Effects of Age and Gender on Cardiovascular Responses to Phenylephrine

Michael J. Turner, Constance M. Mier, Robert J. Spina, and Ali A. Ehsani

The Section of Applied Physiology, Division of Geriatrics and Gerontology, and The Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

Background. The age-associated impairment in left ventricular (LV) systolic function appears to be mostly detectable during exercise or sympathetic stimulation. We hypothesized that the decline in cardiac function could be unmasked by an acute increase in afterload induced by phenylephrine. We further sought to examine whether the deterioration in cardiac function is influenced by gender.

Methods. We studied 17 young (20-31 years old) and 21 older healthy subjects (60-75 years old) who were given infusions of incremental doses of phenylephrine following cardiac muscarinic receptor blockade with atropine. Left ventricular systolic function was assessed with 2-D echocardiography.

Results. The young subjects exhibited a paradoxical increase in heart rate in response to α-adrenergic stimulation, but the older subjects did not (p < 0.01). The increase in systolic blood pressure in response to phenylephrine was influenced by age and gender (i.e., greater in the younger men and older women), whereas the increase in diastolic blood pressure was greater in the younger than the older subjects of both sexes. The changes in LV end-diastolic diameter with phenylephrine were unaffected by age or gender. The slope of the systolic shortening-end systolic wall stress relationship was significantly steeper in the older subjects, suggesting a decline in the contractile response to an acute increase in afterload with aging.

Conclusions. This study's findings suggest that age can significantly influence the cardiovascular responses to α-adrenergic stimulation and that phenylephrine, by acutely increasing afterload, is effective in unmasking the age-associated deterioration in left ventricular systolic function. Further, it appears that the increase in systolic blood pressure in response to an α-adrenergic challenge is significantly influenced not only by age but also by gender.

CARDIOVASCULAR function decreases progressively with advancing age (1-4) and is generally manifested as impaired myocardial contraction and relaxation, increased arterial stiffness, and diminished inotropic and chronotropic responses to catecholamines (1,2,4). In humans, the impaired left ventricular relaxation and diastolic function can generally be detected both at rest and during exercise, and is reflected in diminished left ventricular filling in older subjects (5). In contrast, the age-associated decline in systolic function appears to be mostly detectable during exercise or sympathetic stimulation (4,6). Previous data suggest that resting left ventricular ejection fraction remains normal in older subjects and is similar to that generally seen in younger subjects (7). Therefore, it appears that in order to assess the effect of aging on left ventricular systolic function in humans, it is necessary to use some form of stress to bring about any detectable aging-related effect. In this study, we used phenylephrine to evaluate the effects of aging and gender on left ventricular systolic function. Phenylephrine is a potent α-adrenergic agonist that is effective in acutely increasing afterload. We hypothesized that the age-associated decline in left ventricular systolic function can be unmasked by an acute increase in afterload induced by graded doses of phenylephrine. We further sought to determine whether the age-associated deterioration in cardiac function can be influenced by gender, as previous studies have shown that gender can play a role not only in cardiac responses to acute exercise but also in cardiovascular adaptations to endurance exercise training (8-10).

METHODS

Subjects.—Seventeen young (20-31 years old) and 21 older (60-75 years old) individuals participated in this study. There were 8 men and 9 women in the young group, and 10 men and 11 women in the older group. The ages of the older men and women were 66.4 ± 1.7 years and 64.4 ± 1.0 years, respectively; the young men and women were 24.5 ± 1.1 years and 25.1 ± 1.1 years, respectively. The subject characteristics for each group are summarized in Table 1. All participants were sedentary nonsmokers, and the older subjects were carefully screened for the presence of coronary risk factors and coronary artery disease. All subjects were healthy, asymptomatic, and had normal cardiac examinations; none was taking cardiovascular medications. None of the older women was on hormone replacement therapy. The exclusion criteria were: history of known coronary artery or other cardiac diseases, hypertension, significant elevation of plasma cholesterol (>220 mg/dl), an abnormal glucose tolerance test, exercise-indexed myocardial ischemia manifested as >1 mm horizontal ST depres-
sion and/or exercise-induced myocardial perfusion defect. All subjects signed an informed written consent, and the study protocol was approved by the Human Studies Committee of the Washington University School of Medicine.

**Exercise tests and measurement of maximal oxygen uptake (VO2max).**—Initially, each older subject underwent a graded treadmill exercise test using the Bruce protocol (11). Two weeks later, the subjects performed a maximal treadmill test to determine VO2max, as previously described (12). VO2 was measured continuously by open-circuit spirometry previously validated against the Douglas bag technique (12). Inspiratory volume was measured with a Parkinson CD-4 dry gas meter. O2 and CO2 were sampled from a mixing chamber and their fractional concentrations quantified using electronic O2 (Applied Electrochemistry S3-A, Sunnyvale, CA) and CO2 (Beckman LB-2, Fullerton, CA) analyzers. VO2max was defined as the mean of the two highest consecutive 30 s O2 measurements that met at least two of the following criteria: (a) attainment of a plateau of O2 with increasing exercise intensity, (b) HR < 10 bpm of the age-predicted maximal HR, and (c) a respiratory exchange ratio > 1.10.

**Left ventricular size and systolic performance.**—Left ventricular (LV) size and systolic function were assessed with the use of two-dimensional echocardiography including 2D-guided M-mode images with a 2.5 mHz transducer (Hewlett-Packard Model 2000, Andover, MA). Images were obtained in the supine position using the standard views according to the guidelines recommended by the American Society of Echocardiography (13). The end-diastolic dimension (EDD) and end-systolic dimension (ESD) were measured using standard guidelines (13). Left ventricular mass (LVmass) was estimated using standard equations (14). Fractional shortening (FS) was calculated as FS = (100(EDD – ESD)/EDD. Left ventricular end-systolic wall stress (ores) was estimated as described by Grossman et al. (15): ores = Pr/2h(1+[h/2r]), where P is systolic blood pressure (SBP) expressed as g/cm², r is end-systolic radius (ESD/2), and h is end-systolic posterior wall thickness. Left ventricular contractile performance was assessed using (a) the FS–ores relationship by plotting FS as a function of ors and (b) the σr–EDS relationship by plotting σr as a function of ESD during graded doses of phenylephrine infusion and cardiac muscarinic receptor blockade (atropine), taking into account the changes in EDD, as an index of preload, and heart rate. The reproducibility of these measurements has been reported from our laboratory (16).

**Cardiovascular responses to phenylephrine.**—Following acquisition of baseline echocardiographic data, each subject received 1.0 mg of atropine intravenously. The reason for the use of atropine was to minimize the effect of vagal tone that might alter the LV contractile responses to phenylephrine. Phenylephrine was infused at successive rates of .25, .50, .75, and 1.00 μg·kg⁻¹·min⁻¹ with the use of an infusion pump (Harvard Apparatus, Model 122, South Natick, MA) with simultaneous ECG and blood pressure (BP) monitoring. Each infusion stage lasted for 5 min. Repeat 2-D echocardiographic studies were performed 2 min following atropine administration and in the last 2 min of each stage of the phenylephrine infusion. BP was taken every 2 min with cuff mercury sphygmomanometry simultaneously with echocardiographic recordings in the supine position.

**Data analysis.**—Left ventricular systolic function was assessed by analysis of the slopes of the FS–ores and σr–ESD relationships obtained from each subject.

**Statistics.**—The differences in variables between age groups and genders were compared with the use of a two-way analysis of variance (ANOVA). To assess the differences in physiological responses to phenylephrine, the data were analyzed across the infusion doses with the use of an ANOVA with repeated measures to compare the effects of age, gender, and the interaction between age and gender. An analysis of covariance with repeated measures was utilized if differences existed between groups prior to the phenylephrine infusion. Data are given as means ± SE.

**RESULTS**

**Subject Characteristics**

The subject characteristics are summarized in Table 1. The men were heavier and taller compared to the women, regardless of age (p < .05). Body surface area (BSA) was

| Table 1. Subject Characteristics at Rest and Maximal Exercise (Means ± SE) |
|--------------------------|----------|--------------------------|
| Age (years)              | Young    | Men                      | Older     | Men                      |
| Weight (kg)†             | 25.1 ± 1.1 | 24.5 ± 1.1               | 64.4 ± 1.0 | 66.4 ± 1.7               |
| BSA (m²)‡                | 62.2 ± 2.2 | 78.1 ± 2.8               | 63.3 ± 2.6 | 83.7 ± 4.5               |
| LVmass/BSA (g/m²)*       | 1.66 ± 0.02 | 1.98 ± 0.05             | 1.67 ± 0.04 | 2.01 ± 0.05             |
| h/r                      | 0.35 ± 0.01 | 0.32 ± 0.02             | 0.36 ± 0.02 | 0.36 ± 0.02             |
| VO2max (L/min)†          | 2.37 ± 0.08 | 3.65 ± 0.15             | 1.39 ± 0.06 | 2.33 ± 0.1              |
| VO2max (ml/kg min)†      | 38.5 ± 1.4 | 46.7 ± 0.7              | 22.0 ± 0.7 | 28.0 ± 1.1              |
| HRmax (b/min)*           | 198.8 ± 1.5 | 192.3 ± 3.4             | 163.5 ± 5.9 | 159.3 ± 3.1             |

Notes: BSA = body surface area; LVmass = left ventricular mass; h/r = left ventricular end-diastolic thickness-to-radius ratio; VO2max = maximal oxygen uptake; HRmax = maximal heart rate.

*Different between age groups, p < .05.
†Different between genders, p < .05.
larger in the men than in the women, regardless of age. There were both age and gender effects for VO₂max. The young men had the highest and the older women had the lowest VO₂max. The decrease in VO₂max observed in the older subjects was in part attributable to a slower maximal heart rate (HRmax) compared to the young subjects (Table 1).

**Baseline Hemodynamics and Left Ventricular Size and Function**

**Age effects.**—Baseline HR (Figure 1A), SBP and DBP (Figure 1B), left ventricular septal and posterior wall thicknesses, EDD and ESD, expressed in absolute terms (Table 2) or relative to BSA, were not different between the older and younger subjects. However, the end-systolic wall thickness was significantly different among the groups except for the young men and older women whose differences were not significant (Figure 2). It was the largest in the older men and smallest in the younger women (Figure 2). LV fractional shortening (FS), end-systolic wall stress (σv), and left ventricular wall thickness-to-radius (h/r) ratio were also not different between age groups (Table 2). LV mass normalized for BSA was larger in the older compared to the younger subjects (Table 1).

**Gender effects.**—EDD normalized for BSA was larger in the women (p < .05). LV posterior wall thickness, septal wall thickness, and ESD indexed for BSA were not different between the men and women. Baseline FS (Figure 3A) was significantly higher in the women than in the men (p < .05). Baseline HR, SBP, DBP (Figure 1), and σv (Figure 3B) did not differ between the men and women. Left ventricular wall thickness-to-radius (h/r) ratio and LV mass index were not different between the men and women (Table 1).

**Age × Gender interaction effects.**—There were no significant Age × Gender interaction effects for any of the baseline measures.

**Cardiac Responses Following Vagal Blockade**

**Age effects.**—There was no effect of age on the changes from baseline in EDD, ESD, HR, SBP, and DBP after vagal blockade (Table 2). Fractional shortening increased slightly in the older subjects (0.23 ± 1.01 and 1.66 ± 1.45, women and men, respectively) but decreased in the younger subjects (-2.01 ± 0.75 and -1.19 ± 0.55, women and men, respectively) in response to atropine (Figure 3A). The changes in σv induced by atropine were different in the two age groups, decreasing in the older (-1.52 ± 3.98 and -3.02 ± 2.50, women and men, respectively) and increasing in the younger subjects (6.35 ± 1.87 and 3.57 ± 2.47, women and men, respectively). The different responses in σv probably account for the age-related differences in FS.

**Gender effects.**—The changes in EDD, ESD, FS, σv, SBP, and DBP from baseline in response to vagal blockade were not different between the men and women (Table 2). The increase in HR from baseline in response to vagal...
<table>
<thead>
<tr>
<th>Phenylephrine (ug/kg/min)</th>
<th>Rest</th>
<th>Young</th>
<th>Older</th>
<th>Young</th>
<th>Older</th>
<th>Young</th>
<th>Older</th>
<th>Young</th>
<th>Older</th>
<th>Young</th>
<th>Older</th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDD (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>47.6 ± 1.2</td>
<td>47.8 ± 1.5</td>
<td>46.9 ± 1.0</td>
<td>47.5 ± 1.2</td>
<td>46.4 ± 1.0</td>
<td>47.2 ± 1.4</td>
<td>47.1 ± 1.1</td>
<td>48.1 ± 1.2</td>
<td>48.2 ± 1.1</td>
<td>48.3 ± 1.0</td>
<td>48.7 ± 1.3</td>
<td>48.0 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>52.0 ± 0.9</td>
<td>51.5 ± 1.4</td>
<td>51.3 ± 1.2</td>
<td>51.0 ± 1.4</td>
<td>50.7 ± 1.4</td>
<td>52.2 ± 1.5</td>
<td>51.6 ± 1.4</td>
<td>52.4 ± 1.4</td>
<td>52.7 ± 1.5</td>
<td>53.0 ± 1.4</td>
<td>52.7 ± 1.5</td>
<td>54.0 ± 1.8</td>
<td></td>
</tr>
<tr>
<td><strong>ESD (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>31.0 ± 0.7</td>
<td>30.5 ± 1.0</td>
<td>31.2 ± 0.7</td>
<td>30.8 ± 1.2</td>
<td>31.3 ± 0.8</td>
<td>30.8 ± 1.3</td>
<td>31.8 ± 1.1</td>
<td>32.5 ± 0.7</td>
<td>32.5 ± 0.8</td>
<td>32.2 ± 0.7</td>
<td>32.5 ± 1.3</td>
<td>30.0 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>34.7 ± 0.8</td>
<td>34.3 ± 1.1</td>
<td>34.3 ± 1.4</td>
<td>34.3 ± 1.1</td>
<td>35.4 ± 1.4</td>
<td>36.0 ± 1.2</td>
<td>35.1 ± 1.1</td>
<td>36.5 ± 1.1</td>
<td>36.6 ± 1.2</td>
<td>37.2 ± 1.0</td>
<td>35.3 ± 1.3</td>
<td>37.8 ± 1.3</td>
<td></td>
</tr>
<tr>
<td><strong>F S (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>33.3 ± 1.2</td>
<td>31.4 ± 1.0</td>
<td>32.1 ± 1.4</td>
<td>33.1 ± 1.3</td>
<td>33.3 ± 1.0</td>
<td>31.6 ± 1.0</td>
<td>31.5 ± 1.0</td>
<td>31.6 ± 1.0</td>
<td>31.5 ± 1.0</td>
<td>31.2 ± 1.0</td>
<td>30.4 ± 1.7</td>
<td>29.2 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>44.8 ± 1.4</td>
<td>43.8 ± 1.1</td>
<td>45.8 ± 1.4</td>
<td>45.8 ± 1.4</td>
<td>45.8 ± 1.4</td>
<td>45.8 ± 1.4</td>
<td>46.8 ± 1.4</td>
<td>46.8 ± 1.4</td>
<td>46.8 ± 1.4</td>
<td>46.8 ± 1.4</td>
<td>46.8 ± 1.4</td>
<td>46.8 ± 1.4</td>
<td></td>
</tr>
<tr>
<td><strong>&lt;res (g/cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>61.7 ± 2.8</td>
<td>61.8 ± 5.2</td>
<td>60.8 ± 3.5</td>
<td>61.6 ± 3.7</td>
<td>61.8 ± 3.7</td>
<td>61.5 ± 3.7</td>
<td>61.4 ± 3.7</td>
<td>61.5 ± 3.7</td>
<td>61.4 ± 3.7</td>
<td>61.4 ± 3.7</td>
<td>60.6 ± 3.7</td>
<td>60.7 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>63.8 ± 3.4</td>
<td>63.8 ± 5.1</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td>63.8 ± 3.7</td>
<td></td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>64 ± 2</td>
<td>65 ± 3</td>
<td>95 ± 7</td>
<td>86 ± 4</td>
<td>105 ± 7</td>
<td>81 ± 4</td>
<td>100 ± 8</td>
<td>77 ± 4</td>
<td>104 ± 10</td>
<td>73 ± 3</td>
<td>110 ± 11</td>
<td>72 ± 3</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>59 ± 4</td>
<td>63 ± 2</td>
<td>74 ± 3</td>
<td>83 ± 4</td>
<td>76 ± 3</td>
<td>78 ± 4</td>
<td>76 ± 4</td>
<td>74 ± 4</td>
<td>74 ± 4</td>
<td>76 ± 4</td>
<td>74 ± 4</td>
<td>74 ± 4</td>
<td></td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>108 ± 3</td>
<td>114 ± 4</td>
<td>114 ± 4</td>
<td>114 ± 4</td>
<td>119 ± 4</td>
<td>119 ± 4</td>
<td>120 ± 5</td>
<td>120 ± 5</td>
<td>120 ± 5</td>
<td>120 ± 5</td>
<td>120 ± 5</td>
<td>120 ± 5</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>118 ± 4</td>
<td>119 ± 3</td>
<td>123 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td>122 ± 4</td>
<td></td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>67 ± 4</td>
<td>69 ± 3</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>72 ± 2</td>
<td>69 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td>72 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

Notes: EDD = end-diastolic dimension; ESD = end-systolic dimension; FS = fractional shortening; <res = end-systolic wall stress; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure.

* Different between age groups, p < 0.05.

** Different between genders, p < 0.05.

† Interaction between age groups and genders, p < 0.05.
blockade, however, was greater in the women than in the men, probably because of a greater degree of vagal blockade (Figure 1A). The increase in HR from rest to vagal blockade for all subjects was not correlated to body weight (r = .193, p > .05).

Age ∗ Gender interaction effects.—There were no Age ∗ Gender interaction effects in any of the variables in response to vagal blockade.

Effects of atropine dosage.—There was no aging effect on the dose of atropine normalized for body weight, with no statistically significant differences between the older and younger men and women. However, we found a gender-related difference in the relative dose of atropine with women, young and old alike, receiving a larger dose (p < .05) than the men (young women: 16.3 ± 0.7 mcg/kg, young men: 13.0 ± 0.7 mcg/kg, older women: 16.2 ± 0.6 mcg/kg, and older men: 12.4 ± 0.66 mcg/kg). There was no Age ∗ Gender interaction attributable to atropine.

Cardiovascular Responses to Phenylephrine

Age effects.—EDD and ESD increased to similar extents in response to phenylephrine (Table 2, p < .001) in the young and older subjects. LV fractional shortening decreased in all subjects (Table 2, p < .001), with the young and older subjects responding in a similar manner. End-systolic wall stress increased in response to phenylephrine (Table 2, p < .001) in all groups, but there was a greater increase in σs in the young subjects (p < .01) compared to the older subjects. The left ventricular end-systolic wall thickness decreased in all groups. However, the decrease was significantly greater in the young men and women than in the older subjects (Figure 2), accounting for the smaller increase in σs in the older subjects. The FS–σs relationship (Figures 4 and 5) was linear for both older men and women (r = −.943 ± .021 and −.919 ± .018, respectively) and young men and women (r = −.908 ± .028 and −.896 ± .033, respectively). The young men and women exhibited a markedly less steep slope for the FS–σs relationship (−.06 ± .01 and −.05 ± .01, respectively) compared to the older men and women (−.19 ± .04 and −.16 ± .03, respectively). The young men and women showed a steeper slope for the σs–ESD relationship (16.71 ± 4.52 and 13.79 ± 1.75, respectively) compared to the older men and women (8.03 ± 1.77 and 8.50 ± 2.08, respectively). Therefore, the older subjects exhibited a significantly greater decline in LV systolic shortening in response to a given increase in σs induced by phenylephrine when compared to young subjects (Figure 5). The HR responses to phenylephrine were different between the young and older subjects (Figure 1A), with the young subjects showing an increase but the older subjects showing a decrease in the HR responses even though the doses of atropine normalized for body weight were similar in older and younger subjects (14.3 ± 0.1 and 14.7 ± 0.1 mcg/kg, respectively; p = .66). There were similar increases in SBP in response to phenylephrine in the older and younger subjects (Figure 1B). Diastolic blood pressure also increased progressively with phenylephrine in all groups (Figure 1B, p < .001). The magnitude of the increase in DBP, however, was greater (p < .01) in the young subjects than in the older subjects.

Gender effects.—There were no gender-related differences in the EDD, FS, σs, HR, SBP, and DBP responses to phenylephrine (Table 2). However, the increase in ESD was greater in the men than in the women (Table 2). The slopes of the FS–σs relationship and the σs–ESD relationship were not different between the genders (p > .05).

Age ∗ Gender interaction effects.—There were no Age ∗ Gender interaction effects in the EDD, ESD, FS, σs, HR, and DBP responses to phenylephrine (Table 2). There were no Age ∗ Gender interaction effects on the slopes of the FS–σs relationship and the σs–ESD relationship. The increase in SBP to phenylephrine (Figure 1B) was significantly different, as the young men and older women exhibited greater SBP responses compared to the older men and young women at the two highest doses of phenylephrine.
DISCUSSION

The purpose of this study was to determine whether the phenylephrine-stimulated increase in afterload is useful in identifying the effects of age and gender on left ventricular systolic function. To assess the cardiac effects attributable to aging alone, all older subjects were rigorously screened for the presence of coronary risk factors and myocardial ischemia. Our findings suggest that age can significantly influence the cardiovascular responses to \( \alpha \)-adrenergic stimulation and that phenylephrine, by acutely increasing afterload, is effective in ummasking the age-associated deterioration in left ventricular systolic function. This is evidenced by a steeper slope of the FS-\( \sigma_e \) relationship in older subjects, showing a greater decrease in FS in response to a given increase in \( \sigma_e \), and a less steep slope of the \( \sigma_e \)-ESD relationship in older subjects who exhibited a smaller increase in \( \sigma_e \) in response to a given increase in ESD compared with young subjects. The differences in the slope of the FS-\( \sigma_e \) relationship between the young and older subjects can reflect an age-related decrease in contractile reserve or the differences in the use of the preload reserve, with the younger subjects having the ability to utilize the preload reserve more effectively than the older subjects, therefore preventing the excessive fall in FS in response to an acute increase in left ventricular wall stress (17). However, the role of preload in modulating these changes appears unlikely, because the similarity of the EDD responses to phenylephrine, used as an index of preload, in the older and younger subjects argues against this possibility. The FS-\( \sigma_e \) and \( \sigma_e \)-ESD relationships are reliable measures of LV contractile function provided that preload does not change significantly.

The greater left ventricular end-systolic wall thickness in the older subjects, which did not decrease in response to phenylephrine, was most likely responsible for the blunted increase in \( \sigma_e \), particularly in the older women. This adaptive response provides a useful mechanism to prevent an excessive fall in left ventricular systolic shortening in response to an acute afterload challenge and can, therefore, conceal the age-related decline in LV contractile reserve in the older healthy subjects.

In vitro studies (18,19) using phenylephrine with isolated ventricular preparations have demonstrated a decline in inotropic responsiveness to phenylephrine with age in rats and humans. Phenylephrine is a potent \( \alpha \)-adrenoceptor agonist (20). Although it has some \( \beta \)-adrenergic property, this effect, compared to \( \alpha \)-adrenergic activity, is small (21). A positive inotropic effect with \( \alpha \)-adrenergic stimulation has been shown with phenylephrine (22) in the intact human heart. This positive inotropic effect, however, is not as profound as that observed with \( \beta \)-adrenergic stimulation and accounts for only a small fraction of the increase in contractility compared with \( \beta \)-adrenergic simulation (approximately 8–10% of the \( \beta \)-mediated response) (21). This \( \alpha \)-adrenergic-stimulated increase in contractile state is believed to be only a complementary response to the positive inotropic effect of \( \beta \)-adrenergic stimulation (22). The findings of our study do not distinguish the myocardial effects of phenylephrine (\( \alpha \) and \( \beta \) stimulation) from those attributable to its vasoconstrictive property that can induce a

---

**Figure 4.** A Mean slopes (±SE) of the individual FS-\( \sigma_e \) relationship and B mean slopes (±SE) of the individual \( \sigma_e \)-ESD relationship in response to phenylephrine in the young and older men and women. *Denotes difference between age groups (\( p < .05 \)). OM indicates older men; OW, older women; YM, young men; YW, young women.

**Figure 5.** Mean slopes of the individual fractional shortening versus end-systolic wall stress relationship for older and young individuals during atropine and phenylephrine infusion. The older subjects had a steeper slope (\( p < .05 \)) than the young subjects, showing that for a given increase in end-systolic wall stress (\( \sigma_e \)), there was a greater decrease in fractional shortening (FS).
significant increase in systolic loading and afterload. Therefore, it is possible that the observed age-associated decline in the systolic shortening in response to phenylephrine may be, in part, mediated by a reduction in the number of α- or β-adrenoceptors (18) in the signaling pathway in the senescent heart (23), making the left ventricular myocardium more vulnerable to an afterload stress in older subjects.

The observed paradoxical elevation in HR in the young subjects with increasing doses of phenylephrine is most likely a consequence of vagal blockade. The typical, chronotropic response to phenylephrine is generally a decrease in HR (24–26) in the absence of vagal blockade, and is due to activation of the baroreflex response. A recent study by Saitoh et al. (27) showed results similar to those observed in the current study. These investigators (27) studied the chronotropic response to phenylephrine after both vagal and β-blockade in 44 individuals aged 14 to 75 years. They found an age-associated difference in HR response, with the young subjects showing a paradoxical increase in HR whereas the older subjects exhibited a decrease in HR in response to phenylephrine. We found a similar age-related difference in the HR responses to phenylephrine in this study even though we did not use β-adrenergic blockade.

Age-related differences in the chronotropic response to α-adrenergic stimulation have also been reported in the Purkinje fibers of canine hearts (28) where the smaller increase in the impulse frequency in the senescent heart was attributed to the development of an inhibitory response to α-adrenergic stimulation with cardiac and nerve growth. The positive chronotropic response in the younger subjects may have contributed to greater contractile reserve mediated by the force-frequency relationship.

Research in experimental animals (29,30) has found an age-related decline in vasoconstrictive responsiveness to α-adrenergic stimulation. However, human studies have provided conflicting results showing a decrease (26) or an increase (31) in α-adrenergic-mediated vasoconstrictive responsiveness. Elliott et al. (26) reported an aging-related decline in the mean arterial blood pressure responsiveness to phenylephrine. Our finding of a diminished diastolic blood pressure response to α-adrenergic stimulation in older subjects is in accordance with that of Elliott et al., suggesting a decline in the α-adrenergic-mediated vasoconstrictor responsiveness with aging. Endurance exercise training may restore the age-related decline in the vasopressor responses to α-adrenergic stimulation (24).

The limitations of the current study include a relatively small sample size, the failure to use β-adrenergic blockade, and the differences in the amount of atropine used in the subjects. Although the men were larger than the women regardless of age, resulting in a smaller dosage of atropine relative to body weight used in the men than in the women, there were no gender-related differences in the cardiovascular responses to phenylephrine following vagal blockade.

In conclusion, our findings demonstrate an age-related decline in the LV contractile reserve which can be readily shown by an acute increase in systolic loading and afterload. This effect is associated with a blunted α-adrenergic-mediated vasopressor response. Furthermore, it appears that after even a partial inhibition of the baroreflex, there is a paradoxical positive chronotropic response to an α-adrenergic stimulation in young individuals, which is lost with increasing age.

ACKNOWLEDGMENTS

This research was supported by National Institute on Aging Program Project Grant AG-05562, Claude D. Pepper Older Americans Independence Center Grants AG-13629, RO1 AG-12325, RO1 AG12822, and General Research Center Grant 5-M01-RR-00036. Dr. Michael Turner was supported by Individual National Research Service Award I-F32-AG05756-01.

Address correspondence to Dr. Ali A. Ehsani, Washington University School of Medicine, 4566 Scott Avenue, Campus Box 8113, St. Louis, MO 63110. E-mail: aehsani@imaget.wustl.edu

REFERENCES


Received July 22, 1997
Accepted April 6, 1998

Brown University School of Medicine
Interdisciplinary Fellowships

Unique interdisciplinary fellowship training opportunities in Geriatrics/Gerontology and Health Services Research are available at Brown University for MDs and PhDs. The position requirements are: M.D. and continuation of basic clinical training, or Ph.D. in sociology, epidemiology, economics or other related field; a fundamental understanding of the issues involved in geriatrics/gerontology and an ability to articulate a well-conceived rationale for undertaking the program. The program offers postdoctoral training in health services research/clinical epidemiology. In addition, physicians may opt to pursue an MS degree in epidemiology. Fellows will have the opportunity to participate in ongoing research in one or more substantive areas, including breast cancer, health promotion and prevention, long-term care, and community-based systems of care, health care organizations and methodological approaches to health services research.

Positions are funded by AHCPR and University graduate programs and are jointly sponsored by the Center for Gerontology and Health Care Research and the Departments of Community Health, Family Medicine, Medicine, and Psychiatry. Women, minorities and members of protected groups are encouraged to apply. Term of appointment is for one year, renewable contingent upon funding. Applications received by May 1, 1999 will receive full consideration. Screening will begin on that date and continue until all successful candidates have been identified or the search is closed. Brown University is an equal opportunity/affirmative action employer. For further information contact: Vincent Mor, Ph.D., Director, Center for Gerontology and Health Care Research, Brown University, Box G-B215, Providence, RI 02912; email: Vincent_Mor@brown.edu