Baroreflex Buffering Is Reduced With Age in Healthy Men

Pamela Parker Jones, PhD; Demetra D. Christou, PhD; Jens Jordan, MD; Douglas R. Seals, PhD

Background—Baroreflex buffering is an important mechanism in arterial blood pressure control. The effect of healthy (physiological) aging on tonic baroreflex buffering in humans is unknown.

Methods and Results—Baroreflex buffering was determined in 27 young (aged 25±1 years) and 16 older (aged 65±1 years) healthy normotensive men by measuring the potentiation of the systolic blood pressure (SBP) responses to a phenylephrine bolus (BRBbolus) and incremental infusion (BRBslope) during compared with before ganglionic blockade with trimethaphan. The SBP responses to phenylephrine either were not different or greater in the older men before ganglionic blockade, but smaller during ganglionic blockade. BRBbolus (2.1±0.4 versus 5.1±0.7, P<0.001) and BRBslope (1.6±0.2 versus 3.5±0.4, P<0.0001) were ≈115% smaller in the older men. Baroreflex buffering was not consistently related to mean levels or variability of blood pressure or heart rate, or to cardiovagal baroreflex sensitivity, but correlated with muscle sympathetic nerve activity (BRBbolus: r=-0.55, BRBslope: r=-0.69, P<0.005) and the SBP responses to phenylephrine during ganglionic blockade (BRBbolus: r=0.53; BRBslope: r=0.98, P<0.0001). BRBbolus was also inversely related to the SBP response to phenylephrine before ganglionic blockade (r=-0.78, P<0.0001).

Conclusions—Physiological aging in men is associated with a marked reduction in baroreflex buffering. The decrease in baroreflex buffering with aging is related to increases in basal sympathetic nerve activity and reductions in systemic α1-adrenergic vascular responsiveness. These findings are helpful for interpreting changes in baroreflex buffering in older patients with cardiovascular disease, as well as changes in responsiveness to vasoactive drugs with aging. (Circulation. 2003;107:1770-1774.)

Key Words: autonomic □ sympathetic activity □ vascular responsiveness
Experimental Procedures

Subjects were studied during supine rest beginning at 0800 according to procedures previously described.14 They were instrumented with a radial artery catheter in the non-dominant arm and 2 intravenous catheters in the contralateral arm. BP (mm Hg) was continuously monitored by a pressure transducer connected to the arterial catheter and heart rate by ECG (Hewlett-Packard Merlin Patient Monitoring System). Arterial BP variability was determined over 300 s of the baseline (preganglionic blockade) period with the standard deviation of the beat-to-beat systolic and diastolic peaks of the BP waveforms. Heart rate variability (HRV) was determined as described previously.3,14 The standard deviation of the R-R intervals (time domain measure of HRV) and the high frequency power of the HRV (frequency domain measure of HRV) were used as indicators of tonic cardiac vagal modulation of heart rate. Breathing frequency was not regulated, but did not differ between young and older groups (18±2 versus 16±2 breaths/min, respectively, P=0.49). Cardiovascular baroreflex sensitivity was determined from incremental bolus doses of phenylephrine (25, 50, 100, and 200 μg) administered at 3-minute intervals. R-R intervals were regressed against the corresponding transient increase in systolic blood pressure (SBP) induced by the phenylephrine bolus. Plasma catecholamines were analyzed by high performance liquid chromatography. In a subgroup of the same subjects (n=15 young, n=12 older), after a 12-hour fast on a separate morning, multiunit recordings of muscle sympathetic nerve activity (MSNA) were obtained from the right peroneal nerve at the flabellum with the microneurographic technique as described previously.14,19

Protocol

The protocol was modified from that previously described in detail.14,15,22,23 Briefly, after a stable 30-minute period, baseline measurements were obtained followed by blockade of Nn-cholinergic receptors via continuous intravenous infusion of trimethaphan (Cambridge Laboratories Limited). Complete cardiovascular-autonomic blockade was documented by absence of a change in heart rate in response to bolus injection of phenylephrine (25, 50, and/or 100 μg). After a 20-minute washout period, baseline measurements were repeated. Vascular α-adrenergic responsiveness was determined before and during ganglionic blockade by the increases in systolic and mean arterial blood pressure in response to intravenous administration of: (a) a standard bolus dose of phenylephrine (25 μg), and (b) 6-minute steady-state incremental infusions of phenylephrine (0.02, 0.04, 0.08, 0.16 μg · kg⁻¹ · min⁻¹).

Baroreflex Buffering

Baroreflex buffering15 was measured as: (a) the potentiation of the systolic and mean arterial blood pressure responses to a standard 25-μg bolus dose of phenylephrine (BRBbolus) during, compared with before ganglionic blockade, and (b) the change in the slope of the increase in systolic and mean blood pressure in response to the incremental infusion of phenylephrine (BRBiset) from baseline to ganglionic blockade. Both methods were used because bolus and continuous infusions of vasoactive substances present somewhat different stimuli to the baroreflexes;10 thus, each might provide unique information.

Statistical Analyses

Group comparisons for baseline characteristics and baroreflex buffering were made with the use of t-tests for independent group comparisons. The blood pressure responses to phenylephrine before and during ganglionic blockade were analyzed with a 2-way analysis of variance with repeated measures (age-group x condition [baseline versus autonomic blockade]). Newman-Keuls post hoc analyses were performed when significant interactions were present. Relations of interest were determined from univariate correlations and analyses of covariance (ANCOVA) and partial regression analyses were used to determine how much of the variance in BRB could be explained by the significant correlates. The α was set at 0.05. All data are reported as mean±SE.

Cardiovascular-Autonomic Function During Supine Rest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger (n=27)</th>
<th>Older (n=16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>126±2</td>
<td>125±3</td>
<td>0.35</td>
</tr>
<tr>
<td>SBP variability, SD</td>
<td>4.1±0.2</td>
<td>4.5±0.5</td>
<td>0.23</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>66±1</td>
<td>62±2</td>
<td>0.04</td>
</tr>
<tr>
<td>DBP variability, SD</td>
<td>3.0±0.2</td>
<td>3.2±0.3</td>
<td>0.56</td>
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<tr>
<td>HR, bpm/min</td>
<td>58±2</td>
<td>54±2</td>
<td>0.08</td>
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<tr>
<td>HR variability, SD</td>
<td>691±4.6</td>
<td>51.6±9.8</td>
<td>0.04</td>
</tr>
<tr>
<td>HR variability, high-frequency power</td>
<td>1144±136</td>
<td>770±138</td>
<td>0.04</td>
</tr>
<tr>
<td>Baroreflex sensitivityiset</td>
<td>19.2±2.8</td>
<td>8.7±1.1</td>
<td>0.007</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>24±2</td>
<td>38±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/ml</td>
<td>246±17</td>
<td>390±34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma epinephrine, pg/ml</td>
<td>55±5</td>
<td>50±9</td>
<td>0.62</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure; HR, heart rate; phe, phenylephrine; R-R, interval between ECG R-waves; and MSNA, muscle sympathetic nerve activity

Results

Subject Characteristics

The young and older men did not differ significantly in body mass (76.9±1.4 versus 79.7±2.7 kg, P=0.15), body mass index (24.4±0.5 versus 25.6±0.7, P=0.07), or urinary sodium excretion (134.9±9 versus 143.1±10 mmol/dL, P=0.23).

Resting Cardiovascular-Autonomic Function

Supine resting mean SBP, systolic and diastolic blood pressure variability, and heart rate were not different in the young and older men; mean diastolic blood pressure was slightly lower in the older men (Table 1). HRV was 55% lower in the older men. MSNA and plasma norepinephrine concentrations were 60% higher in the older men (P<0.001). Plasma epinephrine concentrations were not different in the two groups.

Blood Pressure Responses to Phenylephrine Before and During Ganglionic Blockade

Before ganglionic blockade (Figures 1 and 2, left panels), the
The slope of the increase in SBP in response to phenylephrine was greater in the older men (bolus: 7 ± 1 versus 5 ± 1 mm Hg, \( P = 0.03 \); slope: 0.63 ± 0.1 versus 0.66 ± 0.1 mm Hg \( \cdot \) ng \( ^{-1} \) \( \cdot \) min \( ^{-1} \), \( P = 0.81 \)). Trimepraphan infusion caused baseline HR to increase in the young but not the older men (+25 ± 2 versus +4 ± 2 bpm, respectively, \( P < 0.0001 \)), and SBP to decrease in both groups, although more so in the older men (−34 ± 2 versus −54 ± 3, \( P < 0.0001 \)). During ganglionic blockade (Figures 1 and 2, left panels), the increases in SBP in response to phenylephrine were smaller in the older than in the young men (bolus: 12 ± 1 versus 17 ± 1 mm Hg, \( P = 0.001 \); slope: 2.2 ± 0.3 versus 4.1 ± 0.4 mm Hg \( \cdot \) ng \( ^{-1} \) \( \cdot \) min \( ^{-1} \), \( P = 0.001 \)). As such, ganglionic blockade potentiated the SBP responses to the phenylephrine bolus by only 2.1 ± 0.4-fold in the older men compared with 5.1 ± 0.7-fold in the young men (\( P < 0.001 \), Figure 1, right panel). In addition, ganglionic blockade changed the slope of the increase in SBP in response to the incremental infusion of phenylephrine by only 1.6 ± 0.2 mm Hg \( \cdot \) ng \( ^{-1} \) \( \cdot \) ml \( ^{-1} \) in older men compared with 3.5 ± 0.4 in the young men (\( P < 0.001 \), Figure 2, right panel). Similar group differences were observed when the mean arterial blood pressure responses to phenylephrine were examined.

**Correlates of Baroreflex Buffering**

Baroreflex buffering did not correlate with any subject characteristic. In general, baroreflex buffering was not consistently related to mean values or variability in blood pressure or heart rate during supine rest, nor to cardiovagal baroreflex sensitivity. The exceptions included BRB_slope and the high frequency power of HRV (\( r = 0.29 \), \( P = 0.05 \)) and BRB_bolus and cardiovagal baroreflex sensitivity (\( r = -0.49 \), \( P = 0.04 \)).

BRB_slope and BRB_bolus were negatively related to supine resting MSNA (\( r = -0.69 \) and -0.55, \( P < 0.005 \), Figure 3), and BRB_slope was negatively related to plasma norepinephrine concentrations (\( r = -0.40 \), \( P = 0.01 \)). The SBP response to the phenylephrine bolus before ganglionic blockade was inversely and curvilinearly related to BRB_bolus (Figure 4). Baroreflex buffering was positively related to the SBP response to phenylephrine during ganglionic blockade (BRB_slope, \( r = 0.98 \), \( P < 0.0001 \); BRB_bolus, \( r = 0.53 \), \( P < 0.0001 \); Figure 5). The slope of the increase in SBP in response to phenylephrine infusion during ganglionic blockade was inversely related to MSNA (\( r = -0.66 \), \( P = 0.001 \); Figure 6). Adjusting for MSNA with ANCOVA reduced the age-related difference in BRB_slope from 54% (\( P = 0.004 \)) to 23% (\( P = 0.42 \)) and in BRB_bolus from 60% (\( P = 0.003 \)) to 48% (\( P = 0.13 \)). Furthermore, when age was partialed out, BRB_slope remained significantly related to MSNA (partial \( r = -0.51 \), \( P = 0.02 \)).

**Discussion**

The main novel finding from the present study is that aging is associated with a marked reduction in baroreflex buffering in healthy men. We established this with an innovative experimental approach\( ^1 \)\( ^5 \) that takes advantage of the fact that the arterial blood pressure response to vasoactive drugs is mediated by the net effect of vascular sensitivity to the drug (+) and the counter-regulatory actions of the baroreflexes (-). By pharmacologically removing the baroreflexes with trimethaphan, which blocks neurotransmission at the autonomic ganglia, thus interrupting the neural pathway for reflex modulation of cardiac output and vascular resistance, the difference in the pressor response to phenylephrine with and without ganglionic blockade provides a measure of the tonic restraint (buffering capacity) imposed by the baroreflexes.
We found that baroreflex buffering was consistently related to both basal sympathetic activity and systemic $\alpha_1$-adrenergic vascular responsiveness (SBP response to phenylephrine during ganglionic blockade). One possibility is that our findings support the hypothesis\textsuperscript{20,22} that the age-associated increase in basal sympathetic activity is mediated in part by a reduction in tonic baroreflex suppression of central sympathetic outflow. Although most previous investigations\textsuperscript{5,17} including our own work,\textsuperscript{5} have failed to demonstrate differences in the MSNA responses to acute experimental perturbations in blood pressure in young and older healthy adults, these studies did not determine baroreflex buffering per se. Moreover, there are data in experimental animals supporting such a mechanistic association between age-related increases in basal sympathetic activity and reduced tonic baroreflex sympathoinhibition.\textsuperscript{11} Alternatively, it may be that the correlation between baroreflex buffering and basal sympathetic activity is indirect. For example, a chronic increase in sympathetic activity with age may act to desensitize the $\alpha_1$-adrenergic signaling pathway,\textsuperscript{4,12,14} reducing peripheral vasoconstrictor responsiveness and impairing the distal step in the efferent arm of the baroreflex (sympathetic-vascular coupling), thus reducing baroreflex buffering. The inverse relation between basal MSNA and $\alpha_1$-adrenergic vascular responsiveness (Figure 6), and the positive relation between $\alpha_1$-adrenergic vascular responsiveness and baroreflex buffering (Figure 5) together are consistent with this possibility. Impairments in the efferent arm of the baroreflex\textsuperscript{13,18} and changes in central nervous system integration of afferent feedback\textsuperscript{2} also may have contributed to the reductions in baroreflex buffering we observed with age.

Jordan and colleagues\textsuperscript{15} recently observed a strong inverse relation between BRB$_{bolus}$ and the increase in SBP in response to a 25 $\mu$g bolus of phenylephrine before ganglionic blockade in patients with various autonomic-cardiovascular disorders. We found a similarly strong inverse relation among the healthy men varying in age in the present study (Figure 4), suggesting that greater blood pressure responsiveness may reflect reduced baroreflex buffering rather than enhanced vascular sensitivity to the $\alpha_1$-adrenergic agonist. Together these results support the view that an augmented (eg, >5 to 10 mm Hg) SBP response to a standard 25- $\mu$g bolus of phenylephrine can be used to identify both healthy adults and patients with chronic disease who have impaired baroreflex buffering.

Mean levels and variability of arterial blood pressure generally were not different in the young and older men in the present investigation, and were not related to baroreflex buffering or to cardiovasal baroreflex sensitivity. HRV was $\approx$30% lower in the older men, but was not consistently related to baroreflex buffering. The lack of correlation with mean levels of arterial blood pressure is not surprising given the primary role of the kidneys and other mechanisms in chronic blood pressure control. Cardiovasal baroreflex sensitivity has been related to blood pressure (negatively) and HRV (positively), primarily in patients with essential hypertension.\textsuperscript{16,26} However, correlations were modest at best, explaining only 25% or less of the inter-individual variance, and were related in part to baseline blood pressure.\textsuperscript{16} The absence of significant correlations in the present study may be attributed in part to the fact that our subjects were normotensive and/or that cardiovascular variability was measured over a short duration, whereas previous associations were established with 24-hour recordings.\textsuperscript{16} This is consistent with previous findings of reduced cardiovasal baroreflex sensitivity, but no difference in short-term blood pressure variability with aging in normotensive adults.\textsuperscript{25} We have observed modest age-associated increases in daytime and nighttime SBP variability in healthy sedentary women,\textsuperscript{21} and it is possible that this longer-term variability is related to reduced baroreflex buffering.

As established previously,\textsuperscript{6,8,13,17,18,23} cardiovasal baroreflex sensitivity was reduced with age in the present study. However, cardiovasal baroreflex sensitivity was not consistently related to baroreflex buffering, although one correlation was observed. This is consistent with the recent findings of Jordan and colleagues\textsuperscript{15} in patients with autonomic-cardiovascular disorders, and reinforces the concept that cardiovasal baroreflex sensitivity and baroreflex buffering reflect, at least in part, different properties of baroreflex modulation of the circulation.

Our findings have important clinical implications in at least 2 different contexts. First, our results are helpful in interpreting changes in the blood pressure responses to vasoactive drugs with primary (physiological) aging in humans. As we established recently,\textsuperscript{14} systemic $\alpha_1$-adrenergic vascular responsiveness was reduced in the older men as indicated by
smaller blood pressure responses to phenylephrine during ganglionic blockade. Because systemic vascular sensitivity is one of the two major determinants of the blood pressure response to vasoactive drugs in the normal (intact) state, on the basis of this observation one might predict that older adults would be relatively hyporesponsive to pressor agents. However, the baseline SBP responses to phenylephrine in our older men were similar to or greater than that of the young controls, presumably because reduced baroreflex buffering provided less counter-regulation, resulting in a normal or even slightly augmented pressor response in spite of the attenuated vascular sensitivity of the older subjects. White and Leenen observed similar age-associated differences in the cardiac responses to \( \beta \)-adrenergic stimulation in the presence and absence of ganglionic blockade. On the other hand, blood pressure responsiveness to pharmacological agents or physiological stimuli to which vascular sensitivity is not reduced with aging would be expected to be greater in the older adult given their decreased capacity for baroreflex buffering. Second, because baroreflex function is altered in several chronic disease states and most patients with chronic disorders are middle-aged and older, our findings provide baseline data that are essential to separate the respective effects of aging and disease. Specifically, our results demonstrate that because baroreflex buffering is reduced with primary aging, future studies in which patient populations are characterized must include healthy age-matched controls to properly isolate the independent effects of the disease process in question on baroreflex buffering.

There are at least 2 experimental limitations of the present study that should be emphasized. First, we used the SBP response to IV phenylephrine administration during ganglionic blockade as a measure of systemic arterial \( \alpha_1 \)-adrenergic vascular responsiveness. However, the arterial blood pressure response to this \( \alpha_1 \)-adrenergic agonist also can be influenced by venuconstriction, arterial distensibility, and the cardiac response to increased left ventricular impedance, all of which may be affected by aging.4 Second, our results are limited largely to Caucasian men. However, there is no obvious reason to expect qualitatively different changes in baroreflex buffering with age in women and minority populations compared with men.

In summary, the present findings demonstrate for the first time that baroreflex buffering is markedly reduced with primary aging in healthy men. The decrease in baroreflex buffering with advancing age is associated with increases in basal sympathetic activity and reductions in systemic \( \alpha_1 \)-adrenergic vascular responsiveness. These findings may provide novel insight into changes in sensitivity to vasoactive agents with adult human aging in the setting of both health and disease.

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References
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