Carotid Arterial Stiffness and Its Relationship to Exercise Intolerance in Older Patients With Heart Failure and Preserved Ejection Fraction

Dalane W. Kitzman, David M. Herrington, Peter H. Brubaker, J. Brian Moore, Joel Eggebeen, Mark J. Haykowsky

Abstract—Heart failure with a preserved ejection fraction (HFpEF) is the dominant form of heart failure in the older population. The primary chronic symptom in HFpEF is severe exercise intolerance; however, its pathophysiology and therapy are not well understood. We tested the hypothesis that older patients with HFpEF have increased arterial stiffness beyond what occurs with normal aging and that this contributes to their severe exercise intolerance. Sixty-nine patients ≥60 years of age with HFpEF and 62 healthy volunteers (24 young healthy subjects ≤30 years and 38 older healthy subjects ≥60 years old) were examined. Carotid arterial stiffness was assessed using high-resolution ultrasound, and peak exercise oxygen consumption was measured using expired gas analysis. Peak exercise oxygen consumption was severely reduced in the HFpEF patients compared with older healthy subjects (14.1±2.9 versus 19.7±3.7 mL/kg per minute; P<0.001) and in both was reduced compared with young healthy subjects (32.0±7.2 mL/kg per minute; both P<0.001). In HFpEF compared with older healthy subjects, carotid arterial distensibility was reduced (0.97±0.45 versus 1.33±0.55×10−3 mm Hg−1; P=0.008) and Young’s elastic modulus was increased (1320±884 versus 925±530 kPa; P<0.02). Carotid arterial distensibility was directly (0.28; P=0.02) and Young’s elastic modulus was inversely (−0.32; P=0.01) related to peak exercise oxygen consumption. Carotid arterial distensibility is decreased in HFpEF beyond the changes attributed to normal aging and is related to peak exercise oxygen consumption. This supports the hypothesis that increased arterial stiffness contributes to exercise intolerance in HFpEF and is a potential therapeutic target. (Hypertension. 2013;61:112-119.) ● Online Data Supplement

Key words: aging ■ heart failure with preserved ejection fraction ■ arterial stiffness ■ exercise capacity

Approximately 50% or more of heart failure (HF) patients have preserved left ventricular ejection fraction (HFpEF), and the proportion is greater among women and the elderly. The primary symptom in patients with chronic HFpEF, even well compensated, is severe exercise intolerance, which can be measured objectively as decreased peak exercise pulmonary oxygen uptake (VO2). It has been shown in population-based studies that increased arterial stiffness is associated with cardiovascular morbidity and mortality, including in older populations. We and others have shown that increased stiffness of the aorta is associated with exercise intolerance in older patients with either HFpEF or HF and reduced ejection fraction (HFrEF). It is known that arterial function may have substantial regional variation. In HFrEF, it has been shown that the increase in arterial stiffness is generalized and is observed in the peripheral arteries as well as the aorta and has been shown to be modifiable with angiotensin receptor antagonism. Moreover, the pulsatile components of arterial afterload are greater in HFpEF compared with HFrEF and may play a greater role in the pathophysiology of HFpEF compared with HFrEF. It is known that normal aging alone is associated with increased arterial stiffness and that this can be exacerbated in the setting of systemic hypertension. In addition, Borlaug et al and others reported in older HFpEF patients that systemic vascular resistance was increased and appeared to contribute to their reduced peak VO2. However, it is unknown whether arterial stiffness is generalized in HFpEF and whether it contributes to exercise intolerance.

We hypothesized that peripheral arterial stiffness is increased in older HFpEF patients, beyond the extent that occurs with normal aging alone, similar to the changes in the thoracic aorta, and that these changes may contribute to their severe exercise intolerance. To test these hypotheses, we noninvasively measured indices of stiffness of the carotid artery, a large vessel easily accessible by high-resolution ultrasound, and exercise capacity in older patients with HFpEF in comparison with groups of young and old healthy normal volunteers.

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Methods

Subjects

Data regarding flow-mediated arterial dilation have been reported recently from a subset of these subjects. As described previously, HFP EF was defined as HF with normal systolic function (left ventricular [LV] ejection fraction $>50\%$ and no segmental wall motion abnormalities) and no evidence of significant coronary or valvular heart disease or pulmonary disease. The diagnosis of HF was based on clinical criteria as described previously, which included an HF clinical score from National Health and Nutrition Examination Survey I of $\geq 2.5$, and those used by Rich et al., which included a history of acute pulmonary edema, or the occurrence of $\geq 2$ of the following with no other identifiable cause and with improvement following diuresis: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema, or exertional fatigue. Final determination was made by a board-certified cardiologist after review of medical charts, interview, examination, and rest and exercise echocardiography (the latter to exclude inducible ischemia as confounder). There were 69 patients with HFP EF.

As described previously, normal, healthy volunteers were screened and excluded if they had any chronic medical illness, were on any chronic medication, had current symptoms or an abnormal physical examination (including blood pressure $\geq 140/90$ mm Hg), had abnormal results on the screening tests (electrocardiogram, rest and exercise echocardiogram, and spirometry), or were regularly exercising. There were 24 young healthy volunteers (age $<30$ years; YHC) and 38 older healthy participants (age $>60$ years; OHC). Because of the significant influence of atherosclerosis on vascular function, in both patients and healthy subjects, the protocol excluded those at high risk (known hyperlipidemia and cigarette smoking) and those with known or suspected coronary, cerebrovascular, and peripheral arterial disease by record review, history, physical examination, exercise echocardiography, and carotid ultrasound.

Study Protocol

The study protocol was approved by the institutional review board at Wake Forest University Health Sciences. All of the subjects were familiarized with the testing environment and procedures, and informed consent was obtained during the screening visit. During a subsequent visit, patients reported in the morning after an overnight fast and before taking their morning medications, and in a single visit the outcome measures of carotid artery stiffness, LV function, and exercise capacity were obtained. All of the testing was performed by and all of the results were analyzed by individuals blinded to patient groups.

Echocardiography

As described previously, resting echocardiography was performed by an experienced, registered echosonographer using a Philips Sonos 5500 (Andover, MA) ultrasound imaging system fitted with multifrequency transducer. Standard 2-dimensional images were obtained in the parasternal long-axis and short-axis views and apical 4- and 2-chamber views. Offline analyses were performed using a digital analysis workstation according to American Society of Echocardiography standards. Doppler mitral filling patterns were categorized as normal, impaired relaxation, pseudonormal, and restrictive.

Exercise Testing Protocol

As described previously, exercise testing was performed with participants in the upright position on an electronically braked cycle ergometer. A detailed description of the exercise testing protocol methods is available on the online-only Data Supplement.

Carotid Artery Stiffness Measurements

As described previously, standardized longitudinal B-mode images of the left common carotid artery were recorded with the subject in the supine position using a commercially available ultrasound instrument (Sequoia, Accuson, Inc) fitted with a high-frequency (10-MHz) linear probe and using vascular software and optimized settings. A detailed description of the carotid artery stiffness measurements methods is available in the online-only Data Supplement.

Statistical Analysis

Values were expressed as mean±SD unless otherwise noted. Comparisons were performed using ANCOVA. Intergroup comparisons of baseline characteristics and measures of exercise performance and carotid artery stiffness were made using the independent $t$ test for continuous measures and Fisher exact test for categorical measures. Carotid arterial distensibility was selected as the primary outcome measure of arterial stiffness before study initiation. Because of non-normal distribution, carotid stiffness measures were log transformed. Multiple linear regression analysis was performed to determine significant predictors of peak $V_{O2}$ and to determine the independent effects of these variables on peak $V_{O2}$, after adjustment for differences in sex, race, and body mass index. For all of the analyses, a 2-tailed $P$ value of $<0.05$ was required for significance.

Results

Carotid artery imaging and exercise testing were well tolerated in all individuals, and there were no adverse events associated with either.

Participant Characteristics

Characteristics of the HFP EF, YHC, and OHC groups are shown in Table 1. The OHC and HFP EF groups were well matched for age; however, body mass was higher for HFP EF compared with YHC or OHC groups. There was a higher percentage of women in the OHC and HFP EF groups than in YHC. The HFP EF patients had characteristics similar to those reported from population studies and from previous reports from our laboratory. Specifically, they had increased left atrial diameter, LV posterior and septal wall thickness, mass, and mass:volume ratio compared with OHC (Table 1). HFP EF patients were stable, New York Heart Association class II (46%) and III (54%). They had a mean LV ejection fraction by echocardiography of 59±8%, and most had abnormal Doppler mitral flow patterns. Chronic systemic hypertension was present in 90% of HFP EF patients, and diabetes mellitus was present in 28%. HFP EF patients were being clinically treated with the following medications: angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists (45%), digoxin (6%), diuretics (61%), nitrates (12%), β-blockers (21%), and calcium channel blockers (30%). All of the patients were in sinus rhythm.

Exercise Performance

Participants gave an exhaustive exercise effort, and mean peak respiratory exchange ratios were $>1.13$ for all 3 of the groups (Table 2). Peak $V_{O2}$ (in milliliters per minute or milliliters per kilogram per minute) was severely reduced in HFP EF patients compared with OHC subjects and was greater in YHC subjects than in both older groups (Table 2). Peak exercise workload, time, and heart rate were also markedly reduced in HFP EF patients compared with OHC subjects and were greater in YHC subjects than in both older groups (all $P<0.001$). Peak exercise systolic blood pressure was similar in HFP EF patients and OHC subjects ($P=0.42$) and in both was higher than in YHC subjects ($P<0.01$ for both). No significant difference was found between YHC and OHC or OHC and
HFpEF patients for the minute ventilation/V̇\textsubscript{CO}₂ slope (Table 2). Six-minute walk distance was also reduced in HFpEF patients compared with OHC subjects (P < 0.001) and in both was reduced compared with YHC subjects (P < 0.001 for both).

### Carotid Artery Measurements

Arterial and lumen diameters were increased in HFpEF compared with OHC and YHC (P < 0.001; Table 3). Compared with YHC, OHC had significantly increased carotid arterial stiffness indices (decreased arterial compliance, increased Peterson’s elastic modulus, Young’s elastic modulus [YEM], and β-index; Table 3). Compared with OHC, patients with HFpEF had further reductions in arterial distensibility (P = 0.008) and increased YEM (P = 0.018). The decreased carotid arterial distensibility in HFpEF patients appeared primarily because of increased pulse pressure, because phasic arterial diameter change was similar to OHC. Carotid intimal media thickness was increased in OHC compared with YHC and was also similar in HFpEF compared with OHC. These results were not significantly altered after adjustments for sex or medications.

### Relationship of Carotid Arterial Stiffness Indices With Exercise Performance

Indices of carotid arterial stiffness including Peterson’s elastic modulus, YM, β-index and distensibility, adjusted for sex, race, and BMI, were significantly correlated with peak exercise V̇\textsubscript{O}₂ (Figure). Given that HFpEF had significantly lower maximal HR, the relationship between oxygen pulse (equal to V̇\textsubscript{O}₂/HR) and carotid arterial stiffness indices was performed. The oxygen pulse was significantly correlated with carotid arterial distensibility (r = 0.26; P = 0.04) but was not related to Peterson’s elastic modulus (r = −0.20; P = 0.11), YEM (r = −0.20; P = 0.10) or β-index (r = −0.16; P = 0.18). No significant association was found between minute ventilation/VCO₂ slope and carotid arterial distensibility (r = −0.02; P = 0.88), YEM (r = −0.06; P = 0.65), Peterson’s elastic modulus

### Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>YHC (n=24)</th>
<th>OHC (n=38)</th>
<th>HFpEF (n=69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26±3</td>
<td>69±6</td>
<td>70±7</td>
<td>0.65</td>
</tr>
<tr>
<td>Women</td>
<td>12 (50)</td>
<td>25 (66)</td>
<td>52 (77)</td>
<td>0.37</td>
</tr>
<tr>
<td>White</td>
<td>23 (96)</td>
<td>36 (95)</td>
<td>47 (68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>73±15</td>
<td>72±14</td>
<td>87±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.86±0.24</td>
<td>1.80±0.20</td>
<td>1.94±0.23</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24±3</td>
<td>26±3</td>
<td>32±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>–</td>
<td>65±8</td>
<td>59±8</td>
<td>0.01</td>
</tr>
<tr>
<td>Septal wall thickness, cm</td>
<td>–</td>
<td>1.0±0.1</td>
<td>1.4±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>–</td>
<td>0.9±0.1</td>
<td>1.2±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mass, g</td>
<td>–</td>
<td>167±46</td>
<td>261±88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mass/volume ratio</td>
<td>–</td>
<td>2.52±1.06</td>
<td>3.22±1.60</td>
<td>0.07</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
<td>–</td>
<td>3.1±0.5</td>
<td>3.5±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitral early velocity, cm/s</td>
<td>–</td>
<td>68±18</td>
<td>74±20</td>
<td>0.21</td>
</tr>
<tr>
<td>Mitral atrial velocity, cm/s</td>
<td>–</td>
<td>73±13</td>
<td>84±24</td>
<td>0.006</td>
</tr>
<tr>
<td>Early/atrial ratio</td>
<td>–</td>
<td>0.94±0.19</td>
<td>1.01±0.81</td>
<td>0.51</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>–</td>
<td>217±49</td>
<td>228±71</td>
<td>0.41</td>
</tr>
<tr>
<td>Isovolumic relaxation time, ms</td>
<td>–</td>
<td>74±17</td>
<td>82±23</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic filling</td>
<td>Normal</td>
<td>30 (79)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>–</td>
<td>–</td>
<td>62 (90)</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>–</td>
<td>–</td>
<td>19 (28)</td>
<td>–</td>
</tr>
<tr>
<td>ACE Enzyme-converting inhibitors</td>
<td>–</td>
<td>–</td>
<td>27 (39)</td>
<td>–</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>–</td>
<td>–</td>
<td>4 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Digoxin</td>
<td>–</td>
<td>–</td>
<td>4 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Diuretics</td>
<td>–</td>
<td>–</td>
<td>42 (61)</td>
<td>–</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>–</td>
<td>–</td>
<td>15 (22)</td>
<td>–</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>–</td>
<td>–</td>
<td>21 (30)</td>
<td>–</td>
</tr>
<tr>
<td>Nitrates</td>
<td>–</td>
<td>–</td>
<td>8 (12)</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are mean±SD or count (%). P value indicates comparison of HFpEF vs OHC. ACE indicates angiotensin-converting enzyme inhibitor; YHC, young healthy volunteers; OHC, old healthy volunteers; HFpEF, heart failure with preserved ejection fraction.
Discussion

This study demonstrates that, although healthy, normal aging alone is accompanied by increased carotid arterial stiffness and reduced peak $\dot{V}O_2$, and older patients with HFpEF have severely reduced exercise capacity and increased carotid arterial stiffness beyond what occurs with normal nonhypertensive aging. Measures of carotid arterial stiffness performed at rest correlated significantly with peak $\dot{V}O_2$ and 6-minute walk distance. These data support the hypothesis that increased arterial stiffness may play a role in the pathophysiology of HFpEF, the dominant form of HF in the older population. In addition, because exercise intolerance is the primary chronic symptom in HFpEF, these data suggest that increased arterial stiffness may be a potential therapeutic target in older patients with this disorder. To this end, endurance training may be an important therapy to improve arterial stiffness in older HFpEF patients. Finally, because the carotid artery is a large vessel easily assessable by high-resolution ultrasound imaging, this technique may provide a practical means for serial evaluation of arterial stiffness during future clinical intervention trials in HFpEF.

Table 3.  Carotid Artery Stiffness Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>YHC</th>
<th>OHC</th>
<th>HFpEF</th>
<th>YHC vs OHC, P Value</th>
<th>OHC vs HFpEF, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid distensibility ($&gt;10^{-3}$ mm Hg$^{-1}$)</td>
<td>1.96±1.18</td>
<td>1.33±0.55</td>
<td>0.97±0.45</td>
<td>0.211</td>
<td>0.008</td>
</tr>
<tr>
<td>Carotid compliance ($&gt;10^{-3}$ mm mm Hg$^{-1}$)</td>
<td>97.7±57.3</td>
<td>66.3±34.8</td>
<td>58.6±24.0</td>
<td>0.010</td>
<td>0.295</td>
</tr>
<tr>
<td>Peterson elastic modulus, kPa</td>
<td>76±37</td>
<td>194±120</td>
<td>237±129</td>
<td>&lt;0.001</td>
<td>0.131</td>
</tr>
<tr>
<td>Young elastic modulus, kPa</td>
<td>450±229</td>
<td>925±530</td>
<td>1320±884</td>
<td>&lt;0.001</td>
<td>0.018</td>
</tr>
<tr>
<td>$\beta$-index</td>
<td>6.46±3.21</td>
<td>14.61±8.86</td>
<td>16.54±8.35</td>
<td>&lt;0.001</td>
<td>0.315</td>
</tr>
<tr>
<td>Intima-medial thickness</td>
<td>0.57±0.06</td>
<td>0.75±0.12</td>
<td>0.79±0.14</td>
<td>&lt;0.001</td>
<td>0.207</td>
</tr>
<tr>
<td>Systolic arterial diameter</td>
<td>7.12±0.78</td>
<td>7.48±0.94</td>
<td>8.34±0.98</td>
<td>0.169</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic arterial diameter</td>
<td>6.53±0.70</td>
<td>7.14±0.85</td>
<td>7.95±0.97</td>
<td>0.012</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic luminal diameter</td>
<td>6.03±0.83</td>
<td>6.02±0.79</td>
<td>6.80±1.06</td>
<td>0.986</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic luminal diameter</td>
<td>5.59±0.74</td>
<td>5.63±0.71</td>
<td>6.34±1.02</td>
<td>0.885</td>
<td>0.002</td>
</tr>
<tr>
<td>Arterial diameter change</td>
<td>0.59±0.23</td>
<td>0.34±0.17</td>
<td>0.39±0.17</td>
<td>&lt;0.001</td>
<td>0.183</td>
</tr>
<tr>
<td>Luminal diameter change</td>
<td>0.44±0.20</td>
<td>0.39±0.18</td>
<td>0.42±0.18</td>
<td>0.493</td>
<td>0.509</td>
</tr>
</tbody>
</table>

Values are mean±SD. YHC indicates young healthy volunteers; OHC, old healthy volunteers; HFpEF, heart failure with preserved ejection fraction.
pressure were increased, whereas total arterial compliance (measured as stroke volume divided by carotid pulse pressure) was significantly decreased in HFpEF compared with age-and sex-matched healthy control subjects. Arterial sites other than the aorta, including the carotid and radial arteries, have been shown to have increased stiffness in patients with HFrEF. The present findings indicate that arterial stiffness extends beyond the thoracic aorta in HFpEF as well. We have previously reported similar findings in the pathophysiology of HFpEF and HFrEF, including severely reduced exercise capacity, exercise cardiac output, and quality of life and increased neurohormonal activation.

The present study used high-resolution ultrasound to assess carotid arterial stiffness. Although this technique can provide high-quality data at rest, it is not feasible during upright maximal exercise. However, Tartière-Kesri et al recently measured carotid artery stiffness at rest and during low-intensity (30 watts, equal to 39% peak power output) submaximal cycling in older HFpEF patients (n=23) and age-matched healthy controls (n=15). They reported that rest and exercise carotid systolic blood pressure, carotid pulse pressure, and proximal arterial load (carotid Peterson modulus and aortic pulse wave velocity) were significantly increased, whereas arterial compliance was significantly lower in HFpEF patients versus healthy controls. Also, the change in the carotid Peterson modulus from rest to 30-watt cycling was significantly increased in older HFpEF compared with controls (+155% versus −5%, respectively) and was inversely related to peak power output or 6-minute walk distance. We extend these findings by studying a larger group of older HFpEF patients and by including both young and old healthy control subjects to demonstrate that carotid arterial distensibility is decreased in HFpEF beyond the changes attributed to normal aging alone and by correlating these changes with peak exercise VO2 as well as 6-minute walk distance.

The present study also extends previous findings by excluding patients with evidence of significant atherosclerotic plaque on carotid imaging and patients with any history or evidence of cerebrovascular, peripheral vascular, or coronary artery disease. There was also no significant increase in intimal thickness in HFpEF compared with healthy age-matched volunteers, suggesting that the observed changes in arterial stiffness and their relationship with peak VO2 were not necessarily attributed merely to atherosclerosis. The absence of differences in phasic arterial diameter change suggests that the differences in stiffness were attributed primarily to increased pulse pressure, a finding consistent with that found at rest or low-level cycle exercise by Tartière-Kesri et al.

There are a number of potential mechanisms that could be responsible for the altered arterial stiffness in HF patients. First, neurohormonal changes in HF, including activation of the renin-angiotensin system and increased plasma norepinephrine, may cause vasoconstriction and sodium retention in the vascular wall. We and others have shown that HFpEF patients have activation of both renin-angiotensin system and the adrenergic system. Second, the hypertrophic effect of angiotensin II and aldosterone on vascular smooth muscle cells results in changes in vascular wall structure. Endothelial dysfunction also affects vasodilatation properties of the artery.
and proliferation of smooth muscle cells. Finally, atherosclerosis has been associated with impaired arterial elastic properties and may result in decreased distensibility. The above changes can be accelerated by chronic hypertension and diabetes mellitus. Notably, in population-based studies, similar to our patient group, hypertension is found in ≈90% of older HFpEF patients and diabetes mellitus in ≈30%.

Potential Limitations

The present study was designed before publication of the criteria proposed by Paulus et al. However, the inclusion criteria used have been shown to identify patients who have severe abnormalities in key pathophysiological attributes similar to patients with established, severe systolic HF and to have significantly increased rates of death and HF rehospitalization. The criteria from Paulus et al require 3 obligatory features: (1) signs or symptoms of congestive HF; (2) preserved systolic function; and (3) evidence of LV diastolic dysfunction. The first 2 criteria were automatically met by study design. The third criterion as stated by Paulus et al is best fulfilled by either invasive measurements or tissue Doppler and pulmonary venous flow, which are not available in this study. However, Paulus et al acknowledge the finding by Zile et al that, in patients with the combination of a clear history of HF, normal EF, and concentric LV remodeling (all typical of the patients in the present study), 92% were found to have abnormal diastolic function by subsequent invasive measurements. The present study had 2 additional features supported by Paulus et al including formal cardiopulmonary exercise testing with measurement of peak VO₂ to confirm the presence of severely reduced exercise capacity and pulmonary function testing to prevent misdiagnosis attributed to pulmonary disease.

Cardiac medications were withheld the evening before exercise testing and carotid artery imaging in HFpEF patients (≈12–24 hours). Participants also abstained from caffeine ingestion for 24 hours before testing. However, we cannot exclude the potential for residual effects of vasoactive drugs that may confound measures of carotid arterial stiffness. Despite this, most of the medications in the HFpEF patients would be expected to reduce arterial stiffness. By definition, subjects in the healthy older group were taking no chronic medications. Thus, the severity of arterial stiffness observed in the HFpEF patients would be more likely to be underestimated because of medication effects rather than overestimated. Although current (<2-year) smokers were excluded, some participants had been smokers in the past.

In the present study, we did not have an older control group with diabetes mellitus or hypertensive LV hypertrophy without HF; therefore, it is possible that the increased carotid arterial stiffness observed in our elderly HFpEF patients may have been a result of antecedent hypertension. Indeed, Melenovsky et al reported previously that carotid mean blood pressure, carotid augmentation index, and arterial compliance were similar between HFpEF patients and individuals with hypertensive LV hypertrophy without overt HF.

Measures of carotid distensibility were obtained during supine rest, and, therefore, the present data do not exclude additional, more severe abnormalities in vascular function, such as impaired vasodilation, that may occur during exercise and potentially contribute to exercise tolerance. Indeed, our finding of a significant positive (but weak) correlation between peak VO₂ or oxygen pulse (an indirect measure of stroke volume) and carotid distensibility suggests that increased arterial loading may result in the blunted peak exercise stroke volume found in some studies of clinically stable older HFpEF patients. Although these data, taken together with previous reports from our group and other investigators, suggest that there is a generalized increase in systemic arterial stiffness in patients with HFpEF, there can be substantial regional and segmental variations in arterial function. Although the carotid artery is relatively proximal to the left ventricle, there are relatively few data examining its role in determining impedance to ventricular ejection and overall systemic vascular resistance, unlike the case with the aorta.

The finding of abnormal arterial stiffness and significant correlations with exercise tolerance in a cross-sectional study cannot prove a causal relationship. Furthermore, peak VO₂ is determined by a complex interaction of multiple organ systems and physiological responses. Thus, it is not certain that modification of arterial stiffness, if feasible, would lead to improved exercise capacity.

The present study used a variety of indices of arterial stiffness, each of which has somewhat different determinants and implications, and there is lack of consensus in the literature regarding which of the indices is optimal for clinical studies. Carotid arterial distensibility was the preselected primary outcome; however, most of the indices of arterial stiffness were in agreement regarding the key findings of the study.

Perspectives

Carotid arterial distensibility is decreased in older patients with HFpEF beyond the changes that occur with normal aging alone and is correlated with peak exercise VO₂ and 6-minute walk distance. This suggests that a generalized increase in systemic arterial stiffness may contribute to the pathophysiology of exercise intolerance in older patients with HFpEF. Assessment of carotid stiffness by high-resolution ultrasound may provide a practical means for serial assessment of arterial stiffness during clinical studies of therapeutic agents aimed at improving exercise intolerance, the primary chronic symptom in HFpEF.

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Disclosures

Dr Kitzman is a consultant for Relypsa Inc, Boston Scientific Corp, Abbot, and Servier; has received grant support from Novartis; and owns stock in Gilead Sciences.

Reference


What Is New?

• Carotid arterial distensibility is decreased in older patients with HFpEF beyond the changes that occur with normal aging alone and is correlated with exercise capacity.

What Is Relevant?

• Increased arterial stiffness may contribute to the pathophysiology of exercise intolerance, the primary symptom in chronic HFpEF, which is the dominant form of heart failure in the community.

Novelty and Significance

Summary

Carotid arterial distensibility is decreased in older patients with HFpEF beyond the changes that occur with normal aging alone and is correlated with peak exercise \( \text{V}_\text{O}_2 \) and 6-minute walk distance. This suggests that a generalized increase in systemic arterial stiffness may contribute to the pathophysiology of exercise intolerance in older patients with HFpEF.
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Short title: Arterial stiffness and HFPEF

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Supplemental Methods

Exercise Testing Protocol

As previously described,1-6 exercise testing was performed with participants in the upright position on an electronically braked cycle ergometer. Expired gas analysis was carried out using a metabolic cart (CPX 2000, MedGraphics, Minneapolis, MN) which was conducted with a standard gas of known concentration before each test. The initial workload was 12.5 watts for 2 min, followed by 25 watts for 3 min, and advanced thereafter by 25 watts increments in 3-minute stages. Heart rate was measured via continuous electrocardiographic (EKG) monitoring and blood pressure was measured by a mercury sphygmomanometer during the last minute of each stage. Oxygen consumption and carbon dioxide production were measured continuously during exercise and averaged at 15-s intervals. Peak values were averaged from the final 30 sec of the exercise test. A six minute walk test was performed as described by Guyatt et al.7

Carotid artery stiffness measurements

As previously described,8 standardized longitudinal B-mode images of the left common carotid artery were recorded with the subject in the supine position using a commercially available ultrasound instrument (Sequoia, Accuson, Inc.) fitted with a high frequency (10 MHz) linear probe and using vascular software and optimized settings. A ten-second sequence of images was recorded from an optimal interrogation angle which clearly demonstrated the tip of the flow divider at the entrance to the internal and external carotid arteries. The common carotid artery segment located between 10 mm and 20 mm proximal to the tip of the flow divider was placed in the center of the image screen by the sonographer. The four boundaries defining the media-adventitia and blood intima interfaces on the near and far wall (far wall media-adventitia; far wall blood-intima; near wall intima-blood boundary; near wall adventitia-media boundary) were then optimized by small transducer angulations and maintained during the ten-second recording sequence.

The digital images were then loaded to a dedicated workstation for analysis. The locations of the four boundaries were traced on each image over a 4 mm segment. After boundary tracing was completed, the images were reviewed to confirm that the boundaries had been correctly marked. Errors were corrected when detected and the frames reviewed for a second time. The boundary locations were then written to a data analysis file and the following data were computed for each image frame: mean, maximum, and minimum values of the arterial diameter; lumen diameter; far wall thickness; and near wall thickness.

Carotid artery stiffness indexes were measured and calculated using standard formulate as follows8,9: arterial distensibility (AD) = [(SLD-DLD)/DLD]/PP; arterial compliance (AC) = π(DLD)(SLD-DLD)/2PP; Peterson’s elastic modulus (PEM) = [(PP x DAD)/ADC] x 0.133; Young’s elastic modulus (YEM) = [PEM x DAD/(2 x IMT)] and Beta index = Ln (SBP/DBP)/(ADC/DAD), where PP = pulse pressure, SAD = systolic arterial diameter, DAD = diastolic arterial diameter, SLD = systolic lumen diameter, DLD = diastolic lumen diameter, ADC = arterial diameter change during cardiac cycle, LDC = lumen diameter change, IMT = mean wall intimal medial thickness, SBP = systolic blood pressure, DBP = diastolic blood pressure.
Supplemental Reference


