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Age-Related Changes of Baroreflex Function, Plasma Norepinephrine, and Blood Pressure

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SUMMARY **Interrelationships between age, baroreflex sensitivity, plasma norepinephrine levels, and systolic blood pressure were assessed in a group of 54 normal subjects ranging in age from 14 to 77 years. Baroreflex sensitivity was measured by the change in R–R intervals per unit change in systolic blood pressure during phase 4 of the Valsalva maneuver. All correlations among these four variables were statistically significant ($p < 0.05$ or 0.01). To investigate possible causal relationships between age-related changes of baroreflex sensitivity, plasma norepinephrine levels, and blood pressure, partial correlative analysis was then performed. After the effect of age was eliminated, plasma norepinephrine levels were found to be related positively to blood pressure ($r = 0.29$, $p < 0.05$) and negatively to baroreflex sensitivity ($r = -0.34$, $p < 0.05$). The increase in plasma norepinephrine levels could be causally related to the elevation of blood pressure, as plasma norepinephrine levels could provide an index of sympathetic activity. Furthermore, baroreflex sensitivity was found to be negatively related to age ($r = -0.44$, $p < 0.01$) independent of plasma norepinephrine levels, whereas plasma norepinephrine levels were no longer related to age ($r = 0.10$) after adjusting for the effect of baroreflex sensitivity. This finding suggests that an increase in plasma norepinephrine levels with age could be mediated by the age-related change of baroreflex sensitivity. Thus our present data appear to support the hypothesis of age-related alterations in the cardiovascular regulation that an impairment of baroreflex sensitivity would cause a sympathetic activation with an associated increase in plasma norepinephrine levels, which could then contribute to the elevation of blood pressure.**
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KEY WORDS • **aging** • **sympathetic nervous system** • **Valsalva's maneuver** • **hypertension** • **cardiovascular regulation**

TO understand how mechanisms for controlling blood pressure are altered in hypertension, it is crucial to have a full knowledge of the changes in the homeostatic regulation of the cardiovascular system that may occur in the normal aging process. The changes in baroreceptor reflex function and sympathetic nervous activity in hypertension have been studied extensively for many years.[1, 2] Aging also influences these important components in cardiovascular as well as blood pressure control. Baroreceptor reflex sensitivity decreases with age [3] On the other hand, both plasma norepinephrine levels and blood pressure are increased in elderly subjects.[4, 5] Plasma norepinephrine is derived from spillover of the neurotransmitter released from sympathetic nerve terminals and has been used as an index of sympathetic nervous activity.[6] The inhibition of a baroreflex mechanism would result in vagal inhibition and sympathetic stimulation.[7] Thus it has been proposed that an age-related impairment of baroreflex sensitivity would cause a less tonic inhibition of the vasomotor center with an associated increase of neuronal norepinephrine release, which could contribute to the rise in blood pressure.[8, 9] Evidence in support of such a hypothesis might be provided by the presence of a causal relationship between plasma norepinephrine levels and baroreflex sensitivity and between plasma norepinephrine levels and blood pressure in the normal population after adjusting for the effect of age. To our knowledge, few studies have conducted this kind of analysis successfully.[8–10]

In this study, we quantitated baroreflex sensitivity with the use of Valsalva's maneuver,[11] and measured

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plasma norepinephrine levels in a group of healthy subjects of varying age. The interrelationships between these measurements, age, and blood pressure were examined. In addition, age, plasma norepinephrine levels, baroreflex sensitivity and blood pressure were correlated with each other with partial correlation analysis to hold individual variables constant to investigate possible causal relationships between these parameters.

Methods

Fifty-four healthy unmedicated volunteers (35 males and 19 females) ranging in age from 14 to 77 years (49 ± 18 years, mean ± SD) were studied All subjects had a normal cardiovascular (including blood pressure) and respiratory history, electrocardiogram, and chest x-ray; results of physical examination and a fasting blood glucose level also were normal. All subjects had a blood pressure of less than 150/90 mm Hg after supine rest for 30 minutes. Consent for performing all studies was obtained from each subject

The studies were performed the morning after an overnight fast. The subjects lay supine, and a 19-gauge butterfly needle was inserted into one antecubital vein. After subjects had been supine for at least 30 minutes, blood pressure was measured with a standard cuff method. Blood samples, 10 ml, were then collected in prechilled tubes containing ethylenediaminetetraacetic acid for the determination of basal plasma norepinephrine levels. After immediate centrifugation at 4°C, the plasma was separated and frozen at −80°C for analysis at a later time.

The Valsalva maneuver was performed with the subjects supine. The brachial artery was cannulated percutaneously. A polygraph recorded intra-arterial blood pressure, electrocardiogram (lead V_5), and air temperature of the nasal cavity (to monitor respiration) The Valsalva maneuver was conducted by blowing into a rubber tube connected to a mercury column and maintaining a pressure of 40 mm Hg for 15 seconds with glottis open The subjects practiced the maneuver until reproducible hemodynamic responses were obtained. When measurements were made, the recording was carried out at a paper speed of 100 mm/sec.

Baroreflex sensitivity during Valsalva's maneuver was obtained according to the methods of Palmero and co-workers[11] and Goldstein and colleagues[12] as follows. During a later period in phase 4, following the release of the Valsalva maneuver, the increase in blood pressure accompanied a progressive slowing of the heart rate. Here, linear regressions were obtained between systolic blood pressure and R–R intervals with a one-beat delay. In all subjects studied, the correlation coefficients (r) were statistically significant, and the r value was always greater than 0.80. The *baroreflex sensitivity index* was defined as the slope of this linear regression line.

Norepinephrine concentrations were assayed by high-performance liquid chromatography with fluorometric detection.[13] Interassay variability was ±6%. The limit of detection was approximately 20 pg/ml of plasma.

The linear regression line for baroreflex sensitivity was calculated by the least-squares method. An intercorrelation matrix was constructed in which age, systolic blood pressure, plasma norepinephrine levels, and baroreflex sensitivity index were correlated with each other. An adjustment for either age, systolic blood pressure, plasma norepinephrine levels, or baroreflex sensitivity also was made by partial correlation analysis for multiple comparisons in the intercorrelation matrix.

Results

Total Correlations

Intercorrelations among the values for age, systolic blood pressure, plasma norepinephrine levels, and baroreflex sensitivity index are listed in Table 1. All the correlations were statistically significant. Baroreflex sensitivity was inversely related to age ($r = -0.51, p < 0.01$), to plasma norepinephrine levels ($r = -0.43$, $p < 0.01$), and to systolic blood pressure ($r = -0.36$, $p < 0.01$). On the other hand, a positive linear relationship between age and plasma norepinephrine levels ($r = 0\ 30$, $p < 0.05$) and between age and blood pressure ($r = 0.42$, $p < 0.01$) was present in these subjects. Plasma norepinephrine levels also were related to systolic blood pressure ($r = 0\ 37, p < 0.01$). All these linear relationships are illustrated in Figure 1.

Partial Correlations

Because systolic blood pressure, plasma norepinephrine levels, and baroreflex sensitivity all were related significantly to age, correlations between these three measurements would be expected. Therefore, we analyzed the relationships between blood pressure, plasma norepinephrine levels, and baroreflex sensitivity by a partial correlation analysis to eliminate the effect of age. Table 2 shows that after adjusting for the effects of age, the relationship between plasma norepinephrine levels and blood pressure ($r = 0\ 29$, $p <$

TABLE 1. *Intercorrelations Among Age, Baroreflex Sensitivity Index, Plasma Norepinephrine Levels, and Systolic Blood Pressure in 54 Normal Subjects*

Parameter	r	p (two-tailed, %)	Level
BRSI-Age	−0 51	0 01	†
BRSI-PNE	−0 43	0 11	†
BRSI-SBP	−0 36	0 76	†
Age-PNE	0 30	2 86	*
Age-SBP	0 42	0 15	†
PNE-SBP	0 37	0 53	†

*$p < 0\ 05$.
†$p < 0\ 01$
BRSI = baroreflex sensitivity index; level = the level of significance, PNE = plasma norepinephrine levels, r = correlation coefficient, SBP = systolic blood pressure

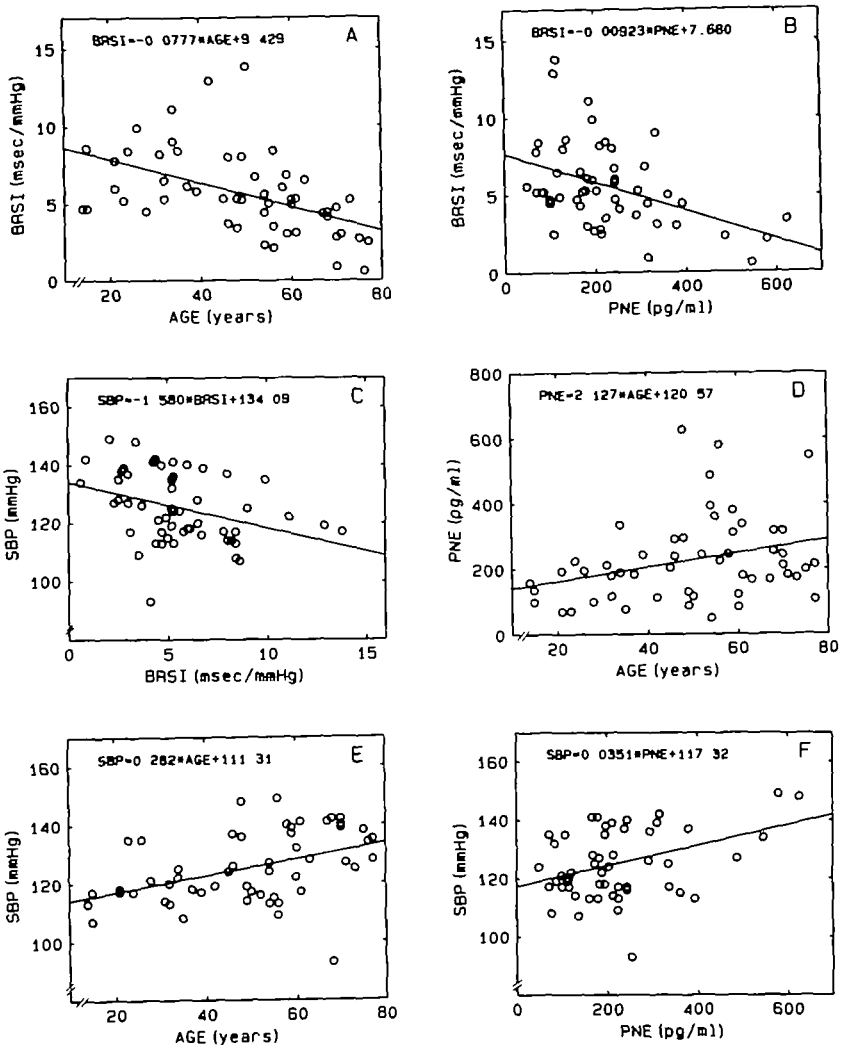

FIGURE 1 *Linear relationships between age, baroreflex sensitivity index (BRSI), plasma norepinephrine levels (PNE), and systolic blood pressure (SBP) in 54 normal subjects. Correlation coefficients and statistical significance for these parameters are listed in Table 1*

0.05) and between plasma norepinephrine levels and baroreflex sensitivity ($r = -0.34$, $p < 0.05$) remained significant, but weak. After the effect of age was eliminated, however, systolic blood pressure was no longer significantly related to baroreflex sensitivity ($r = -0.19$).

Table 2 also shows similar partial correlation analyses where the effect of either systolic blood pressure, plasma norepinephrine levels, or baroreflex sensitivity was eliminated from the relationship between the other three variables. The correlation between age and baroreflex sensitivity ($r = -0.42$, $p < 0.01$) and between plasma norepinephrine levels and baroreflex sensitivity ($r = -0.34$, $p < 0.05$) remained statistically significant after adjusting for the effects of blood pressure. The correlation between age and baroreflex sensitivity ($r = -0.44$, $p < 0.01$) and between age and systolic blood pressure ($r = 0.35$, $p < 0.01$) was also significant even after the effect of plasma norepinephrine levels was eliminated. After adjusting for the effect of baroreflex sensitivity, however, only the correlation between age and systolic blood pressure ($r = 0.30$, $p < 0.05$) was significant.

Blood Pressure and Heart Rate Responses to Valsalva's Maneuver

The decline of systolic blood pressure induced by Valsalva's maneuver (i.e., the systolic blood pressure before the maneuver minus the lowest systolic pressure attained post-Valsalva release) was 45.8 ± 23 mm Hg (mean ± SD) and was significantly related to age ($r = 0.35$, $p < 0.01$). On the other hand, the subsequent blood pressure overshoot (i.e., the highest systolic blood pressure attained in phase 4 minus the systolic pressure before the maneuver) was 30.3 ± 21 mm Hg, and was significantly inversely related to age ($r = -0.50$, $p < 0.0001$). The average change in R–R intervals during phase 4 was 281.8 ± 176 msec. This change was also inversely correlated with age ($r = -0.75$, $p < 0.0001$).

Discussion

Several techniques have been used to measure baroreflex sensitivity.[12] The present method, which uses phase 4 of the Valsalva maneuver, originally was proposed by Pickering and Sleight.[14] Palmero and col-

TABLE 2 *Partial Correlation Analysis Between Age, Baroreflex Sensitivity Index, Plasma Norepinephrine Levels, and Systolic Blood Pressure After Eliminating the Effect of Either of the Variables*

Parameter	r	p (two-tailed, %)	Level
Age-independent			
SBP-PNE	0 29	3 55	*
SBP-BRSI	−0.19	18 08	
PNE-BRSI	−0 34	1.14	*
SBP-independent			
Age-PNE	0 17	22 78	
Age-BRSI	−0 42	0 14	†
PNE-BRSI	−0 34	1 09	*
PNE-independent			
Age-SBP	0 35	0 93	†
Age-BRSI	−0 44	0 08	†
SBP-BRSI	−0 24	8 60	
BRSI-independent			
Age-SBP	0.30	2 93	*
Age-PNE	0 10	47 22	
SBP-PNE	0 26	5 78	

Abbreviations are the same as in Table 1
*$p < 0\ 05$
†$p < 0\ 01$

leagues[11] recently compared this method with that which employs an injection of a vasoconstrictor agent, phenylephrine, and found that the results obtained by these two methods were highly correlated ($r = 0.91$). In our experience, the reproducibility of this technique was high and the linearity between the changes in the R–R interval and the systolic pressure was almost always excellent Thus, although Goldstein and colleagues[12] recently have demonstrated significant but relatively low intercorrelations among several measures to assess a baroreflex sensitivity in the same subjects and have cautioned against interpreting the results on the basis of a single measurement technique, the data obtained in the present study certainly seem to provide an accurate measure for the baroreflex sensitivity in a certain aspect of the complex reflex system. It should be noted that this maneuver involves not only the carotid and aortic baroreceptors, but also other receptors, including cardiopulmonary low pressure receptors as well as various thoracic stretch receptors.

The age-related increase in plasma norepinephrine levels, the rise in systolic blood pressure, and the decrease in the baroreflex sensitivity have been described previously.[3–5] We also found a significant inverse relationship between plasma norepinephrine levels and baroreflex sensitivity whether or not the age factor was included. This relationship was also significant independently of systolic blood pressure. Goldstein[10] recently has demonstrated a significant negative relationship between plasma norepinephrine levels and baroreflex sensitivity among hypertensive subjects, but not among normotensive subjects. In his study, the effect of age was not adjusted for this correlation analysis and plasma norepinephrine levels did not correlate significantly with age in the hypertensive or normotensive groups. These findings are in contrast with our study. We found a significant relationship between the age-related decrease in the baroreflex sensitivity and the age-related increase in plasma norepinephrine levels in normal subjects even after the effect of age was eliminated. This finding might suggest a causal relationship between the changes of these two variables; however, such a causality, if any, may be explained in two ways The inhibition of baroreceptor reflex would result in the stimulation of sympathetic nervous system and vagal inhibition [9, 15] Therefore, an attenuated baroreflex sensitivity could be a cause of the elevated basal plasma norepinephrine levels in elderly subjects. An alternative causal relationship (i.e., the decrease in baroreflex sensitivity owing to the increase in the sympathetic neural activity) also is possible, as attenuation of the vagally mediated baroreflex sensitivity has been described during increased adrenergic activity.[16] Our data show that when the effect of plasma norepinephrine levels was eliminated in the partial correlation analysis, baroreflex sensitivity was still significantly correlated with age ($r = -0\ 44$), which indicates that advancing age could be related to the progressive inhibition of baroreflex sensitivity, independent of the sympathetic activity. Furthermore, when the effect of baroreflex sensitivity was eliminated in the partial correlation analysis, plasma norepinephrine levels were no longer related to age. This finding indicates that an apparent significant relationship between age and plasma norepinephrine levels could be mediated by the level of baroreflex sensitivity. Our results, therefore, are in favor of the concept that aging causes a reduction of baroreflex sensitivity, which could then result in the increase of plasma norepinephrine levels.

We also found a weak, but significant, positive relationship between plasma norepinephrine levels and systolic blood pressure, even after adjusting for the effect of age. The correlation coefficient of this partial correlation analysis ($r = 0.29$) surprisingly agreed with the value for the age-independent correlation between plasma norepinephrine levels and mean arterial blood pressure reported by Pfeifer and co-workers ($r = 0.28$).[8] The increase in plasma norepinephrine levels could be causally related to the elevation of blood pressure, as its age-related change in concentration could be due to an increased rate of neuronal norepinephrine release rather than to a decrease in clearance from the circulation.[6, 17] Some controversy, however, still exists regarding norepinephrine kinetics.[18] Moreover, our data show that systolic blood pressure was significantly related to age ($r = 0.35$) after adjusting for the effect of plasma norepinephrine levels. These results indicate that the age-related increase in systolic blood pressure also could be mediated by some other mechanisms independent of the sympathetic activity. Structural vascular changes are the most likely explanation for this mechanism.

In summary, the present intercorrelation analysis based on the study of healthy, normal subjects appears to support, or at least is consistent with, the hypothesis of age-related alterations in the cardiovascular regulation that an impairment of baroreflex sensitivity would cause a sympathetic activation associated with an increased plasma norepinephrine level, which in turn could contribute to the elevation of blood pressure.[8, 9]

It should be noted that when the effect of age was eliminated, the correlation between systolic blood pressure and baroreflex sensitivity was not statistically significant. High blood pressure has been well documented to reduce the sensitivity of the baroreceptor reflex independently of age,[3] but these changes have been observed principally among hypertensive subjects. In addition, the level of blood pressure per se was not related to the baroreflex sensitivity in the same individuals.[19] Thus our data suggest that blood pressure would affect the baroreflex sensitivity exclusively in hypertensive patients and that its reduction with age in subjects without high blood pressure could be related to factors other than blood pressure level. This concept is supported by the present finding that age was significantly related to baroreflex sensitivity independently of systolic blood pressure. The goal of this study was not to investigate what causes the reduction of baroreflex sensitivity in elderly normal subjects. Changes in baroreflex control could result from alterations at any level of the baroreflex arc, including the baroreceptors themselves, vessel wall distensibility, central neural integration, efferent autonomic pathways, or any combination of these.[3, 20] Because heart rate changes associated with brief baroreflex stimulation probably result from changes in vagal outflow,[21] the results are consistent with a decreased parasympathetic nervous activity in the heart in older subjects.[8]

Another interesting finding in our study was the demonstration of an age-related decrement in blood pressure and heart rate responses to Valsalva's maneuver. Aging caused an increase in the decline of blood pressure post-Valsalva release as well as a decrease in blood pressure overshoot or bradycardia during phase 4. The age-related changes in both cardiac and vascular responses to Valsalva's maneuver may represent generalized disturbances in the functions of the cardiovascular autonomic nervous system reflexes with aging.

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