group.[7] Expired gases were sampled using a mouthpiece-mounted sensor and were analysed to continuously measure oxygen (O_2) uptake. The highest 10 s interval average value within the final 30 s of exercise was used to define peak oxygen consumption (VO_2) and expressed as (i) an absolute value (mL/kg); (ii) an indexed by body weight (mL/kg/min); and (iii) a percent (%) of predicted values according to age, gender, and ideal body weight. Subjects in whom exertion was limited by angina (with or without ECG changes), uncontrolled hypertension, or arrhythmias were excluded.

Data were reported as median and interquartile range. Correlations between two variables were analysed using the Spearman correlation test. Multivariable linear regression analysis with a stepwise approach was used to assess for collinearity and associations between the dependent and independent variables.

Results

Table 1 shows the demographic characteristics of the subjects. Twelve (75%) were women; median age was 55

Table 1 Characteristics of the subjects

Age, years	55 (51–60)
Sex, male/female	4 (25%)/12 (75%)
Race, Caucasian/African–American	7 (44%)/9 (56%)
Body mass index (kg/m^2)	41 (37–46)
Arterial hypertension	13 (81%)
Diabetes mellitus	11 (69%)
NT-proBNP (ng/mL)	174 (70–308)
NYHA functional class, II/III	7 (44%)/9 (56%)
DASI score	21.4 (11.4–31.3)
MLWHF score	66.5 (45.5–74.5)
Echocardio-Doppler parameters	
Left ventricular ejection fraction, %	60 (57–65)
Stroke volume, mL	69 (58–74)
Longitudinal strain (tissue Doppler), cm/s	7.9 (6.9–8.1)
E′ velocity, cm/s	6.9 (5.2–9.1)
E/E′ ratio	10.7 (8.6–15.1)
E/A ratio	1.1 (0.9–1.5)
DT, ms	230 (192–288)
E′ indexed by DT (E'_{DT})	0.034 (0.021–0.047)
Exercise E′ velocity, cm/s	10.1 (8.2–12.5)
Exercise E/E′	10.7 (8.0–12.5)
Diastolic functional reserve index (DFRI)	18.5 (9.2–31.3)
Functional capacity	
Exercise time, min	8.2 (7.0–9.7)
Respiratory exchange ratio	1.09 (1.04–1.13)
Peak oxygen consumption (VO_2), mL/min	1,742 (1,534–2,193)
Peak oxygen consumption (VO_2), mL/kg/min	15.8 (13.5–17.9)
Peak oxygen consumption (VO_2), mL/kg/min; % predicted	57 (46–72)

DASI, Duke Activity Status Index; DFRI: Diastolic functional reserve index; DT, Deceleration time of the early filling at transmitral flow pulsed waved Doppler; E, Early velocity of transmitral flow at pulsed wave Doppler; E′, Early velocity of the mitral annulus at pulsed wave tissue Doppler; MLWHF, Minnesota Living with Heart Failure; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; NYHA, New York Heart Association; Peak VO_2, peak oxygen consumption at cardiopulmonary exercise testing.

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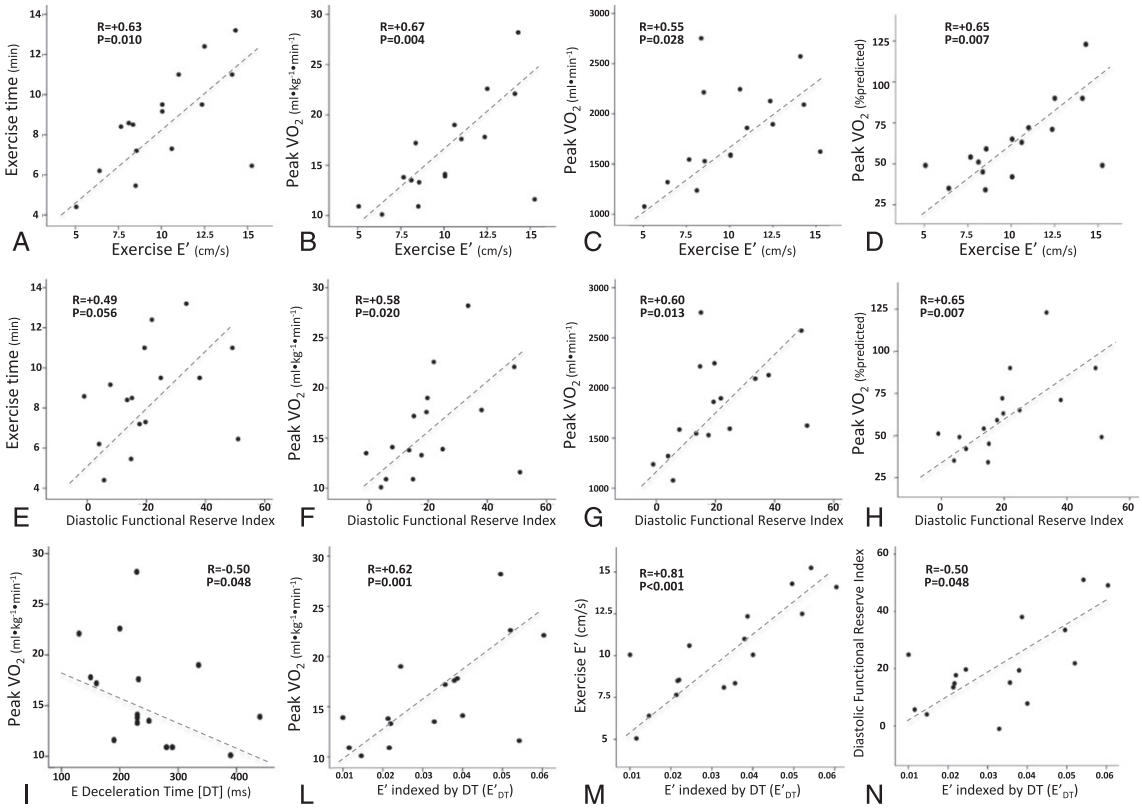
Figure 1 Correlation between echocardio-Doppler derived measures of impaired myocardial relaxation and aerobic exercise capacity in patients with heart failure and preserved ejection fraction.



(51–60) years. The duration of exercise was 8.5 min (6.6–10.6) with a peak VO_2 of 14.0 (12.0–18.7) mL/kg/min. LVEF was 60% (57–65).

Median E′ at rest and peak exercise were 6.9 cm/s (5.2–9.1) and 10.1 cm/s (8.2–12.5) ($P = 0.001$ for the change), respectively, whereas the E/E′ ratio at rest and peak exercise were 10.7 (8.6–15.1) and 10.7 (8.0–12.5) ($P = 0.28$), respectively.

E′ velocity, at rest and at peak exercise, and the DFRI ($=E'_{rest} \bullet \Delta E'_{exercise}$) positively correlated with exercise time and peak VO_2 expressed in relative (mL/kg/min), absolute (mL/min), and percent (%) of predicted values (*Figure 1*), whereas exercise E/E′ was inversely correlated with exercise time ($R = -0.51$, $P = 0.042$) and peak VO_2 ($R = -0.45$, $P = 0.079$).

While both E′ velocity at rest and E wave DT at rest significantly correlated with peak VO_2 ($R = +0.52$, $P = 0.040$ and $R = -0.50$, $P = 0.048$, inversely), the E′ velocity indexed by DT (E'_{DT}) at rest more strongly correlated with peak VO_2 ($R = +0.62$, $P = 0.010$).

We found no statistically significant association between end-diastolic or end-systolic volumes, stroke volume, ejection fraction, or longitudinal systolic strain at tissue Doppler and exercise time or peak VO_2 (all $P > 0.30$).

A multivariable analysis that included E/A, DT, E′, E'_{DT}, E/E′ at rest, E′ and E/E′ with exercise, $\Delta E'_{exercise}$, $\Delta E/E'_{exercise}$, and DFRI found exercise E′ was the only independent predictor of peak VO_2 ($P = 0.005$)—such analysis, however, may be limited by collinearity and should be considered as explorative only.

Of note, E′ velocity ($R = +0.71$, $P = 0.002$), DT ($R = -0.56$, $P = 0.023$), and, even more strongly, E'_{DT} ($R = +0.81$, $P < 0.001$) at rest predicted exercise E′ (*Figure 1*).

Conclusions

Impaired diastolic reserve, measured as an inadequate increase in myocardial relaxation, is considered a hallmark of HFpEF and is associated with a progressive decline in exercise capacity.[1,5,8] However, measuring diastolic parameters only at rest may not reveal the severity of limitation in patients suffering from this syndrome. In the current study, we found that impaired myocardial relaxation during exertion, measured with the E′ velocity at peak exercise, is a strong and independent predictor of aerobic exercise capacity as measured by peak VO_2 in a cohort of relatively young obese female patients with HFpEF. It has been shown that E′ correlates with the invasively measured constant of isovolumetric relaxation time (τ), which is almost universally abnormal in HFpEF.[9] The correlation between E′ and τ is

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independent of the left ventricular filling pressure,[10] and E′ is a strong independent predictor of outcomes,[11] thus representing an ideal marker of myocardial relaxation. In conditions of normal filling pressures, the E wave DT also linearly correlates with τ,[4,5] and as such, it predicted impaired peak VO_2 in our cohort. Exercise E′ showed the strongest and independent association with peak VO_2 at multivariable analysis, and this is likely related to the fact that the E′ velocity at peak exercise is dependent upon both the E′ velocity at rest and the ability to accommodate increased venous return with exercise. While other studies have shown increased left ventricular filling pressures during exercise, this study specifically shows that the impairment in myocardial relaxation, measured with E′ velocity, is abnormal and drives exercise intolerance in HFpEF. Measuring E′ velocity at peak exercise is a challenge considering the potential difficulty in obtaining apical pulsed-wave Doppler recording at peak exercise. In our data, we find that exercise E′ could be predicted by resting E′ and the E wave DT, both independent markers of impaired relaxation. When indexing E′ by DT, to reflect both peak velocity of volume accommodation and the delay in myocardial relaxation, the E'_{DT} at rest appeared to be a strong predictor of exercise E′. The link between E'_{DT} at rest and exercise E′ provides both a physiologic explanation of an impairment in the augmentation of E′ due to a prolonged DT and also a means to estimate peak VO_2 using resting data (i.e. E′ and DT).

Altogether, the predictive behaviour of E'_{DT} and exercise E′ provides the link between abnormal myocardial relaxation with exercise and impaired aerobic exercise capacity in patients with HFpEF. This small single study has important limitations that may limit external validity, primarily because it included mainly moderately-to-severely obese female patients with controlled hypertension and levels of NT-proBNP that in many cases would not exceed the proposed cut-off value for HFpEF, a phenotype that may differ from older female patients with uncontrolled hypertension and/or severe left ventricular hypertrophy. Nevertheless, these findings may have diagnostic, prognostic, and therapeutic implications. From a diagnostic standpoint, the association of the diastolic parameters and in particular of the E′ velocity with impaired functional capacity reinforces the view that impaired diastolic function is key phenomenon in this HFpEF subgroup.[1,11] The close association between E′ velocity with exercise, and of E'_{DT}, with peak VO_2, a well-validated prognostic indicator in HF,[6] supports the concept that the severity of the impaired myocardial relaxation is an important factor in the pathophysiology of HFpEF. Therefore, therapies that enhance myocardial relaxation and diastolic functional reserve function may provide a novel approach to improve symptoms of exertional intolerance in a subgroup of patients with HFpEF.

Conflict of interest

None declared.

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