Altered Autonomic Support of Arterial Blood Pressure With Age in Healthy Men

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Background—Primary aging is associated with changes in the autonomic nervous system (ANS), but the functional significance of these changes for systemic circulatory control of arterial blood pressure (BP) is unknown. We tested the hypothesis that ANS support of BP is altered in healthy older humans.

Methods and Results—A total of 23 young (aged 24±1 years; systolic/diastolic BP, 126±2/66±1 mm Hg) and 16 older (aged 65±1 years; systolic/diastolic BP, 125±3/62±2 mm Hg) healthy men were studied before and during ganglionic blockade (intravenous trimethaphan). The reduction in mean BP (radial artery catheter) with trimethaphan was almost twice as great in the older men (−33±2 versus −19±2 mm Hg; −40% versus −22% of baseline; P<0.01) due to a lack of increase in heart rate (3±2 versus 25±2 bpm; P<0.001) and cardiac output (−0.42±0.19 versus 1.01±0.26 L/min; P<0.001); the decreases in systemic vascular resistance were not different. The absence of tachycardia in the older men was associated with reduced baseline heart rate variability (HRV, P<0.05); the change in heart rate with trimethaphan correlated with the standard deviation of the R-R intervals (HRVSD R-R interval; r=0.57, P<0.001). Among individual subjects (pooled groups), the reductions in mean BP with trimethaphan were most strongly related to measures of sympathetic activity (r=0.58 to 0.67, P<0.005), change in mean BP with intravenous phenylephrine (r=0.57, P<0.001), and HRVSD R-R interval (r=−0.40, P<0.01).

Conclusions—ANS support of BP is altered with age in healthy men due to less cardiac vagal inhibition of heart rate and cardiac output. Basal sympathetic activity and α-adrenergic vascular sensitivity are also key physiological correlates of ANS support of BP in healthy men. (Circulation. 2001;104:2424-2429.)

Key Words: nervous system, autonomic ➔ cardiac output ➔ heart rate
was obtained from all subjects, and the experimental protocol was approved by the Colorado Multiple Institutional Review Board and the University of Colorado at Boulder Human Research Committee.

**Experimental Procedures**

Subjects were admitted to the University of Colorado Adult General Clinical Research Center the evening before pharmacological testing. For the preceding 48 hours, subjects consumed a eucaloric, controlled sodium (150 mEq/d) and potassium (70 mEq/d) diet. All were studied during supine rest beginning at 8:00 AM. Radial artery catheterization (20G, 5-cm catheter; Arrow) was performed under local anesthesia (1% lidocaine) using standard aseptic procedures; the catheter was flushed with heparinized saline (2 U/mL) at 3 cc/h. Two intravenous catheters were placed in the contralateral arm for drug infusions.

**Measurements**

Plasma volume was measured by a modified Evans Blue dye technique (New World Trading), with total blood volume calculated from simultaneous measurements of plasma volume and hematocrit in triplicate. During pharmacological testing, BP was continually monitored by a pressure transducer connected to the arterial catheter, and heart rate was monitored by ECG (Hewlett-Packard Merlin Patient Monitoring System). The ECG, BP, and respiratory signals were digitized (CODAS, Datasq Instruments) at 500 Hz.

Heart rate variability (HRV) was determined as described previously by our laboratory. Heart rate, mean R-R interval, and the standard deviation of the R-R intervals (HRVSD R-R Interval, a time domain measure of HRV) were computed from the beat-to-beat R-R intervals, whereas frequency domain measures of HRV were obtained using power spectral analysis.

Cardiac output was measured as previously described using 2D echocardiography (Hewlett-Packard Ultrasonography 2500) with a 3.5-Mz phased-array transducer using the parasternal short-axis view. Care was taken to measure the maximal flow velocity of the left ventricular outflow tract parallel to the flow envelope. The velocity envelope was integrated over time (velocity time integral) to yield a mean cardiac output. All measurements were made by a certified echotechnician according to the guidelines of the American Association of Echocardiography. Systemic vascular resistance and cardiac output were repeated under ANS blockade. Arterial blood samples were collected intravenously in 6-minute steady-state doses (0.02, 0.04, 0.08, 0.16 µg·kg⁻¹·min⁻¹) until mean BP increased 25 mm Hg from baseline. After a 20-minute washout period, measurements of heart rate, BP, and cardiac output were repeated under ANS blockade. Arterial blood samples were drawn at rest and during ANS blockade, 30 to 40 minutes after the bolus injection of phenylephrine. Differences between baseline and trimethaphan were taken as the measure of ANS support. To determine vascular α-adrenergic responsiveness, while still under ganglionic blockade phenylephrine was infused intravenously in 6-minute steady-state doses (0.02, 0.04, 0.08, 0.16 µg·kg⁻¹·min⁻¹) until mean BP increased 25 mm Hg above baseline. On completion of all measurements, trimethaphan infusion was stopped, and subjects were monitored until completely recovered.

**Muscle Sympathetic Nerve Activity**

To confirm the presence of age-associated elevations in tonic peripheral SNS activity, on a separate day we measured muscle sympathetic nerve activity (MSNA) in a subset of 12 older (66±2 years) and 10 young (27±1 years) men from the original groups. Multinuit recordings of MSNA were obtained from the right peroneal nerve at the fibular head using the microneurographic method, as described previously. Subjects were studied in the supine position after a 12-hour fast. Ten-minute resting levels of MSNA were obtained subsequent to a stable 10-minute baseline period.

**Muscle Sympathetic Nerve Activity**

Group comparisons for baseline characteristics were made using unpaired t tests. Responses to trimethaphan were analyzed using a 2-way ANOVA with repeated measures [age group×condition (baseline versus autonomic blockade)]. Relations of interest were determined using univariate correlations. The slope of the increase in mean BP with incremental phenylephrine infusion was used to determine α-adrenergic vascular sensitivity. All data are reported as mean±SE.

**Results**

**Subject Characteristics**

Body mass index and plasma norepinephrine concentration were higher and blood volume and diastolic BP were lower in the older men (all P<0.05; Table). There were no other differences between the groups. Basal supine MSNA was higher in the older men (38±2 versus 24±3 bursts/min; P<0.001).

**Responses to Ganglionic Blockade**

Systolic, diastolic, and mean BP decreased (P<0.001) in response to trimethaphan in both groups; each of the decreases was greater in the older men (P<0.001). Mean BP decreased 33±2 mm Hg (40%) from baseline in the older men compared with only 19±2 mm Hg (22%) in the young men (Figure 1).
The greater fall in mean BP in the older men was due to an 10% decrease in cardiac output compared with a 20% increase in the young men (P<0.001); the decreases in systemic vascular resistance (increases in systemic vascular conductance) were not different. Stroke volume decreased similarly in the 2 groups during trimethaphan. Therefore, the decrease in cardiac output in the older men was solely due to a lack of increase in heart rate (2 bpm; P<NS versus baseline), whereas the increase in cardiac output in the young controls was mediated by significant tachycardia (25 bpm; P<0.001 versus baseline). Baseline HRV was lower in the older men (HRV SD R-R interval, 51 vs 41 ms; P<0.05; high frequency power of HRV, P=0.01). In all subjects, the change in heart rate with trimethaphan was positively related to baseline HRV SD R-R interval (r=0.57, P<0.001; Figure 1) and high frequency power of HRV (r=0.41, P<0.01).

Plasma norepinephrine concentration decreased from baseline during trimethaphan in both groups (P<0.001); the decrease was greater in the older men (1.29 vs 0.62 nmol/L; P<0.001) due to their higher baseline values. Plasma vasopressin concentrations increased during trimethaphan in both groups (P<0.001); the increase was greater in the older men (62 vs 16 ng/L; P<0.05).

Vascular α-Adrenergic Sensitivity

The slope of the increase in mean BP in response to incremental phenylephrine infusion during ganglionic blockade was lower in the older men (2.1 vs 3.2 mm Hg · mL⁻¹ · mL⁻¹; P<0.01; Figure 3A).

Discussion

The primary finding from the present study is that ANS support of BP is altered with age in healthy men. This seems to be primarily mediated by reduced tonic cardiac vagal inhibitory modulation of heart rate and cardiac output. Moreover, basal SNS activity and α-adrenergic vascular sensitivity seem to be important physiological correlates of ANS support of BP among young and older healthy men. Thus, our results demonstrate that changes in the ANS with healthy adult aging have a functionally significant effect on tonic BP maintenance in humans. Our findings also provide insight into some of the mechanisms involved.

**Figure 1.** Responses to ganglionic blockade in young men (open bars) and older men (shaded bars). SBP, DBP, and MAP indicate systolic, diastolic, and mean arterial BP, respectively; SVR and SVC, systemic vascular resistance and conductance; and HFP HRV, high frequency power of heart rate variability. Values are means±SE.

**Figure 2.** Univariate relation showing the change in heart rate with ganglionic blockade as a function of baseline HRV SD R-R interval.

**Figure 3.** A, Slopes of the increases in mean BP (MAP) with incremental intravenous infusions of phenylephrine (phe) in the young and older men. Values are means±SE. B, Univariate relation showing the change in mean BP with ganglionic blockade as a function of the slope of the increase in mean BP with incremental intravenous infusions of phenylephrine.
ANS Support of BP with Healthy Aging

To our knowledge, the present findings are the first to demonstrate that tonic ANS support of BP, as determined by the short-term reduction in BP with ganglionic blockade, is altered in healthy older men compared with young men. Our data indicate that the key mechanism underlying this effect is an age-associated reduction in tonic cardiac vagal suppression of heart rate and cardiac output. Specifically, the greater decrease in mean BP with ganglionic blockade in the older men was mediated solely by a lack of increase in heart rate which, along with a modest decrease in stroke volume, resulted in a slight reduction in cardiac output (compared with the increase observed in young men). In the present study, the change in heart rate with ganglionic blockade among the individual men was positively related to baseline HRV, suggesting that basal cardiac vagal tone was an important determinant of the chronotropic response to the removal of ANS input.

It might be expected that ANS support of BP would be greater in older adults due to their elevated basal SNS activity, which could produce tonically elevated peripheral vasoconstriction. Indeed, baseline SNS activity and the decrease in that activity during trimethaphan were significant correlates of the reduction in mean BP with ganglionic blockade. However, although the elevated SNS activity in the older men was an important determinant of their ANS control of BP, it did not seem to play a predominant role in the tonic support of systemic vascular resistance. Rather, our results suggest that vascular α-adrenergic desensitization with age counteracted the vasoconstrictor effects of chronically elevated peripheral SNS activity in the older men. This contention is consistent with the facts that (1) the reduction in systemic vascular resistance (increase in conductance) during ganglionic blockade was not different in the 2 groups, despite greater reductions in SNS activity in the older men, and (2) in the absence of counter-regulatory reflexes, the increase in mean BP in response to systemic infusion of phenylephrine, a nonspecific α-adrenergic agonist, was smaller in the older compared with the young men.

The difference in BP between the intact and ganglionic blocked states has been reported to be greater in healthy adults with a mean age of 60 compared with younger controls, whereas the difference in heart rate was smaller in the older subjects. This previous investigation differed from the present study in several ways. First, the intact and ganglionic blocked conditions were studied in separate sessions at least 4 days apart (fixed order) compared with our measurements, which were performed in the same experimental session. Second, BP was determined noninvasively using an automated monitor, as opposed to our direct intra-arterial measurements. Third, the numbers of subjects studied (n=8 per group) were much smaller than in the present study (n=16 to 23 per group). Finally and importantly, the sex distribution was markedly different in the young and older groups in this earlier study (preliminary data from our laboratory suggest that the BP reduction with ganglionic blockade may be related to sex). Thus, although selective results of this prior investigation are consistent with those reported here, we believe that the findings of the present study provide the first definitive insight into changes in ANS support of BP with healthy aging in adult humans. Our results also provide additional information on the nature of the cardiovascular and ANS mechanisms involved.

Experimental Considerations

There are several experimental considerations that should be noted. First, regarding ANS control of heart rate, one might expect higher resting heart rates in the older men due to their apparent lower cardiac vagal modulation. However, consistent with the literature, supine resting heart rate was similar in our young and older men. We think that the reduction in intrinsic sinus node rate (intrinsic heart rate) with aging likely explains the lack of group differences observed. Our data also do not differentiate between age-related differences in vagal input to the sinoatrial node and tissue responsiveness. As such, the age-related decline in HRV could reflect either, although recent evidence indicates that chronotropic responsiveness to vagal stimulation is not affected by age in healthy adult humans. Moreover, our data do not allow us to determine a potential role of basal cardiac sympathetic tone in the support of heart rate, cardiac output, and BP. Although the change in heart rate with ganglionic blockade was also related to the low frequency and total power of HRV (data not presented), the interpretation of these measures as indicators of cardiac sympathetic modulation of heart rate is unclear.

Second, age-associated differences in humoral and local factors could have exerted some influence on the change in BP with ganglionic blockade. For example, because cardiac output increased in the young, but not in the older, subjects during ganglionic blockade, it is possible that there was a greater stimulus for flow-mediated endothelium-dependent vasodilation in the young men. In addition, there was a greater increase in plasma vasopressin in the older compared with the young subjects. In rats, the reduction in BP with
trimethaphan is greater in the presence of a vasopressin receptor antagonist. This raises the possibility that vasopressin partially counteracts the fall in BP and causes ANS support to be underestimated.\textsuperscript{1,15,30,31} It is not known if trimethaphan-evoked vasopressin release similarly modulates the depressor response to ganglionic blockade in humans. However, the increase in plasma vasopressin concentration during ganglionic blockade in the present study was positively related to the corresponding reduction in mean BP ($r=0.57$, $P<0.01$). This suggests that vasopressin release is responding to the trimethaphan-induced BP decrease, not vice versa. It also indicates that the greater decrease in BP with ganglionic blockade in the older subjects is not due to an attenuated vasopressin release (ie, less vasooactive hormone counter-regulation) compared with the young men. Therefore, any influence of these factors actually would have diminished the observed age-related difference in the BP reduction with trimethaphan by increasing the magnitude of decline in young subjects (via greater flow-mediated vasodilation) and by counteracting the decrease in older subjects (via greater vasopressin response), thus causing the increase in ANS support of BP with age to be underestimated. Accordingly, we believe that our interpretation that the greater BP reductions with trimethaphan in the older men reflect a true age-related difference in tonic ANS support with age is valid.

Finally, we can provide little mechanistic insight into the similar reductions in stroke volume with ganglionic blockade in our young and older men in the present study, despite marked differences in the heart rate responses. However, the reduced stroke volume in the ganglionic blocked compared with the intact state is associated with a similarly decreased left ventricular end-diastolic volume index in healthy men and women varying in age.\textsuperscript{14} This suggests that similar reductions in left ventricular preload may have been responsible for the lack of difference observed in the stroke volume response to ganglionic blockade in our young and older men.

**Clinical Significance**

The ANS plays an important role in the pathogenesis of several cardiovascular disorders, including congestive heart failure, essential hypertension, and ventricular tachyarrhythmias.\textsuperscript{32–34} The incidence of these cardiovascular disorders increases markedly with advancing age. Moreover, w\textsuperscript{24,6,9,10,12,19,35} and others\textsuperscript{3,4} have shown that numerous changes in ANS behavior occur with age, even in healthy humans. However, a lack of information concerning the effects of such ANS changes on cardiovascular function has made it difficult to discern the respective contributions of biological (primary) aging and disease processes to changes in circulatory physiology and pathophysiology with advancing age. The findings of the present study provide new insight into ANS-mediated effects on cardiovascular control of BP with healthy aging from which the independent effects of cardiovascular disease can be determined.

Our results also may have relevance for interactions between age and the effects of antihypertensive medications. For example, the risk of orthostatic hypotension in response to some BP-lowering drugs is augmented in the elderly and is the source of substantial morbidity.\textsuperscript{36,37} The present data are consistent with and may provide a physiological basis for this augmented hypotensive effect in older adults.

**Conclusions**

In conclusion, we have shown that healthy older adults have altered tonic ANS support of arterial BP compared with young adults. This is mediated by a complex interaction among reduced cardiac vagal modulation of heart rate, chronically elevated SNS activity, and vascular $\alpha$-adrenergic desensitization. Our results provide important new insight into the effects of primary aging per se on ANS support of BP, which should be of benefit in interpreting age-associated changes due to cardiovascular disease.

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