Effects of Exercise on Left Ventricular Systolic and Diastolic Properties in Patients with Heart Failure and a Preserved Ejection Fraction versus Heart Failure and a Reduced Ejection Fraction

Zile et al: Exercise in Heart Failure

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Abstract

Background—The purpose of the current study was to define exercise-induced changes in indices of left ventricular (LV) systolic and diastolic properties in patients with chronic heart failure (HF), compare these changes in patients with HF and a reduced ejection fraction (HFrEF) versus HF and a preserved EF (HFpEF), and compare the hemodynamic responses to activities of daily living versus symptom limited upright exercise.

Methods and Results—HFpEF subjects (n=8) and HFrEF subjects (n=5) underwent symptom limited Naughton protocol treadmill exercise tests. Implantable hemodynamic monitor (IHM) data and echocardiographic data were obtained prior to exercise and at peak exercise. IHM data were obtained during activities of daily living over a 24 hour time period. In HFrEF patients, limited exercise time (639±164 seconds) was associated with a marked rise in right ventricular (RV) systolic, diastolic, and estimated pulmonary artery diastolic (ePAD) pressures and an increase in LV end diastolic volume (EDV). LV systolic properties; EF, end systolic elastance (Ees), stroke work (SW), preload recruitable SW all decreased. The ePAD/EDV ratio increased; to a large extent this was dependent on an increase in EDV. By contrast, in HFpEF, limited exercise time (411±128 seconds) and the marked rise in RV systolic, diastolic, and ePAD pressures were associated with no change in LV EDV. LV systolic properties increased or were unchanged; ePAD/EDV ratio increased during exercise but the increase was independent of a change in EDV. The ranges of RV systolic, diastolic, and ePAD pressures during activities of daily living were higher than the ranges of these values during the exercise stress test.

Conclusions—While exercise limitations were similar between HFrEF and HFpEF, there were significant differences in exercise-induced changes in LV systolic and diastolic properties. These differences likely reflect the different pathophysiology of these clinical syndromes of heart failure.

Key Words: heart failure, exercise, systolic function, diastolic function
Exercise intolerance is a cardinal symptom of patients with chronic heart failure (CHF). Symptoms of exertional fatigue and dyspnea are universally present and present to a comparable extent in patients with heart failure and a reduced ejection fraction (HFrEF) and patients with heart failure and a preserved ejection fraction (HFpEF) (1, 2). These symptoms are attributed to an inability to fill the left ventricle at typically low pressures during exercise and the inability to increase cardiac output sufficiently to meet the metabolic demands of exercise. Healthy middle aged subjects can augment diastolic filling while maintaining normal diastolic pressure during exercise and increase cardiac output approximately four fold through a combination of increased heart rate and stroke volume (3, 4). Previous studies using symptom limited exercise testing have suggested that an abnormal response to exercise in CHF patients may be associated with changes in left ventricular (LV) systolic properties, diastolic properties and / or chronotropic incompetence (5-13). However, whether these functional changes are comparable in patients with HFrEF versus HFpEF has not been completely defined. In addition, recent studies have suggested that even activities of daily living in CHF patients can result in large changes in hemodynamic profile (14). However, whether the hemodynamic response to daily activity is comparable to the hemodynamic response to symptom limited exercise in patients with HFrEF versus HFpEF has not been clearly defined. Defining these exercise-induced changes in systolic properties and diastolic properties in different forms of heart failure may have both diagnostic and therapeutic clinical implications. The purpose of the current study was to define the exercise-induced changes in left ventricular (LV) systolic and diastolic properties in patients with CHF, compare these changes in patients with HFrEF versus HFpEF, and compare the hemodynamic responses to activities of daily living versus symptom limited upright exercise.
Methods

Patients

The current study was a sub-study of the COMPASS-HF trial (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) (15). After completion of the six month randomization period and when the patients were clinically stable, they were enrolled in the exercise sub-study. Eight COMPASS-HF subjects who had documented HFrEF (EF ≥ 50%) and 5 subjects with HFrEF (EF < 50%) were enrolled. The inclusion and exclusion criteria for the COMPASS-HF study have been described previously (15). Briefly, patients were eligible for the study if they were ≥ 18 years old, had New York Heart Association (NYHA) class III or IV heart failure, were managed in a heart failure program with optimized medical therapy for at least 3 months prior to enrollment, and had at least 1 heart failure related hospitalization or emergency department visit necessitating intravenous treatment within the previous 6 months. Patients were excluded from the study if they had severe chronic obstructive or restrictive pulmonary disease, primary pulmonary hypertension; a major cardiovascular event within 3 months prior to enrollment; known atrial or ventricular septal defects, tricuspid or pulmonic stenosis, or mechanical right heart valves; a severe, non-cardiac condition limiting 6 month survival; serum creatinine ≥ 3.5 mg/dL or chronic renal dialysis; or were likely to undergo cardiac transplantation within 6 months of enrollment, were receiving continuous positive inotropic therapy, were presently implanted with an incompatible pacemaker or implantable cardioverter-defibrillator, were receiving cardiac resynchronization therapy that had not achieved optimal programming for 3 months; or were of childbearing age and were not using reliable contraceptive measures.
For the exercise sub-study the following criteria were added; the subject must have been able to perform a Naughton exercise protocol, must not have had unstable angina within past 8 weeks, recent MI or bypass, or valvular surgery (within 8 weeks) or symptomatic aortic stenosis. The Naughton protocol was chosen to ensure that an adequate stress was imposed and a sufficient time of the treadmill would be possible in a group of subjects with severe heart failure.

The investigational review board of each participating institution approved the study and sub-study protocols, and all patients provided written informed consent for both study and sub-study.

Study Design and Measurements

Patients enrolled in the exercise sub-study underwent a symptom limited, upright, graded exercise test using a Naughton protocol on a treadmill. Implantable hemodynamic monitor (IHM) derived pressure data, heart rate data, blood pressure data and echocardiographic data were obtained at baseline prior to exercise and at peak exercise. In addition, IHM data were obtained during activities of daily living over 24 hour time periods from 7 days before the day of exercise study.

The IHM measurements made in this study included two sets of data: a- those associated with activities of daily living (ambulatory), and b- those associated with the treadmill test (exercise). For ambulatory activities of daily living, the median, minimum, and maximum values during each 24 hour period from 7 days prior to the day of exercise testing were obtained (16). For the treadmill exercise, values were obtained just before, during, and after the exercise treadmill test.

The IHM used in this study measured right ventricular (RV) systolic pressure, RV diastolic pressure, RV pulse pressure, an estimate of pulmonary artery diastolic pressure (ePAD),
maximum positive and negative change in pressure over time (+ and - dP/dt), heart rate and activity. The system components, implantation procedure, monitoring, storage and retrieval methods, and pressure analysis methods have been previously described (15). While the specific implantable hemodynamic monitoring (IHM) device used in the current study is no longer under development, there are currently at least 2 IHM technologies under development and study. These include pulmonary artery and left atrial pressure monitors. None of these technologies are currently approved for clinical use in the USA, but each is being examined in randomized clinical trials. Prior to beginning the exercise test, the IHM device was programmed to a high resolution data mode which allowed the device to capture hemodynamic data every 2 seconds. At the end of the study the IHM device was programmed to restore the original setting for continued heart failure management.

A baseline echocardiogram, performed in a supine position, captured the short and long parasternal views, apical 2, 4 and 5 chamber views; however, Doppler and Tissue Doppler studies were not done as part of this exercise protocol. After the initial echocardiogram, the patient performed a Naughton protocol on an exercise treadmill. At peak exercise the subject dismounted the exercise treadmill, returned to the supine position, and a second echocardiogram was immediately performed. Echocardiographic views were captured in the following order: apical 4 chamber, parasternal short, parasternal long, apical 2 and 5 chamber views. At the end of the second echocardiogram, the IHM data was uploaded and saved to a disk. Blood pressure was measured with the BP cuff at baseline, during each exercise stage, at peak exercise, and during the recovery period.

Echocardiographically determined LV dimensions and wall thickness were measured according to the recommendations of the American Society of Echocardiography (17, 18).
Calculations of LV volume and mass were made using standard published methods (17, 18). Analysis of the echocardiographic data was performed in a core laboratory at the Medical University of South Carolina. All images were coded and interpreted by a single research sonographer who was blinded to patient identity and the order of study. No normal referent control subjects were included in this study because there would not have been an indication for placement of an IHM and they would not have been candidates for the COMPASS-HF study. Therefore, hemodynamic, structural and functional data examined in HFrEF and HFpEF patients in the current study were qualitatively compared to the normal ranges for these parameters that were published recently as part of the I-Preserve echo-substudy (19).

The systolic properties of the left ventricle were assessed and evaluated by examining indices that reflect LV performance, function, and contractility (20). LV systolic performance was assessed by calculating stroke volume (SV, end diastolic volume - end systolic volume) and stroke work (SW, LV pressure-volume area). The pressure-volume area was calculated using data from 4 time points: mitral valve opening (MVO), MV closure (MVC), aortic valve opening (AVO), AV closure (AVC), using methods similar to previous studies. The pressures and volumes at each of these time points were calculated as follows:

- at MVO, LV volume = ESV, LV pressure = ePAD/2,
- at MVC, LV volume = EDV, LV pressure = ePAD,
- at AVO, LV volume = EDV, LV pressure = mean BP and,
- at AVC, LV volume = ESV and LV pressure = mean BP.

Using the latter method (rather than SV x mean BP) allows consideration of changes in diastolic compliance to be taken into account. The rationale for estimating LV pressure at end systole as ePAD/2 is based on previous studies in both HFrEF and HFpEF demonstrating that early
diastolic pressure at MVO is \( \frac{1}{2} \) the value at end diastole (21). LV systolic function was assessed as LV ejection fraction and preload recruitable stroke work (PRSW, single beat method) (20). LV contractility was assessed as end systolic elastance (Ees) which was defined as the slope of the end systolic pressure–volume relationship (ESPVR) calculated using a single beat method of (20). Effective arterial elastance (Ea) was assessed as the ratio of ESP versus SV and was used in the calculation of an arterial-ventricular coupling index: Ea/Ees (20).

The diastolic properties of the left ventricle were assessed by measuring ePAD, end diastolic stress, and the ratio of ePAD to EDV; the ePAD/EDV ratio was used to reflect operative end diastolic distensibility.

**Statistical Analysis**

Due to the small sample size in this study, five HFrEF patients and eight HFpEF patients, interpretation of the concepts presented were driven primarily by the descriptive statistics. Statistical tests were also conducted to aid in the interpretation of the data. Due to the small sample size, non-parametric statistical tests were chosen.

Statistical comparison of demographic, hemodynamic, structural, and functional data at baseline *between* HFrEF vs. HFpEF patients was made using a Wilcoxon Rank Sum test. Similarly, changes in IHM pressures, blood pressure and echocardiographic data before to after exercise or during activities of daily living *between* HFrEF and HFpEF groups were made using a Wilcoxon Rank Sum test. Changes in IHM pressures, blood pressure and echocardiographic data *within* a group before and after exercise or during activities of daily living were compared using a Wilcoxon Signed Rank test. P-values presented are two-sided and nominal. P-values \( \leq 0.05 \) or \(<0.1\) are provided in Tables 1-2. These 2 partition values indicating level of statistical
significance were chosen because of the small sample sizes and the limits of the non-parametric
to detect a P-values < 0.05 under these circumstances. Data presented in the tables are mean ±
SD and median, minimum, maximum. Data presented in the figures are mean ± SE. Spearman’s
correlation coefficient was used to calculate correlation. Statistical analyses were also performed
using parametric tests consisting of two-sample t-tests and Person’s correlation; these are
presented in supplement one. Data management and statistical analyses were conducted by the
study’s sponsor, Medtronic, Inc. An independent core lab at MUSC blinded to the patient and
timing of the echo was utilized for echo analysis. The authors had full access to and take full
responsibility for the integrity of the data. All authors have read and agree to the manuscript as
written.

Results

Demographics

The HFrEF patients were 55±17 years old, 4 male and 1 female, and had a BSA of 2.2±0.3 m².
All patients were being treated with a β-blocker, angiotension converting enzyme inhibitor or
angiotension receptor antagonist, and a diuretic. Three patients had a history of hypertension, 3
had diabetes, 3 had coronary artery disease, and all were NYHA class III.

The HFpEF patients were 61±7 years old, 3 male and 5 female, and had a BSA of 2.4±0.2
m². All patients were being treated with a β-blocker, angiotension converting enzyme inhibitor
or angiotension receptor antagonist, and a diuretic. All patients had a history of hypertension, 4
had diabetes, 3 had coronary artery disease, and all were NYHA class III.
Baseline Structure and Hemodynamics

HFrEF patients were characterized by eccentric remodeling with an increased EDV of 236±58 ml and LV mass of 314±75 g, and decreased relative wall thickness of 0.29±0.09 cm compared with published referent control values (19, 22). RV systolic, diastolic, and ePAD pressures were increased at baseline (Table 1).

HFpEF patients were characterized by concentric remodeling with a normal EDV of 130±33 ml, increased LV mass of 237±40 g and increased relative wall thickness of 0.45±0.06 cm. RV systolic, diastolic, and ePAD pressures were increased at baseline. Compared with HFrEF, patients with HFpEF had a smaller volume and mass, a larger mass / volume ratio but similar abnormalities in RV systolic, diastolic, and ePAD pressures. Heart rate was normal in both HFrEF and HFpEF patients. Systolic and diastolic arterial pressures were lower in HFrEF compared to HFpEF.

Response to Exercise in HFrEF Patients

On average, patients with HFrEF exercised on the treadmill for 639±164 seconds (Table 1). This limited exercise time was associated with a small rise in heart rate and blood pressure but a marked rise in RV systolic, diastolic, pulse, and ePAD pressures. EDV, ESV and CO increased during exercise compared with baseline. LV systolic properties decreased during exercise compared with baseline; EF, Ees, SW, PRSW all decreased (Table 2). The ePAD/EDV ratio increased during exercise compared with baseline; to a large extent the increase in ePAD/EDV was dependent on an increase in EDV (Table 2 and Figures 1 and 2). There was an inverse relationship between the increase in EDV and the baseline ePAD; the larger baseline ePAD, the smaller the change in EDV (r = - 0.72).
The ranges of ambulatory and exercise RVSP, ePAD, RVDP and RVPP for HFrEF patients are illustrated in Figure 3. The shaded bars show the range of ambulatory pressures averaged over seven days before the day of the exercise testing. The solid bars show the range of pressures from rest to peak exercise during symptom limited treadmill exercise. For all variables, the range in pressures was larger during ambulatory activities of daily living than during symptom limited treadmill exercise. With the exception of maximum values of RVPP, the maximum values during symptom limited exercise were lower and the minimum pressures during symptom limited exercise were higher then the corresponding maximum and minimum pressures seen during ambulatory activities.

Both during exercise and ambulatory measurements the heart rate ranged from minimum values of 60 ± 10 to maximum values of 122 ± 19 bpm (in both the HFrEF and HFpEF patients). These data suggest that the degree of exertion during activities of daily living was of a comparable scale to the degree of exertion during symptom limited exercise testing and that this extent of exertion was limited by comparable symptoms.

**Response to Exercise in HFpEF Patients**

On average patients with HFpEF exercised on the treadmill for 411±128 seconds (Table 1). This limited exercise time was associated with a rise in heart rate and blood pressure and a marked rise in RV systolic, diastolic, pulse and ePAD pressures. These changes in RV pressures were similar in HFpEF vs. HFrEF. EDV did not change in patients with HFpEF, ESV decreased and CO increased during exercise compared with baseline. LV systolic properties increased or were unchanged during exercise compared with baseline; EF, Ees, SW increased, PRSW was unchanged (Table 2). Ees and Ea were also calculated using peak aortic pressure (instead of
mean aortic pressure). Both increased with exercise. The ePAD/EDV ratio increased during exercise compared with baseline; the increase in ePAD was independent of a change in EDV. The baseline value and the exercise value of the ePAD/EDV ratio were higher in HFpEF vs. HFrEF (Table 2 and Figures 1 and 2).

The ranges of RVSP, ePAD, RVDP and RVPP for HFpEF patients are illustrated in Figure 3. The ranges were comparable between HFpEF and HFrEF patients. For all variables in HFpEF patients, the range was larger during ambulatory activities of daily living than during symptom limited treadmill exercise. It is of particular note that the maximum values during symptom limited exercise were lower and the minimum pressures during symptom limited exercise were higher than the corresponding maximum and minimum pressures seen during ambulatory activities. In both HFpEF and HFrEF patients, peak RVPP during symptom limited exercise tended to reach a comparable level to the peak values seen in ambulatory activities.

Discussion

Data from the current study support the following conclusions. First, there was a similar impairment in the ability to sufficiently increase cardiac output and maintain low LV diastolic pressure during exercise in HFrEF and HFpEF patients. Second, in both HFrEF and HFpEF patients, the hemodynamic response to ambulatory activities of daily living had larger ranges, larger maximum values and smaller minimum values than those that occurred during the symptom limited upright exercise. Third, in HFrEF patients, exercise was associated with a significant decrease in LV systolic properties and a volume-dependent increase in LV diastolic pressure. The exercise-induced increase in stroke volume, albeit limited, appeared to result from the ability to recruit the Frank-Starling mechanism (increased end diastolic volume) in spite of
the fall in contractility (increased end systolic volume). The inability to maintain or decrease end systolic volume during exercise occurred even though there was an increase in heart rate of 46% and at least the potential for an enhanced force-frequency response. Fourth, in contrast to HFrEF, in HFP EF patients, exercise was associated with small increases in LV systolic properties and a volume-independent increase in LV diastolic pressure. The exercise-induced increase in stroke volume, albeit limited, appeared to result from increased contractility (decreased end systolic volume) or a preserved force-frequency response (HR increased 69%) without an ability to recruit the Frank-Starling mechanism (unchanged end diastolic volume). Therefore, while exercise limitations were present in both HFrEF and HFP EF, there were significant differences in exercise-induced changes in LV systolic and diastolic properties. These differences likely reflect the different pathophysiologies of these clinical syndromes of heart failure.

Normal Response to Exercise

In the age group examined in the current study, a normal response to exercise is characterized by an increase in LV systolic properties and an augmentation in LV diastolic relaxation and filling. Under normal circumstances, exercise results in a 10% increase in LV end diastolic volume, a 10% decrease in LV end systolic volume, a 15-20% increase in stroke volume and a 3.5-4 fold increase in CO with no significant change in LV mean diastolic or end diastolic pressure (3). The decrease in LVESV results from an exercise-induced increase in contractility (as evidenced by an increase in Ees) driven at least in part by an increase in sympathetic activation and the force versus frequency relationship. The increase in LVEDV with no significant change in mean or end diastolic pressures results from an increase in the rate of LV diastolic pressure decline, an increase in early diastolic suction and recoil and an increase in diastolic filling. Additional
mechanisms that allow this dynamic rightward shift in the diastolic pressure-volume relationship during exercise may also include exercise induced increases in adrenergic tone and enhanced myocardial nitric oxide bioavailability. Increased LVEDV allows recruitment of Frank-Starling forces to increase SV. Thus, in normal subjects, augmentation of both systolic and diastolic properties combine to increase stroke volume without a significant increase in diastolic pressure. Compared with this normal response to exercise, both the HFrEF and HFpEF patients examined in the current study had an abnormal response to exercise.

Previous Studies of Diastolic Properties in HFpEF Patients

In their seminal study in 1991, Kitzman et al were the first to examine a group of patients with HFpEF and compare their response to normal control subjects (13). In these patients, many of whom had hypertrophic cardiomyopathy or amyloidosis, exercise was characterized by a blunted increase in cardiac index, an inability to recruit Frank-Starling mechanism (no change in EDV or SV), and a volume-independent increase in pulmonary capillary wedge pressure, all of which are concordant with the results in the present study of HFpEF patients. In a more recent study by some of the same investigators, exercise in HFpEF patients resulted in a 10% increase in LV EDV (5). The reason for the differences between these 2 studies is not clear but may be related to the patient populations examined. In addition, the more recent study did not measure LV pressures and may not have had the same severity of disease. All other studies, by a variety of investigators, are concordant with the current study and demonstrate that exercise in HFpEF patients is associated with little or no change in EDV and an inability to recruit Frank-Starling mechanisms (10, 11, 23-25). Other studies have examined changes in the diastolic pressure-volume relationship during exercise in patients with HFpEF and compared them with referent
controls (11, 24, 26). One found no differences in HFpEF patients compared with control (26) while the other showed changes similar to those found in the current study (11, 24). These differences in outcomes may be dependent on the differences between upright and supine exercise, other methodological issues, or differences in baseline hemodynamic conditions. For example, the extent of baseline diastolic dysfunction may affect the ability to recruit starling forces (in both HFpEF and HFrEF) where higher baseline LV diastolic pressures, higher operative stiffness, and/or the presence of a very restrictive filling pattern may limit filling and an exercise induced increase in LV EDV. Neither of the previous studies discussed above compared the exercise response in HFpEF to patients with HFrEF or ambulatory to exercise hemodynamic responses.

**Previous Studies of Systolic Properties in HFpEF Patients**

Borlaug et al were among the first to compare changes in systolic properties during exercise in a group of HFpEF patients using a largely African American female population that they compared to normal controls (10). They found that HFpEF patients had a reduced chronotropic, vasodilator, and cardiac output reserve response to exercise. Compared with the normal controls, HFpEF patients had a blunted increase in Ees but a similar increase in power index compared with normal controls. Additional studies examined exercise responses in LV systolic properties in patients with HFpEF and compared these responses to referent controls (5, 9, 10, 24, 27-30). In some of these studies, blunted exercise responses in LV systolic properties were seen in patients with HFpEF compared with controls; however, in others, there were no differences in the exercise response in LV systolic properties between HFpEF and control patients (29).
Whether the differences between these studies were caused by differences in patient selection or some other methodological difference is unclear.

**Previous Studies Comparing Ambulatory to Exercise Hemodynamics in HFrEF Patients**

Studies of Braunschweig et al used IHM data obtained from patients with HFrEF and compared RV systolic, diastole and ePAD pressure responses during 6-minute walk tests to responses seen during ambulatory activities of daily living (14). Ohlsson et al examined differences between 6 minute hall walk, submaximal and maximal exercise using IHM technology in HFrEF patients (31). These studies demonstrate that the ambulatory ranges of hemodynamic values were larger (with higher maximum and lower minimum values) than seen with 6-minute hall walk, submaximal or maximal exercise tests. These data suggest that daily ambulatory ranges of pressures in patients with HFrEF are large and that exercise tests encompass only a portion of the physiological range of the haemodynamic load experienced during daily living activities in HF patients. Data from the current study are concordant with these previous studies and demonstrate for the first time that these same conclusions apply to patients with HfpEF. It is possible that activities of daily living include modest but sustained activity that involve combinations of higher sympathetic tone, mixed changes in body position or posture and mixed isometric and dynamic exercise that in aggregate induce a large (or larger) hemodynamic response compared with controlled treadmill exercise.

**Limitations**

A number of studies have specifically examined patients with HfpEF or HFrEF and compared them with normal control subjects. The current study did not examine referent control subjects in
part because participation in the COMPASS-HF study required implantation of an implantable hemodynamic monitor. Implantation of such a device in referent control subjects would not have been ethical. Therefore results from the current study must be interpreted based on published data for comparison to control subjects (19, 22). The number of subjects studied was also limited by the number of available patients after the end of the COMPASS-HF study who had IHM devices that were functional and patients that qualified for an exercise study. None-the-less, while the number of subjects studies were limited, each was studied in a thorough fashion using technology not widely available.

The use of stress echocardiography to quantitate LV structure and function imposes certain limitations. Images must be obtained immediately after peak exercise; there is a time limited opportunity to obtain images. However, these are now standardized and reproducible. The effects of exercise on echocardiographic parameters of diastolic function were not measured. Given a limited amount of imaging time available to assess post-exercise function, we chose to focus on views of the left ventricle rather than Doppler or Tissue Doppler.

The pressure-volume loop data were composed of four time points and a number of reasonable assumptions were used to quantitate pressure and volume at each point. Most of these assumptions have been validated in previous studies (19, 22). For example, while ePAD is not completely equivalent to LV end diastolic pressure, it is reasonably equivalent to mean pulmonary capillary wedge pressure (PCWP) in the absence of intrinsic pulmonary vascular disease (which was an exclusion criteria for this study). Thus, LV diastolic pressures were reasonably represented by ePAD. These assumptions provided an important conceptual framework for the analyses presented. For example, stroke work (the P-V area) in a group of heart failure patients with very abnormal diastolic function, was described using 4 points and the
diastolic pressure-volume relationship was appropriately subtracted from the calculated SW. This provides a more accurate representation of SW compared with methods that use the product of SV x mean blood pressure.

The changes in heart rate both during exercise and during activities of daily living (ambulatory) were limited by treatment with β-blockade. However, the range of heart rates from minimum to maximum were similar in HFrEF and HFpEF patients both during exercise and ambulatory activities.

Epidemiologic studies have demonstrated that patients with HFpEF are older and more often women. This was true in the patients enrolled in this study. However, given the limited sample sizes there were no statistical differences between groups with respect to age and gender. Nonetheless, the effects of age and gender on reported results must be considered. We are not aware of a gender effect on the parameters measured; increased age may amplify the underlying abnormalities seen in HFpEF and magnify its effects on exercise parameters. Additional studies will be required to address these gender and age issues.

It was not the purpose of the current study to define the mechanisms causing the exercise limitation present in these patients with heart failure. Therefore, no attempt to do so was made. The specific focus was on the differences in exercise induced changes in LV systolic and diastolic function.

Conclusions

Data from the current study examining patients with HFpEF are largely concordant with the previous studies discussed above. However, the current study adds important new data. In the current study, both systolic and diastolic properties are examined, HFpEF patients are compared
to HFrEF patients, and the hemodynamic response to activities of daily living were compared with symptom limited exercise stress tests in the same patients. These additional data provided new and unique insights into our understanding of exercise-induced changes in systolic and diastolic properties. For example, while the increase in cardiac output was blunted in both HFrEF and HFpEF patients, the mechanisms underlying this limitation were significantly different. In HFrEF, systolic properties fell during exercise but the recruitment of Frank-Starling mechanisms allowed some increase in stroke volume. By contrast, in HFpEF patients there was no recruitment of Frank-Starling mechanisms but a small increase in LV systolic properties allowed an increase in stroke volume. LV diastolic pressures rose in both HFrEF and HFpEF patients; however, this was a volume-dependent change in HFrEF patients but a volume-independent change in HFpEF patients. These data support the conclusion of an editorial by Paulus in which he suggested that while a number of mechanisms limit exercise in HFpEF, “chief among the gang (of potential mechanisms) are the abnormalities in diastolic function” (6). By contrast, while a number of mechanisms limit exercise in HFrEF, one dominant mechanism is the abnormalities in systolic function. These data may serve to underscore the differences in pathophysiology of the clinical syndrome of HFrEF versus HFpEF.

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Disclosures
Drs. Zile, Aaron, Abraham, Bourge received research grants from and served as consultants to Medtronic, Inc.
Dr. Baicu has no disclosures.

Dr. Kjellstrom was a Medtronic employee at the time this research was conducted but since 2009 is working at the Karolinska Institute, Stockholm, Sweden, with no conflict of interest. Drs. Cho and Bennett and Mr Kueffer are Medtronic employees.

References

18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MSJ, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005, 18:1440–1463.
Table 1. Hemodynamic Responses to Exercise in Patients with HFrEF vs. HFpEF

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<td>20±14 *</td>
<td>(16, 11-45)</td>
<td>22±16 **</td>
<td>(25, 3-48)</td>
</tr>
<tr>
<td>RV PP (mmHg)</td>
<td>28±12</td>
<td>(24, 18-49)</td>
<td>22±3</td>
<td>(23, 18-26)</td>
</tr>
<tr>
<td></td>
<td>42±17 *</td>
<td>(40, 38-54)</td>
<td>40±6 **</td>
<td>(39, 33-49)</td>
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<tr>
<td>(+) RV dP/dt (mmHg/s)</td>
<td>327±11</td>
<td>(327, 314-340)</td>
<td>335±74</td>
<td>(300, 261-471)</td>
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<td></td>
<td>998±339</td>
<td>(964, 643-1429)</td>
<td>943±436 **</td>
<td>(801, 561-1432)</td>
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<tr>
<td>(-) RV dP/dt (mmHg/s)</td>
<td>340±81</td>
<td>(355, 236-415)</td>
<td>274±78</td>
<td>(271, 163-420)</td>
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<tr>
<td></td>
<td>650±155</td>
<td>(710, 423-754)</td>
<td>525±104 **</td>
<td>(610, 417-714)</td>
</tr>
<tr>
<td>LV EDV (mL/m²)</td>
<td>111±42</td>
<td>(96, 61-164)</td>
<td>55±14 **##</td>
<td>(57, 37-83)</td>
</tr>
<tr>
<td></td>
<td>121±39 *</td>
<td>(109, 72-171)</td>
<td>55±13 ##</td>
<td>(56, 38-80)</td>
</tr>
<tr>
<td>LV ESV (mL/m²)</td>
<td>73±37</td>
<td>(63, 32-131)</td>
<td>24±7 **##</td>
<td>(23, 14-38)</td>
</tr>
<tr>
<td></td>
<td>86±41 *</td>
<td>(75, 44-154)</td>
<td>21±6 **####</td>
<td>(21, 12-32)</td>
</tr>
<tr>
<td>Exercise Time (s)</td>
<td>639±164</td>
<td>(686, 450-859)</td>
<td>411±128 **##</td>
<td>(392, 270-581)</td>
</tr>
</tbody>
</table>

Abbreviations: HFrEF = heart failure with a reduced ejection fraction (EF), HFpEF = heart failure with a preserved EF, LV = left ventricular, RV = right ventricular, EDV = end diastolic volume, ESV = end systolic volume, BP = blood pressure, dP/dt = rate of change of pressure versus time, SP=systolic pressure, DP=diastolic pressure, PP=pulse pressure, Data=Mean ± SD, (median, min, max). *= p<0.10; ** = p < 0.05 versus corresponding baseline, # = p < 0.10; ## = p < 0.05 versus corresponding HFrEF.
Table 2. Effects of Exercise on LV Systolic and Diastolic Function

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<tr>
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<th>HFrEF Exercise</th>
<th>HFpEF Baseline</th>
<th>HFpEF Exercise</th>
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<tr>
<td><strong>Diastolic Properties</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ePAD (mmHg)</td>
<td>23±3 (22, 19-28)</td>
<td>44±8 * (44, 36-52)</td>
<td>22±7 (21, 13-32)</td>
<td>46±12 ** (44, 33-72)</td>
</tr>
<tr>
<td>ePAD/EDV (mmHg/mL)</td>
<td>0.10±0.03 (0.10, 0.08-0.15)</td>
<td>0.17±0.03 * (0.17, 0.14-0.21)</td>
<td>0.17±0.03 ## (0.16, 0.14-0.24)</td>
<td>0.36±0.05 **## (0.37, 0.27-0.42)</td>
</tr>
<tr>
<td>End Diastolic Stress (g/cm²)</td>
<td>53±22 (50, 28-86)</td>
<td>126±57 * (99, 69-207)</td>
<td>29±12 # (27, 13-46)</td>
<td>58±19 **## (49, 41-92)</td>
</tr>
<tr>
<td><strong>Systolic Properties</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>37±11 (36, 20-48)</td>
<td>31±13 * (33, 10-42)</td>
<td>56±5 ## (54, 52-63)</td>
<td>62±4 **## (61, 56-68)</td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>6.0±2.3 (5.7, 4.0-9.6)</td>
<td>8.6±4.1 (8.2, 3.6-14.9)</td>
<td>5.4±1.5 (4.9, 3.6-7.8)</td>
<td>10.0±3.2 ** (9.1, 7.3-16.8)</td>
</tr>
<tr>
<td>Ea (mmHg/mL)</td>
<td>0.94±0.20 (0.99, 0.63-1.16)</td>
<td>1.21±0.72 (0.96, 0.67-2.47)</td>
<td>1.20±0.31 # (1.33, 0.78-1.58)</td>
<td>1.37±0.35 * (1.39, 0.89-1.94)</td>
</tr>
<tr>
<td>Ees (mmHg/mL)</td>
<td>0.55±0.22 (0.50, 0.29-0.91)</td>
<td>0.46±0.15 (0.44, 0.27-0.69)</td>
<td>1.57±0.51 ## (1.55, 0.91-2.53)</td>
<td>2.23±0.68 **## (2.17, 1.33-3.44)</td>
</tr>
<tr>
<td>Ea/Ees</td>
<td>1.99±1.15 (1.77, 1.10-3.97)</td>
<td>3.25±3.23 * (2.06, 1.38-9.00)</td>
<td>0.79±0.14 # (0.85, 0.59-0.92)</td>
<td>0.63±0.11 **## (0.64, 0.48-0.78)</td>
</tr>
<tr>
<td>Stroke Work (Kgf/cm)</td>
<td>5.81±2.46 (5.40, 3.04-9.55)</td>
<td>3.43±1.58 * (3.48, 0.92-5.07)</td>
<td>5.67±1.08 (5.55, 4.23-6.96)</td>
<td>5.83±1.11 ## (5.56, 4.18-7.50)</td>
</tr>
<tr>
<td>PRSW (g/cm²)</td>
<td>46.9±17.0 (45.8, 22.8-69.5)</td>
<td>26.9±11.6 * (29.6, 6.9-36.5)</td>
<td>61.1±10.5 (59.4, 48.1-79.4)</td>
<td>62.9±12.7 ## (64.2, 37.4-75.6)</td>
</tr>
<tr>
<td>End Systolic Stress (g/cm²)</td>
<td>113±39 (116, 57-166)</td>
<td>154±55 * (142, 86-238)</td>
<td>45±7 ## (42, 37-60)</td>
<td>44±6 ## (44, 35-52)</td>
</tr>
</tbody>
</table>

Abbreviations: HFrEF = heart failure with a reduced ejection fraction (EF), HFpEF = heart failure with a preserved EF, ePAD = estimated pulmonary artery diastolic pressure, EDV = left ventricular (LV) end diastolic volume, Ea = effective arterial elastance, Ees = end systolic elastance, PRSW =
preload recruitable stroke work, Data=Mean ± SD (median, minimum-maximum), * = p<0.10; ** = p<0.05 versus Baseline, # = p<0.10; ## = p<0.05 versus corresponding HFrEF.
Figure Legends

Figure 1. Pressure versus volume data during diastole in patients with heart failure and a preserved ejection fraction (HFrEF, squares) versus patients with heart failure and a reduced ejection fraction (HFrEF, circles) at baseline (solid lines) and during exercise (dashed lines). Estimated pulmonary artery diastolic pressure (ePAD) increased during exercise in all heart failure patients; pressure increased without an increase in LV diastolic volume in HFrEF but with an increased in LV diastolic volume in HFrEF. Data points = Mean ± SE. Connecting lines between data points were stylized curved lines rather than straight lines.

Figure 2. Pressure versus volume throughout the cardiac cycle in patients with heart failure and a preserved ejection fraction (HFrEF, circles) versus patients with heart failure and a reduced ejection fraction (HFrEF, squares) at baseline (solid lines) and during exercise (Dashed lines). Data points = Mean ± SE. Connecting lines between data points were stylized curved lines rather than straight lines.

Figure 3. Ambulatory (grey box) versus symptom limited exercise (black line) pressures in patients with heart failure and a preserved ejection fraction (HFrEF) versus patients with heart failure and a reduced ejection fraction (HFrEF). RVSP = right ventricular systolic pressure; ePAD = estimated pulmonary artery diastolic pressure, RVDP = right ventricular diastolic pressure, RVPP= right ventricular pulse pressure. * = p < 0.05 maximum values during exercise versus ambulatory, # = p < 0.05 minimum values during exercise versus ambulatory. The maximum values during symptom limited exercise were lower and the minimum pressures during symptom limited exercise were higher than the corresponding maximum and minimum pressures seen during ambulatory activities.
HFpEF

RVSP  ePAD  RVDP  RVPP

HFrEF

RVSP  ePAD  RVDP  RVPP

Pressure (mmHg)

Ambulatory  Symptom Limited Exercise

*p<0.05 Peak exercise vs. Max ambulatory

#p<0.05 Resting prior to exercise vs. Min ambulatory
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Michael R. Zile, Barbro Kjellstrom, Tom Bennett, Yong Cho, Catalin F. Baicu, Mark F. Aaron, William T. Abraham, Robert C. Bourge and Fred J. Kueffer

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Supplemental Material

Supplemental Table 1. Hemodynamic Response to Exercise in Patients with HFrEF vs. HFpEF

<table>
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<td>Heart rate (bpm)</td>
<td>74±9</td>
<td>108±24 *</td>
<td>74±14</td>
<td>125±16 *#</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>94±8</td>
<td>110±9 *</td>
<td>115±13 #</td>
<td>154±9 *#</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>64±5</td>
<td>60±2</td>
<td>67±9</td>
<td>79±13 *#</td>
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<tr>
<td>RV SP (mmHg)</td>
<td>38±19</td>
<td>63±11 *</td>
<td>36±10</td>
<td>61±15 *</td>
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<td>RV DP (mmHg)</td>
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<td>End Diastolic Stress (g/cm²)</td>
<td>52.5±22.4</td>
<td>126.4±57.4 *</td>
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<td>57.8±19.5 *#</td>
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