Effect of Systolic Blood Pressure and Carotid Stiffness on Baroreflex Gain in Elderly Subjects

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Background. Aging is associated with diminished baroreflex sensitivity (gain), which predisposes elderly people to orthostatic hypotension, syncope, and cardiovascular morbidity. Aging is also associated with systolic blood pressure (SBP) elevation and carotid artery stiffness, which may both affect baroreflex gain.

Methods. We examined the relation between SBP, carotid artery stiffness, and baroreflex gain in 34 healthy elderly (71 ± 4 years) and 10 healthy young (31 ± 3 years) subjects. SBP (Finapres) and carotid artery stiffness (ultrasound measures of relative carotid artery diameter changes during each blood pressure pulse) were measured. The gain of the transfer function relating the R-R interval to SBP fluctuations at a frequency of 0.05–0.15 Hz was used to assess cardiovagal baroreflex gain.

Results. Elderly subjects had higher carotid artery stiffness (14.2 ± 5.1 vs 6.6 ± 1.8, p < .05), higher SBP (146 ± 24 vs 125 ± 8 mmHg, p = .012), and lower baroreflex gain (8.2 ± 6.4 vs 16.3 ± 7.4, p < .05) than young subjects. Among all subjects, SBP and carotid artery stiffness both correlated with baroreflex gain (r = −.39, p = .02 for both). Although SBP was related to stiffness across all subjects, this relation was not present among the elderly subjects. Within the elderly group, only SBP was independently related to baroreflex gain (R² = .51, p = .009).

Conclusions. SBP elevation in elderly people may affect the neural or cardiac response to blood pressure fluctuations, independent of the mechanical properties of barosensory regions in the carotid artery. Future studies should examine the effect of pharmacologic treatment of hypertension on baroreflex gain in elderly people.

Both aging and hypertension are associated with reduced baroreflex sensitivity (1), which may increase cardiovascular mortality (2) and predispose hypertensive elders to the development of hypotension during physiologic stresses that unload arterial baroreceptors. Aging and hypertension are also associated with increased carotid artery stiffness (3,4). Vascular stiffness in barosensitive regions of the carotid artery may play an important role in reducing baroreflex sensitivity by mechanically restricting the stretch and relaxation of baroreceptors during physiologic changes in arterial pressure. We therefore hypothesized that age- and hypertension-related declines in baroreflex sensitivity may be mediated through increases in carotid artery stiffness. Accordingly, we investigated the contributions of systolic blood pressure and carotid stiffness to baroreflex sensitivity in elderly persons.

Methods

Subjects

Thirty-four elderly subjects (71 ± 4 years) and 10 young subjects (31 ± 3 years) were recruited from among volunteers responding to newspaper advertisements and members of the Harvard Cooperative Program on Aging subject registry. All subjects were carefully screened with a medical history, physical examination, and electrocardiogram (ECG) to exclude acute medical conditions other than hypertension. Subjects were excluded if they smoked cigarettes or took cardiovascular medications. A carotid Doppler study was performed on all subjects to rule out significant (>50%) carotid artery stenosis. The experimental protocol was approved by the Clinical Investigations Committee of the Hebrew Rehabilitation Center for Aged, and all subjects provided informed consent.

Experimental Protocol

Subjects reported to the cardiovascular laboratory in the postabsorptive state, ≈2 hours after their last meal, and refrained from alcohol and caffeine ingestion during the 24 hours before the study. While the subject was resting supine on a tilt table, ECG electrodes were attached to the subject’s chest, and a photoplethysmographic arterial pressure cuff (Finapres, Ohmeda, CO) was attached to the middle finger of the nondominant hand. The Finapres cuff was maintained at the level of the right atrium at all times by supporting the forearm in a sling.

After a 10-minute supine rest, carotid artery imaging was performed by a trained investigator for 1 minute with a Hewlett-Packard SONOS 2500 ultrasound imaging system (Hewlett-Packard, Palo Alto, CA). A high-resolution linear array transducer (7.5 MHz) and vascular enhancement software were used to provide longitudinal B-mode images of the carotid artery, approximately 1 cm proximal to the bulb. The transducer was positioned parallel to the vessel to obtain clear visualization of the anterior wall media-adventitial interface and the posterior wall intima–lumen interface. Ultrasound images were directly digitally recorded to a computer in real time for subsequent analysis.
Vessel image acquisition was gated on the R wave of the electrocardiogram, and 15 images (of a 30-Hz video signal) were captured for each R wave, while beat-by-beat arterial pressure was simultaneously recorded. This technique allowed measurement of vascular diameter over approximately the first 500 milliseconds of each cardiac cycle.

After baseline beat-by-beat carotid artery recording was completed, subjects were tilted upright to 60° on an electrically driven table with footboard. After a 1-minute stabilization period, the continuous ECG and arterial pressure waveforms were recorded for 5 minutes. These signals were digitized at 500 Hz and stored for later analysis by using commercial hardware and software (Windaq, Dataq Instruments, Akron, OH).

**Carotid Artery Stiffness**

We used a custom image-analysis program developed in the laboratory to measure carotid diameter (Castanon AN, Ghosh S, Cohen MA. Personal communications.). This entailed three steps. First, the user scrolled through the image set to determine the region of the vessel wall with the greatest clarity. Then, a single image was used to orient this extracted region along an axis of symmetry. Subsequently, our software program projected the region of interest for the entire image set along the axis, and identified candidate edges in this projection by points at which the change in pixel intensity was maximum; then, it assessed the possible diameters by using a cost function defined over paths through possible candidate pixels that is minimized by a Viterbi search (5). (This technique is successfully used in speech processing to track formants and to identify a Viterbi search (5). (This technique is successfully used in speech recognition.) The cost function chooses the candidate edges and thus the diameters by penalizing for lack of continuity of each individual edge, dimness of the edges, distance of edges from each image center, and large changes in computed diameter from adjacent images. The recursive nature of this Viterbi search and the limited number of candidate edges identified allows this algorithm to operate almost in real time. We compared our carotid diameter results with those obtained manually by using the method of Statler and colleagues (6) For individual images with adequate resolution and stable diameters, the $R^2$ comparing our results with manually determined diameters was >0.9.

Within each cardiac cycle, we measured the largest diameter (Ds), smallest diameter (Dd), systolic blood pressure (SBP), and diastolic blood pressure (DBP) to calculate the carotid artery stiffness index according to the following formula (4):

\[
\text{Stiffness Index} = \log_e \left( \frac{\text{SBP/DBP} \times \text{Dd}}{\text{Ds} - \text{Dd}} \right).
\]

The average of stiffness values for each cardiac cycle over 1 minute of recording was used as the measure of carotid artery stiffness.

**Baroreflex Sensitivity**

Beat-to-beat R-R interval and SBP were determined from the R wave of the ECG and the maximum of the arterial pressure waveform during 5 minutes of data collection in both the supine and the 60° head-up tilt position. All data segments were visually inspected and edited for artifact, and only stationary data were used for the analysis. The time series of R-R interval and SBP were linearly interpolated and resampled at 5 Hz to provide a 1500-point signal for frequency analysis. A power spectrum analysis of each signal was calculated by means of Welch’s averaged, modified periodogram method (7). First, the interpolated signal was divided into five equally overlapping segments of 500 points each. Each individual window was then linearly detrended, smoothed by means of a Hanning window, and fast Fourier transformed to produce its magnitude squared. Cross-spectral estimates between variables were calculated from cross-spectral densities derived with the same parameters used to estimate power spectra. Coherence was computed as $(\text{cross-spectra}^2/\text{input signal autospectrum}) \times (\text{output signal autospectrum})$. The signals were considered coherent over the frequency at which coherence values exceeded 0.5. Transfer magnitude was calculated for each subject over the frequency range meeting this criterion, with MATLAB software (The Mathworks, Inc., Natuck, MA). The baroreflex gain was determined by using a modification of the method of Robbe and associates (8) as the mean transfer magnitude between SBP and R-R interval in the low-frequency range (0.05–0.15 Hz) where the coherence between these signals was greater than 0.5. Baroreflex gain determined by this method (8) is highly correlated with results of the phenylephrine method ($R = .94$).

**Statistical Analysis**

All variables were compared between elderly and young subjects by t tests. As transfer gain data in elderly subjects were not normally distributed, the data were transformed to the natural log for subsequent statistical analysis. As a way to examine the effects of SBP and stiffness on baroreflex sensitivity without confounding by age, the relations between these variables were evaluated with linear and multiple regression analysis only in elderly subjects. Because results of the regression analysis were similar when baroreflex gain was used in the supine or tilted position, only correlations using the supine gains are presented. Data are expressed as mean ± SD and a value of $p \leq .05$ was considered statistically significant.

**RESULTS**

**Effects of Age**

Table 1 compares the cardiovascular characteristics of young and elderly subjects. Heart rate, DBP, and mean arterial blood pressure were not different between elderly and young subjects. SBP was higher in elderly subjects compared with that in young subjects ($p = .012$). Changes in SBP, DBP, and mean arterial blood pressure from supine to 60° tilt were similar between groups; however, the acceleration in heart rate was greater in young subjects than in elderly subjects ($p < .01$). Systolic and diastolic (maximum and minimum) carotid diameters were both larger in elderly subjects than in young subjects ($p < .001$, for both). Carotid artery stiffness was higher and baroreflex gain was lower in elderly subjects than in young ones ($p < .001$ and $p < .01$, respectively).
Baroreflex gain was significantly lower in the tilt than supine position for both groups ($p < .0013$).

### Effects of SBP and Stiffness on Baroreflex Gain in Elderly Subjects

Because there was very little overlap of carotid artery stiffness between young and elderly subjects, and a narrow distribution of pressure and carotid artery stiffness values in the young, we examined the independent relationships among SBP, carotid artery stiffness, and baroreflex gain in only the elderly group of subjects. On bivariate analyses, only SBP correlated with baroreflex gain in elderly subjects ($r = 0.51$, $p = .002$) (Figure 1). SBP was not correlated with carotid artery stiffness. Entering stiffness and SBP into a multiple regression analysis adjusted for age (within the elderly group) showed that only SBP was independently related to baroreflex gain (Model $R^2 = .51$, $p = .009$).

### DISCUSSION

Our results not only confirm that carotid artery stiffness is higher and baroreflex sensitivity is lower in elderly subjects compared with young, but also show that SBP is independently related to baroreflex sensitivity in elderly people. Although we postulated that the age-related decline in baroreflex sensitivity is mediated by elevations in blood pressure, which in turn reduce arterial compliance, our data indicate that pressure exerts an independent effect on the baroreflex arc. In previous work, Hunt and associates (9) demonstrated separate mechanical and neural components of the vagal baroreflex. Therefore, it is possible that systolic pressure elevation in elderly people primarily affects neural pathways in autonomic centers of the brain or cardiac responsiveness to sympathetic or vagal outflow.

Despite the age-related decline in baroreflex gain observed in our study, there was a similar blood pressure change during tilt in young and elderly subjects. However, the heart rate response to tilt was smaller in elderly subjects than in young subjects. These results agree with several previous studies (10–12). Furthermore, they suggest that the cardiovagal, rather than the vascular-sympathetic, component of the baroreflex was impaired in our elderly subjects. It is likely that the vascular response to baroreflex activation during tilt was preserved, enabling these subjects to prevent orthostatic hypotension, by means of vasoconstriction.

Gribbin and colleagues reported that both age and mean arterial blood pressure are independently related to baroreflex gain (1). Lage and associates reported a relationship between carotid artery stiffness and baroreflex sensitivity in middle-aged normotensive and hypertensive subjects combined (4). However, when these groups of subjects were analyzed separately, there was no correlation between the baroreflex slope and carotid stiffness within either the normotensive or hypertensive group. These investigators concluded, as we do, that reduced arterial compliance is not solely responsible for baroreflex dysfunction in hypertensive subjects.

### Table 1. Cardiovascular Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elderly</th>
<th>Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>70 ± 4</td>
<td>31 ± 3*</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/14</td>
<td>6/4</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>66 ± 10</td>
<td>70 ± 14</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>146 ± 24</td>
<td>125 ± 8*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>70 ± 13</td>
<td>69 ± 7</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>95 ± 15</td>
<td>87 ± 8</td>
</tr>
<tr>
<td>Diast. diam. (mm)</td>
<td>6.85 ± 0.87</td>
<td>5.62 ± 0.36*</td>
</tr>
<tr>
<td>Syst. diam. (mm)</td>
<td>7.25 ± 0.85</td>
<td>6.17 ± 0.28*</td>
</tr>
<tr>
<td>Carotid stiff. (units)</td>
<td>14.2 ± 5.1</td>
<td>6.6 ± 1.8*</td>
</tr>
<tr>
<td>Baroreflex gain</td>
<td>8.2 ± 6.4</td>
<td>16.3 ± 7.4*</td>
</tr>
<tr>
<td>Tilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in HR (bpm)</td>
<td>8 ± 6</td>
<td>20 ± 10*</td>
</tr>
<tr>
<td>Change in SBP (mm Hg)</td>
<td>5 ± 19</td>
<td>−1 ± 12</td>
</tr>
<tr>
<td>Change in DBP (mm Hg)</td>
<td>7 ± 8</td>
<td>8 ± 10</td>
</tr>
<tr>
<td>Change in MBP (mm Hg)</td>
<td>5 ± 12</td>
<td>6 ± 10</td>
</tr>
<tr>
<td>Baroreflex gain</td>
<td>4.6 ± 3.5</td>
<td>8.3 ± 3.0*</td>
</tr>
</tbody>
</table>

Notes: Cardiovascular characteristics of the subjects are shown as mean ± SD. There were 34 elderly subjects and 10 young ones. HR = heart rate; SBP and DBP = systolic and diastolic blood pressure; MBP = mean arterial blood pressure.

* $p < .05$ vs elderly subjects.
In healthy young subjects, Bonyhay and colleagues reported that baroreflex sensitivity is related to carotid artery distensibility, but not systolic pressure (13). Monahan and associates reported that reduced carotid artery compliance was the strongest independent physiological correlate of the age-associated decrease in carotidovagal baroreflex sensitivity, explaining 51% of the variance across an age span of 19 to 76 years (3). Because aging increases both arterial pressure and stiffness, we examined their independent relationship to baroreflex gain over a relatively narrow age range of 65–80 years, and we found in this age group that systolic pressure contributes independently to reduced baroreflex gain.

Hypertension is a well-known risk factor for the development of atherosclerosis. In animals (14) and man (4), carotid compliance is markedly reduced by hypertension. In their 4-year prospective study, Lakka and colleagues reported that elevated SBP accelerates the progression of intima–media thickness in the common carotid artery (15). Our results in elderly subjects may have failed to show a significant relationship between SBP and carotid stiffness because aging itself changes arterial elastic properties through collagen deposition, elastin fiber degeneration, intima–media hyperplasia, and vascular calcification (16). Any incremental effect of hypertension may not be evident in an elderly population already affected by age-related changes in vascular compliance.

We used the technique of cross-spectral analysis to measure carotidovagal baroreflex gain. Several reports comparing the standard phenylephrine test to this noninvasive method in normotensive or hypertensive subjects have reported good agreement between the methods (8,17,18). The noninvasive assessment of baroreflex sensitivity by spectral analysis has several advantages over the phenylephrine method. First, this noninvasive method imposes less risk and discomfort on the subjects. Although the risk associated with vasoactive drug injection is small in healthy subjects, this risk may be increased in subjects with blood pressure elevation. Second, the maintenance of patent intravenous lines and the injection process itself can be associated with increased anxiety in some individuals. This increased anxiety may affect baroreflex sensitivity (19). Furthermore, because the spectral method requires only 5 minutes of ECG and blood pressure recording, this technique is more practical than the pharmacological methods and can be performed in a broad range of research settings.

Potential limitations of this study include its small sample size and relatively few subjects with high SBPs and high arterial stiffness values. Ideally, we would have studied a large cohort of healthy subjects across the entire adult age spectrum. However, there are several practical limitations to such a study. Unless all age groups have similar distributions of arterial pressure and stiffness and are not being treated for blood pressure elevation, it is difficult to avoid the confounding effects of age and medications on the analysis. To our knowledge, the current study is the first to examine these relationships in healthy subjects over the age of 65, who have a broad range of arterial pressures and stiffness.

Another potential limitation of our study was the necessary reliance on finger pressure to compute carotid artery stiffness and baroreflex gain. Amplification of the peripheral finger pressure waveform as a result of wave reflection may result in overestimation of the central carotid artery systolic pressure. Unfortunately, the only available noninvasive tool to estimate carotid pressure is carotid artery tonometry, which is also limited by the need for indirect calibration, its sensitivity to placement and movement, and its stimulation of carotid baroreceptors, which can produce significant cardiac slowing. Pulse wave amplification could partially explain the differences in carotid stiffness we observed between young and old subjects; however, it would have less of an impact on our within-group correlations among pressure, stiffness, and baroreflex gain in elderly subjects. Moreover, among elderly subjects, SBP was not correlated with carotid artery stiffness, suggesting that within-group differences in pulse wave reflection did not affect our stiffness index. Our measure of baroreflex gain also was probably unaffected by pulse wave amplification, because this measure relies on beat-to-beat changes in pressure, rather than its absolute value. We assessed subjects in the resting supine position, where they were likely to be in the same vascular state, without large hemodynamic and neurohumoral changes that could affect pulse wave amplification.

Conclusions

The results of this study point to systolic hypertension as a potentially modifiable factor that reduces baroreflex gain. In fact, combination antihypertensive therapy has recently been shown to improve baroreflex sensitivity in patients aged 45 to 63 with systemic hypertension (20). One would hope that these findings will motivate future studies designed to determine whether antihypertensive therapy will improve baroreflex function and associated cardiovascular health in elderly people.

Acknowledgments

This research was supported by the Hebrew Rehabilitation Center for Aged (HRCA) and the HRCA/Harvard Research Nursing Home Program Project under Grant AG04390 from the National Institute on Aging.

The authors are grateful to Drs. Janice Weinberg, ScD, and L. Adrienne Cupples, PhD, from Boston University Medical School for statistical consultation, and to Drs. J. Andrew Taylor and Michael Cohen for providing the software for carotid image analysis.

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Received September 17, 2002
Accepted October 28, 2002