Differential Hemodynamic Effects of Exercise and Volume Expansion in People With and Without Heart Failure

Andersen et al: Hemodynamic Stress Testing in Heart Failure

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Abstract

Background—Invasive hemodynamic exercise testing is commonly used in the evaluation of patients with suspected heart failure with preserved ejection fraction (HFpEF) or pulmonary hypertension. Saline loading has been suggested as an alternative provocative maneuver, but the hemodynamic changes induced by the two stresses have not been compared.

Methods and Results—Twenty-six subjects (aged 67±10 years, n=14 HFpEF, n=12 control) underwent right heart catheterization at rest, during supine exercise, and with acute saline loading in a prospective study. Exercise and saline each increased cardiac output (CO) and pressures in the right atrium (RAP), pulmonary artery (PAP), and pulmonary capillary wedge positions (PCWP). Changes in heart rate, blood pressure, rate-pressure product and CO were greater with exercise compared to saline. In controls subjects, RAP, PAP and PCWP increased similarly with saline and exercise, while in HFpEF subjects, exercise led to ~2-fold greater increases in RAP (10±4 vs 6±3mmHg, p=0.02), PAP (22±8 vs11±4mmHg, p=0.0001) and PCWP (18±5 vs 10±4mmHg, p<0.0001) compared to saline. Systolic reserve assessed by stroke work and cardiac power output was lower in HFpEF subjects with both exercise and saline. Systemic and pulmonary arterial compliances were enhanced with saline but reduced with exercise.

Conclusions—Exercise elicits greater PCWP elevation compared to saline in HFpEF but not controls, suggesting that hemodynamic stresses beyond passive stiffness and increased venous return explain the development of pulmonary venous hypertension in HFpEF. Exercise testing is more sensitive than saline loading to detect hemodynamic derangements indicative of HFpEF.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT01418248.

Key Words: heart failure, hemodynamics, hemodynamic stress, exercise physiology, exercise testing
Dyspnea and exercise intolerance are common symptoms that can be caused by cardiovascular and non-cardiovascular diseases. Diagnosis can be challenging in patients with normal ejection fraction (EF) because of the difficulties in noninvasively assessing left ventricular (LV) filling pressures and pulmonary artery (PA) pressures.1-6 Patients with early stage heart failure and preserved EF (HFrEF) and/or pulmonary hypertension (PH) may display normal hemodynamics rest, with abnormalities developing only when the cardiovascular system is stressed.1, 3, 7 Invasive hemodynamic exercise testing has been shown to greatly enhance diagnosis of HFrEF and PH.1, 7 Because this testing modality is not universally available, it has recently been proposed that saline loading may provide an alternative provocative maneuver.8, 9 However, it remains unknown how closely saline loading reflects the hemodynamic changes associated with exercise, or how sensitive saline is compared with exercise to detect the cardiovascular reserve limitations that are present in early stage HFrEF.10

Elevation in left ventricular (LV) filling pressures with exercise is well-described in HFrEF,1, 3, 11, 12 yet its mechanisms remain poorly understood. Exercise and saline loading share the common stress of increased venous return, but exercise presents other unique hemodynamic stresses, including shortening in the diastolic filling period, increases in myocardial wall stress, elevations in contractility and myocardial oxygen demand, and alterations in resistive and pulsatile arterial load. Comparison of the hemodynamic changes observed with these two stresses may also allow for greater insight into the mechanisms of pulmonary venous hypertension in HFrEF. Accordingly, we performed a prospective comparison of the hemodynamic responses associated with acute volume loading to responses observed with exercise in subjects with and without HFrEF.
Methods

Subjects referred to the Mayo Clinic catheterization laboratory for invasive hemodynamic exercise stress testing were enrolled in this prospective study between August 2011 and July 2013. Written informed consent was provided by all patients prior to participation in study-related procedures. The study was approved by the Mayo Clinic Institutional Review Board and the study was registered (NCT01418248).

Study Population

HFP EF was defined by clinical symptoms of chronic HF (dyspnea, fatigue), normal EF (≥50%), and elevated left heart filling pressures (pulmonary capillary wedge pressure, PCWP) at rest (>15mmHg) and/or with exercise (>25mmHg). Subjects with significant valvular heart disease (>mild stenosis, >moderate regurgitation), cor pulmonale, significant pulmonary disease, congenital heart disease, left to right shunt, unstable coronary artery disease, myocardial infarction within 60 days, hypertrophic or infiltrative cardiomyopathy, primary renal or hepatic disease, high output heart failure and constrictive pericarditis were excluded. Control subjects were referred for invasive exercise assessment for exertional dyspnea but displayed no demonstrable cardiac pathology after thorough clinical evaluation and invasive hemodynamic assessment, including normal rest and exercise pulmonary artery (PA) pressures (rest<25mmHg, exercise<40mmHg) and normal rest and exercise PCWP.

Study Protocol

After providing consent, subjects underwent history and physical examination, and comprehensive resting echocardiogram. Subjects were studied on their chronic medications in the fasted state after minimal sedation in the supine position as previously described. Cardiac
catheterization was then performed with simultaneous expired gas analysis at rest and during supine exercise starting at 20-Watt (W) workload (5 minutes) followed by 10W increments in 3-minute stages to subject-reported exhaustion. During the same procedure and after return to steady-state baseline values, subjects then underwent reassessment of hemodynamics immediately preceding and immediately following rapid infusion (150 ml/min) of pre-warmed 0.9% normal saline administered directly into the central circulation (superior vena cava-right atrial junction) to a total volume of 10 ml/kg.8

Catheterization Protocol

Right heart catheterization was performed through a 9-French sheath via the internal jugular vein. Transducers were zeroed at mid-axilla, measured using laser calipers. Pressures in the right atrium (RAP), PA, and PCWP were measured at end expiration (mean of ≥3 beats) using 2-French high fidelity micromanometer-tipped catheters (Millar Instruments, Houston, TX) advanced through the lumen of a 7-French fluid-filled catheter (Arrow). Mean RAP and PCWP were taken at mid A wave. PCWP position was verified by typical waveforms, appearance on fluoroscopy, and direct oximetry (saturation ≥94%). Continuously recorded pressure tracings were digitized (240 Hz) and analyzed offline by one investigator (BAB).

Arterial blood pressure (BP) was measured continuously through a 4-6 French radial arterial cannula. Oxygen consumption (VO₂) was measured from expired gas analysis (MedGraphics, St. Paul, MN) interpreted offline in a blinded fashion by one investigator (TPO). Arterial-venous O₂ content difference (AVO₂diff) was measured directly as the difference between systemic arterial and PA O₂ content.11 Cardiac output (CO) was determined by the direct Fick method (CO = VO₂/ AVO₂diff). Stroke volume (SV) was determined from the
quotient of CO and heart rate (HR). Pulmonary vascular resistance (PVR= [mean PA-PCWP]/CO), PA compliance (PAC= SV/[PA pulse pressure]), systemic vascular resistance (SVR= [mean BP-RAP]*80/CO), total arterial compliance (TAC= SV/systemic pulse pressure) were calculated using standard formulas. Myocardial oxygen consumption was estimated by the rate pressure product (HR*SBP) and LV systolic function by stroke work ([mean BP-PCWP]*SV*0.0136) and cardiac power output ([mean BP-PCWP]*CO).

Statistical Analysis

Results are reported as mean (SD) or number (%). Within-group differences are assessed by paired t test. Between group differences were tested using Student’s t-test or Fisher’s exact test. Group differences in the change in hemodynamic parameters with exercise as compared to changes with saline infusion were made using Hotelling’s T^2 test, with correction for multiple comparisons made using Holm’s adjustment. All tests were two-sided, with a P-value < 0.05 considered significant. Analyses were performed using JMP 10.0.0 SAS Institute, Cary, NC, USA.

Results

Twenty-six subjects (aged 67±10 years, 58% female, 14 HFpEF, 12 controls) were enrolled. Compared to controls, subjects with HFpEF were more likely to have a history of hypertension, be treated with anti-hypertensive medicines, and display more LV diastolic dysfunction on echocardiography, evidenced by higher E wave velocities, higher E/e’ ratio and larger left atrial volumes (Table 1). There were no differences in age, sex, body size, symptom severity, cardiac structure, or other medical comorbidities between HFpEF and controls. Based upon
echocardiographic alone, 21% of HFpEF subjects and 8% of control subjects met currently proposed diagnostic criteria for HFpEF (p=0.6).13

Hemodynamic responses with exercise and saline infusion in Controls

Increases in HR, BP, and CO were 3 to 10-fold greater with exercise as compared to saline infusion in control subjects (Table 2, Figure 1). However, increases in RAP and PCWP were similar with saline and exercise in controls, while increases in PA pressure tended to be greater with exercise (Figure 1). Compared to saline infusion, exercise was also associated with >20-fold greater increases in estimated myocardial oxygen demand (rate pressure product increase +540±1280 vs +12500±3900 mmHg/min; p<0.0001, Table 3) and 4-fold greater increases external LV work rate (cardiac power output increase +150±130 vs +700±250 mmHg*L/min; p<0.0001).

Arterial resistance in both circulations dropped with exercise and saline in controls, but the magnitude of SVR reduction was greater in with exercise (Figure 2). In contrast, arterial compliance in the systemic and pulmonary circulations showed diverging effects: systemic and pulmonary compliances increased with saline loading but decreased with exercise (Figure 2). There were no differences in the changes in SV with exercise and saline in the control group (Table 3).

Differential Responses in HFpEF

Subjects with HFpEF had higher baseline RAP, PCWP and PAP compared to controls, with similar resting HR, BP, SV, and CO (Table 2). Systemic and pulmonary arterial compliances and resistances were similar in HFpEF and control subjects at rest.
Similar to controls, subjects with HFpEF displayed less increase in HR, BP, CO, rate pressure product and cardiac power output with saline as compared to exercise (Tables 2 and 3). However, unlike controls where diastolic filling pressure responses were similar to both stresses, HFpEF subjects experienced ~2-fold greater increase in PCWP with exercise compared to saline (Hotelling’s $T^2$ test $p<0.0001$, Figure 3). These differential responses remained significant after adjusting for beta-blocker use and hypertension ($p=0.13$ for PCWP difference with saline, $p<0.0001$ for difference with exercise after adjustment). Bland-Altman analysis revealed substantial bias in the HFpEF group but not the control group comparing exercise and saline PCWP (Supplemental Figure 1). While PCWP was higher in HFpEF during saline (Table 2), the absolute change in PCWP from baseline to saline infusion was not different in HFpEF and controls, in striking contrast to exercise differences (Figure 3).

Exercise was also associated with 2-fold greater increases in RAP and PAP compared to saline in the HFpEF group, again in contrast to the similar responses observed with the two maneuvers in controls (Figure 4). Two of the control subjects (17%) with no significant increase in PCWP with exercise developed an elevated PCWP ($\geq 15$mmHg) with saline infusion. The slope of increase in PCWP relative to the volume of saline infused was not statistically different in HFpEF and controls, whereas the slope of increase in PCWP relative to exercise performed at matched workload (20W) was ~3-fold greater in HFpEF compared to controls (Figure 5).

Similar to diastolic reserve impairments, subjects with HFpEF displayed systolic reserve impairment, with blunted increases in CO, stroke work and cardiac power output compared to controls in response to both exercise and saline infusion (Table 3). Vascular reserve dysfunction was also observed in HFpEF compared to controls, with less reduction in PVR and less increase
in TAC with saline, and greater reduction in PA compliance with both exercise and saline infusion (Table 3).

**Discussion**

This prospective study is the first direct comparison of hemodynamic responses with exercise and acute volume loading within the same individuals, including participants with both HFrEF and non-cardiac etiologies of dyspnea. Exercise and saline produced significant hemodynamic alterations compared to baseline, but changes with exercise were much more dramatic, with greater increases in heart rate, blood pressure, myocardial oxygen demand and LV work. Despite these differences, increases in RAP and PCWP were similar with saline loading and exercise in control subjects. In contrast, increases in PCWP with exercise were ~2-fold greater than what was observed with saline loading in HFrEF subjects, while PCWP changes with saline were not different comparing cases and controls. In addition to diastolic reserve limitation, subjects with HFrEF displayed systolic reserve impairment, manifest by blunted increases in stroke work, cardiac output and cardiac power output compared to controls in response to both exercise and saline. These data show that exercise is the more sensitive maneuver to identify hemodynamic derangements present in the early stages of HFrEF, and that hemodynamic stresses associated with exercise above and beyond increased passive LV chamber stiffness importantly contribute to the development of pulmonary venous hypertension in HFrEF.

**Pathophysiologic Implications**

Heart failure is characterized by an inability to pump blood to the body at a rate commensurate with its needs, or to do so only at the expense of elevated filling pressures. Diagnosis of HF relies on objective assessment of these abnormalities, which may be evident based upon history,
physical examination, radiography, natriuretic peptide testing and echocardiography. However, these noninvasive tests have limited sensitivity, particularly for the presence of high filling pressures.\textsuperscript{2-5, 14, 15} Diagnosis is further complicated by patients with compensated HFpEF, who frequently display normal hemodynamics at rest, with elevations in PCWP and PA pressures that develop only during stress.\textsuperscript{1, 3, 16}

Exercise is the most commonly-encountered stress in everyday life and represents the ultimate test of diastolic reserve. With physical exertion, increases in venous return are coupled to tachycardia-mediated shortening of the diastolic period, such that the ventricle must fill to a larger end diastolic volume in a shorter period of time, without increasing left ventricular filling pressures.\textsuperscript{17} The normal heart achieves this by enhancing relaxation and suction, effectively “pulling” blood into a compliant LV chamber from the left atrium, with little or no increase in pulmonary venous pressure.\textsuperscript{18-20} The LV diastolic pressure volume relationship is, on average, shifted upward and/or to the left in patients with HFpEF, indicating an increase in passive chamber stiffness.\textsuperscript{21-23} This increase in passive stiffness has been proposed to be the dominant contributor to the increase in LV filling pressures with stress.\textsuperscript{24}

However, if stress-induced PCWP elevation in HFpEF were explained solely by a stiff ventricle, one would expect that isolated increases in venous return associated with rapid saline infusion would replicate the PCWP increases observed during exercise. The current data show that is not the case; exercise was associated with a 2-fold greater rise in PCWP as compared to saline in HFpEF subjects, while increases in PCWP were similar in controls with exercise and saline loading. In addition, exercise at the same workload (20W) produced a 3-fold steeper increase in PCWP relative to work performed in HFpEF compared to controls, while the slope of increase in PCWP relative to weight-matched saline infused was not statistically different from
controls. An alternative explanation for the discrepant PCWP responses with exercise could be greater increases in central blood volume mobilized during exercise in HFpEF subjects—a possibility that we cannot discount from this study design. Nonetheless, from these data we can conclude that factors beyond passive LV stiffening alone contribute to the development of pulmonary venous hypertension with stress in HFpEF.

Similar to diastolic reserve, LV systolic reserve was impaired in HFpEF subjects compared to controls, confirming and extending upon recent noninvasive studies. Inadequate stroke volume responses, coupled to chronotropic incompetence, compromised the ability increase in cardiac output in HFpEF subjects. This cardiac output reserve impairment may have also contributed to the increased filling pressures if cardiac outflow was exceeded by venous return due to systolic reserve limitation, in addition to diastolic abnormalities.

Diagnostic Implications

While invasive exercise testing has emerged as a powerful diagnostic test to evaluate for suspected HFpEF or PH, equipment and expertise to perform invasive exercise testing is not universally available. Acute volume loading has recently been proposed as an alternative stressor. Fujimoto et al. compared the saline-induced increase in PCWP in 11 subjects with HFpEF to young and age-matched controls. In contrast to the current study, they observed a significantly greater slope of increase in PCWP relative to volume infused in HFpEF compared to both young and older healthy controls. There are several potential reasons for the differing results in the current study. Fujimoto et al. administered a smaller total volume of saline to the HFpEF subjects (6.1±1.9 mL/kg) as compared to the current study (10 ml/kg), meaning the change in PCWP they observed was being divided by a smaller number. In addition, the control
group utilized by Fujimoto and colleagues was free of any cardiovascular disease, in contrast to our control group that included 25% with a history of coronary disease, 42% with hypertension, and 25% with diabetes mellitus—prevalences that are typical of an older adult US population. Consistent with the greater comorbidity burden in our controls, we observed a steeper slope of PCWP relative to saline infused (17±8 mmHg·L⁻¹·m⁻²) as compared to the rigorously-screened healthy controls in the Fujimoto study (14±5 mmHg·L⁻¹·m⁻²).

Robbins et al. recently reported that 22% of patients with presumed pulmonary arterial hypertension developed an increase in PCWP to 15mmHg or greater with acute saline loading, suggesting that a component of left heart disease is present in these people that may contribute to PH. However, it is not clear what degree of PCWP elevation with saline is pathologic. Indeed, in the current study, 17% of control subjects with no significant PCWP elevation on exercise had an elevation of PCWP to this level with saline. These results suggest that in addition to being more sensitive, exercise testing may be more specific in the evaluation of suspected HFpEF compared with saline.

The current data clearly show that exercise is the more sensitive provocative maneuver to detect stress-induced pulmonary venous hypertension in people with dyspnea due to HFpEF. The greater hemodynamic stresses observed during exercise likely account for the differences, including greater increases in heart rate, higher myocardial oxygen demand (rate-pressure product), greater increases in contractility (stroke work and cardiac power output), and increases in pulsatile arterial loading reflected by reductions in arterial compliance. The current data indicate that people with HFpEF are less able to maintain normal cardiac filling pressures, cardiac output, and PA pressures with these physiologic stresses compared to subjects without HF.
Vascular Responses to Exercise and Saline

Similar to Fujimoto et al., we observed reductions in systemic vascular resistance and pulmonary vascular resistances with saline infusion. However, systemic and pulmonary arterial compliances showed differential responses—being enhanced with saline but decreased by exercise. These responses may serve to variably compensate for increases in central blood volume with stress, but the lack of directly measured central arterial waveforms and use of ‘lumped’ estimates of vascular stiffness limits our ability to completely reconcile the potential arterial contribution to the primary findings.

Limitations

Given the relatively small size of this study, the absence of difference in saline PCWP response between HFpEF and controls may be due to Type II error, though this does not compromise the primary conclusion that exercise increases PCWP and PA pressure much more than saline in HFpEF. The study is subject to bias in that participants had all been referred for invasive hemodynamic assessment. Hemodynamics were assessed in the supine position during exercise and saline loading, where the absolute peak VO₂ achieved is lower, venous return is closer to maximal at rest, and where there are significant differences as compared to upright exercise. Subjects with HFpEF were more likely to be hypertensive and be treated with antihypertensive medicines, but it is unlikely that this would account for the differential response to saline and exercise stress, and results were similar after adjusting for these baseline differences. Because the study groups were defined by pressure tracings during exercise there could be no blinding on the part of the hemodynamic interpretations.
Conclusion

Exercise presents a much greater hemodynamic stress as compared to saline loading, which is associated with more profound increases in left and right heart filling pressures and pulmonary artery pressures in people with HFpEF. The greater increase in PCWP with exercise as compared to volume loading in HFpEF suggests that factors beyond passive LV diastolic chamber stiffness underlie the development of pulmonary venous and arterial hypertension in people with HFpEF. Invasive exercise testing is the more sensitive and physiologically relevant provocative maneuver to help diagnose or exclude HFpEF in patients presenting with dyspnea and normal EF.

Sources of Funding

This research was funded through a competitive grants program within the Mayo Clinic Division of Cardiovascular Diseases.

Disclosures

None.
References


Table 1: Baseline Characteristics

<table>
<thead>
<tr>
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<th>Control (n=12)</th>
<th>HFP EF (n=14)</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>63±11</td>
<td>70±9</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>7 (58%)</td>
<td>8 (57%)</td>
<td>&gt;0.99</td>
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<tr>
<td><strong>Body surface area, m²</strong></td>
<td>1.88±0.26</td>
<td>2.04±0.23</td>
<td>0.11</td>
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**Comorbidities, Signs and Symptoms**

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<th>Control (n=12)</th>
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<tr>
<td><strong>Coronary disease, n (%)</strong></td>
<td>3 (25%)</td>
<td>4 (29%)</td>
<td>&gt;0.99</td>
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<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>5 (42%)</td>
<td>13 (93%)</td>
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<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>3 (25%)</td>
<td>5 (36%)</td>
<td>0.68</td>
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<tr>
<td><strong>NYHA class</strong></td>
<td>2.3±0.8</td>
<td>2.6±0.5</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Edema&gt;2+, n (%)</strong></td>
<td>2 (17%)</td>
<td>4 (29%)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Dyspnea (1-5) &gt;3</strong></td>
<td>7 (58%)</td>
<td>8 (57%)</td>
<td>&gt;0.99</td>
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**Medications**

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<tr>
<td><strong>ACEI or ARB, n (%)</strong></td>
<td>3 (25%)</td>
<td>10 (71%)</td>
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<td><strong>BB, n (%)</strong></td>
<td>2 (17%)</td>
<td>10 (71%)</td>
<td>0.008</td>
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<tr>
<td><strong>Any diuretics, n (%)</strong></td>
<td>2 (17%)</td>
<td>8 (57%)</td>
<td>0.05</td>
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**Echocardiography**

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<tr>
<td><strong>LVEDD (mm)</strong></td>
<td>49±3</td>
<td>48±6</td>
<td>0.47</td>
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<tr>
<td><strong>LV mass index (g/m²)</strong></td>
<td>89±21</td>
<td>85±20</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>LV ejection fraction, (%)</strong></td>
<td>61±8</td>
<td>64±5</td>
<td>0.41</td>
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<tr>
<td><strong>Left atrial volume index (mL/m²)</strong></td>
<td>31±10</td>
<td>41±20</td>
<td>0.19</td>
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<tr>
<td><strong>Mitral E velocity (cm/s)</strong></td>
<td>64±19</td>
<td>85±20</td>
<td>0.009</td>
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<tr>
<td><strong>Mitral E/A ratio</strong></td>
<td>0.95±0.32</td>
<td>1.16±0.59</td>
<td>0.27</td>
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<tr>
<td><strong>Mitral e’ velocity (cm/s)</strong></td>
<td>8.3±1.6</td>
<td>6.9±1.4</td>
<td>0.03</td>
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<tr>
<td><strong>E/e’ ratio</strong></td>
<td>8±3</td>
<td>13±4</td>
<td>0.002</td>
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NYHA, New York Heart Association; ACEI, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; LV, left ventricle; EDD, end-diastolic diameter. P values calculated using students’ T-test for Gaussian distributed variables and Fisher’s exact test for categorical values.
Table 2: Baseline, Exercise and Saline Hemodynamics

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<tr>
<td></td>
<td>Baseline</td>
<td>Exercise</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>67±13</td>
<td>118±19‡</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>142±29</td>
<td>187±33‡</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>92±14</td>
<td>113±14‡</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>9653±3075</td>
<td>22192±5734‡</td>
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<tr>
<td>Respiratory exchange ratio</td>
<td>-</td>
<td>1.09±0.13</td>
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<tr>
<td>Peak work (Watts)</td>
<td>-</td>
<td>73±27</td>
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<tr>
<td>VO₂ (ml/min)</td>
<td>195±46</td>
<td>1166±429</td>
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**Diastolic and Pulmonary pressures**

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<th>HFpEF (n=14)</th>
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<tr>
<td>RA pressure (mmHg)</td>
<td>4±2</td>
<td>8±4‡</td>
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<tr>
<td>PA systolic pressure (mmHg)</td>
<td>27±7</td>
<td>40±10‡</td>
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<tr>
<td>PA mean pressure (mmHg)</td>
<td>16±5</td>
<td>26±7‡</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>7±3</td>
<td>13±5‡</td>
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**Systolic Function**

<table>
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<tr>
<td>Cardiac output (L/min)</td>
<td>5.2±1.9</td>
<td>11.7±3.6‡</td>
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<tr>
<td>Stroke volume (mL)</td>
<td>79±25</td>
<td>99±28‡</td>
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<tr>
<td>LV stroke work (g/beat)</td>
<td>90±34</td>
<td>131±30‡</td>
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<tr>
<td>Cardiac power output (mmHg·L/min)</td>
<td>446±205</td>
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**Vascular Function**

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<tr>
<td>PVR (mmHg/L/min)</td>
<td>1.8±0.9</td>
<td>1.2±0.7‡</td>
</tr>
<tr>
<td>PA compliance (mL/mmHg)</td>
<td>4.4±1.1</td>
<td>4.2±1.4</td>
</tr>
<tr>
<td>SVR (dynes/s/m⁻⁵)</td>
<td>1485±540</td>
<td>812±347‡</td>
</tr>
<tr>
<td>TAC (mL/mmHg)</td>
<td>1.1±0.4</td>
<td>1.0±0.4</td>
</tr>
</tbody>
</table>

*p<0.05 vs exercise, †p<0.05 vs Control, ‡p<0.05 vs baseline.

BP, blood pressure; RA, right atrial; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure; LV, left ventricular; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; TAC, total arterial compliance.
**Table 3: Systolic and Vascular Changes with Exercise and Saline**

<table>
<thead>
<tr>
<th></th>
<th>Exercise Changes</th>
<th>Saline Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>HFpEF</td>
</tr>
<tr>
<td>ΔHeart rate (bpm)</td>
<td>+51±17</td>
<td>+37±12</td>
</tr>
<tr>
<td>ΔMean blood pressure (mmHg)</td>
<td>+21±8</td>
<td>+20±11</td>
</tr>
<tr>
<td>ΔRate pressure product (mmHg/min)</td>
<td>+12500±3900</td>
<td>+9630±3620</td>
</tr>
</tbody>
</table>

**Systolic Reserve**

<table>
<thead>
<tr>
<th></th>
<th>Exercise Changes</th>
<th>Saline Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔStroke volume (mL)</td>
<td>+21±22</td>
<td>+8±19</td>
</tr>
<tr>
<td>ΔCardiac output (L/min)</td>
<td>+6.5±2.6</td>
<td>+3.7±2</td>
</tr>
<tr>
<td>ΔLV stroke work (g/beat)</td>
<td>+41±29</td>
<td>+11±22</td>
</tr>
<tr>
<td>ΔCardiac power output (mmHg*L/min)</td>
<td>+700±247</td>
<td>+306±193</td>
</tr>
</tbody>
</table>

**Vascular Reserve**

<table>
<thead>
<tr>
<th></th>
<th>Exercise Changes</th>
<th>Saline Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPVR (mmHg/L/min)</td>
<td>-0.6±0.7</td>
<td>-0.3±0.8</td>
</tr>
<tr>
<td>ΔPAC (mL/mmHg)</td>
<td>-0.11±1.22</td>
<td>-1.45±1.07</td>
</tr>
<tr>
<td>ΔSVR (dynes/s/m$^5$)</td>
<td>-673±290</td>
<td>-503±391</td>
</tr>
<tr>
<td>ΔTAC (mL/mmHg)</td>
<td>-0.15±0.25</td>
<td>-0.22±0.20</td>
</tr>
</tbody>
</table>

LV, left ventricular; PVR, pulmonary vascular resistance; PAC, pulmonary artery compliance; SVR, systemic vascular resistance; TAC, total arterial compliance
Figure Legends

**Figure 1.** Tukey boxplot showing hemodynamic changes in the control group in response to saline infusion (green) and exercise (blue) for [A] heart rate (ΔHR), [B] mean systemic blood pressure (ΔmBP), [C] cardiac output (ΔCO), [D] pulmonary capillary wedge pressure (ΔPCWP), [E] right atrial pressure (ΔRAP), and [F] mean pulmonary arterial pressure (ΔmPAP).

**Figure 2.** Tukey boxplots showing [A] absolute changes in the control group for systemic and pulmonary vascular resistance (ΔSVR, ΔPVR) in response to saline (green) and exercise (blue). [B] Absolute changes in total arterial compliance (ΔTAC) and pulmonary arterial compliance (ΔPAC).

**Figure 3.** Tukey boxplot showing increases in pulmonary capillary wedge pressures (PCWP) with exercise were much greater in HFpEF (red) compared to controls (black) while changes in PCWP with saline were similar in cases and controls. Hotelling’s T² test compares changes with saline and exercise between groups. Individual p values are post Holm adjustment.

**Figure 4.** Tukey boxplots showing [A,B] increases in right atrial pressure (RAP) and mean pulmonary artery pressure (mPAP) were much greater with exercise in HFpEF (red) compared to controls (black) while changes with saline loading were similar. Hotelling’s T² test compares changes with saline and exercise between groups. Individual p values are post Holm adjustment.

**Figure 5.** [A] The slope of increase in pulmonary capillary wedge pressure (PCWP) relative to the volume of saline infused was similar in HFpEF (red) and controls (black). In contrast, the increase in PCWP relative to matched dose of exercise workload was much greater in HFpEF [B]. Error bars reflect SEM.
Figure 1

A. ΔHR (bpm)
- ΔHR: [Saline, Exercise]
  - Saline: [0, 20]
  - Exercise: [40, 60]
  - p < 0.0001

B. ΔmBP (mmHg)
- ΔmBP: [Saline, Exercise]
  - Saline: [0, 10]
  - Exercise: [20, 30]
  - p < 0.0001

C. ΔCO (L/min)
- ΔCO: [Saline, Exercise]
  - Saline: [5, 10]
  - Exercise: [10, 15]
  - P = 0.0001

D. ΔPCWP (mmHg)
- ΔPCWP: [Saline, Exercise]
  - Saline: [4, 6]
  - Exercise: [8, 10]
  - P = 0.52

E. ΔRAP (mmHg)
- ΔRAP: [Saline, Exercise]
  - Saline: [2, 4]
  - Exercise: [6, 8]
  - p = 0.92

F. Δmean PAP (mmHg)
- Δmean PAP: [Saline, Exercise]
  - Saline: [0, 2]
  - Exercise: [5, 10]
  - p = 0.0004
Figure 2

Comparison of ΔSVR, ΔPVR, ΔTAC, and ΔPAC between Saline and Exercise groups.

- ΔSVR: p=0.01
- ΔPVR: p=0.61
- ΔTAC: p=0.0004
- ΔPAC: p=0.04

Saline vs. Exercise: ΔDyne*sec*cm⁻⁵
ΔSVR: -1500 to 500
ΔPVR: -1000 to 0
ΔTAC: -500 to 3
ΔPAC: -2 to 1
Figure 3

Hotelling’s $T^2$ $p<0.0001$

- Controls HFpEF vs Controls: $p<0.0001$
- Controls HFpEF vs Saline: $p=0.14$
- Controls HFpEF vs Exercise: $p=0.52$

$\Delta$PCWP (mmHg)
Hotelling's $T^2$ $p=0.0001$

$\Delta$RAP (mmHg)

Controls HFpEF Controls HFpEF

$p=0.02$

$p=0.90$

$p=0.018$

Exercise Saline

$\Delta$mPAP (mmHg)

Controls HFpEF Controls HFpEF

$p=0.06$

$p=0.02$

$p=0.0003$

Exercise Saline

Figure 4
Figure 5

A

PCWP (mmHg)

Saline (L/m²)

p=0.11

B

PCWP (mmHg)

Watts

p<0.0001

Controls

HFpEF
Differential Hemodynamic Effects of Exercise and Volume Expansion in People With and Without Heart Failure
Mads J. Andersen, Thomas P. Olson, Vojtech Melenovsky, Garvan C. Kane and Barry A. Borlaug

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Supplemental Material
Supplemental Figure 1: Bland-Altman plots showing bias and limits of agreement between exercise and saline pulmonary capillary wedge pressure (PCWP) in controls [A] and HFpEF subjects [B].
구혈률보존 심부전 환자에서 운동부하 검사는 식염수부하 검사에 비해 쌍기정맥압 상승을 더 잘 반영한다

김석연 과장 · 서울의료원 순환기내과

초록

배경

일반적으로 침습적인 혈류역학적 운동부하 검사는 초기 구혈률보존 심부전 (heart failure with preserved ejection fraction, HFpEF) 환자 혹은 폐동맥 고혈압 환자의 진단을 위해 사용되고 있다. 식염수부하(saline loading)를 통한 검사가 대체진단법으로 제안되고 있으나, 식염수부하 검사와 운동부하 검사 간의 혈류역학적 변화는 비교된 바 없다.

방법 및 결과

본 전향적 연구에서는 26명(67± 10세; HFpEF 환자군 14명; 대조군 12명)을 대상으로 심도자술을 시행하면서 운동부하 검사와 식염수부하 검사를 진행하였다. 운동부하와 식염수부하 검사는 심박출량(cardiac output, CO), 우심방압(right atrium pressure, RAP), 폐동맥압(pulmonary artery pressures, PAP), 폐모세혈관쐐기압(pulmonary capillary wedge pressure, PCWP)을 증가시켰다. 심박수, 혈압, 심근 산소소모량(rate-pressure product), CO의 변화는 운동부하 검사 시 식염수부하 검사보다 더 크게 나타났다. 대조군에서는 RAP, PAP, PCWP의 증가가 양부하 검사 간에 차이가 없었지만, HFpEF군에서는 RAP(10±4 vs. 6±3mmHg; P=0.02), PAP(22±8 vs. 11±4mmHg; P<0.0001), PCWP(18±5 vs. 10±4mmHg; P<0.0001)가 운동부하 검사에서 식염수부하 검사에 비해 2배 정도 증가하였다. 두 검사 모두에서 수축기압과 cardiac power output은 HFpEF군에서 낮았다. 전신 또는 폐동맥 compliance는 식염수부하 검사에서는 증가되었지만 운동부하 검사에서는 감소되었다.

결론

HFpEF군에서 운동부하는 식염수부하에 비해 PCWP를 더 크게 증가시키며, 혈류역학적 스트레스와 증가된 정맥환류(venous return)는 폐정맥압을 설명한다. 따라서, HFpEF군에서 운동부하 검사는 식염수부하 검사에 비해 혈류역학적 변화를 예측하는 데 더욱 민감하게 이용될 수 있다.