Does Reduced Vascular Stiffening Fully Explain Preserved Cardiovagal Baroreflex Function in Older, Physically Active Men?

Brian E. Hunt, PhD; William B. Farquhar, PhD; J. Andrew Taylor, PhD

Background—We measured cardiovagal baroreflex gain and its vascular mechanical and neural components during dynamic baroreflex engagement in 10 young untrained men, 6 older untrained men, and 12 older, physically active men.

Methods and Results—Our newly developed assessment of beat-to-beat carotid diameters during baroreflex engagement estimates the mechanical transduction of pressure into barosensory stretch (Δdiameter/Δpressure), the neural transduction of stretch into vagal outflow (ΔR-R interval/Δdiameter), and conventional integrated cardiovagal baroreflex gain (ΔR-R interval/Δpressure). Integrated gain was lower in older untrained men than in young untrained men (6.8±1.2 versus 15.7±1.8 ms/mm Hg) due to both lower mechanical (9.1±1.0 versus 17.1±2.4 mm Hg/μm) and lower neural (0.57±0.10 versus 0.90±0.10 ms/μm) transduction. Integrated gain in older active men (13.3±2.7 ms/mm Hg) was comparable to that in young untrained men. This was achieved through mechanical transduction (12.1±1.4 mm Hg/μm) that was modestly higher than that in older untrained men and neural transduction (1.00±0.20 ms/μm) comparable to that in young untrained men. Across groups, both mechanical and neural components were related to integrated gain; however, the neural component carried greater predictive weight (β=0.789 versus 0.588).

Conclusions—Both vascular and neural deficits contribute to age-related declines in cardiovagal baroreflex gain; however, long-term physical activity attenuates this decline by maintaining neural vagal control. (Circulation. 2001;103:2424-2427.)

Key Words: aging — nervous system, autonomic — carotid arteries

A recent report suggested aerobic exercise attenuates carotid arterial stiffening with age.1 The importance of this observation is the impact stiffness may have on cardiovascular function. It has been hypothesized that barosensory vessel stiffening would profoundly affect autonomic circulatory control2 and reduce cardiovagal baroreflex gain with age.3,4 Indeed, some data indicate a direct relation between arterial compliance and cardiovagal baroreflex control.5,6 However, basal estimates of vascular stiffness may not represent the mechanical stresses placed on barosensory vessels during the dynamic pressure changes that characterize baroreflex engagement.7–9 Moreover, compromised neural function may play as prominent a role as decreased vascular mechanical function in reducing baroreflex gain with age.10

We determined the impact of altered carotid stiffness with age and habitual physical activity on baroreflex function using our recently developed, novel approach to quantify vascular and neural components during dynamic baroreflex engagement.11 Concurrent beat-by-beat arterial pressures, carotid diameters, and R-R intervals during vasoactive drug infusions provide insight into key steps of cardiovagal baroreflex regulation: mechanical transduction of pressure into barosensory vessel stretch and neural transduction of stretch into vagal outflow. On the basis of previous observations,1 we hypothesized that lower cardiovagal baroreflex gain in older untrained men would most strongly relate to reduced mechanical transduction. Further, we hypothesized that high levels of habitual physical activity in older men would preserve baroreflex gain primarily through maintained mechanical transduction. We found both mechanical and neural transduction contribute importantly to cardiovagal baroreflex gain in older adults; however, contrary to our hypothesis, the neural component in older active men seemed to be most responsible for maintaining gain at levels similar to those in young untrained men.

Methods

Ten young untrained men (aged 25±1 years), 6 older untrained men (aged 63±3 years), and 12 older, physically active men (aged 59±2 years) were studied. Untrained men participated in <60 minutes of aerobic exercise per week, whereas physically active men were competitive runners, averaging ≥150 minutes of endurance training per week. Aerobic capacity reflected these differences (Table).
Subjects were not hypertensive (by oscillometric Dinamap measurements), obese (by skinfold), smokers, or taking cardiovascular medications. Older volunteers were free from cardiovascular disease, as assessed by resting and treadmill exercise electrocardiograms. The Hebrew Rehabilitation Center for Aged institutional review board approved all protocols. The nature, purpose, and risks of the study were explained to each subject, and written informed consent was obtained.

We devised a new approach to arterial baroreflex function in humans.11 This technique, when properly applied, provides robust linear gain estimates of the mechanical and neural baroreflex components. Importantly, our estimates are unaffected by set-point differences that can produce erroneous differences in gain. When the set point lies near the midrange of the sigmoid relations, as in young healthy adults, linear gain estimation by increasing pressure from resting levels is appropriate. However, when the set point lies near saturation, as in highly trained individuals, these simple linear gains may represent a misestimation.10 With our approach, the exclusion of threshold and saturation values allows for the identification of the linear portion of the sigmoid relation. Briefly, concurrent beat-by-beat arterial pressures (Finapres), carotid diameters (B-mode ultrasonography), and R-R intervals (ECG lead II) are acquired during sequential bolus injections of 100 μg of nitroprusside and 150 μg of phenylephrine (modified Oxford technique).1 This allows an estimation of the mechanical transduction of pressure into barosensory stretch, the neural transduction of stretch into barosensory stretch, and conventional integrated cardiovagal baroreflex gain.11 To compare our dynamic mechanical transduction with the static index previously reported,1 we calculated pulsatile carotid vascular stiffness. From 1 minute of beat-by-beat data before each of 3 cardiovagal baroreflex tests, we derived stiffness [log (systolic pressure/diastolic pressure)/(pulsatile diameter/diastolic diameter)].6 Values were averaged across trials for each subject.

Group comparisons were made by ANOVA with Bonferroni post-hoc analysis. Univariate correlations across subjects provided insight into potential links between vascular function, neural transduction, and cardiovagal baroreflex gain. Variables with significant univariate correlations to integrated gain were included in forward, stepwise, multiple linear regression analysis to determine the gain variance explained by these variables. Because β-coefficients are metric-dependent, we repeated stepwise regression analysis with variables expressed as z-scores. β-Coefficients from this approach provided the relative importance of each baroreflex component in explaining differences in integrated cardiovagal baroreflex gain; older, physically active men had gains twice that of their untrained, age-matched peers. These gains were comparable to those of young untrained men. This greater integrated gain resulted from both mechanical and neural components. Mechanical pressure transduction in older, physically active men tended to be greater than that in older untrained men (P=0.09) but still less than that in young untrained men. However, neural transduction was 75% greater than that in their untrained peers and equal to that in young untrained men.

Pulsatile stiffness was ∼200% greater in older untrained men (22.0±7.1) than in both young untrained men (8.5±0.9)

### Results

Figure 1 shows the means for integrated cardiovagal baroreflex gain and its mechanical and neural components. Integrated gain in older untrained men was less than half of that in young untrained men. This seemed to derive from both lower mechanical transduction and lower neural transduction. Physical activity blunted the age-related decline in integrated cardiovagal baroreflex gain; older, physically active men had gains twice that of their untrained, age-matched peers. These gains were comparable to those of young untrained men. This greater integrated gain resulted from both mechanical and neural components. Mechanical pressure transduction in older, physically active men tended to be greater than that in older untrained men (P=0.09) but still less than that in young untrained men. However, neural transduction was 75% greater than that in their untrained peers and equal to that in young untrained men.

Pulsatile stiffness was ∼200% greater in older untrained men (22.0±7.1) than in both young untrained men (8.5±0.9)
and older, physically active men (5.0±1.8). However, stiffness was only marginally related to integrated cardiovagal baroreflex gain (r=−0.32, P=0.09), probably because it does not relate to the dynamic index of mechanical function (r=−0.23, P=0.23). In contrast, dynamic mechanical transduction was related to integrated gain (r=0.48), as was neural transduction, although more strongly (r=0.71). Stepwise multiple linear regression resulted in the following model: integrated gain=(0.666×mechanical transduction)+(8.437×neural transduction)−3.95. This equation indicates that both components contribute independently to the integrated response and account for 85% of the total variance. To determine the relative contribution of each component, data were standardized (z-scores) to remove the influence of each variable’s metric on β-coefficients. As before, this model accounted for 85% of the total variance in the integrated response. It further revealed that the neural component accounted for 53% of the variance and carried ∼34% greater weight in predicting the integrated cardiovagal response when compared with the mechanical component (β=0.789 versus 0.588). Although both components significantly contribute to the integrated response (Figure 2), the neural component was a greater determinant of cardiovagal baroreflex gain and, thus, it is a key mechanism for differences associated with physical activity in older humans.

Discussion
Our results indicate that deficits in both the mechanical and neural components of baroreflex contribute to lower integrated cardiovagal gain in untrained older men but that age-related declines may be mitigated by habitual physical activity. This seems to result from preserved neural control in the face of vascular stiffening with advancing age. We are aware of no previous data providing direct insight to the impact of vessel stiffness on dynamic cardiovagal baroreflex function in older humans.

Aging decreases baroreflex gain and increases vascular stiffness. Building on these findings, we clearly established that dynamic arterial function is important in age-related cardiovagal baroreflex declines. Although previous studies reported that basal levels of arterial vascular stiffness modestly relate to cardiovagal baroreflex gain, our estimates of carotid stiffness showed no obvious relation. This may reflect inaccuracies in measures derived from only small pulsatile changes, which can overestimate the distension capacity of large arteries, particularly in older adults. Thus, estimates based on resting values may provide limited insight into age-related differences in vascular mechanics during the pressure changes that characterize baroreflex engagement. This is underscored by the lack of relation between basal pulsatile stiffness and mechanical pressure transduction in our young untrained, older untrained, and older, physically active subjects.

Although the ability of barosensory vessels to transduce arterial pressure changes into vessel stretch is key to baroreflex function, our data highlight the critical role of neural function. Our index of neural transduction encomasses baroreceptor output, afferent neural conduction, central integration, efferent autonomic outflow, and sinoatrial node responsiveness, which broadly index cardiovagal neural function. Lower neural transduction in our older untrained men is consistent with evidence of altered central autonomic integration, reduced vagal outflow, and lower muscarinic sinoatrial node receptor density with advancing age. The strong relation between cardiovagal baroreflex gain and its neural component may reflect some or all of these declines.

It is possible that age-related changes in extracarotid sinus baroreceptors reduce neural transduction. Our stimulus did not account for the possible engagement of cardiopulmonary baroreceptors or the contribution of aortic baroreceptors. For example, if aortic baroreceptors primarily determine cardiovagal gain, then aortic baroreflex declines may drive age-related reductions. However, it seems likely that our carotid estimates have significance for baroreflex function because age-related vascular stiffening of the aorta and carotid arteries occurs in parallel.

The present and previous studies suggest exercise training improves vascular function. The only longitudinal study to date reported 3 months of exercise that did not improve aerobic capacity but fully reversed age-related carotid stiffness in middle-aged men. Our cross-sectional data suggest regular aerobic conditioning (training duration from 21 to 56 years) is indeed related to lesser carotid stiffness. However, our findings challenge the notion that reduced arterial stiffness fully explains preserved cardiovagal baroreflex function in older, physically active men. Instead, our data demonstrate that in the face of unremitting vascular stiffening, neural function predominately determines baroreflex gain, both with age and in response to endurance training. Physical activity induces neurological adaptations much sooner than structural adaptations, particularly in older adults. Therefore, improvements in neural function with short-term exercise training are likely to have the greatest impact on autonomic function in older adults. Our results provide some of the first data to indicate that neural plasticity with advancing age may be maintained and plays a critical role in preserving auto-
nomic cardiovascular regulation in the face of declining vascular function.

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**References**

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