Arterial vasodilatory and ventricular diastolic reserves determine the stroke volume response to exercise in elderly female hypertensive patients

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Arterial function; heart failure with preserved ejection fraction; hyper-risk of HFpEF in these patients.

Hypertension affects up to two-thirds of the population in the western world and is a major risk factor for heart failure with preserved ejection fraction (HFpEF; Refs. 20, 36). Diastolic impairment, which is common in hypertension, was originally believed to be the cause of HFpEF. However, the connection between HFpEF and diastolic impairment has recently been challenged based on experimental data from animal models and humans (4, 33, 34). Instead, as many of these patients are elderly hypertensive females characterized by elevated pulse pressure and stiffened arteries, (12, 24, 28), it has been proposed that the arterial tree may play a role in the pathogenesis of HFpEF (52, 56).

Arterial function in hypertension is characterized by reduced compliance and increased resistance, leading to elevation of left ventricular (LV), afterload. This greatly influences LV performance and cardiac output (CO; Ref. 51), as reacknowledged in recent publications in this field (3, 52, 56). Based on a framework developed by Sunagawa et al. (47) the LV and arterial compartment may be viewed as two elastic chambers. Chamber stiffness is referred to as elastance, and lumped LV afterload is represented by effective arterial elastance (Ea), incorporating arterial compliance, systemic vascular resistance (SVR), aortic characteristic impedance (Zc), and cardiac timing intervals (22). LV end-systolic elastance (Ees), on the contrary, represents a relatively load-independent index of LV contractility. Interestingly, elderly hypertensive females have been shown to exhibit coupled increases in Ea and Ees that are larger than in men (41), and experimental data suggest that arterial load increases more in females in response to physical exercise, associated with a smaller increase in stroke volume (SV; 37). This raises the possibility that hypertension-induced vascular-ventricular stiffening makes HFpEF patients susceptible to afterload mismatch during physical exercise, leading to poor SV reserve and ultimately HFpEF (14). We wished to investigate the importance of arterial load for SV reserve in elderly female patients with long-standing hypertension, a group proposed to suffer from presymptomatic HFpEF (18).

METHODS

Patients. Outpatients were screened for inclusion using ICD-10 code I109 (Essential Hypertension). Inclusion criteria were as follows: female sex, age > 65 yr, and hypertension defined as blood pressure >140/90 despite ≥2 antihypertensive medications. Exclusion criteria were as follows: secondary hypertension, LV ejection fraction (LVEF) <55%, serious comorbidities affecting cardiopulmonary function and/or interfering with the ability to perform supine bicycle exercise, and nonsinus rhythm. Protocols were submitted to, and approved by, the regional independent ethics committee in Stockholm, Sweden, and all participants provided written informed consent.

Protocol. Patients avoided intake of vasoactive substances at ≥24 h before participation including all antihypertensive and statin treatments, as well as caffeinated drinks. All patients were screened for cardiac disease before participation using 12-lead electrocardiography and history. Blood tests were drawn before and 5 min after exercise for J) N-terminal pro-brain natriuretic peptide (NT-proBNP), a powerful predictor of future progression to clinically overt heart failure (53), using an assay with a coefficient of variability (CV) < 6% (normal <220 ng/l); and 2) high-sensitivity troponin T (hsTnT; both Roche Diagnostics Scandinavia, Bromma, Sweden). Serum creatinine was recalculated to estimated glomerular filtration rate using the
Cockcroft-Gault formula. Resting investigations were performed after a 5-min supine rest. Patients were positioned supine and tilted leftwards on a bicycle ergometer (Ergoline D-72475, Bitz, Germany), brachial blood pressure was measured by sphygmomanometry, and echocardiography and tonometry were performed as described below. Pedaling load given as power output was started at 0 W and increased by 10 W each min until completion of the test. During exercise, data acquisition (echocardiography and tonometry) commenced when the heart rate exceeded 110 min⁻¹. Cycling was stopped once apical views during stress had been recorded. Repeat blood tests were performed for NT-proBNP and hsTnT ~5 min after exercise had finished. Natriuretic peptides were combined with echocardiography to judge whether evidence of HFpEF was present (38).

Echocardiography. All echocardiograms were performed using a Vivid E9 system (GE Healthcare, Horten, Norway). Studies were saved onto digital medium and postprocessed using a dedicated workstation (EchoPAC; GE Healthcare, Horten, Norway). LV dimensions and Doppler data were recorded as recommended by the American Society of Echocardiography including LV outflow tract (LVOT) diameter, which was measured at the same position as the pulsed-wave Doppler sample volume was placed (26). LVOT Doppler forward volume flow was recorded as SV. CO was calculated as

\[ CO = SV \cdot \text{heart rate}. \] (1)

SV was divided by LVEF to obtain LV end-diastolic volume (15) as done previously in studies using similar methodology (4, 5, 12). LVEF was calculated using Simpson’s biplane method, taking great care to avoid foreshortening when acquiring apical images. CVs of our laboratory for Simpson’s biplane method have been published previously as intraobserver CV: 2.3–3.8% and interobserver CV: 7.5–8.4% (45). Dynamic mitral regurgitation was specifically excluded using Doppler imaging (32) Color-coded tissue Doppler data were obtained by postprocessing at a dedicated workstation (EchoPAC; GE Healthcare, Horten, Norway). All cardiac dimensions, blood flow, and velocities were analyzed in triplicate. All volume measurements were indexed for body surface area (BSA) using Mosteller’s formula (BSA = [3,600(weight-height)²]). Echocardiograms were read after blinding for all other data.

Arterial tonometry. Applanation tonometry was performed at the right radial artery (Millar SPT-301) using brachial blood pressures for calibration. A generalized transfer function was applied that synthesizes central aortic blood pressure (AtCor Medical, Sydney, Australia), which has been validated for use both at rest (9, 21) and during hemodynamic alterations by exercise (16, 46). Augmentation pressure (AP) was calculated as the magnitude of the pressure increase above the inflection point. Altered augmentation at elevated heart rate was accounted for by using the variable AP₇₅, which constitutes a heart-rate normalized measure of augmentation that corrects for tachycardia (54).

Noninvasive measures of ventriculo-arterial coupling. We calculated Eₐ as described previously (1, 8, 47, 48):

\[ E_a = \frac{LVESP}{SV}. \] (2)

Kelly et al. (22) validated this method and demonstrated that LV end-systolic pressure (LVESP) could be approximated as

\[ \text{LVESP} = 0.9 \cdot \text{brachial systolic blood pressure (SBP)}. \] (3)

\[ E_{LV} = \frac{DBP - [E_{N\text{aest}} \cdot \text{SBP} \cdot 0.9]}{(SV \cdot E_{N\text{aest}})} \] (4)

where DSP is diastolic blood pressure.

The volume axis intercept (V₀) of the Eₐ line was calculated as

\[ V_0 = \frac{(LVESV \cdot E_{LV} - LVESP)}{E_{LV}}. \] (5)

Indexed stroke work (SWI) was calculated as

\[ \text{SWI} = \frac{SI \cdot LVESP}{SV}. \] (6)

where SI is stroke index.

Arterial hemodynamic parameters. Echocardiographic systolic LVOT Doppler jet velocity was analyzed offline by dedicated software to manually trace Doppler envelopes (Precision Image Digitizer; Michael Robinson, Shelton, CT). Central pressure data were exported from the SphygmoCor device into an Excel spreadsheet. (Microsoft, Redmond, WA) Aortic characteristic impedance (Zc) was calculated in the time-domain as

\[ Z_c = \frac{P_2 - P_1}{Q_2 - Q_1}. \] (7)

where P and Q refer to pressure and volume flow in the interval t₁ = 10 to t₂ = 30 ms after aortic valve opening (13, 23).

Systemic vascular resistance (SVR) was obtained based on the three-element windkessel model of arterial load, (8)

\[ \text{SVR} = R_T - Z_c, \] (8)

where R_T is total arterial resistance approximated as

\[ R_T = \frac{\text{MAP}}{\text{CO}}. \] (9)

Arterial compliance constitutes the ratio between volume and pressure in the arterial compartment. Compliance was estimated using the traditional linear method (C_lin) based on arterial pulse pressure (PP) as

\[ C_{lin} = \frac{SV}{PP}. \] (10)

However, as arterial pressure relates nonlinearity to arterial volume and compliance, estimates of compliance made using linear assumptions are liable to overestimation (44). Therefore, the method of Yin and colleagues (29, 55) was also used, which gives an estimate of C_nonlin as a nonlinear function of pressure, (29)

\[ C_{nonlin} = \left( b \cdot SV \cdot e^{h \cdot P} \right) \div \left( \left( \frac{A_S + A_P}{A_P} - Z_c \cdot SV / A_D \right) \left[ e^{h \cdot ESP} - e^{h \cdot EDP} \right] \right) \] (11)

where the nonlinear parameter b may be approximated as ~0.0131 (29); ESP and EDP are end-systolic and end-diastolic aortic pressure, respectively; and A_S and A_P are the systolic and diastolic areas under the pressure waveform as obtained by integration, respectively. As compliance is the pressure derivative of volume, the effective arterial volume was obtained by integrating compliance with respect to pressure.

Statistics. Data are presented as means ± SD. Normality was tested using Shapiro-Wilk’s method, and skewed variables were log transformed. Subgroups were tested for baseline differences in basic characteristics using unpaired t-test or Mann-Whitney U-test as appropriate. All variables recorded at rest and during stress were analyzed using two-way repeated-measures ANOVA. The presence of SV reserve was entered as a fixed factor, and main effects analyzed using linear analyses [Spearman’s or Pearson’s correlation coefficient (r)]. All analyses were performed using PASW Statistics for Windows version 18 (SPSS, Chicago, IL). Statistical significance was considered present for P values < 0.05.

RESULTS

The study population included 21 female hypertensive patients aged 70 (66–71) yr [median (interquartile range)]. Electrocardiograms did not show any evidence of ischemic heart disease or conduction disease in any patient. Bicycle stress was
well tolerated, and the stress test did not provoke clinical chest pain or regional wall motion abnormalities in any patient. Based on SV reserve, the study population was dichotomized into two subgroups: patients with intact SV reserve (≥15%; Res; n = 11) vs. patients with reduced SV reserve (<15%; NoRes; n = 10) patients. An example of pressure and flow recorded in two patients is shown in Fig. 1. As shown in Table 1, basic characteristics including age, LV mass, and power output were similar in the two subgroups. Hypertension had been present for an average of 9 (5–12) yr, similarly in Res and NoRes patients [8.5 (7.0–12) vs. 7.5 (3–12) yr, respectively]. Antihypertensive therapy included 3 drugs or more in 11 (52%) patients, of which 6 were in the Res subgroup (55% of n = 11) and 5 were in the NoRes subgroup (50% of n = 10; P = 0.65). Mild LV hypertrophy (LVH) was present in two subjects and severe LVH in one patient. Elevated levels of NT-proBNP (>220 ng/l) were detected in six patients of whom five were in the NoRes subgroup (Fisher’s exact test, P = 0.06). Criteria for HFpEF based on echocardiography and natriuretic peptides were positive in a similar proportion of Res and NoRes patients

Table 1. Basic characteristics of study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 21)</th>
<th>SV Reserve (n = 11)</th>
<th>No SV Reserve (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67 ± 9.0</td>
<td>68 ± 10</td>
<td>67 ± 7.2</td>
</tr>
<tr>
<td>eGFR, ml/min</td>
<td>98 ± 33</td>
<td>105 ± 38</td>
<td>88 ± 24</td>
</tr>
<tr>
<td>Interventricular septal thickness, mm</td>
<td>11 ± 1.7</td>
<td>10 ± 1.3</td>
<td>11 ± 2.1</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>68 ± 16</td>
<td>65 ± 17</td>
<td>72 ± 15</td>
</tr>
<tr>
<td>Left atrial area, cm²</td>
<td>18 ± 4</td>
<td>18 ± 5</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Test duration, s</td>
<td>377 ± 125</td>
<td>382 ± 147</td>
<td>370 ± 95</td>
</tr>
<tr>
<td>Test power output, W</td>
<td>59 ± 20</td>
<td>59 ± 24</td>
<td>59 ± 16</td>
</tr>
<tr>
<td>HFpEF, n (%)</td>
<td>12 (57%)</td>
<td>5 (46%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>10 (48)</td>
<td>5 (45)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, n (%)</td>
<td>16 (76)</td>
<td>6 (55)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Angiotensin II-receptor blocker, n (%)</td>
<td>5 (24)</td>
<td>4 (36)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Calcium channel blocker, n (%)</td>
<td>9 (43)</td>
<td>4 (36)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>12 (57)</td>
<td>5 (45)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Other antihypertensive, n (%)</td>
<td>2 (10)</td>
<td>2 (18)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are shown as means ± SD or as number and percentage [n (%)]. Subgroups are dichotomized based on the presence or absence of stroke volume reserve, defined as an increase with exercise ≥15% from baseline. SV, stroke volume; eGFR, estimated glomerular filtration; LV, left ventricle; HFpEF, heart failure with preserved ejection fraction. P values for all variables ≥0.13.
as shown in Table 1 (P = 0.39). Levels of NT-proBNP increased significantly [total population at rest 115 (93–197) ng/l vs. poststress 122 (99–216) ng/l; P < 0.01] with a trend to a difference between subgroups [Res and NoRes at rest: 98 (84–142) ng/l vs. 197 (115–248) ng/l, respectively; P = 0.08]. Cardiac hsTnT did not change significantly with stress [4.4 (3.0–9.8) ng/l vs. 4.7 (3.0–10.6) ng/l in the whole population; P = 0.35] and was similar between subgroups [Res vs. NoRes: 4.4 (3.0–6.3) ng/l vs. 7.0 (3.0–13.6) ng/l; P = 0.18]. No patient had more than trivial mitral regurgitation at rest, and dynamic mitral regurgitation during exercise was not present in any patient.

**LV function.** During exercise, Res patients exhibited augmentation of EDV that was highly significant as shown in Table 2 (interaction, P < 0.01). Greater SV reserve in Res patients translated into greater augmentation of CO and cardiac stroke work in spite of similar tissue velocities (Table 2; between-subgroup, P > 0.46) and similar recruitment of LV elastance (Table 3; between-subgroup, P = 0.60). In unpaired testing, there was no between-subgroup difference in ELV reserve (average ELV increased by 54 vs. +34% in Res vs. NoRes patients, respectively; P = 0.32). In spite of Res patients having higher LVEF at rest (P = 0.02), the between-subgroup ANOVA main effects for EDV and SV were not significant (P for both >0.05). To further explore this question, unpaired testing for differences between subgroups was performed post hoc, demonstrating that Res patients had higher LVEF during exercise (P = 0.002) but not at rest (P = 0.21).

**Arterial hemodynamics.** As shown in Table 3, exercise had differential effects on EA, which increased by an average of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 21)</th>
<th>SV Reserve (n = 11)</th>
<th>No SV Reserve (n = 10)</th>
<th>Exercise P Value</th>
<th>Group P Value</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, rest, ml</td>
<td>95 ± 24</td>
<td>91 ± 26</td>
<td>100 ± 22</td>
<td>0.01</td>
<td>0.81</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EDV, exercise, ml</td>
<td>104 ± 27</td>
<td>102 ± 26</td>
<td>101 ± 29</td>
<td>0.99</td>
<td>0.83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESV, rest, ml</td>
<td>36 ± 18</td>
<td>18 ± 16</td>
<td>28 ± 15</td>
<td>0.01</td>
<td>0.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESV, exercise, ml</td>
<td>32 ± 17</td>
<td>11 ± 11</td>
<td>21 ± 11</td>
<td>0.21</td>
<td>0.07</td>
<td>0.28</td>
</tr>
<tr>
<td>LVEF, rest, %</td>
<td>68 ± 13</td>
<td>72 ± 13</td>
<td>64 ± 11</td>
<td>0.11</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>LVEF, exercise, %</td>
<td>73 ± 12</td>
<td>80 ± 8</td>
<td>65 ± 10</td>
<td>0.60</td>
<td>0.50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SV, rest, ml</td>
<td>59 (55–67)</td>
<td>59 (57–68)</td>
<td>59 (53–67)</td>
<td>0.001</td>
<td>0.19</td>
<td>0.001</td>
</tr>
<tr>
<td>SV, exercise, ml</td>
<td>71 (54–94)</td>
<td>79 (72–105)</td>
<td>75 (53–62)</td>
<td>0.001</td>
<td>0.43</td>
<td>0.001</td>
</tr>
<tr>
<td>SI, mmHg/ml</td>
<td>33 (31–37)</td>
<td>32 (28–37)</td>
<td>34 (31–39)</td>
<td>0.001</td>
<td>0.43</td>
<td>0.001</td>
</tr>
<tr>
<td>SI, mmHg/ml</td>
<td>36 (33–52)</td>
<td>46 (36–53)</td>
<td>33 (32–36)</td>
<td>0.001</td>
<td>0.43</td>
<td>0.001</td>
</tr>
<tr>
<td>CI, l/min⁻¹·m⁻²</td>
<td>2.6 ± 0.6</td>
<td>2.5 ± 0.4</td>
<td>2.7 ± 0.9</td>
<td>&lt;0.001</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, l/min⁻¹·m⁻²</td>
<td>5.7 ± 1.5</td>
<td>6.4 ± 1.4</td>
<td>4.8 ± 1.0</td>
<td>0.001</td>
<td>0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>SWI, rest, mmHg·ml⁻¹·m⁻²</td>
<td>4.585 ± 1.072</td>
<td>4.226 ± 0.969</td>
<td>4.960 ± 1.199</td>
<td>&lt;0.001</td>
<td>0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>SWI, exercise, mmHg·ml⁻¹·m⁻²</td>
<td>5.674 ± 1.406</td>
<td>5.921 ± 1.392</td>
<td>5.364 ± 1.452</td>
<td>0.001</td>
<td>0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>E wave, rest, cm/s</td>
<td>72 (67–83)</td>
<td>71 (62–83)</td>
<td>79 (70–84)</td>
<td>0.01</td>
<td>0.30</td>
<td>0.38</td>
</tr>
<tr>
<td>E wave, exercise, cm/s</td>
<td>97 (76–112)</td>
<td>83 (66–108)</td>
<td>105 (18–92)</td>
<td>0.001</td>
<td>0.41</td>
<td>0.73</td>
</tr>
<tr>
<td>E/A ratio, rest</td>
<td>0.85 (0.75–0.96)</td>
<td>0.77 (0.71–0.95)</td>
<td>0.90 (0.85–0.96)</td>
<td>0.41</td>
<td>0.31</td>
<td>0.73</td>
</tr>
<tr>
<td>E/A ratio, exercise</td>
<td>0.91 (0.83–1.08)</td>
<td>0.91 (0.83–1.00)</td>
<td>0.96 (0.83–1.12)</td>
<td>0.001</td>
<td>0.46</td>
<td>0.47</td>
</tr>
<tr>
<td>Tissue Doppler imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sm, rest, cm/s</td>
<td>5.8 ± 1.7</td>
<td>6.1 ± 1.3</td>
<td>5.2 ± 2.0</td>
<td>0.009</td>
<td>0.63</td>
<td>0.23</td>
</tr>
<tr>
<td>Sm, exercise, cm/s</td>
<td>7.0 ± 1.6</td>
<td>6.9 ± 1.5</td>
<td>7.8 ± 2.0</td>
<td>0.001</td>
<td>0.63</td>
<td>0.23</td>
</tr>
<tr>
<td>Em, rest, cm/s</td>
<td>5.8 ± 2.3</td>
<td>12.6 ± 2.1</td>
<td>5.7 ± 2.1</td>
<td>0.001</td>
<td>0.46</td>
<td>0.47</td>
</tr>
<tr>
<td>Em, exercise, cm/s</td>
<td>11.8 ± 4.4</td>
<td>12.8 ± 4.6</td>
<td>11.1 ± 4.5</td>
<td>0.001</td>
<td>0.46</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Data shown as means ± SD or median (interquartile range) as appropriate. Tissue velocities shown are those from the lateral mitral annulus. Subgroups are as shown in Table 1. P values are as shown in Table 2. EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; SI, stroke index; CI, cardiac index; SWI, stroke work index; E wave, early diastolic filling; A wave (A), late diastolic filling; Sm, peak systolic shortening velocity; Em, early diastolic lengthening velocity.
22% in NoRes patients and decreased by an average of −11% in Res patients (P < 0.001). Arterial pressure was higher in NoRes patients but increased similarly in both subgroups (interaction, P = 0.54; Table 4). A pulse pressure ≥65 mmHg was detected in n = 14 patients of whom 8 were in the Res subgroup (Fisher’s exact test, P = 0.61).

Table 5 lists the components of the 3-element windkessel model: Res patients exhibited larger reductions in RT and SVR than NoRes patients (mean −55 vs. −36% and −58 vs. −40%; P < 0.01 for both). Groups differed in terms of ZC overall (ANOVA main effect, P = 0.02) but increased to a similar degree with exercise (+25 vs. +35%; P = 0.89; Table 5). Arterial compliance estimated by linear methodology was significantly higher than with the nonlinear method proposed by Liu et al. (29); mean difference at rest +44% (P < 0.001) and during exercise +31% (P = 0.02). Figure 2 shows arterial compliance at end-systole estimated using nonlinear methodology and averaged for each subgroup. The fact that Res patients exhibited higher end-systolic compliance during exercise after accounting for effects of pressure is demonstrated by an apparent upwards shift of the arterial pressure-compliance curve. This was explained by the fact that exercise did in fact alter effective arterial volume: +29 vs. −19% in Res vs. NoRes patients, respectively (P < 0.01; Table 5).

Higher Ea correlated with higher Zc and lower end-systolic (nonlinear) compliance (r = 0.73 and r = −0.81; P for both < 0.001), smaller estimated arterial volume (−0.78; P < 0.001), and higher NT-proBNP (r = 0.52; P = 0.02).

Lastly, the data presented above suggest that exercise produced simultaneous alterations of LV preload, afterload, and contractility. As these are three key determinants of global LV function and SV, their interaction is shown schematically as a classic force-velocity diagram in Fig. 3 (11).

DISCUSSION

We investigated the determinants of cardiac SV reserve in elderly females with long-standing hypertension, a group

![Table 4. Blood pressures at rest and during exercise](http://ajpheart.physiology.org/)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 21)</th>
<th>SV Rest (n = 11)</th>
<th>No SV Rest (n = 10)</th>
<th>Exercise P Value</th>
<th>Group P Value</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, rest, mmHg</td>
<td>116 ± 12</td>
<td>111 ± 8</td>
<td>120 ± 16</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>MAP, exercise, mmHg</td>
<td>130 ± 12</td>
<td>122 ± 8</td>
<td>136 ± 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, rest, mmHg</td>
<td>162 ± 20</td>
<td>158 ± 19</td>
<td>167 ± 25</td>
<td>&lt;0.001</td>
<td>0.19</td>
<td>0.70</td>
</tr>
<tr>
<td>SBP, exercise, mmHg</td>
<td>193 ± 18</td>
<td>185 ± 14</td>
<td>202 ± 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, rest, mmHg</td>
<td>87 ± 9</td>
<td>86 ± 6</td>
<td>89 ± 11</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>0.10</td>
</tr>
<tr>
<td>DBP, exercise, mmHg</td>
<td>92 ± 8</td>
<td>89 ± 7</td>
<td>96 ± 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central blood pressures</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP, rest, mmHg</td>
<td>150 ± 19</td>
<td>143 ± 12</td>
<td>156 ± 27</td>
<td>&lt;0.001</td>
<td>0.05</td>
<td>0.53</td>
</tr>
<tr>
<td>SBP, exercise, mmHg</td>
<td>167 ± 18</td>
<td>156 ± 10</td>
<td>176 ± 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, rest, mmHg</td>
<td>89 ± 9</td>
<td>87 ± 5</td>
<td>91 ± 12</td>
<td>&lt;0.001</td>
<td>0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>DBP, exercise, mmHg</td>
<td>96 ± 9</td>
<td>92 ± 8</td>
<td>100 ± 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESP rest, mmHg</td>
<td>133 ± 16</td>
<td>125 ± 8</td>
<td>138 ± 21</td>
<td>0.01</td>
<td>0.03</td>
<td>0.54</td>
</tr>
<tr>
<td>ESP, exercise, mmHg</td>
<td>141 ± 15</td>
<td>132 ± 10</td>
<td>147 ± 14</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Central pressure augmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APr, rest, mmHg</td>
<td>18 (13–22)</td>
<td>18 (16–20)</td>
<td>18 (14–32)</td>
<td>0.006</td>
<td>0.16</td>
<td>0.97</td>
</tr>
<tr>
<td>APr, exercise, mmHg</td>
<td>25 (21–34)</td>
<td>21 (20–24)</td>
<td>25 (21–25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation index, rest, %</td>
<td>147 (136–161)</td>
<td>146 (127–154)</td>
<td>149 (138–177)</td>
<td>&lt;0.001</td>
<td>0.19</td>
<td>0.85</td>
</tr>
<tr>
<td>Augmentation index, exercise, %</td>
<td>129 (116–143)</td>
<td>119 (113–133)</td>
<td>134 (128–144)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Data are shown as means ± SD or median (interquartile range) as appropriate. Subgroups and P values are as in Table 1. MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESP, end-systolic pressure; APr, augmentation pressure shown after normalization to heart rate 75 min⁻¹.

![Table 5. Arterial hemodynamics at rest and during exercise](http://ajpheart.physiology.org/)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 21)</th>
<th>SV Rest (n = 11)</th>
<th>No SV Rest (n = 10)</th>
<th>Exercise P Value</th>
<th>Group P Value</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, rest, min⁻¹</td>
<td>77 (70–82)</td>
<td>77 (71–82)</td>
<td>77 (63–83)</td>
<td>&lt;0.001</td>
<td>0.25</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart rate, exercise, min⁻¹</td>
<td>137 (123–145)</td>
<td>138 (133–169)</td>
<td>126 (119–143)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rv, rest, mmHg · s · ml⁻¹</td>
<td>1.58 ± 0.47</td>
<td>1.43 ± 0.17</td>
<td>1.70 ± 0.70</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rv, exercise, mmHg · s · ml⁻¹</td>
<td>0.81 ± 0.28</td>
<td>0.64 ± 0.15</td>
<td>1.03 ± 0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zc, rest, mmHg · s · ml⁻¹</td>
<td>0.08 ± 0.03</td>
<td>0.06 ± 0.02</td>
<td>0.10 ± 0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.50</td>
</tr>
<tr>
<td>Zc, exercise, mmHg · s · ml⁻¹</td>
<td>0.10 ± 0.05</td>
<td>0.08 ± 0.03</td>
<td>0.12 ± 0.06</td>
<td></td>
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</tr>
<tr>
<td>SVR, rest, mmHg · s · ml⁻¹</td>
<td>1.51 ± 0.45</td>
<td>1.36 ± 0.18</td>
<td>1.72 ± 0.63</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR, exercise, mmHg · s · ml⁻¹</td>
<td>0.73 ± 0.26</td>
<td>0.56 ± 0.14</td>
<td>0.97 ± 0.18</td>
<td></td>
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</tr>
<tr>
<td>Compsys, rest, ml/mmHg</td>
<td>0.91 ± 0.30</td>
<td>0.92 ± 0.28</td>
<td>0.90 ± 0.34</td>
<td>&lt;0.01</td>
<td>0.29</td>
<td>0.025</td>
</tr>
<tr>
<td>Compsys, exercise, ml/mmHg</td>
<td>0.78 ± 0.27</td>
<td>0.89 ± 0.22</td>
<td>0.64 ± 0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic comp, rest, mmHg</td>
<td>0.66 ± 0.29</td>
<td>0.70 ± 0.26</td>
<td>0.61 ± 0.34</td>
<td>0.33</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>End-systolic comp, exercise, mmHg</td>
<td>0.63 ± 0.29</td>
<td>0.79 ± 0.26</td>
<td>0.41 ± 0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic arterial volume, rest, ml</td>
<td>228 ± 92</td>
<td>227 ± 74</td>
<td>231 ± 120</td>
<td>0.71</td>
<td>0.25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-systolic arterial volume, exercise, ml</td>
<td>244 ± 108</td>
<td>289 ± 104</td>
<td>180 ± 81</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as means ± SD or median (interquartile range) as appropriate. Subgroups are as in Table 1. P values are as in Table 2. Rv, total arterial resistance; Zc, characteristic impedance; SVR, systemic vascular resistance; Compsys, compliance based on assumption of linearity between pressure and volume in arterial tree; end-systolic comp, compliance at end-systole without assuming linearity.
whose risk of developing HfPEF is so high that it has been proposed that they should be referred to as having presymptomatic HfPEF (18). The key findings were that the presence of SV reserve was associated with the following: 1) the ability to augment LVEDV during exercise (i.e., intact preload reserve), coupled with 2) a reduction of global afterload (E_A) owing to lesser resistance (Z_C, SVR) and increased compliance (C_{nonlin}) of the arterial tree.

Effects of exercise on LV systolic and diastolic function. In the present study, patients were dichotomized based on whether SV reserve was present (Res) or not (NoRes). Failure to augment SV with physical exercise is considered a hallmark of early heart failure (10), which may stem from several principally different etiologies affecting cardiac preload, afterload, and contractility. Contractility was estimated using a noninvasive, single-beat estimate of LV end-systolic elastance. In spite of the differences in SV reserve between Res and NoRes patients, similar elevations in E_LV were seen in the two subgroups. We found similar levels of E_LV as did Borlaug et al. (4) in a group of predominantly hypertensive subjects, in whom E_LV increased from 3.8 mmHg/ml at rest by ~20% during light exercise. Interestingly, somewhat at variance with reports from patients with overtly symptomatic, later stage HfPEF (5, 37, 50), our results indicate that patients with hypertensive heart disease at high risk of HfPEF may be unable to augment SV in spite of adequate contractile reserve. Future research in this field will need to focus on LV contractile function in hypertensive heart disease and its role in the progression to HfPEF.

It is noteworthy that, in spite of relatively long-standing hypertension, Lvh was absent in a majority of our patients, and tissue velocities were preserved and almost identical to values found in the general population (35). This may indicate a degree of recruitment bias in favor of relatively physically active subjects and/or the presence of a particular genetic make-up that protects against hypertensive LV remodeling.

SV reserve during exercise is also known to reflect the presence of preload reserve (39). In the present study, Res patients demonstrated exercise-induced augmentation of end-diastolic volume. Our findings are in agreement with a previous study (42) in physically active elderly individuals, in whom greater utilization of Frank-Starling preload reserve compensated for poor chronotropic function during exercise. Loss of preload reserve in the elderly may thus not primarily be due to the ageing process per se but to an associated sedentary lifestyle (42).

Effects of exercise on arterial function. In the present study, increased SV and CO in the Res subgroup were associated with both lower vascular resistance and greater arterial compliance. Integration of compliance with respect to pressure demonstrated that arterial volume decreased during physical exercise in NoRes but increased in Res patients, i.e., subgroups differed in their vasodilatory reserve. This may be related to abnormalities at the microvascular level or due to a disordered response of the large arterial tree. Possible mechanisms include 1) microvascular reserve and local regulation of feed arteries in exercising muscle, 2) endothelial function, and 3) neural effects and receptor stimulation.

We found that peripheral resistance in Res patients was lower at rest and a larger decrease was seen during exercise than in NoRes patients, implying that small-caliber arteries were differentially regulated during exercise. Indeed, global SVR has been shown to be a key determinant of overall CO during exercise (6). This is important for the present study, as patients performed large-muscle exercise and the increase in CO would have been directed largely to exercising muscle. Regulation of feed arteries supplying capillary beds in muscle is complex and incompletely understood. Firstly, nitric oxide bioavailability is an important determinant of microvascular function and small artery caliber during exercise (19). This may be of relevance for the present study, as endothelial dysfunction has been shown to be common in elderly hypertensives (49), and, furthermore, patients with HfPEF do appear to suffer from an inability to reduce SVR during exercise. (14)

However, Borlaug et al. (5) tested microvascular endothelial function in HfPEF patients before and during exercise and found nonsignificant differences compared with patients with “uncomplicated” hypertension. Similarly, Hundley et al. (17)
studied middle-sized artery endothelial function and did not find a difference between HFpEF patients and healthy controls.

Neural mechanisms are hugely important for blood flow regulation during exercise and rely on afferent signals from a variety of receptors including mechano- and metabo-receptors in skeletal muscle (40). Elderly hypertensive patients have elevated sympathetic tone at rest, and there is some evidence there is an enhanced response to further augmentation of sympathetic outflow during exercise (25). Muscle blood flow can only increase if sympathetic-excitatory transmission is overridden by locally produced factors within the exercising muscle: functional sympatholysis. Moreover, sympathetic tone may be augmented during exercise by poor SV reserve through activation of arterial baroreceptors (7). The respective roles of functional sympatholysis and baroreceptor activation will need to be explored in future research in these patients.

Arterial compliance is a measure of the distensibility of central, elastic arteries. To examine the impact of physical exercise on arterial compliance, one must account for the direct effects of elevation of pressure. This is important as a progressively greater proportion of vascular load is borne by collagen fibers when arterial pressure rises and the elastic modulus of the vessel wall therefore increases progressively as arteries distend (2). We estimated compliance based on the assumption that arterial pressure and volume are not linearly related but exponentially (29). This method was previously applied in hypertensive patients using invasive pressure waveforms and yielded virtually identical values to our transfer function-derived (i.e., noninvasive) data [present study: 0.61 ml/mmHg; Liu et al (30): 0.6 ml/mmHg].

During exercise, arterial compliance increased in Res patients but decreased in NoRes patients. There are few published reports on the impact of exercise on arterial compliance derived from central pressure waveforms. Maeda et al. (31) studied sedentary elderly women and found that compliance was not affected by exercise at baseline. However, following a training program it was noted that compliance did increase during exercise (31). Laskey et al. (27) studied 11 normal subjects (53 ± 7 yr) and found a significant increase in arterial compliance during exercise. While the present study did not include a group of normal controls, the findings of Laskey et al. are similar to the response seen in Res patients, which likely reflects normal arterial physiology.

Limitations. The present study has several limitations. Owing to stringent inclusion criteria, the study population may have been biased in favor of patients with preserved exercise tolerance. The study design did not incorporate a control group. Based on the noninvasive nature of this study, key variables were derived from echocardiography, tonometry, and sphygmomanometry, all of which are operator dependent and susceptible to measurement error especially during exercise. SphygmoCor-derived central pressure waveforms were used and not direct aortic catheterization. SV was estimated based on the assumption that the LVOt is circular and that the flow profile is flat, neither of which is strictly true.

Conclusions. We studied a group of elderly female patients with long-standing hypertension at high risk of HFpEF fulfilling previously proposed criteria for stage A to B heart failure (18). Poor SV reserve was associated with greater increase in central pressure, lesser arterial vasodilatation, and decreased arterial compliance. As the presence of preload reserve was closely coupled to arterial vasodilatory function, we conclude that poor SV reserve was secondary to simultaneous failure of vascular and ventricular reserve functions (5), producing a state of afterload mismatch (43). Unresolved questions in this field include the underlying culprit behind vasodilatory failure and what the mechanistic and pathophysiological link is between the reserve functions of the heart and arteries.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES