Congestive heart failure with preserved ejection fraction is associated with severely impaired dynamic Starling mechanism

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Submitted 22 July 2010; accepted in final form 3 February 2011

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HEALTHY, SEDENTARY AGING leads to increased cardiovascular stiffening, which can be ameliorated by sufficient amounts of lifelong exercise training. An even more extreme form of cardiovascular stiffening can be seen in heart failure with preserved ejection fraction (HFpEF), which comprises ~40~50% of elderly patients diagnosed with congestive heart failure. There are two major interrelated hypotheses to explain heart failure in these patients: 1) increased left ventricular (LV) diastolic stiffness and 2) increased arterial stiffening. The beat-to-beat dynamic Starling mechanism, which is impaired with healthy human aging, reflects the interaction between ventricular and arterial stiffness and thus may provide a link between these two mechanisms underlying HFpEF. Spectral transfer function analysis was applied between beat-to-beat changes in LV end-diastolic pressure (LVEDP; estimated from pulmonary artery diastolic pressure with a right heart catheter) and stroke volume (SV) index. The dynamic Starling mechanism (transfer function gain between LVEDP and the SV index) was impaired in HFpEF patients (n = 10) compared with healthy age-matched controls (n = 12) (HFpEF: 0.23 ± 0.10 ml·m⁻²·mmHg⁻¹ and control: 0.37 ± 0.11 ml·m⁻²·mmHg⁻¹, means ± SD, P = 0.008). There was also a markedly increased (3-fold) fluctuation of LV filling pressures (power spectral density of LVEDP) in HFpEF patients, which may predispose to pulmonary edema due to intermittent exposure to higher pulmonary capillary pressure (HFpEF: 12.2 ± 10.4 mmHg² and control: 3.8 ± 2.9 mmHg², P = 0.014). An impaired dynamic Starling mechanism, even more extreme than that observed with healthy aging, is associated with marked breath-by-breath LVEDP variability and may reflect advanced ventricular and arterial stiffness in HFpEF, possibly contributing to reduced forward output and pulmonary congestion.

cardiovascular variability

METHODS

HFpEF Patients

Subjects were defined as having HFpEF by the following criteria: 1) an index hospitalization for documented congestive heart failure, 2) meeting Framingham criteria for congestive heart failure during the event (21), and 3) ejection fraction measured by echocardiography of >50% at the time of index hospitalization. These criteria were confirmed by chart review, patient history, and a review of medical records with the individual treating physicians. Subjects were enrolled into the study after they were clinically stable and discharged; therefore, all subjects were studied when stable and well compensated.

Exclusion criteria for the study included the following: 1) significant obstructive coronary artery disease as determined by provokable ischemia during exercise electrocardiogram and echocardiogram, 2) significant valvular heart disease by echocardiogram, 3) renal dysfunction (serum creatinine > 2.5 mg/dl), 4) previous coronary
artery bypass surgery, 5) arrhythmias such as atrial fibrillation/flutter and left bundle branch block, 6) lung disease (pulmonary hypertension or chronic obstructive pulmonary disease), 7) untreated thyroid disorders, and 8) warfarin use.

The most recent epidemiological studies (4, 26, 27, 37, 41) have shown that the prototypical patient with HFpEF is elderly, female, obese, hypertensive, and often diabetic. Since the primary purpose of the present study was to address this population, we did not exclude patients with diabetes, hypertension, or body mass index (BMI) >30 for the recruitment of HFpEF patients. We recruited 4 male patients and 6 female patients with HFpEF, and all of them were older than 65 yr. The detailed patient characteristics, recruitment process, and demographics along with static Starling and pressure-volume curves for these patients have been reported previously (28). The physiological variables from the patients with HFpEF were compared with those of age- and gender-matched controls and young healthy individuals as a reference (31).

Previous work from our group focused on the effects of aging and physical activity on cardiovascular function using both cross-sectional and longitudinal approaches (25). Briefly, our laboratory conducted 1 yr of endurance exercise training in sedentary but otherwise healthy elderly subjects (>65 yr old), in which subjects gradually increased their exercise level and finally achieved weekly exercise training up to 4–6 h at the end of the year, including long distance and maximal steady-state and interval training. The results of the beat-to-beat dynamic Starling mechanism from this previous study (31) were published and are reproduced, in part, in Fig. 3. Of note, the exclusion criteria for this study were the same as in the present study except for the fact that we also excluded 1) obesity (BMI > 30), 2) diabetes, and 3) hypertension in these healthy volunteers. Moreover, we applied the same protocol to quantify the physiological variables, so that they could serve as appropriate controls without exposing additional volunteers to the risk of right heart catheterization.

The experimental procedures were explained to all subjects with informed consent obtained as approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center (Dallas, TX) and Presbyterian Hospital (Dallas, TX).

Peak O₂ Uptake
A modified Astrand-Saltin incremental treadmill protocol was used to determine the peak exercise capacity as previously described (3, 25). β-Blockers were stopped at least 48 h before testing to avoid chronotropic effects of β-blockade limiting exercise performance. Other medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and insulin, were not stopped to avoid severe hypertension and/or hyperglycemia during exercise.

Dynamic and Static Hemodynamics

Cardiac preload. A 6-Fr balloon-tipped, fluid-filled catheter (Swan-Ganz, Baxter) was placed through an antecubital vein into the pulmonary artery under fluoroscopic guidance. Pulmonary artery pressure (PAP) and right atrial pressure (RAP) were referenced to atmospheric pressure with the pressure transducer (Transpac IV, Abbott) zero reading set at 5 cm below the sternal angle. The static measurement of PCWP was performed by arterial negative pressure (≤0.5 mmHg) and normal saline infusion (10–15 and 20–30 ml/kg), during which PAP and PCWP ranged from ~2.0 to 24 mmHg (28). There was a strong linear relationship between PCWP versus PAD with slopes approximating unity in both sedentary elderly individuals (R²: 0.93 ± 0.19, slope: 0.92 ± 0.13) and patients with HFpEF (R²: 0.99 ± 0.01 and slope: 0.97 ± 0.10).

SV. Cardiac output was measured with the C2H2 rebreathing method (15), and SV was calculated from the cardiac output and corresponding heart rate. Cuff blood pressure was measured at the brachial artery (Suntech, SunTech Medical) during cardiac output measurements.

Photoplethysmography (Portapres, FMS, Amsterdam, The Netherlands) was used to measure finger arterial blood pressure continuously. Beat-to-beat changes in SV were calculated from the finger arterial pressure waveform reconstructed to a central arterial waveform using pulse contour analysis with the Modelflow method (BeatScope, FMS) (36). The Modelflow method has been well validated to estimate SV changes even in patients with coronary heart disease when the baseline SV was calibrated (5, 14, 40). Patients with coronary heart disease are likely to show similar comorbidities as patients with HFpEF, such as hypertension and diabetes, supporting the validity of the Modelflow method for HFpEF. Each Modelflow SV computed from the finger arterial pressure waveform was calibrated by a constant, the ratio of mean Modelflow SV to baseline SV with the C2H2 rebreathing method (5, 36, 40). SV index (SV divided by body surface area; Mosteller’s equation) (38) was used to minimize the effects of differences in body size between individuals.

Experimental protocol. All experiments were performed in the morning at least 2 h after a light breakfast in a quiet environmentally controlled laboratory with an ambient temperature of 25°C. Subjects were asked to refrain from heavy exercise and caffeinated or alcoholic beverages for at least 24 h before the tests. Patients with HFpEF recruited for this study were taking cardiovascular medications such as diuretics, β-blockers, Ca²⁺ channel blockers, ACE inhibitors, ARBs, HMG-CoA reductase inhibitors, whereas none of control subjects were. β-Blockers were withdrawn 48 h before the study to avoid their direct effects on diastolic function. In addition, diuretics were withheld the morning of the study, although they were given as soon as the study was over. Since virtually all of these patients had hypertension, we chose to keep them on drugs such as ARBs, ACE inhibitors, and/or Ca²⁺ channel blockers for two reasons: 1) patient safety and 2) we felt that the direct effects of the drugs on ventricular-arterial coupling would be less than the effects of acute hypertension in the laboratory. Hemodynamic measurements were made as previously described (31, 32). Briefly, after confirmation of hemodynamic stability and steady-state hemodynamic measurements, subjects were asked to breathe at a controlled frequency (0.2 Hz, 12 breaths/min) for 8 min to collect beat-to-beat SV index, mRAP, and PAD. The last 6 min of data were used for the transfer functional and power spectral analysis.

Data analysis for dynamic hemodynamics. Spectral transfer function analysis between PAD versus SV index and transmural pressure versus SV index were applied to obtain gain, phase, and coherence as previously described (31, 32). Mean values of gain, phase, and coherence were calculated in the respiratory range (0.18–0.22 Hz) and averaged for all subjects in each group. The phase ranges from −π to +π and yields a negative value when changes in the input precede changes in the output at each frequency. Phase zero indicates complete synchrony between the input and output. The gain, similar conceptually to the slope of a linear regression, reflects changes in the output against a unit change of the input at each frequency. Thus, the gain between PAD and SV index was used as an index of the dynamic
Starling mechanism that reflects a function of beat-to-beat modulations of SV against changes in LV preload pressures. The reliability of the linear transfer function estimation was evaluated by estimates of coherence function, which ranges between 0 and 1. A value of unity indicates a perfectly linear relationship between the input and output at each frequency, conceptually similar to the r² value of a linear regression. The spectral power of PAD, transmural pressure (PAD – RAP), and SV index was also calculated in the respiratory frequency range (0.18–0.22 Hz) by integrating the corresponding autospectra (31, 32).

Statistical Analysis

Numerical data are presented as means ± SD except for graphics, in which means ± SE is used. A Student’s t-test was performed between HFpEF and age-matched controls.

RESULTS

Subject Characteristics

All patients had hypertension and were being treated with antihypertensive medications; seven patients had diabetes, six patients were being treated with medication and one patient with diet therapy; five patients had a BMI > 30. Patients with HFpEF had lower maximal O₂ consumption and higher body weight and BMI compared with age-matched controls (Table 1).

Steady-State Hemodynamics

Patients with HFpEF had higher pulse pressure and lower diastolic blood pressure than age-matched controls. Patients also had higher PCWP, PAD, and transmural pressure (PCWP – RAP) than age-matched controls. SV as well as SV index were comparable between HFpEF and age-matched controls. Time series SDs of beat-to-beat PAD as well as beat-to-beat transmural pressure (PAD – mRAP) were higher in patients with HFpEF than age-matched controls (Table 2).

Dynamic Hemodynamics

The input variable of the dynamic Starling mechanism (spectral power of PAD and transmural pressure) at the respiratory frequency was substantially higher in patients with HFpEF than age-matched controls (Fig. 1). The output variable of the dynamic Starling mechanism (namely, spectral power of SV index variability at the respiratory frequency) was comparable between patients and controls (Table 2). The dynamic Starling mechanism (transfer function gain between PAD and SV index) was lower in patients than controls (Fig. 2A). Even when controlling for respiratory-induced changes in intrathoracic pressure using transmural pressure as the input variable to the transfer function, the gain remained much lower in HFpEF patients (Fig. 2B).

Table 2. Hemodynamic variables

<table>
<thead>
<tr>
<th></th>
<th>HFpEF Patients</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>74 ± 22</td>
<td>67 ± 9</td>
<td>0.356</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>145 ± 12</td>
<td>136 ± 15</td>
<td>0.227</td>
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<tr>
<td>DBP, mmHg</td>
<td>70 ± 11*</td>
<td>79 ± 8</td>
<td>0.039</td>
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<tr>
<td>MBP, mmHg</td>
<td>95 ± 10</td>
<td>98 ± 10</td>
<td>0.426</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>75 ± 10*</td>
<td>59 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>16 ± 5*</td>
<td>12 ± 2</td>
<td>0.012</td>
</tr>
<tr>
<td>PCWP – RAP, mmHg</td>
<td>6.0 ± 2.9*</td>
<td>3.4 ± 1.5</td>
<td>0.011</td>
</tr>
<tr>
<td>PAD mean, mmHg</td>
<td>13.7 ± 4.0*</td>
<td>7.6 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD SD, mmHg</td>
<td>4.1 ± 1.3*</td>
<td>2.2 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trans-P mean, mmHg</td>
<td>6.0 ± 1.7*</td>
<td>2.6 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trans-P SD, mmHg</td>
<td>2.8 ± 0.7*</td>
<td>1.2 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV mean, ml</td>
<td>87 ± 22</td>
<td>73 ± 19</td>
<td>0.129</td>
</tr>
<tr>
<td>SV, ml</td>
<td>4 ± 2</td>
<td>3 ± 1</td>
<td>0.108</td>
</tr>
<tr>
<td>SVi mean, ml/m²</td>
<td>45 ± 15</td>
<td>40 ± 8</td>
<td>0.310</td>
</tr>
<tr>
<td>SVi SD, ml/m²</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>0.300</td>
</tr>
<tr>
<td>PSD SVi</td>
<td>0.88 ± 0.091</td>
<td>0.66 ± 0.53</td>
<td>0.499</td>
</tr>
<tr>
<td>Coherence PAD-SVi</td>
<td>0.78 ± 0.18</td>
<td>0.74 ± 0.09</td>
<td>0.492</td>
</tr>
<tr>
<td>Phase PAD-SVi</td>
<td>0.15 ± 0.93</td>
<td>-0.15 ± 0.77</td>
<td>0.409</td>
</tr>
<tr>
<td>Coherence Trans-P-SVi</td>
<td>0.71 ± 0.21</td>
<td>0.66 ± 0.11</td>
<td>0.529</td>
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<tr>
<td>Phase Trans-P-SVi</td>
<td>-0.16 ± 1.1</td>
<td>-0.43 ± 0.48</td>
<td>0.476</td>
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</table>

Values are means ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; PCWP, pulmonary capillary wedge pressure measured at end inspiration; RAP, right atrial pressure measured at end expiration; PAD mean, mean of beat-to-beat PAD during fixed breathing at 0.2 Hz; PAD SD, time series SD of PAD; Trans-P mean, mean of beat-to-beat PAD-RAP; Trans-P SD, time series SD of Trans-P; SV mean, mean of beat-to-beat stroke volume; SV SD, time series SD of SV; SVi mean, mean of beat-to-beat SV index; SVi SD, time series SD of SVi; PSD SVi, power spectral density of SVi at the respiratory frequency; coherence PAD-SVi, coherence function between PAD and SVi at respiratory frequency; phase PAD-SVi, transfer function phase between PAD and SVi at respiratory frequency; coherence Trans-P-SVi, coherence function between transmural pressure (Trans-P) and SVi at respiratory frequency; phase Trans-P-SVi, transfer function phase between Trans-P and SVi at respiratory frequency. *P < 0.05 vs. controls.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>HFpEF Patients</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women</td>
<td>4/6</td>
<td>6/6</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>73 ± 7</td>
<td>70 ± 3</td>
<td>0.177</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163 ± 10</td>
<td>168 ± 10</td>
<td>0.236</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>89 ± 22*</td>
<td>73 ± 11</td>
<td>0.042</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>33.3 ± 7.0*</td>
<td>25.8 ± 2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.00 ± 0.29</td>
<td>1.85 ± 0.18</td>
<td>0.153</td>
</tr>
<tr>
<td>Maximal O₂ consumption, ml·min⁻¹·kg⁻¹</td>
<td>13.7 ± 3.5*</td>
<td>21.9 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD. HFpEF patients, patients with congestive heart failure with preserved ejection fraction; controls, age-matched control subjects. *P < 0.05 vs. controls.

DISCUSSION

The dynamic Starling mechanism is impaired with healthy sedentary aging (31). The key new finding from the present study was that the dynamic Starling mechanism was even more impaired in patients with HFpEF than sedentary but healthy age-matched controls. This finding suggests that an impaired dynamic Starling mechanism reflects the essential pathophysiology of HFpEF, i.e., enhanced LV and arterial stiffness, and provides a rationale as to how sedentary cardiovascular aging may contribute to the pathogenesis of HFpEF.

Dynamic Starling Mechanism in HFpEF

There are two major interrelated hypotheses that have been advanced to explain HFpEF (6, 8, 16, 42). Both of these
suggest static functional impairments in either LV diastolic compliance or end-systolic elastance (EDPVR and ESPVR in Fig. 4) (20). Zile et al. (42–44) argued that patients with HFpEF have abnormal LV relaxation and increased LV passive stiffness. Therefore, this syndrome conventionally has been called “diastolic heart failure.” Conversely, Kawaguchi et al. (16) showed that increased LV end-systolic elastance leads to the appearance of diastolic dysfunction, that is, a steeper ESPVR results in a steeper EDPVR in patients with HFpEF. Conversely, a steeper EDPVR results in a steeper ESPVR (2, 45). Since EDPVR and ESPVR interact via a beat-to-beat LV pressure-volume relationship, it is difficult to distinguish the primary changes of either EDPVR or ESPVR from the secondary changes that occur from their interdependence via LV pressure-volume loops (16, 20, 45). Intriguingly, it is recognized by both major hypotheses that both EDPVR and ESPVR become steeper in patients with HFpEF regardless of the specific mechanisms. Since the beat-to-beat dynamic Starling mechanism reflects time-varying ventricular-arterial stiffness, this novel index may quantify the integrated feature of HFpEF by unifying the previous two interrelated hypotheses (Fig. 4).

Our previous report (28) using many of these same patients showed that the static Starling mechanism was not different between patients with HFpEF and healthy age-matched controls. Although the mechanisms underlying this discrepancy between static versus dynamic LV function are not clear in the present study, this is not so surprising since the dynamic nature of LV as well as vascular compliance/stiffness are different from static behavior. This fact emphasizes the importance of the evaluation of the dynamic nature of the Starling mechanism in HFpEF.

Increased central arterial stiffness and LV load have been observed in patients with congestive heart failure (10, 23, 24) and those with HFpEF (11), as evidenced by augmented reconstructed central pulse pressure, aortic characteristic impedance, and central pulse wave velocity consistent with the steeper ESPVR in patients with HFpEF (6, 16). The calculation of SV using the ModelFlow method in this study estimates the central aortic pressure waveform similar in many respects to this previous work. Moreover, the extent of beat-to-beat changes in SV in response to changes in LV preload and contractile work is primarily determined by the relationship between aortic flow and pressure. Thus, the impaired dynamic Starling mechanism conceptually reflects increased pulsatile load as characterized by aortic impedance. Therefore, our work is a natural extension of previous work by further addressing the integrated dynamic feature of ventricular-arterial coupling accompanied with an invasive measurement of changes in LV preload.

**Prominent Fluctuation of LV Filling Pressure in HFpEF**

The input variable of the dynamic Starling mechanism, that is, spectral power of LVEDP at the respiratory frequency, was prominently higher in patients with HFpEF than controls (Fig. 1). The Starling mechanism functions to modulate cardiac

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**Fig. 1.** A: mean autospectra of pulmonary artery diastolic pressure (PAD) for congestive heart failure (CHF) with preserved ejection fraction (CHF-pEF) and controls. The shaded bar shows enhanced 0.18–0.22 Hz. B: means ± SE of power spectral density of PAD (PSD PAD) at 0.18–0.22 Hz. The PSD PAD of young individuals is shown as a reference. C: mean autospectra of transmural pressure (Trans-P) for CHF-pEF patients and controls. D: means ± SE of PSD Trans-P at 0.18–0.22 Hz. The PSD trans-P of young individuals is shown as a reference.
output depending on LV preload. One outcome of the failure of the Starling mechanism is higher LVEDP and PCWP and pulmonary edema, which is one of the common features for patients with congestive heart failure, as observed in patients with HFpEF in the present study. As a consequence, failure of the dynamic Starling mechanism may result in a marked increase in LVEDP variability at the respiratory frequency since the beat-to-beat dynamic Starling mechanism modulates beat-to-beat fluctuations of LV preload. Importantly, the higher LVEDP variability in HFpEF implies that patients with HFpEF are intermittently exposed to higher cardiac filling pressure during the respiratory cycle as blood flows into a noncompliant LV. Moreover, when given a transient volume challenge or increased cardiac output, such as during exercise, these patients experience a larger rise in filling pressures (7). We speculate that not only higher mean PCWP but also these dynamic mechanisms may predispose patients with HFpEF to pulmonary edema, although, of course, both the dynamic and static mechanisms are interrelated with each other.

**Effects of Aging and Physical Activity on HFpEF**

Intriguingly, the difference of the dynamic Starling mechanism between young and healthy but sedentary elderly subjects...
subject to patients with HFpEF (31). One implication of this vascular stiffening ranging from the highly trained elderly Together, these observations suggest a continuum of cardio-

namic Starling mechanism with aging, whereas the effect is somewhat limited when training is started later in life (31).

Masters athletes (elderly fit), and sedentary young individuals (young unfit) from the present study and a previous study (31).

(~75%) was much larger than that between HFpEF patients and their age-matched controls (~38%; Fig. 2A). These results emphasize the important impact of aging on HFpEF, consistent with epidemiological findings that patients with HFpEF are more common in the elderly population than younger individuals (26, 27, 37). Moreover, age-related cardiovascular stiffening may be one of the key mechanisms for the occurrence of HFpEF. Ventricular-arterial stiffening with human aging is accelerated by obesity, diabetes, hypertension, and changes in sex hormones by promoting the accumulation of cross-linked collagen in cardiovascular tissues (18, 22, 29, 33). Therefore, these findings provide one explanation as to why the prototypical patient with HFpEF is elderly, female, obese, hypertensive, and more often diabetic (4, 26, 27, 37, 41).

Masters athletes functioned with a dynamic Starling mechanism much greater than that of the sedentary elderly population. Even though the dynamic Starling mechanism increased after 1 yr of exercise training in previously sedentary elderly subjects, this value remained substantially lower than that of Masters athletes (Fig. 3) (31). These findings suggest that lifelong exercise training prevents the impairment of the dynamic Starling mechanism with aging, whereas the effect is somewhat limited when training is started later in life (31). Together, these observations suggest a continuum of cardiovascular stiffening ranging from the highly trained elderly subject to patients with HFpEF (31). One implication of this continuum is that daily exercise training begun in youth or middle age is a possible strategy to fundamentally ameliorate the substrate for HFpEF, that is, ventricular-arterial stiffening with aging, although this hypothesis would have to be tested prospectively.

The classic Starling mechanism is, of course, widely appreciated, and its failure contributes substantially to all forms of heart failure (particularly systolic heart failure). However, the dynamic nature of the Starling mechanism as it adjusts output of the heart to the ebb and flow of cardiac filling on a breath-by-breath basis is less well appreciated and rarely considered clinically. Since patients are continuously exposed to these dynamic changes during daily life, the recognition that filling pressure fluctuates widely in HFpEF patients even during quiet respiration is novel and clinically relevant. That this dynamic function is so severely impaired in patients with HFpEF provides new insights into the underlying mechanism for HFpEF, and the presentation in the context of a broad range of healthy individuals of varying ages and fitness levels further emphasizes the importance of aging and physical activity on ventricular-arterial coupling.

**Technical Considerations and Limitations**

The coherence function was higher than 0.9 at respiratory frequencies and transfer function phase was negative and close to zero in patients with HFpEF as well as their age-matched controls. These results imply that 1) >90% of changes in SV are correlated with fluctuation of PAD and 2) higher (or lower) LV preload pressure precedes higher (or lower) SV with zero or one beat delays. Therefore, the majority of SV variability due to respiration is most likely caused by the dynamically operating Starling mechanism and fluctuation of LV preload. However, ventricular interdependence and/or changes in intrapleural pressure due to respiration may confound the relationship between LV preload and SV. To account for this possibility, we also estimated the transmural pressure as an input variable for the dynamic Starling mechanism (34). The dynamic Starling mechanism estimated by the transmural pressure was also impaired with aging and even more impaired in patients with HFpEF than in their peers, similar to that estimated by the LV preload pressure referenced to the atmosphere. Thus, the effects of ventricular interdependence and intrathoracic pressure due to respiration on the beat-to-beat dynamic Starling mechanism are, if any, relatively small, although we cannot exclude the possibility that the impaired

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**Fig. 3. Means ± SE of transfer function gain between PAD and SVi (gain PAD-SVi) at 0.18–0.22 Hz for CHF-pEF patients, sedentary elderly (elderly unfit) subjects, sedentary elderly subjects after exercise training (elderly post-Ex), master athletes (elderly fit), and sedentary young individuals (young unfit) from the present study and a previous study (31).**

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**Fig. 4. Effects of aging, exercise training, and CHF-pEF on the dynamic Starling mechanism. Each loop represents the left ventricular (LV) pressure-volume relationship during one cardiac cycle. The end-systolic pressure-volume relationship (ESPVR; LV end-systolic pressure-LV end-systolic volume relationship) reflects LV end-systolic stiffness and thus arterial stiffness, whereas the end-diastolic pressure-volume relationship (EDPVR; LV end-diastolic pressure-LV end-diastolic volume relationship) reflects LV end-diastolic stiffness or compliance.**
dynamic Starling mechanism is affected by changes in ventricular interdependence in patients with HFpEF.

The absolute value of PAD may not be a robust surrogate for left atrial pressure in patients with HFpEF. However, it is important to emphasize that the present study focused on the changes in PAD as a measure of changes in PCWP rather than the absolute values. Most importantly, to address this concern, we compared the relationship between PAD and PCWP directly and found a strong linear relationship with a slope approaching unity. These data strongly support our contention that there is a close 1:1 relationship between changes in PAD and changes in PCWP over a broad physiological range of preload and defend our strategy in this experiment in patients with HFpEF.

We applied an indirect approach for the measurement of SV. However, this approach has been validated and widely accepted in either clinical settings or physiological studies (5, 36, 40). The validity of SV changes with the Modelflow method was first demonstrated in patients with coronary disease, who often have diabetes and/or hypertension, supporting the validity of the Modelflow method for our patient population (40). Direct measurements of beat-to-beat SV and LVEDP, such as left heart catheterization and direct aortic flow measurement, may be needed to confirm these findings, although they are too invasive for outpatients with HFpEF and healthy individuals. Our approaches without left heart catheterization enabled us to compare the prototypical HFpEF patients with healthy age-matched controls using the same methodologies without any potential complication or referral bias.

Subject Recruitment

We excluded patients with atrial fibrillation and/or coronary artery disease, although epidemiological studies (27, 37) have shown that ~50% of HFpEF have coronary artery disease and that ~40% of HFpEF have atrial fibrillation. Since coronary artery disease is likely to impair the dynamic Starling mechanism via an impairment of diastolic function (9), and atrial fibrillation impairs the beat-by-beat dynamic relationship itself, especially at short R-R intervals, the dynamic Starling mechanism may be underestimated in subjects with coronary artery disease and/or atrial fibrillation. Therefore, it was essential to exclude patients with these comorbidities to test our hypothesis. Moreover, this recruitment strategy ensured a clear diagnosis of HFpEF since rapidly conducted atrial fibrillation may elevate left atrial pressure even though cardiac function is normal, and intermittent ischemia is known to cause large and rapid increases in left atrial pressure (30).

We did not exclude patients with BMI > 30 because obesity is one of the common characteristics in patients with HFpEF. There were no significant differences in dynamic Starling gain between patients with normal BMI (n = 5) versus patients with higher BMI (n = 5) (gain LVEDP – SV index, 0.20 ± 0.08 vs. 0.27 ± 0.12 ml·m⁻²·mmHg⁻¹, P = 0.335). Also, even if we selectively compared patients with normal BMI versus age-matched controls, a clear difference was observed in the dynamic Starling gain (gain LVEDP – SV index, 0.20 ± 0.08 vs. 0.37 ± 0.11 ml·m⁻²·mmHg⁻¹, P = 0.006), indicating that the effects of different body size on the findings were, if any, negligible. Nevertheless, we cannot exclude the possibility that the impaired dynamic Starling mechanism in patients with HFpEF is influenced at least in part by the cardiovascular effects of obesity.

The small number of patients with HFpEF recruited could be considered one limitation of the present study to apply this concept to larger population. However, the fact that we found a significant difference in the dynamic Starling mechanism despite the small number of patients recruited rather strengthens our hypothesis. Our thorough inclusion criteria may have increased the statistical power by reducing confounding factors and limited the number of patients undergoing the risks of right heart catheterization. Some of the key studies by other researchers in this field also recruited the same (13, 16) or even smaller numbers (17) of patients with HFpEF to address pathophysiology of HFpEF.

As previously reported (28), the patients with HFpEF recruited for this study were taking cardiovascular medications such as diuretics, β-blockers, Ca²⁺ channel blockers, ACE inhibitors, ARBs, and HMG-CoA reductase inhibitors. Since ACE inhibitors and ARBs were not held during the study to avoid uncontrolled hypertension, and these drugs by themselves may improve ventricular and/or arterial stiffness, the impairment of the dynamic Starling mechanism in patients with HFpEF might have been underestimated due to drugs in the present study.

Conclusions

An impaired dynamic Starling mechanism associated with marked breath-by-breath LVEDP variability in elderly patients with HFpEF is likely to be explained by advanced ventricular and arterial stiffening, consistent with two previous major hypotheses. Our results also suggest that ventricular-arterial stiffening with sedentary aging contributes to the prevalence of HFpEF in the elderly population.

ACKNOWLEDGMENTS

The authors thank Colin Connor and Daniel Creson for the nursing care of the patients and healthy subjects during the study, Diane Bedenkop for invaluable efforts in recruiting subjects, Cyrus Oufi and Murugappan Ramana-than for engineering support, and finally Robin Shook and Tiffany VanGundy for assistance in performing the experiments.

GRANTS

This study was supported by National Institute on Aging Grant AG17479-02 and National Space Biomedical Research Institute Postdoctoral Fellowship Grant PR01101 through NASA NCC 9-58.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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