Central Arterial Compliance Is Associated With Age- and Habitual Exercise–Related Differences in Cardiovagal Baroreflex Sensitivity

Kevin D. Monahan, PhD; Hirofumi Tanaka, PhD; Frank A. Dinenna, PhD; Douglas R. Seals, PhD

Background—Cardiovagal baroreflex sensitivity (BRS) declines with age but is favorably modulated by habitual aerobic exercise. We tested the hypothesis that compliance (transducing capacity) of an elastic artery in which baroreceptors are located is associated with these age-exercise interactions.

Methods and Results—Nine young (28 ± 6 years old) and 9 older (65 ± 1) sedentary and 10 young (27 ± 1) and 9 older (63 ± 2) endurance-trained healthy men were studied. Cardiovagal BRS was assessed conventionally (R-R interval–systolic blood pressure [SBP] relation) by the Oxford technique. Because of age-associated increases in central arterial stiffness, cardiovagal BRS was expressed with both peripheral (Finapres) and central (applanation tonometry) SBP values. The change in carotid artery end-systolic lumen diameter (ultrasonography) per unit increase in SBP and the slope of the R-R interval–carotid artery diameter relation also were determined. Cardiovagal BRS declined with age in both sedentary (≈65%) and endurance-trained (≈40%) men but was higher in endurance-trained than sedentary older men regardless of the SBP values used (all P<0.05). Changes in carotid artery lumen diameter per unit increase in SBP mirrored these differences in cardiovagal BRS (all P<0.05). Thus, R-R interval prolongation per unit increase in carotid artery diameter was not different among the groups (P>0.70).

Conclusions—These results demonstrate that age- and habitual exercise–related differences in cardiovagal BRS are associated with corresponding differences in carotid artery compliance among healthy men. (Circulation. 2001;104:1627-1632.)

Key Words: baroreceptors ■ nervous system, autonomic ■ arteries ■ ultrasonics ■ aging

Rapid transient increases in systolic blood pressure (SBP) evoke arterial baroreflex–mediated R-R interval prolongation. The slope of the R-R interval–SBP relation during this rise in SBP has been used as a measure of cardiac vagal baroreflex sensitivity (BRS).1 Reduced cardiac vagal BRS is associated with impaired regulation of arterial blood pressure (BP)2 and, in the presence of myocardial ischemia, with increased risk of ventricular tachyarrhythmias and sudden cardiac death.3,4 Thus, factors that affect cardiac vagal BRS in humans and the mechanisms underlying those influences are of both physiological and clinical interest.

Sedentary aging is associated with marked reductions in cardiac vagal BRS,5 even in healthy adults.6 In contrast, we demonstrated that habitual aerobic exercise favorably modulates age-associated declines in cardiac vagal BRS.6,7 Specifically, decreases in cardiac vagal BRS with age are attenuated in endurance-trained compared with sedentary adults.6 Moreover, cardiac vagal BRS is greater in middle-aged and older adults who exercise regularly than in their inactive peers.5,7

The mechanisms by which aging reduces cardiac vagal BRS and regular aerobic exercise modifies such changes have not been determined. One possibility that could account for both effects involves differences in arterial compliance. The compliance of large elastic arteries in which the arterial baroreceptors are located (carotid and aorta) decreases with advancing age in adult humans.8 This has led to the postulate that corresponding reductions in the ability of these reflexogenic regions to transduce signals generated by acute changes in intravascular pressure may explain age-related decreases in cardiac vagal BRS.9 Although long hypothesized, this theory has not been proved experimentally. Moreover, we recently showed that habitual exercise status modulates age-associated decreases in carotid arterial compliance.10 Taken together, these observations are consistent with the concept that the effects of sedentary aging and regular exercise on central arterial compliance could explain their associations with cardiac vagal BRS.

In the present study, we isolated the influence of central arterial compliance on cardiac vagal BRS using the Oxford technique.1 We first determined cardiac vagal BRS using the conventional approach of assessing the slope of the R-R interval–SBP relation. Because of age-associated increases in central arterial stiffness, cardiovagal BRS was expressed with both peripheral (Finapres) and central (applanation tonometry) SBP values. The change in carotid artery end-systolic lumen diameter (ultrasonography) per unit increase in SBP and the slope of the R-R interval–carotid artery diameter relation also were determined. Cardiovagal BRS declined with age in both sedentary (≈65%) and endurance-trained (≈40%) men but was higher in endurance-trained than sedentary older men regardless of the SBP values used (all P<0.05). Changes in carotid artery lumen diameter per unit increase in SBP mirrored these differences in cardiac vagal BRS (all P<0.05). Thus, R-R interval prolongation per unit increase in carotid artery diameter was not different among the groups (P>0.70).

Conclusions—These results demonstrate that age- and habitual exercise–related differences in cardiac vagal BRS are associated with corresponding differences in carotid artery compliance among healthy men. (Circulation. 2001;104:1627-1632.)

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interval–SBP relation. Furthermore, advances in arterial applanation tonometry\(^{11}\) allow estimation of carotid SBP. Thus, the true pressure stimulus in the carotid artery (ie, that to which the arterial baroreceptors are exposed) can be used to assess cardiovascualar BRS more precisely. To remove potential influences of group differences in arterial compliance, we then determined arterial baroreflex–mediated R-R interval responses as a function of changes in carotid lumen diameter (wall deformation) produced by increases in SBP.\(^{12}\) There were no longer any group differences in cardiovascualar BRS after corresponding differences in carotid arterial compliance had been accounted for. These results provide experimental support for the concept that age- and habitual exercise–related differences in cardiovascualar BRS are associated with central arterial compliance in healthy men.

### Methods

#### Subjects

Thirty-seven healthy men volunteered for the present study. Subjects were classified into 1 of 4 groups based on their age and habitual exercise status: “young” (20 to 35 years old) and “older” (55 to 75 years old) and “sedentary” (no regular exercise) and “endurance-trained” (regular aerobic exercise).\(^{6}\) Young and older endurance-trained subjects had been training for \(77 \pm 10\) and \(55 \pm 2\) min/session, at 5.8 \pm 0.4 and 5.1 \pm 0.5 sessions/wk, for 7.2 \pm 3 and 19 \pm 3 years, respectively. All subjects were normotensive, nonobese, nonsmokers, nonmedicated, and had no overt disease. Older subjects were further evaluated by physical examination and maximal exercise ECGs. Subjects who had cholesterol levels \(>220\) mg/dL, significant intima-media thickening, and/or other characteristics of atherosclerosis were excluded. The experimental protocol was approved by the Human Research Committee, and written informed consent was obtained.

#### Measurements

Before the experimental protocol, subjects refrained from food and caffeine consumption for a 4-hour period. Endurance-trained subjects did not exercise for a minimum 16-hour period before testing to avoid potential acute effects of exercise.

#### Resting Brachial BP and Heart Rate

Arterial BP at rest was determined noninvasively over a brachial artery (Dinamap XL, Johnson & Johnson) after 30 minutes in the supine position. Resting heart rate was determined from the ECG during this period.

#### Maximal Oxygen Consumption

Maximal oxygen consumption was measured by online computer-assisted open-circuit spirometry during incremental treadmill exercise.

#### Body Composition

Body composition was determined by dual-energy x-ray absorptiometry (Lunar Radiation).

#### Carotid Artery Compliance and Diameter

Carotid artery compliance was measured under resting supine conditions as recently described in detail.\(^{10}\) Carotid lumen diameters were measured from images obtained from an ultrasound machine (Toshiba SSH-140) equipped with a high-resolution linear-array transducer. A longitudinal image of the common carotid artery was acquired to 2 cm proximal to the carotid bulb. These images were recorded directly to the hard drive of a PC computer with image acquisition software (CVI Acquisition, Information Integrity) through a frame grabber (DT-3152, Data Translations). Images were collected at 30 Hz for the first \(\approx 475\) ms of the cardiac cycle as triggered by the R wave from the ECG. This allowed measurement of both maximal and minimal lumen diameters from the media-adventitia border of the near wall to the intima-lumen interface of the far wall (CVI Analysis, Information Integrity). To minimize variability, points along both the near and far walls of the computer image were inserted manually, and an edge-detection algorithm was applied to calculate arterial diameter across this length of arterial segment. Minimal and maximal diameters were identified by scrolling through images acquired at \(\approx 33\) ms intervals. The same investigator, blinded to the subject’s group assignment, performed all analyses. Simultaneously with image acquisition, central BP waveforms were obtained noninvasively by arterial applanation tonometry using a pencil-type probe with a high-fidelity strain-gauge transducer (TCB-500, Millar Instruments) over the contralateral common carotid artery. This technique provides waveforms with the same harmonic content as those obtained invasively in humans.\(^{11}\) Furthermore, waveforms derived from an exposed artery do not differ from those recorded intra-arterially.\(^{12}\) Because this technique is dependent on hold-down pressure, mean BP from the periphery was used to calibrate the central arterial waveform to the same mean BP.\(^{13}\) Calculations of carotid arterial compliance and \(\beta\)-stiffness index were performed as previously described.\(^{10}\) \(\beta\)-Stiffness provides an index of arterial compliance adjusted for BP. In our laboratory, the day-to-day coefficients of variation for these measures are 2 \pm 1\%, 7 \pm 3\%, and 5 \pm 2\% for carotid artery diameter, pulse pressure, and arterial compliance, respectively.

#### Beat-by-Beat BP and R-R Interval

Peripheral BP for assessment of cardiovascualar BRS was measured with a Finapres (Ohmeda) and central SBP by applanation tonometry. R-R interval was measured from the ECG. Signals were analog-to-digital–converted at 500 Hz (Datqax) and stored on a PC computer for later analysis.

#### Protocol

Cardiovascualar BRS was assessed by the Oxford technique.\(^{1,5}\) After a 30-minute period in the supine position, phenylephrine was administered rapidly (\(\approx 1\) second) as a bolus (0.75 to 1.5 mL IV). A sufficient dose (75 to 150 \(\mu\)g) was administered to increase BP \(\approx 15\) to 25 mm Hg. The hand used for continuous BP monitoring with the Finapres monitor was positioned at a level to match the mean arterial pressure measured noninvasively via the brachial artery (Dinamap) shortly before drug administration. This protocol was repeated 3 times in each subject at 10-minute intervals. The correlation coefficients between trials were consistently high and similar (range \(r=0.81 \pm 0.01\) to \(0.85 \pm 0.01\)) for the 3 measures and across the 4 groups. Therefore, for each expression, the average slope for the 3 trials was used as the measure of cardiovascualar BRS for each subject.

#### Data Analysis

Several components of the baroreflex response were determined. First, SBPs measured in the periphery were regressed against corresponding R-R intervals starting at the time that SBP began to increase and continued to the maximal R-R interval.\(^{1}\) Cardiovascualar BRS is reported as the slope of the R-R interval–SBP relation (ms/mm Hg) during this period. Second, R-R intervals were regressed against corresponding central SBP values during this period. Third, carotid arterial end-systolic lumen diameter was plotted as a function of the corresponding R-R interval\(^{14}\) and reported as the slope (ms/mm).\(^{12}\) Typical results of linear regressions are presented in Figure 1.

#### Statistical Analysis

Main effects were examined via 2-way (age×habitual exercise status) ANOVA with Newman-Keuls post hoc analyses. ANCOVA was performed to remove influences of 1 variable from the relation between 2 other variables. Relations between variables of interest were determined with univariate correlation and regression analyses. Data are presented as mean±SEM.
Results

Subject Characteristics

Values are shown in the Table. There were no group differences in brachial SBP. Diastolic BP, mean BP, and central SBP were higher in the older men (P<0.01). Heart rate at rest did not differ with age but was lower in the endurance-trained men (P<0.01). Carotid lumen diameter increased with age in both sedentary and endurance-trained men (P<0.05). Carotid artery compliance was lower and the \( \beta \)-stiffness index higher in older men within each exercise status (P<0.05), but age-associated differences were smaller in endurance-trained men (P<0.05). Carotid artery compliance also was lower with age in subgroups of young (n=8) and older (n=8) men matched for mean BP (0.19±0.01 versus 0.14±0.01 mm\(^2\)/mm Hg; P<0.05). Carotid artery compliance was greater and the \( \beta \)-stiffness index lower in the endurance-trained than the sedentary older men (P<0.05) but did not differ with exercise status in the young men.

Influence of External Probe Placement Near Barosensory Regions

Because cardiovagal BRS was assessed while both applplanation tonometry and ultrasound probes were placed in close proximity to barosensory regions, responses may have been influenced by their placement. To rule out this possibility, we measured cardiovagal BRS in 10 subjects (5 young and 5 older) both with and without probes in place. Cardiovagal BRS, assessed as the slope of the relation between R-R interval and Finapres-derived SBP during the phenylephrine-induced rise in SBP, was not different between the 2 conditions in either young (32±5 versus 29±7 ms/mm Hg, with and without probes in place) or older (14±3 versus 14±5 ms/mm Hg) subjects.

Selected Subject Characteristics

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<tr>
<th>Variable</th>
<th>Sedentary</th>
<th>Endurance-Trained</th>
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<td>Older (n=9)</td>
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<td>Carotid lumen diameter, mm</td>
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<td>Carotid arterial compliance, mm(^2)/mm Hg</td>
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<td>0.11±0.01*</td>
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<td>( \beta )-Stiffness index, U</td>
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<td>3.5±0.1*</td>
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<tr>
<td>Maximal oxygen consumption, mL·kg(^{-1})·min(^{-1})</td>
<td>45±2</td>
<td>29±1*</td>
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</table>

Values are mean±SEM.

*P<0.05 vs young men of same physical activity status.
†P<0.05 vs age-matched sedentary men.
Cardiovagal BRS

In response to bolus infusion of phenylephrine, both Finapres-derived SBP ($\Delta 18 \pm 2$ versus $\Delta 21 \pm 2$ mm Hg) and carotid SBP ($\Delta 17 \pm 2$ versus $\Delta 22 \pm 2$ mm Hg) increased similarly in young and older subjects, respectively. As shown in Figure 2A, cardiovagal BRS was reduced with age in the sedentary men ($P<0.05$), but age-associated declines were smaller in endurance-trained men ($P<0.05$). Cardiovagal BRS was greater in endurance-trained than sedentary older men ($P<0.05$) but did not differ with exercise status in young men. Similar age and exercise group differences were noted when cardiovagal BRS was assessed by use of carotid SBP (Figure 2B). Values for central SBP-estimated cardiovagal BRS did not differ from Finapres-derived cardiovagal BRS for any group. Baseline carotid artery compliance was related to cardiovagal BRS ($r=0.69, P<0.001$) and central SBP-estimated cardiovagal BRS ($r=0.71, P<0.001$).

R-R Interval and Carotid Lumen Diameter Responses to Baroreceptor Stimulation

The peripheral and carotid SBP responses to phenylephrine did not differ in any group. Therefore, carotid SBP was used for these measurements. Increases in carotid lumen diameter per unit increase in SBP were greater in young than older sedentary and endurance-trained men and in the endurance-trained compared with the sedentary older men (all $P<0.05$; Figure 2C). When carotid lumen diameter changes in response to phenylephrine were accounted for by expressing R-R interval prolongation as the slope of the relation between R-R interval and carotid lumen diameter, all group differences were no longer significant (all $P>0.7$, Figure 2D). Baseline carotid artery compliance was related to increases in carotid artery internal diameter per unit increase in SBP ($r=0.65, P<0.001$). To exclude the possibility that age-associated increases in baseline carotid lumen diameter influenced our results, we matched a subgroup of young ($n=11$) and older ($n=11$) subjects for carotid lumen diameter ($6.7 \pm 0.1$ versus $6.9 \pm 0.1$ mm, respectively). The R-R interval prolongation in response to increases in carotid artery end-systolic diameter remained insignificant ($543 \pm 31$ versus $590 \pm 63$ ms/mm; $P>0.05$).

Discussion

The key new finding from the present study is that age- and habitual exercise-associated differences in cardiovagal BRS are associated with corresponding differences in the compliance of the carotid artery among healthy men. The main evidence for this conclusion is that the significant group differences in the R-R interval response to baroreceptor stimulation in older sedentary men compared with young control subjects and endurance-trained older men were no longer significant when corresponding stimulus-evoked differences in carotid artery diameter (deformation) were accounted for.

The present findings are consistent with but substantially extend previous observations from our laboratory and others. First, Bonyhay and colleagues\textsuperscript{15} reported that cardiovagal BRS was strongly related to baseline carotid artery distensibility among young adults. Second, decreases in cardiovagal BRS and measures of central arterial compliance with age appear to demonstrate similar temporal patterns.\textsuperscript{6,7,10} Moreover, we have shown that these respective age-associated declines are significantly attenuated in endurance-trained men.\textsuperscript{6,7,10} Third, there is a strong positive correlation between cardiovagal BRS and carotid arterial compliance among healthy men of increasing age.\textsuperscript{16} The present findings provide experimental evidence directly supporting the influence of arterial compliance on cardiovagal BRS that was suggested by these previous correlational observations.

The mechanism linking cardiovagal BRS to arterial compliance probably involves the ability of the artery to deform in response to acute changes in intravascular pressure. Specifically, the arterial baroreceptors are located within the walls of the carotid sinus and aortic arch. Deformation of the walls of these reflexogenic regions during changes in BP, rather than alterations in intravascular pressure per se, are necessary to evoke a baroreflex response.\textsuperscript{17} Thus, because of lower baseline arterial compliance, smaller increases in carotid lumen diameter in response to acute increases in central SBP in older sedentary men in the present study would be
expected to result in a correspondingly smaller R-R interval response.

There are at least 4 alternative mechanisms that may have explained age- and habitual exercise–related differences in cardiovagal BRS. First, it is possible that efferent vagal responsiveness could be nonspecifically attenuated with sedentary aging. Recent findings, however, suggest that this may not be the case in humans. Second, central processing of the afferent feedback from the arterial baroreceptors (afferent-efferent coupling) could be impaired with age. In humans, it is not possible to isolate this step in the baroreflex loop. There is no obvious physiological basis, however, for postulating that sedentary aging would depress and habitual exercise would augment central processing of baroreceptor afferent feedback. Third, it is possible that reduced β-adrenergic responsiveness with age may have contributed to group differences in cardiovagal BRS. We do not believe this to be the case because the reflex bradycardia induced by bolus infusion of phenylephrine is nearly abolished by muscarinic receptor blockade and unchanged or augmented by β-adrenergic blockade. Fourth, parallel differences in local or humoral modulation of baroreceptor activity with age and habitual exercise may have been involved. On the basis of the limitations imposed by the present study design, this remains a possibility.

A common criticism of conventional BRS assessment by use of peripheral BP values is that they might not be representative of the intravascular pressure stimulus for the arterial baroreceptors. Moreover, we demonstrated that resting carotid SBP can increase progressively with age in the absence of elevations in resting peripheral SBP, thus dissociating these measures of chronic SBP under conditions of human aging. Therefore, we assessed cardiovagal BRS using both peripherally and centrally estimated SBP. Our results indicate that any differences in baseline SBP with these 2 measures do not affect age- and exercise-associated group differences in cardiovagal BRS assessed during a BP perturbation.

Our findings may have important physiological and clinical implications. Arterial BP control can be altered in the presence of reduced cardiovagal BRS. For example, BP variability, an independent risk factor for cardiovascular disease, is inversely related to cardiovagal BRS. SBP variability increases with advancing age in sedentary adults but is smaller in habitually exercising middle-aged and older adults compared with their sedentary peers. Moreover, data from animals suggest that low levels of cardiovagal BRS are related to an increased propensity for ventricular fibrillation and cardiac sudden death in the presence of myocardial ischemia. The prevalence of lethal ventricular tachyarrhythmias increases with advancing age but is lower in middle-aged and older physically active adults than in sedentary adults. These observations suggest that arterial compliance–associated differences in cardiovagal BRS may contribute to these population differences in resistance to electrical instability and adverse cardiac events. This hypothesis warrants further investigation.

At least 3 additional experimental considerations should be noted. First, we did not assess diameter and BP changes in the aorta, which is also richly innervated with arterial baroreceptors. Because the stimulus to these 2 receptor regions is directionally similar during phenylephrine administration and both vessels demonstrate similar mechanical and hemodynamic properties, this should not represent a significant confound in the present study. We cannot exclude this possibility, however.

Second, if baseline carotid lumen diameter differed between groups at baseline, this could bias our measure of R-R interval prolongation to carotid artery lumen diameter increases with phenylephrine. For example, a larger baseline lumen diameter in older than young sedentary men could have resulted in a smaller increase in arterial diameter with age in response to SBP elevation, independent of differences in compliance via a ceiling effect. At least 4 lines of experimental evidence, however, do not support this possibility. First, baseline carotid lumen diameter did not correlate with the change in lumen diameter in response to phenylephrine-evoked BP elevations. Second, when subgroups of young and older subjects were matched for baseline carotid artery diameter, the results were not affected. Third, when we accounted for baseline differences in carotid diameter statistically (ANCOVA), group differences in the slope of the relation between R-R interval and carotid lumen diameter remained insignificant. Fourth, older exercising men had higher mean values for baseline carotid lumen diameter than their sedentary peers but demonstrated greater increases in lumen diameter in response to SBP elevations, thus effectively dissociating these events. Collectively, these observations suggest that differences in baseline carotid lumen diameter did not influence our results.

Third, it may be argued that age-related reductions in carotid arterial compliance may be influenced by an upward shift onto a less steep portion of the pressure-volume curve in our group of older subjects. At least 2 lines of evidence, however, argue against such an explanation. Carotid arterial compliance may be a pressure-dependent measure. There are measures of arterial compliance, however, that remove the pressure dependency of this relation. One such method is the β-stiffness index. When carotid arterial compliance was calculated by use of the β-stiffness index, arterial compliance remained reduced with age in both sedentary and endurance-trained men. A second line of evidence is that when we selected subgroups of young and older men matched for mean BP, the age-associated decline in carotid arterial compliance persisted. Collectively, these results suggest, albeit do not prove, that the age-associated declines in carotid artery compliance were not dependent on corresponding differences in resting BP. Rather, as previously discussed, we believe that alterations in vasoactive hormone levels and/or endothelium-derived vasoactive substances may figure importantly in the reductions in central arterial compliance with age.

In conclusion, the present results provide experimental support for the role of reduced central arterial compliance as an important mechanism underlying age- and habitual exercise–associated modulation of cardiovagal BRS in healthy men. As such, aging may impair and regular exercise may improve cardiovagal BRS by contrasting effects on central arterial compliance.
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References

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