THE EFFECT OF AGING ON PHENYLEPHRINE RESPONSE IN NORMAL SUBJECTS

Kenneth M. Madden, Wayne C. Levy, Arnold Jacobson, and John R. Stratton
Division of Cardiology, Department of Medicine and
Division of Nuclear Medicine, Department of Radiology
Seattle Veterans Affairs Medical Center and University of Washington
Seattle, Washington

ABSTRACT

INTRODUCTION: With aging, cardiac responses to β-adrenergic stimulation decline but the responses to α1-stimulation are less clear. Moreover, whether aging, in the absence of disease, influences the left ventricular response to an increase in afterload is unclear. This study examined the effect of aging on heart rate (HR), blood pressure (BP), cardiac index (CI) and several left ventricular contractility measurements during α1-stimulation with a phenylephrine infusion. METHODS: Subjects were rigorously screened to be normal by history, physical, blood tests, ECG, ETT and echocardiogram. Twelve young (mean 26 years, all male) and 15 aged (69 years, 11 males) subjects were studied during 10 minute infusions of phenylephrine at 0.5 and 1.0 mcg/kg/min. HR, BP and radionuclide ventriculographic cardiac volumes were measured. RESULTS: Systolic BP increased more in the young than in the young (22 vs. 13%, p=0.003), while heart rate (16 vs. 21%, p=0.05) fell less. Contractile responses to phenylephrine, including EF, stroke volume index (SVI), stroke work index and left ventricular contractility index were not altered with aging. Systemic vascular resistance (SVR) was higher at baseline and at each infusion rate, but there was no age-associate change in the response to PE. CONCLUSIONS: In a healthy normal aged population, a preserved SVI response in the setting of a higher baseline SVR results in an increased SBP response to α1-stimulation. Contractile responses to increased afterload are not altered with aging. Age-associated differences in the response to α1-stimulation are small and are explained by altered baroreflex sensitivity and a stiffer vasculature.

INTRODUCTION

Autonomic regulation of cardiovascular function changes with aging. For example, human and animal studies have consistently shown a decrease in beta adrenergic responsiveness with aging, with reduced heart rate, ejection fraction, blood pressure and cardiac output responses to beta adrenergic stimulation with isoproterenol. In addition, there is abundant evidence of reduced cardiac vagal tone with aging as manifested by reduced heart rate variability. Whether alpha adrenergic responsiveness alters with aging is less clear. In vitro animal studies have shown both an increased[1], reduced[2,3] or unchanged[4] α1-mediated phenylephrine response. In vitro human studies have shown an increased[5] or reduced[6] α1-mediated phenylephrine response in isolated artery preparations. In vivo examination of the vascular response to α1-stimulation has been found to be reduced with age in the rat hindlimb[7] but unchanged by aging in the beagle hindlimb[8]. Human in vivo studies have shown an age-associated reduction in α1-mediated phenylephrine response in forearm blood flow[9] but an overall increase in the blood pressure response to phenylephrine with increasing age[10]. Thus, the effect of aging on the cardiovascular response to α1-stimulation varies with the portion of the vascular bed examined. In addition, conflicting results in prior human studies may also be due to the rigor with which confounding diseases such as hypertension are excluded.

Alpha receptors are of two types. The majority of myocardial alpha receptors are of the α1 subtype[11]; α1 receptors mediate smooth muscle constriction, arterial vasconstriction, and cause a positive inotropic effect. Alpha 2 receptors mediate inhibition of sympathetic neurotransmission in the heart by inhibiting norepinephrine release at the presynaptic level. Although most studies at rest have shown no age-associated reduction in ejection fraction with aging[12,13], some have postulated that this can be "uncovered" by maneuvers that increase afterload, such as mental stress[14] or phenylephrine infusion[15]. Phenylephrine is an α1 selective agonist and causes at least some inotropic effect but also causes vasoconstriction leading to an increase in blood pressure and afterload. Unfortunately these prior investigations showing an age-associated change in contractility have
been limited by the use of echocardiographically-derived measures of cardiac contractility[15], confounded by drugs used to block the arterial baroreceptors[15], and had insufficiently rigorous methods of screening for confounding cardiac disease[14].

The purposes of this study were to determine whether α responses are altered with aging and whether the contractile response to an increased afterload declines with aging. We hypothesized that the older adult population will demonstrate an increased systemic blood pressure (SBP) response to phenylephrine and that the use of more reproducible radionuclide angiographic measures will demonstrate preserved contractile responses to an increase in afterload in older subjects.

METHODS

Subjects

The subjects studied consisted of 12 young (aged 22 to 33) and 18 older (aged 63 to 80) healthy adults. All 12 of the younger subjects and 11 of the older subjects were male. Subjects were excluded if they had any history of angina, myocardial infarction, stroke, hypertension, chronic pulmonary disease, diabetes, current medication use (prescription or over the counter), current smoking, or exercise-limiting orthopedic impairment. Entry requirements included a normal blood pressure, a normal physical exam, normal resting ECG, normal M-mode and two-dimensional echocardiograms showing no more than mild valvular regurgitation, a normal Bruce protocol maximal exercise treadmill stress test, and a normal hematocrit, fasting blood glucose, total cholesterol, and creatinine. Two older subjects were excluded on the basis of this screening and an additional older subject was excluded secondary to problems with line placement. Therefore a total of 12 young subjects and 15 older subjects received phenylephrine infusion.

This study was approved by the Human Subjects Committee of the University of Washington, and all subjects gave informed consent.

Study Protocol

Intravenous catheters were inserted into a right hand vein and a right antecubital vein of each subject, after which they rested supine for 30 minutes before collection of baseline data. All studies were performed with the subject supine, and all were performed at the same time of day (10 AM to 12 noon). After the collection of baseline data, serial infusions of phenylephrine at 0.5 and 1.0 mcg/kg/min were given for 10 minutes each with a Medfusion 2010 infusion pump. The infusion solution was prepared by diluting a sufficient amount of phenylephrine in 0.5N saline to achieve a total injectate volume of 20 mL at each infusion level. Phenylephrine infusions were halted if the diastolic blood pressure (DBP) became greater than 100 mm Hg or if the systolic blood pressure (SBP) became greater than 200 mm Hg. No complications occurred, and all younger subjects received all two doses. One older subject did not receive the 1.0 mcg/kg/min phenylephrine dose since her blood pressure increased to 210/102.

Data Collection and Processing:

At rest and during the final 2 minutes of each infusion dose, cardiac blood pool images, heart rate, and blood pressure (using Ohmeda 2300 Finapres) were recorded. For radionuclide angiography, blood was obtained at the time of intravenous catheter placement and labeled with 20-30 mCi of 99mTc as previously described[16]. Images were acquired in the left anterior oblique projection, which offered the best septal definition, with a high-sensitivity parallel hole collimator and a General Electric 300 small-field-of-view camera interfaced to a Microdelta imaging terminal. Radionuclide images were acquired in 20-msec frames by forward and backward reconstruction with ±20% arrhythmia rejection; a single beat was dropped after each rejected beat[16]. Ejection fraction, end-diastolic volume index, and end-systolic volume index were calculated by previously described methods[16]. Cardiac index was obtained by multiplying the stoke volume index times the mean heart rate during the acquisition.

Derived Measurements

Mean arterial pressure (MAP) was calculated as [SBP + 2XDBP]/3. Total systemic vascular resistance (SVR) was calculated as MAP x 80 / CO. Stroke work index (SWI) was calculated as stroke volume index (SVI) X SBP; rate pressure product (RPP) as SBP X HR; left ventricular contractility index (LVCl) as SBP/ESVI. Effective E, an estimate of afterload that takes into account pulsatile flow was calculated as [2XSBP+DBP]/3 X SV. Root mean square difference (RMS Diff), which is calculated by taking the root mean square of the difference of successive RR-intervals, is a measure of heart rate variability used as a marker for vagal tone. Baroreceptor sensitivity (BRS) was calculated by performing a linear regression of the relationship between RR interval and SBP during the phenylephrine infusion[14,17,18].

Statistical Analysis

Results are expressed as the mean ± standard error. The results in all young and older subjects were compared by ANOVA for repeated measures. The reported probability values are those for phenylephrine effect, overall young/old effect and the interaction term (old versus young times dose). A value of p<0.05 was considered significant.

<table>
<thead>
<tr>
<th>Table 1—Subject Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SEM</strong></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
</tr>
<tr>
<td><strong>Body Surface Area (m²)</strong></td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
</tr>
</tbody>
</table>

The symbol * designates a significant difference (p<0.05) between age groups.