Influence of age on cardiac baroreflex function during dynamic exercise in humans

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1Department of Medical Pharmacology and Physiology, 2Dalton Cardiovascular Research Center, 3Department of Internal Medicine, 4Department of Radiology, University of Missouri, Columbia, and 5Harry S. Truman Memorial Veterans Hospital, Department of Veterans Affairs Medical Center, Columbia, Missouri; and 6Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas

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Fisher JP, Ogoh S, Ahmed A, Aro MR, Gute D, Fadel PJ. Influence of age on cardiac baroreflex function during dynamic exercise in humans. Am J Physiol Heart Circ Physiol 293: H777–H783, 2007. First published April 20, 2007; doi:10.1152/ajpheart.00199.2007.—We investigated the influence of aging on cardiac baroreflex function during dynamic exercise in seven young (22 ± 1 yr) and eight older middle-aged (59 ± 2 yr) healthy subjects. Carotid-cardiac baroreflex function was assessed at rest and during moderate-intensity steady-state cycling performed at 50% heart rate reserve (HRR). Five-second pulses of neck pressure and neck suction from +40 to −80 Torr were applied to determine the operating point gain (GOP) and maximal gain (GMAX) of the full carotid-cardiac baroreflex function curve and examine baroreflex resetting during exercise. At rest, mean arterial pressure (MAP) and heart rate were similar between the younger and older subjects. In contrast, the resting GOP and GMAX were significantly lower in the older subjects. The increase in MAP from rest to exercise was greater in the older subjects (Δ ±20 ± 2 older vs. Δ +6 ± 3 younger mmHg; P < 0.001). However, the GMAX was similar in both groups during exercise because of a reduction in the younger subjects. In contrast, GMAX was unchanged from rest and therefore remained lower in older subjects (−0.19 ± 0.05 older vs. −0.42 ± 0.05 younger beats·min−1·mmHg−1; 50% HRR; P < 0.001). Furthermore, exercise resulted in an upward and rightward resetting of the cardiac baroreflex function curve in both groups. Collectively, these findings suggest that the cardiac baroreflex function curve appropriately resets during exercise in older subjects but operates at a reduced GMAX primarily because of age-related reductions in carotid-cardiac baroreflex control at rest.

arterial baroreceptors; aging; heart rate

HEALTHY AGING HAS BEEN associated with impaired arterial baroreflex control of heart rate (HR; see Refs. 10, 17, 25, 33), vasomotor tone (8), and blood pressure (23) under resting conditions. However, little is known about how aging alters baroreflex function during dynamic exercise. Importantly, alterations noted at rest cannot simply be extrapolated to exercise because peripheral feedback from skeletal muscle (i.e., exercise pressor reflex; EPR) and feedforward central neural inputs (i.e., central command) modulate arterial baroreflex control during exercise, influencing reflex sensitivity and also contributing to the resetting of the baroreflex function curve (13, 27). Moreover, EPR function may be attenuated in older subjects (24), thereby leading to decreases in input from the EPR to the baroreflex, potentially altering baroreflex sensitivity and resetting characteristics. In addition, it is possible that an age-related enhancement of central command may also modify the baroreflex during exercise (5). Thus it is important to consider the influence of healthy aging on baroreflex function and resetting during dynamic exercise. This is particularly relevant from a clinical standpoint since older subjects are increasingly being encouraged to exercise and decreases in baroreflex control of HR can increase the occurrence of ventricular arrhythmias during physical activity (1, 38).

Limited studies have attempted to investigate age-related alterations in autonomic control of the heart during dynamic exercise, and of these studies only one specifically examined baroreflex regulation (12, 22, 34, 42). Lucini et al. (22) reported that cardiac baroreflex sensitivity assessed via the α-index was reduced in older middle-aged subjects (52 ± 1 yr) compared with young subjects during low-intensity incremental supine cycling exercise. However, given that each exercise stage was performed for just 4 min, it is unclear whether steady-state conditions were reached (43). Furthermore, both young and older subjects performed the same absolute workloads. Because peak work rate and aerobic capacity commonly decrease with age (16), it is possible that the older subjects were exercising at a greater relative intensity. This is an important consideration since cardiac baroreflex sensitivity at the operating point of the cardiac baroreflex function curve decreases during exercise in an intensity-dependent manner as the operating point moves toward the threshold of the reflex to a location of reduced sensitivity, even though maximal gain is maintained (30). In this regard, how aging alters the resetting and general parameters of the cardiac baroreflex function curve during dynamic exercise is unknown.

Given the limited information regarding aging and baroreflex function during exercise, the present study was designed to examine cardiac baroreflex function during dynamic exercise in young and older healthy subjects. The application of neck pressure (NP) and neck suction (NS) was used to determine the operating point gain and maximal gain of the full carotid-cardiac baroreflex function curve and examine baroreflex resetting during moderate-intensity cycling. We hypothesized that decreases in the operating point gain would be similar in young and older subjects during exercise performed at an equivalent relative intensity, indicative of a resetting-induced shift of the operating point toward the threshold and to a locus of lesser gain on the carotid-cardiac baroreflex function curve.

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Furthermore, the carotid-cardiac maximal gain would be reduced in older subjects at rest, and this reduction would persist during exercise.

METHODS

Seven young (22 ± 1 yr) and eight older (59 ± 2 yr) middle-aged healthy subjects were recruited from the University of Missouri-Columbia and the surrounding community. Both young and older subjects were recreationally active, typically engaging in low (e.g., walking)- and moderate (e.g., jogging, stationary bike)-intensity aerobic activities (2–3 days/wk), but importantly none were competitive athletes. All experimental procedures and protocols conformed to the Declaration of Helsinki and were approved by the University of Missouri-Columbia Health Sciences Institutional Review Board and the Research and Development Committee at the Harry S. Truman Memorial Veterans’ Hospital. Each subject provided written informed consent. All subjects completed a medical health history questionnaire, and a physical exam was conducted by a physician investigator before participation. In addition, older subjects underwent Duplex ultrasound imaging within the University Radiology department to screen for significant carotid artery plaques and identify the location of the carotid sinus bifurcation before performing NP and NS (see below). No subject had a history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease and were not using prescribed or over-the-counter medications. Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least a day before any experimental sessions. On experimental days, the subjects arrived at the laboratory a minimum of 2 h following a light meal. All subjects were familiarized with the equipment and procedures before experimental sessions.

Experimental Measurements

HR was continuously monitored using a lead II electrocardiogram (ECG). Beat-to-beat blood pressure was measured using photoplethysmography obtained from the middle finger of the left hand positioned at the level of the right atrium in the midaxillary line (Finometer; Finapres Medical Systems, Amsterdam, Netherlands). Previous work has demonstrated that the changes in mean arterial pressure (MAP) measured by photoplethysmography are not different from direct arterial blood pressure measurements both at rest and during dynamic exercise (19, 40). In the present study, Finometer measurements were validated with absolute blood pressure measurements obtained by a modified sphygmomanometer (SunTech Medical Instruments, Raleigh, NC). Briefly, before Finometer recordings were obtained, the diastolic blood pressure (DBP) of the Finometer was matched with DBP measurements obtained from the brachial artery of the right arm using the automated sphygmomanometer. In addition, brachial artery blood pressures were measured every minute throughout exercise. Importantly, this sphygmomanometer has previously been shown to provide accurate blood pressure measurements during dynamic exercise (4). MAP was calculated as DBP plus one third of pulse pressure. The ECG signal and arterial blood pressure waveform were sampled at 1,000 Hz (Powerlab; ADInstruments, Bella Vista, NSW, Australia), and beat-to-beat values of HR, systolic blood pressure (SBP), MAP, and DBP were stored for off-line analysis (Chart version 5.2; AD Instruments).

Incremental maximal exercise test. Subjects performed a continuous incremental exercise test to ascertain peak HR for the determination of the steady-state cycling workload and to exclude the possibility of any exercise-induced arrhythmias or blood pressure abnormalities. To accomplish the latter, subjects were instrumented with a 12-lead ECG, and blood pressure was measured using automated sphygmomanometry. Subjects were seated in a semi-recumbent position on a medical exam table equipped with an electrically braked cycle ergometer with toe clips (Angio V2; Lode, Groningen, Netherlands). Following a 3-min warm-up period of cycling at 60 revolutions/min (rpm), the workload was increased by 25 Watts every minute. Peak responses were determined at the power output where the subject could no longer maintain a pedal frequency of 60 rpm despite strong verbal encouragement. All subjects gave a maximal rating of perceived exertion (i.e., 19–20) at exhaustion using the standard 6–20 Borg scale (2).

Carotid baroreflex control of HR. Full carotid-cardiac baroreflex function curves were derived at rest and during moderate-intensity cycling, as previously described (14, 30, 36). Briefly, following instrumentation for HR and blood pressure measurements, subjects were fitted with a malleable lead neck collar that encircled the anterior 2/3 of the neck for the application of NP and NS. Appropriate neck chamber placement was ensured by first fitting the subjects based on observed neck size and then performing resting trials of NP and NS to determine directionally appropriate and consistent HR and MAP responses. Carotid baroreflex (CBR) function was determined by applying random-ordered single 5-s pulses of NP and NS ranging from +40 to −80 Torr (i.e., +40, +20, −20, −40, −60, and −80 Torr). To minimize respiratory-related modulation of HR, the 5-s pulses of pressure and suction were delivered to the carotid sinus during a 10- to 15-s breath hold at end-expiration under resting conditions. However, during exercise, the breath hold was eliminated as previous work has identified no differences between the responses to neck collar stimuli during inspiration and expiration at a breathing frequency of >24 breaths/min (11). Four to five trials of NP and NS were performed at rest, whereas, during exercise, two to three perturbations were performed. The reduced time for carotid sinus stimulation during exercise (~13–15 min) was designed to allow subjects to be at steady state before CBR testing began and also to minimize any confounding effects of cardiovascular drift on CBR function (29). A minimum of 45 and 30 s of recovery was allotted between NP-NS trials at rest and during exercise, respectively, to allow all physiological variables to return to prestimulus values. The exercise bout began with a low workload (25–30 Watts), which was then adjusted to elicit a target HR corresponding to 50% HR reserve while pedal frequency was maintained at 60 rpm. Once the target HR was achieved, subjects exercised for 6 min to assure steady-state conditions, after which CBR function was assessed.

Derivation of CBR function curves. At rest, carotid-cardiac responses were evaluated by plotting the peak and nadir changes in HR or R-R interval evoked by NP and NS, respectively, against the estimated carotid sinus pressure (ECSP), which was calculated as MAP minus neck chamber pressure. However, during exercise, HR was only used to assess CBR-mediated cardiac responses to avoid the mathematical constraint of the hyperbolic relationship between R-R interval and HR, whereby for a given change in HR the corresponding changes were evaluated by plotting the peak and nadir changes in HR against the estimated carotid sinus pressure (ECSP), which was calculated as MAP minus neck chamber pressure. The ECG signal and arterial blood pressure waveform were sampled at 1,000 Hz (Powerlab; ADInstruments, Bella Vista, NSW, Australia), and beat-to-beat values of HR, systolic blood pressure (SBP), MAP, and DBP were stored for off-line analysis (Chart version 5.2; AD Instruments).

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\[
HR = A_t \times \{1 + \exp[A_s \times (ECSP - A_d)]\}^{-1} + A_n, \quad (1)
\]

where HR is the dependent variable, \(A_t\) is the HR range of response (maximum–minimum), \(A_2\) is the gain coefficient, \(A_3\) is the carotid sinus pressure required to elicit an equalpressor and depressor response (centering point), and \(A_4\) is the minimum HR response. The data were fit to this model by nonlinear least-squares regression (using a Marquardt-Levenberg algorithm), which minimized the sum of
squares error term to predict a curve of “best fit” for each set of raw data. The overall fit of the curves was similar in the young and older subjects with \( r^2 \) values of 0.992 ± 0.002 vs. 0.970 ± 0.009, respectively, at rest and 0.984 ± 0.004 vs. 0.986 ± 0.003, respectively, during exercise. Although these values are very high, it is notable that the \( r^2 \) of the overall model is influenced by the number of parameters employed and therefore does not necessarily mean that all parameters are significant. The coefficient of variation for the overall fit of this model to the individual responses was 15% for the younger subjects and 19% for the older subjects. The carotid-cardiac maximal gain and operating point gain were calculated using the following equations:

\[
G_{\text{MAX}} = -\frac{A_1A_2}{4}
\]

\[
G_{\text{OP}} = A_1A_2 \exp[A_3(\text{ECSP}_{\text{OP}} - A_3)]/\{1 + \exp[A_3(\text{ECSP}_{\text{OP}} - A_3)]\}^2
\]

where \( G_{\text{MAX}} \) is the maximal gain of CBR function curve, \( G_{\text{OP}} \) is the gain of CBR function curve at the operating point, and \( \text{ECSP}_{\text{OP}} \) is the ECSP at the operating point (i.e., prestimulus MAP). The \( G_{\text{MAX}} \) was calculated as the gain at the centering point and used as an index of overall CBR responsiveness, whereas the \( G_{\text{OP}} \) was calculated as the gain at the operating point and used to provide a measure of responsiveness at the operating point of the CBR function curve. The latter measure becomes important during exercise as the operating point moves away from the centering point to a locus of reduced responsiveness (30, 36). The threshold (THR), point where no further increase in HR occurred despite reductions in ECSP, and the saturation (SAT), point where no further decrease in HR occurred despite increases in ECSP, were calculated by applying equations described by McDowell and Dampney (26):

\[
\text{THR} = -2.944/A_2 + A_1
\]

\[
\text{SAT} = 2.944/A_2 + A_3
\]

These calculations of THR and SAT are the carotid sinus pressure at which HR is within 5% of the upper or lower plateau of the sigmoid function.

Statistical Analysis

Statistical comparisons of physiological variables were made using a two-way repeated-measures ANOVA test, and a Student-Newman-Keul’s test was employed post hoc to investigate main effects and interactions. Statistical significance was set at \( P < 0.05 \). Results are presented as means ± SE. Analyses were conducted using SigmaStat (Jandel Scientific Software; SPSS, Chicago, IL) for Windows.

RESULTS

Subject Characteristics

There were no significant differences in body mass index, blood urea nitrogen, plasma sodium, or plasma potassium between the young and older subjects, but as expected the peak HR response to the incremental exercise test was significantly higher in younger subjects (Table 1). In addition, although cholesterol and triglycerides tended to be higher in the older subjects, both values were within the normal range for healthy individuals.

Cardiovascular Responses at Rest and During Exercise

Resting HR (63 ± 3 older vs. 63 ± 3 younger beats/min; \( P > 0.05 \)) and MAP (92 ± 3 older vs. 86 ± 1 younger mmHg; \( P > 0.05 \)) measurements were similar between the younger and older subjects. During dynamic leg cycling, the MAP responses were greater in the older subjects (change from rest of +20 ± 2 older vs. +6 ± 3 younger mmHg; \( P < 0.001 \)). SBP was also increased during exercise and was significantly greater in older subjects (118 ± 4 to 179 ± 6 older vs. 115 ±

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Older</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>22.1</td>
<td>59 ± 2*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 3</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170 ± 3</td>
<td>173 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>162 ± 15</td>
<td>199 ± 10</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>78 ± 9</td>
<td>97 ± 14</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>12 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Plasma Na+, meq/l</td>
<td>140 ± 0.8</td>
<td>139 ± 0.4</td>
</tr>
<tr>
<td>Plasma K+, meq/l</td>
<td>3.7 ± 0.1</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>Peak heart rate, beats/min</td>
<td>185 ± 3</td>
<td>158 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; BUN, blood urea nitrogen.

*\( P < 0.05 \) vs. young.

Carotid-Cardiac Baroreflex Function Curves and Parameters

Original records depicting carotid-cardiac responses to NP and NS at rest and during exercise in a young and older subject are presented in Fig. 1. The stimulus-response relationships for ECSP and HR at rest and during exercise in young and older subjects are shown in Fig. 2. The logistic model parameters and derived variables describing carotid-cardiac baroreflex control in young and older individuals at rest and during exercise are presented in Tables 2 and 3, respectively. The response range (\( A_1 \)), \( G_{\text{MAX}} \), and \( G_{\text{OP}} \) were all significantly attenuated in the older subjects with 

\( 2 \) to \( 150 \) younger mmHg; \( P < 0.001 \)). In young subjects, DBP was reduced from rest during moderate-intensity cycling (\( -8 \) to \( 3 \) mmHg, \( P < 0.05 \)). In contrast, in older subjects, DBP was unaltered from rest during exercise. As expected, HR was significantly higher in younger subjects during exercise. Ratings of perceived exertion were similar between groups (12 ± 0.4 older vs. 11 ± 0.5 younger AU).

DISCUSSION

The present study is the first to examine measures of cardiac baroreflex function and baroreflex resetting in healthy older and younger subjects during steady-state dynamic exercise in comparison with rest. First, we found that operating point gain and the maximal gain of the carotid-cardiac baroreflex function curve were both reduced in older subjects at rest. In contrast, the operating point gain obtained during exercise was generally similar in young and older subjects, primarily because of marked reductions in the young subjects. Furthermore, because the maximal gain of the carotid-cardiac baroreflex function
curve was unchanged from rest to exercise in both groups, it remained significantly lower in older subjects during exercise. Importantly, similar to young subjects, the cardiac baroreflex function curve was reset in an upward and rightward manner in older subjects during exercise but operated at a reduced maximal gain and responding range. Collectively, these findings indicate that aging results in a reduced capacity to regulate HR via the baroreflex during exercise primarily because of age-related reductions in carotid-cardiac control manifest at rest.

It is well known that resting baroreflex control of HR is reduced with healthy aging (10, 17, 25, 33). However, limited studies have examined how aging modulates cardiac baroreflex function during dynamic exercise. In the present study, we found that, although the G_{OP} of the carotid-cardiac baroreflex function curve was lower in older subjects at rest, the G_{OP} was not different between young and older subjects during moderate exercise. This was primarily because of a greater reduction in G_{OP} in the younger subjects as the operating point moved toward the threshold of the reflex and to a point of reduced gain. Careful examination of the carotid-cardiac baroreflex function curves indicates that even at rest the G_{OP} is away from the centering point and closer to the threshold in older subjects, likely contributing to the reduction in resting cardiac baroreflex sensitivity. The reason for this shift at rest is unclear but likely has to do with the reduction in resting parasympathetic tone that occurs with aging (41). Indeed, the relationship between the operating and centering point of the cardiac baroreflex function curve has been shown to be dependent on the degree of parasympathetic tone (30).

From a functional standpoint, perhaps the most striking age-related difference in cardiac baroreflex control was the ~50% reduction in maximal gain in the older subjects at rest, clearly indicating that aging results in a reduced capacity to regulate HR via the baroreflex. This finding for carotid-cardiac baroreflex control was similar when the dependent variable was expressed as R-R interval. Interestingly, similar age-related decreases in resting cardiac baroreflex control have been identified using pharmacological manipulations of blood pressure (25). More importantly, we now provide evidence that the significant reduction in maximal gain of the cardiac baroreflex function curve persists during exercise. Thus, even though the operating point gain is similar between young and older subjects during exercise, the older subjects still have an impaired cardiac baroreflex function because of the reduction in

Table 2. Comparison of logistic model parameters describing carotid baroreflex control of HR in young and older subjects at rest and during moderate-intensity cycling

<table>
<thead>
<tr>
<th></th>
<th>A_1, beats/min</th>
<th>A_2</th>
<th>A_3, mmHg</th>
<th>A_4, beats/min</th>
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</thead>
<tbody>
<tr>
<td>Rest Young</td>
<td>17±2</td>
<td>0.09±0.01</td>
<td>91±3</td>
<td>53±4</td>
</tr>
<tr>
<td>Rest Older</td>
<td>8±1</td>
<td>0.09±0.01</td>
<td>102±6</td>
<td>57±3</td>
</tr>
<tr>
<td>Exercise Young</td>
<td>15±3</td>
<td>0.14±0.03</td>
<td>112±5</td>
<td>111±4*</td>
</tr>
<tr>
<td>Exercise Older</td>
<td>8±1</td>
<td>0.11±0.02</td>
<td>129±5</td>
<td>105±4*</td>
</tr>
<tr>
<td>*P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>0.600</td>
<td>0.094</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group</td>
<td>0.004</td>
<td>0.641</td>
<td>0.013</td>
<td>0.872</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.432</td>
<td>0.602</td>
<td>0.387</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; A_1, response range; A_2, gain coefficient; A_3, centering point; A_4, minimum response. *P < 0.05 vs. rest.
or metabolic modulation of sympathetic outflow directed to the subjects. Although age-related impairments in vasodilatation jects, whereas it was significantly reduced from rest in young vasomotor tone, was unchanged during exercise in older sub-

this regard, in the present study, DBP, which primarily reflects increases in vascular tone are not effectively limited and would baroreflex function during dynamic exercise could mean that this protection was impaired since the movement of the operating point toward the threshold of the reflex in both young and older subjects. Nevertheless, the results of the present study provide novel insight into cardiac baroreflex function and resetting during dynamic exercise as one advances in age.

In summary, although the operating point gain was similar during exercise in young and older subjects, the maximal gain of the carotid-cardiac baroreflex function curve was signifi-...
cantly lower in older subjects primarily because of reductions at rest. More importantly, by defining the logistic model parameters and derived variables for CBR control of HR, we have identified for the first time that the carotid-cardiac baroreflex function curve was reset in an upward and rightward manner during exercise in older subjects. However, due primarily to decreases in maximal gain and responding range, it appears that aging results in a reduced capacity to regulate HR via the baroreflex during exercise. Collectively, these findings suggest that the cardiac baroreflex function curve appropriately resets during exercise in older subjects but operates at a reduced maximal gain primarily because of age-related reductions in carotid-cardiac control manifest at rest.

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GRANTS

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