Published in final edited form as:

Exp Physiol. 2009 April ; 94(4): 447–458. doi:10.1113/expphysiol.2008.044867.

Spontaneous baroreflex measures are unable to detect age-related impairments in cardiac baroreflex function during dynamic exercise in humans

James P. Fisher^{1,5}, Shigehiko Ogoh⁶, Chelif Junor³, Azamuddin Khaja³, Mindy Northrup⁴, and Paul J. Fadel^{1,2,5}

¹ Department of Medical Pharmacology & Physiology, University of Missouri, Columbia, MO

² Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO

³ Department of Internal Medicine, University of Missouri, Columbia, MO

⁴ Department of Radiology, University of Missouri, Columbia, MO

⁵ Harry S. Truman Memorial Veterans Hospital, Department of Veterans Affairs Medical Center, Columbia, MO

⁶ Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, TX

Abstract

The dynamic relationship between “spontaneous” fluctuations in arterial blood pressure (BP) and heart rate (HR) is increasingly being used to provide an estimate of resting cardiac baroreflex sensitivity. Given the ease of use and clinical utility, spontaneous methods are now also being used to examine cardiac baroreflex sensitivity in distinct subject groups during various laboratory stressors and tasks encountered during daily life, such as physical activity. However, the utility of such spontaneous measures to estimate cardiac baroreflex function during exercise remains unclear, particularly when comparing groups. Therefore, we tested the ability of spontaneous indices to detect age-related differences in cardiac baroreflex function during dynamic exercise. Beat-to-beat HR and BP were measured in eighteen young (24 ± 1 yr) and sixteen older (59 ± 1 yr) healthy middle-aged subjects at rest and during steady-state leg cycling. Estimates of spontaneous cardiac baroreflex sensitivity using the sequence technique (G_{SEQ}) and low frequency transfer function gain (G_{TF}) were compared to the operating point (G_{OP}) and maximal gain (G_{MAX}) of the full carotid-cardiac baroreflex function curve. At rest G_{SEQ} , G_{TF} , G_{OP} and G_{MAX} were all significantly lower in older subjects. During moderate intensity steady-state exercise no differences were observed in G_{SEQ} and G_{TF} (0.26 ± 0.03 older vs. 0.32 ± 0.04 younger bpm/mmHg; $P > 0.05$), whereas G_{OP} and G_{MAX} (-0.21 ± 0.02 older vs. -0.39 ± 0.03 younger bpm/mmHg; $P < 0.05$) remained lower in older subjects. These data indicate that spontaneous measures of cardiac baroreflex sensitivity alone provide limited information when comparing age-groups during exercise making actual differences in baroreflex function difficult to identify.

Please send correspondence to: Paul J Fadel, Ph.D., Department of Medical Physiology and Pharmacology, One Hospital Drive, MA415 Medical Sciences Building, University of Missouri, Columbia, MO, 65212, USA. Tel: (573) 814-6000 ext. 53660, Fax: (573) 884 4276, fadelp@health.missouri.edu.
Present address for J. P. Fisher: School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

Keywords

arterial baroreflex; ageing; autonomic nervous system

INTRODUCTION

The dynamic relationship between “spontaneous” fluctuations in arterial blood pressure (BP) and heart rate (HR) is increasingly being used to provide an estimate of resting cardiac baroreflex sensitivity (Parati *et al.*, 2001; La Rovere *et al.*, 2008). This is primarily a result of the collection and analysis of spontaneous oscillations of BP and HR being noninvasive, cost effective and inherently straightforward (Parati *et al.*, 2000; Parati *et al.*, 2006; Taylor & Studinger, 2006). In addition, studies suggest that decreases in cardiac baroreflex sensitivity may be prognostic for increased risk of arrhythmias and cardiac mortality (Mortara *et al.*, 1997; La Rovere *et al.*, 1998; La Rovere *et al.*, 2001). Given this ease of use and clinical utility, spontaneous methods such as the sequence technique and transfer function analysis are now also being used in distinct subject groups to examine cardiac baroreflex sensitivity during various laboratory stressors and tasks encountered during daily life, including physical activity (Parati *et al.*, 2000; Carrington & White, 2002; Lucini *et al.*, 2004; Iellamo *et al.*, 2005; Dietrich *et al.*, 2006). However, the utility of such spontaneous measures to estimate cardiac baroreflex function during dynamic exercise remains unclear, particularly when comparing groups.

Importantly, spontaneous indices of cardiac baroreflex function estimate baroreflex sensitivity from beat-to-beat oscillations of BP which are centered around the prevailing HR and BP (i.e., operating point of the full baroreflex function curve) (Ogoh *et al.*, 2005). Under resting conditions, the operating point is typically located near the centering point of the baroreflex curve, which is the point of maximal baroreflex sensitivity (i.e., gain) (Potts *et al.*, 1993; Fadel *et al.*, 2003; Ogoh *et al.*, 2005; Raven *et al.*, 2006). However, during exercise the operating point for the baroreflex control of HR has been shown to move away from the centering point and towards the threshold of the reflex to a locus of reduced gain, even though maximal gain is well maintained (Potts *et al.*, 1993; Fadel *et al.*, 2003; Ogoh *et al.*, 2005; Raven *et al.*, 2006). Thus, due to the movement of the operating point during exercise, whether spontaneous estimates can accurately reflect baroreflex sensitivity during exercise and appropriately detect differences in cardiac baroreflex function remains unclear and requires careful examination.

Given this background, the purpose of the present study was to examine the utility of spontaneous measures of cardiac baroreflex sensitivity during dynamic exercise. Since previous studies have demonstrated a clear reduction in the arterial baroreflex control of HR in older individuals (Gribbin *et al.*, 1971; Ebert *et al.*, 1992; Parati *et al.*, 1995; Matsukawa *et al.*, 1996; Fisher *et al.*, 2007), we used aging as a model to determine if spontaneous cardiac baroreflex sensitivity indices can detect group differences in cardiac baroreflex function at rest and during exercise. First, to comprehensively examine spontaneous cardiac baroreflex sensitivity during dynamic exercise the sequence technique (G_{SEQ}) and low frequency transfer function gain (G_{TF}) between changes in BP and HR were estimated during low, moderate, and high intensity leg cycling and compared to rest in young and older healthy subjects. Second, to better understand the value of the spontaneous cardiac baroreflex sensitivity measures, G_{SEQ} and G_{TF} measurements were compared to the operating point gain and maximal gain of the full carotid-cardiac baroreflex function curve in young and older healthy subjects at rest and during moderate intensity steady-state cycling. We hypothesized that estimates of spontaneous cardiac baroreflex sensitivity would be unable to detect age-related differences in maximal cardiac baroreflex gain during

dynamic exercise and would be more closely related to the gain around the operating point of the cardiac baroreflex function curve.

METHODS

Subjects

Eighteen young (24 ± 1 yr; 12 men and 6 women) and sixteen older (59 ± 1 yr; 9 men and 7 women) healthy middle-aged subjects participated in the present study after providing written informed consent. 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 completed a medical health history questionnaire and underwent a physical exam by a physician investigator which included a 12-hour fasting blood chemistry screening. Both young and older subjects were moderately active and typically engaged in low (e.g., walking) and moderate (e.g., jogging, stationary bike) intensity aerobic activities (2–3 days/wk), but none were competitive athletes. No subject had a history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease. Subjects were not using prescribed or over the counter medications, apart from one older woman who was using hormone replacement therapy. There were no significant age-group differences in body mass index, triglycerides, or high-density lipoprotein, whereas total cholesterol, low-density lipoprotein (LDL), and glucose tended to be higher in the older subjects. However, values for the latter variables were within the normal range for healthy adults (Grundy *et al.*, 1999). Subjects were requested to abstain from caffeinated beverages for 12 hours and strenuous physical activity and alcohol for at least a day prior to any experimental sessions. All subjects were familiarized with the equipment and procedures before an actual experimental session.

Experimental Measurements

Heart rate (HR) was continuously monitored using a lead II electrocardiogram (ECG; model Q710, Quinton Instrument Co, Bothell, WA). Beat-to-beat arterial blood pressure (BP) was measured using photoplethysmography obtained from the left finger positioned on an adjustable bedside table in the midaxillary line at the level of the right atrium (Finometer, Finapres Medical Systems, Amsterdam, Netherlands). Before recordings were started diastolic BP of the Finometer was matched with measurements obtained from the brachial artery using an automated sphygmomanometer equipped with a microphone for the detection of Kortokoff sounds (Tango⁺, SunTech Medical Instruments, Raleigh, NC). In addition, brachial artery blood pressures were measured every minute throughout exercise. Importantly, this sphygmomanometer has previously been shown to provide accurate BP measurements during dynamic exercise (Cameron *et al.*, 2004). Ratings of perceived exertion (RPE) were obtained using the standard 6–20 Borg scale (Borg, 1982). The ECG signal and BP waveform were sampled at 1000Hz and beat-to-beat values of HR and BP were stored for off-line analysis (Powerlab, Chart v5.2, AD Instruments, Bella Vista, NSW, Australia).

Experimental Procedures

Incremental maximal exercise test—All subjects performed a continuous incremental exercise test to ascertain peak HR for the determination of steady-state exercise workloads. Subjects were seated in a semi-recumbent position on a medical exam table equipped with an electrically braked cycle ergometer (Angio V2, Lode, Groningen, Netherlands), while HR (12 lead ECG) and BP (automated sphygmomanometer) were measured. Following a 3 minute warm-up period of cycling at 60 revolutions per minute (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.

Protocol 1: “Spontaneous” cardiac baroreflex sensitivity during steady-state exercise—Twelve young (9 men) and eleven older (7 men) subjects performed three bouts of semi-recumbent cycling exercise at steady-state heart rates corresponding to 30, 50 and 70% of HR reserve (HRR), representing low, moderate, and high intensity exercise (Mazzeo *et al.*, 1998; Fletcher *et al.*, 2001). Subjects cycled at a pedal frequency of 60 rpm and the workload was gradually increased until the target HR was achieved (~3–5 min), after which 15 minutes of steady-state cycling was performed. During the last minute of each exercise bout subjects provided a rating of perceived exertion. The order of the low, moderate and high intensity trials was randomized and subjects were allowed to fully recover between exercise bouts (minimum of 30 min).

Data Analyses—For each exercise trial, five minute steady-state data segments were used for the calculation of average cardiovascular parameters, and spontaneous measures of cardiac baroreflex sensitivity via the sequence technique and transfer function analysis. All data segments were obtained after six minutes of cycling at the target workload to ensure steady-state conditions (Whipp, 1994). In addition, these same data segments were used to assess HR variability using time and frequency domain indices of parasympathetic control of HR, a key component of cardiac baroreflex sensitivity. To be comprehensive and allow for comparison with previous studies, spontaneous measures were calculated using both systolic (SBP) and mean (MBP) BP as well as HR and RR interval (Potts *et al.*, 1993; Ogoh *et al.*, 2003; Ogoh *et al.*, 2005). However, we are cognizant of the non-linear relationship between RR interval and HR and the potential concerns of using changes in RR interval when comparing conditions with different basal heart rates such as rest and exercise (O’Leary, 1996; Fadel *et al.*, 2001; Raven *et al.*, 2006). Measurements obtained during exercise were compared to those derived from five minute resting data segments collected after the subject had rested quietly for a minimum of fifteen minutes.

Sequence technique for cardiac baroreflex sensitivity—At rest and during each exercise bout the beat-to-beat time series of SBP or MBP and HR or RR interval were analyzed off-line using a customized computer algorithm (Spike 2, Cambridge Electronic Design, Cambridge, UK). Briefly, sequences of three or more consecutive beats where BP and HR change in the opposite direction or BP and RR interval change in the same direction were identified as arterial baroreflex sequences. A linear regression was applied to each individual sequence and only those sequences in which r^2 was >0.85 were accepted. The slopes of the SBP-HR (or RR interval) and MBP-HR (or RR interval) were calculated as measures of spontaneous cardiac baroreflex sensitivity (G_{SEQ}).

Transfer function analyses for cardiac baroreflex sensitivity—The transfer function gain (G_{TF}) between fluctuations in SBP and HR (or RR interval) as well as MBP and HR (or RR interval) were also calculated as a measure of spontaneous cardiac baroreflex sensitivity at rest and during exercise as described in detail previously (Saul *et al.*, 1991; Zhang *et al.*, 2002; Iwasaki *et al.*, 2004; Ogoh *et al.*, 2005). Briefly, transfer function analysis estimates baroreflex gain during the spontaneously occurring beat-to-beat oscillations of BP and therefore, reflects a measure of gain centered around the operating point of the baroreflex function curve. Beat-to-beat SBP, MBP, HR and RR interval were obtained by integrating analog signals within each cardiac cycle, and then linearly interpolated and re-sampled at 2 Hz for spectral analysis. The transfer function $H(f)$ between

SBP and HR or RR interval was computed from the cross spectrum between SBP and HR or RR interval variability and the autospectrum of SBP variability using the Welch method:

$$H(f) = S_{xy}(f) / S_{xx}(f), \quad (1)$$

where $S_{xx}(f)$ is the autospectrum for SBP variability and $S_{xy}(f)$ is the cross-spectrum between SBP and HR or RR interval variability. The real $H(f)$ and imaginary components $H_i(f)$ of the complex transfer function $H(f)$ were used to calculate the magnitude or gain $|H(f)|$ between the SBP and HR or RR interval signals as follows:

$$|H(f)| = [H_r(f)^2 + H_i(f)^2]^{1/2} \quad (2)$$

In order to determine the linear relation between the two signals, the squared coherence function (MSC(f)) was estimated as $MSC(f) = |S_{xy}(f)|^2 / (S_{xx}(f) S_{yy}(f))$, where $S_{yy}(f)$ is the autospectrum for HR or RR interval variability. Similar analyses were performed for MBP and HR or RR interval. Spectral power of SBP, MBP, HR, mean value of transfer function gain, phase and coherence function were calculated in the low frequency range (LF, 0.04–0.15 Hz) (Zhang *et al.*, 2002; Ogoh *et al.*, 2005). The BP fluctuations in the LF range are independent of the respiratory frequency and primarily reflect baroreflex mechanisms, whereas BP fluctuations in the high frequency range (HF, 0.15–0.4 Hz) can be influenced by changes in respiration and HR (Saul *et al.*, 1991; Zhang *et al.*, 2002; Iwasaki *et al.*, 2004). Furthermore, the very low frequency range (VLF, <0.04 Hz) of BP variability appears to reflect multiple physiological mechanisms that confound interpretation (Malliani *et al.*, 1991; Task Force, 1996). Thus, we used the LF range of each variable for the spectral analysis, to identify spontaneous cardiac baroreflex sensitivity at rest and during exercise.

Heart rate variability analyses—Time domain analysis of HR variability (HRV) was performed using the standard deviation of normal-to-normal R-R intervals (SDNN) and the square root of the mean of the sum of successive differences (RMSSD). These indices have been recommended for the estimation of overall variability (SDNN) and short-term high-frequency variability (RMSSD) of HR (Task Force, 1996). In addition, power spectral analysis, using Fast Fourier transformation, was performed to calculate HRV in the LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) ranges. LF and HF power are expressed in absolute units (ms^2) and normalized units (nLF and nHF, respectively) calculated as the relative power at a particular frequency in proportion to total power, minus the power at the very low frequency range (<0.04Hz). It is well accepted that HF power predominantly represents parasympathetic tone, while LF power reflects both parasympathetic and sympathetic activity (Malliani *et al.*, 1991; Task Force, 1996).

Protocol 2: Carotid baroreflex control of heart rate during steady-state exercise—In order to compare spontaneous measures of cardiac baroreflex sensitivity with full carotid-cardiac baroreflex function curves, thirteen young (7 men) and eleven older (6 men) subjects returned to the laboratory on a separate day for the application of neck pressure (NP) and neck suction (NS) at rest and during moderate intensity cycling (50% HRR), an exercise intensity commonly prescribed for developing and maintaining cardiorespiratory fitness (Mazzeo *et al.*, 1998; Fletcher *et al.*, 2001). All 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 prior to performing NP and NS. On the experimental day, after instrumentation for HR and BP 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 BP 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, -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 (Eckberg *et al.*, 1980). 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. 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 pre-stimulus values. Similar to protocol 1, the exercise bout began with a low workload (25–30Watts), which was then adjusted to elicit a target HR corresponding to 50% HRR, 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—Carotid-cardiac baroreflex responses were evaluated by plotting the peak and nadir changes in HR evoked by NP and NS, respectively against the estimated carotid sinus pressure (ECSP), which was calculated as MBP minus neck chamber pressure. Beat-to-beat changes in MBP measured by photoplethysmography were uniformly corrected to the absolute BP recorded via automated sphygmomanometry to provide accurate estimates of ECSP. The CBR stimulus-response data were fitted to the logistic model described by Kent *et al.* (Kent *et al.*, 1972). This function incorporates the following equation:

$$HR = A_1 \{1 + \exp[A_2(ECSP - A_3)]\}^{-1} + A_4 \quad (3)$$

where HR is the dependent variable, ECSP is the estimated carotid sinus pressure, A_1 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 equal pressor and depressor response (centering point), and A_4 is the minimum HR response. The data were fit to this model by non-linear 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-squared values of 0.981 ± 0.008 vs. 0.973 ± 0.007 , respectively at rest and 0.982 ± 0.003 vs. 0.982 ± 0.005 , respectively during exercise. The carotid-cardiac maximal gain and operating point gain were calculated using the following equations:

$$G_{MAX} = -A_1 A_2 / 4 \quad (4)$$

$$G_{OP} = -A_1 A_2 \exp[A_2(ECSP_{OP} - A_3)] / \{1 + \exp[A_2(ECSP_{OP} - A_3)]\}^2 \quad (5)$$

where G_{MAX} is the maximal gain of CBR function curve, G_{OP} is the gain of CBR function curve at the operating point and $ECSP_{OP}$ is the ECSP at the operating point (i.e., pre-

stimulus MBP). The G_{MAX} was calculated as the gain at the centering point and used as an index of overall carotid baroreflex responsiveness, whereas the G_{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 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 McDowall & Dampney (McDowall & Dampney, 2006): $THR = -2.944/A_2 + A_3$ and $SAT = 2.944/A_2 + A_3$. These calculations of THR and SAT are the carotid sinus pressure at which HR is within 5% of upper or lower plateau of the sigmoid function.

Statistical analysis

Statistical comparisons of physiological variables were made using a two-way repeated measures analyses of variance (ANOVA) test and a Student-Newman-Keuls test was employed *post hoc* to investigate main effects and interactions. Statistical significance was set at $P < 0.05$. Due to logistical reasons we were unable to collect data in three younger and two older subjects during the high intensity exercise trial of Protocol 1. Missing data were substituted with the mean of the respective group to retain statistical power (Donders *et al.*, 2006). Correlation coefficients relating cardiac-baroreflex gain measurements derived from the different methodologies were obtained using Spearman Correlation Analyses. Results are presented as means $\pm$ standard error (SEM). Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Cardiovascular responses to exercise

During dynamic leg cycling the MBP responses were greater in the older subjects during all exercise intensities with the greatest difference being observed during high intensity exercise (change from rest of $+33 \pm 2$ vs. $+16 \pm 2$ mmHg, in older and younger subjects, respectively, $P < 0.001$, Table 1). Similarly, SBP was increased during all exercise intensities and was significantly greater in the older subjects (Table 1). In young subjects DBP was not altered from rest during low and moderate dynamic exercise and tended to decrease during high intensity exercise (-5 ± 2 mmHg, $P = 0.055$, Table 1). In contrast, in older subjects DBP was significantly increased from rest during low, moderate and high intensity exercise ($+6 \pm 2$, $+8 \pm 2$, $+8 \pm 3$ mmHg, respectively, $P < 0.05$, Table 1). HR was significantly higher in younger subjects during all exercise intensities (Table 1). Ratings of perceived exertion were progressively increased during low, moderate and high intensity exercise with no significant difference between groups.

Spontaneous cardiac baroreflex sensitivity

The sequence technique—Figure 1A summarizes the spontaneous cardiac baroreflex sensitivity measures using the sequence technique (G_{SEQ}). Resting G_{SEQ} was significantly lower in the older subjects compared to the younger subjects. However, no age-group differences in G_{SEQ} were observed during low, moderate or high intensity exercise. This primarily reflected the greater reduction from rest to exercise in the younger subjects. The results were comparable with the use of HR or RR interval as the dependent variable with the major difference being a significant reduction during low, moderate and high intensity exercise in the older subjects with RR interval compared to HR. The percentage of cardiac cycles associated with baroreflex sequences was progressively and significantly reduced from rest ($24 \pm 3\%$) to low ($14 \pm 2\%$), moderate ($10 \pm 2\%$) and high ($8 \pm 2\%$) intensity exercise. Similar results were found when SBP or MBP was used as the independent variable.

Transfer function analysis—Similar to the sequence technique measures, resting cardiac baroreflex sensitivity assessed via low frequency transfer function gain (G_{TF}) was significantly lower in the older subjects compared to the younger subjects (Figure 1B). The coherence of the low frequency range was above 0.5 in all subjects under resting conditions (0.61 ± 0.02 , range 0.53 to 0.66 older vs. 0.63 ± 0.02 , range 0.51 to 0.74 younger; $P > 0.05$). Using HR as the dependent variable, G_{TF} was significantly reduced from rest in young subjects during all exercise bouts while older subjects only exhibited a significant decrease during high intensity exercise (Figure 1B). In comparison to young subjects the G_{TF} was lower in the older subjects during low intensity exercise, whereas there were no significant age-group differences during moderate and high intensity exercise. The use of RR interval as the dependent variable lead to significant decreases in G_{TF} from rest during all exercise bouts in older subjects and eliminated the age-group difference during low intensity exercise. As at rest, coherence remained above 0.5 in both groups during all exercise conditions (0.57 ± 0.01 , range 0.52 to 0.61 older vs. 0.58 ± 0.02 , range 0.54 to 0.66 younger; $P > 0.05$). Similar results were found when SBP or MBP was used as the independent variable.

Heart rate variability analysis—At rest RMSSD, SDNN, high (HF) and low (LF) frequency power were all significantly greater in the younger subjects (Table 2). Exercise produced decreases in RMSSD, SDNN, HF, and LF at the low, moderate and high exercise intensities that were much more robust in the young compared to the older subjects (Table 2). In contrast, normalized HF and LF power were unchanged from rest in older subjects at any intensity of exercise, while in the young subjects nHF was reduced and nLF increased during all exercise conditions.

Carotid-cardiac baroreflex function curves and parameters—Table 3 summarizes the logistic model parameters and derived variables describing carotid-cardiac baroreflex control in the young and older individuals who consented to the variable pressure neck collar procedure. The stimulus-response relationship for ECSP and HR at rest in the young and older subjects is shown in Figure 2. The response range (A_1), G_{MAX} and G_{OP} were all significantly lower in the older subjects at rest and these variables all remained lower in older subjects during exercise (Figure 3).

Overall comparison of cardiac baroreflex indices—Under resting conditions, an age-related decrease in cardiac baroreflex sensitivity was detected using either the spontaneous measurements (G_{SEQ} or G_{TF}) or the variable pressure neck collar technique (G_{OP} and G_{MAX} ; Figure 2). However, during moderate intensity exercise a pronounced age-group difference was only observed in G_{MAX} , while the spontaneous measures of baroreflex sensitivity were relatively similar between the young and older subjects (Figure 3). These exercise-induced changes were mainly due to robust reductions in G_{SEQ} and G_{TF} in the young subjects, associated with the movement of the operating point away from the centering point of the baroreflex function curve, and a subsequent decrease in G_{OP} (Figures 2 and 3). Indeed, the G_{SEQ} , G_{TF} and G_{OP} were all significantly reduced during exercise ($\Delta -78 \pm 7\%$, $\Delta -58 \pm 7\%$ and $\Delta -45 \pm 5\%$, respectively) in young subjects. In contrast, the G_{MAX} of young subjects remained relatively unchanged from rest to exercise (-0.42 ± 0.06 rest vs. -0.39 ± 0.03 exercise bpm/mmHg; $P < 0.05$). Thus, while spontaneous measures are related to the G_{OP} of the carotid cardiac baroreflex function curve at rest and during exercise (G_{OP} vs. G_{TF} $r = -0.57$, $P < 0.05$; G_{OP} vs. G_{SEQ} $r = 0.66$, $P < 0.05$), no such relationship exists between the spontaneous indices and G_{MAX} (G_{MAX} vs. G_{TF} $r = -0.09$, $P > 0.05$; G_{MAX} vs. G_{SEQ} $r = -0.002$, $P > 0.05$; Figure 4). Similar relationships were apparent in the older subjects however, the age-related reductions in all the measures of cardiac baroreflex sensitivity minimized the range of data for the correlation analyses.

DISCUSSION

To our knowledge this is the first study to examine the utility of spontaneous measures of cardiac baroreflex sensitivity to detect group differences in cardiac baroreflex function during steady-state dynamic exercise. The data demonstrate that although age-related decreases in cardiac baroreflex sensitivity can be detected with spontaneous indices under resting conditions, these measurements were unable to consistently identify the reduced cardiac baroreflex function present in older subjects during exercise. Furthermore, the data suggest that this is primarily a result of the spontaneous measures corresponding to the operating point gain (G_{OP}) of the full baroreflex function curve. Together, these findings indicate that a reliance purely on spontaneous indices of cardiac baroreflex sensitivity (i.e., G_{SEQ} or G_{TF}) would lead to the erroneous conclusion that aging does not result in significant impairments in cardiac baroreflex sensitivity during exercise, while in fact the maximal gain (G_{MAX}) as well as the G_{OP} of the carotid-cardiac baroreflex function curve was significantly attenuated in older individuals. Thus, when comparing subject groups during exercise spontaneous measures of cardiac baroreflex sensitivity alone provide limited information making actual differences in baroreflex function difficult to identify.

In the present study, we employed two commonly used measures of cardiac baroreflex sensitivity (i.e., the sequence technique and transfer function gain) in young and older subjects and compared these measures to the operating point and maximal gains of the full carotid-cardiac baroreflex function curve. The data highlight the importance of using caution when interpreting spontaneous baroreflex measures during exercise. This appears to be the result of these measures closely reflecting the gain at the operating point of the full baroreflex function curve which moves towards the threshold of the reflex during exercise to a location of lesser gain, which has been associated with reductions in parasympathetic tone (Potts *et al.*, 1993; Fadel *et al.*, 2003; Ogoh *et al.*, 2005; Raven *et al.*, 2006). In this regard, the G_{SEQ} , G_{TF} , and G_{OP} were all significantly lower at rest in older subjects along with the G_{MAX} of the carotid baroreflex function curve. However, during exercise the G_{SEQ} and G_{TF} measures, similar to the G_{OP} of the CBR, were reduced in young subjects leading to similarities in the G_{SEQ} and G_{TF} between young and older subjects during exercise. In contrast, the G_{MAX} did not change from rest to exercise in either group and therefore, remained diminished in older subjects during exercise. As such, if our conclusions were based solely on the baroreflex gains derived from the sequence technique and transfer function analysis, we would have reported that the younger and older subjects have similar cardiac baroreflex control during exercise. However; this clearly was not the case because of the profound reduction in maximal gain found in the older subjects both at rest and during exercise.

The reason the spontaneous measures were only slightly reduced in the older subjects but significantly and robustly decreased in the younger subjects from rest to exercise is unclear but likely has to do with differences in resting parasympathetic tone which are eliminated with exercise (Table 2). In this regard, there is some discussion on whether spontaneous baroreflex measures provide information beyond that provided by HR variability derived parasympathetic measurements alone (Diaz & Taylor, 2006; Taylor & Studinger, 2006). Clearly vagal activity is critical for the baroreflex control of HR however; the extent to which other mechanisms both mechanical and neural contribute to spontaneous cardiac baroreflex sensitivity measures at rest and during exercise is unclear and requires further studies (Chapleau *et al.*, 1995; Brodde *et al.*, 1998; Hunt *et al.*, 2001; Monahan *et al.*, 2001).

Overall, there is considerable debate on the utility of spontaneous baroreflex measures with some studies demonstrating correlations with traditional measures of cardiac baroreflex function (i.e., vasoactive drug infusion) (Robbe *et al.*, 1987; Parlow *et al.*, 1995), while

others have reported weak relationships (Pitzalis *et al.*, 1998; Colombo *et al.*, 1999; Lipman *et al.*, 2003). Of note, these studies were all performed under resting conditions. In the current study, we combined the spontaneous gain measurements with the full carotid-cardiac baroreflex function curve to better understand the usefulness of spontaneous indices to investigate cardiac baroreflex function during exercise. We found that although spontaneous measures are related to the operating point gain of the carotid cardiac baroreflex function curve at rest and during exercise, no such relationship exists between the spontaneous indices and maximal gain. Overall our findings indicate that care should be taken when spontaneous gain measurements are used as a primary measure of cardiac baroreflex function during exercise. While these measurements are noninvasive, cost effective, inherently straightforward and may have value during isometric or dynamic exercise of a small muscle mass (Iellamo *et al.*, 1997; Iellamo, 2001; Carrington & White, 2002), the current results demonstrate that during large muscle dynamic exercise (i.e., two-legged cycling) further measures that drive the baroreflex system and attempt to “open” the closed loop system by evoking clear baroreflex-mediated responses and derive a measure of maximal gain are needed, particularly when comparing subject groups. Furthermore, although the use of spontaneous measures has been advocated for low intensity exercise (Rimoldi *et al.*, 1992; Iellamo, 2001; Lucini *et al.*, 2004), our results suggest that even at low intensities consistent results are lacking as G_{TF} was lower in older subjects whereas there were no age-group differences in G_{SEQ} .

Previous studies have identified a clear reduction in the arterial baroreflex control of HR in healthy older individuals under resting conditions (Gribbin *et al.*, 1971; Ebert *et al.*, 1992; Parati *et al.*, 1995; Matsukawa *et al.*, 1996). More recently, our laboratory extended these findings to include dynamic exercise in which we demonstrated an ~50% reduction in maximal carotid-cardiac baroreflex gain in older compared to younger subjects during leg cycling (Fisher *et al.*, 2007). However, in that study operating point gains of the CBR during exercise were similar in young and older subjects, whereas in the current study the G_{OP} remained significantly reduced in the older subjects during exercise. While the reason for this discrepancy between our studies is unclear, it likely has to do with the greater operating point gains for some of the young subjects in the current study as can be seen in Figure 4. Nevertheless, our results indicate that there is a clear reduction in cardiac baroreflex function in older subjects during dynamic exercise that cannot be detected with spontaneous indices of cardiac baroreflex sensitivity. We suggest that these findings may be applicable to comparisons of other groups during exercise (such as diabetic, hypertensive and chronic heart failure patients) and care should be taken when interpreting results based on spontaneous measures of cardiac baroreflex sensitivity alone. This may be a particular concern in patient groups with known reductions in resting parasympathetic tone (Pagani *et al.*, 1988; Malliani *et al.*, 1991; 1996).

An important methodological issue that needs to be considered when comparing cardiac baroreflex function between rest and exercise is the use of HR vs. R-R interval, as previously discussed in detail (O’Leary, 1996; Fadel *et al.*, 2003; Raven *et al.*, 2006). Briefly, due to the non-linear relationship between HR and RR interval, the use of changes in RR interval will bias the interpretation when HR is significantly elevated such as during exercise. While the use of RR interval is justified when examining changes in vagal control of the heart (Parker *et al.*, 1984), studies have suggested that HR appears to be more appropriate when investigating baroreflex control mechanisms since HR provides important information regarding baroreflex-mediated changes in cardiac output (Ogoh *et al.*, 2002; Ogoh *et al.*, 2003). Nevertheless, in the present study we used both HR and RR interval in our analyses to be more comprehensive. For the most part the major difference was the greater reduction in cardiac baroreflex sensitivity from rest to exercise when RR interval

was used compared to HR. However, this effect was similar in both young and older subjects and therefore, did not effect interpretation of the age-group results.

In summary, the findings of the present study indicate that the sole use of spontaneous indices of cardiac baroreflex sensitivity (i.e., G_{SEQ} or G_{TF}) to detect age-group differences would lead to the erroneous conclusion that aging does not result in significant impairments in cardiac baroreflex sensitivity during exercise, while in fact the maximal gain of the carotid-cardiac baroreflex function curve was significantly attenuated in older individuals. Thus, when comparing subject or patient groups during exercise spontaneous measures of cardiac baroreflex sensitivity alone provide limited information making actual differences in baroreflex function difficult to identify.

Acknowledgments

The authors appreciate the time and effort expended by all the volunteer subjects. We thank Dr. David McIntyre, School of Sport and Exercise Sciences, University of Birmingham, UK, for writing the Spike 2 script files. This research is the result of work supported with resources and the use of facilities at the Harry S. Truman Memorial Veterans Hospital in Columbia, MO and by NIH Grant # HL-093167 to PJF, and by an American Heart Association Postdoctoral Fellowship Award to PJF.

References

- Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* 1982; 14:377–381. [PubMed: 7154893]
- Brodde OE, Kanschak U, Becker K, Ruter F, Poller U, Jakubetz J, Radke J, Zerkowski HR. Cardiac muscarinic receptors decrease with age. In vitro and in vivo studies. *J Clin Invest.* 1998; 101:471–478. [PubMed: 9435320]
- Cameron JD, Stevenson I, Reed E, McGrath BP, Dart AM, Kingwell BA. Accuracy of automated auscultatory blood pressure measurement during supine exercise and treadmill stress electrocardiogram-testing. *Blood Press Monit.* 2004; 9:269–275. [PubMed: 15472500]
- Carrington CA, White MJ. Spontaneous baroreflex sensitivity in young and older people during voluntary and electrically evoked isometric exercise. *Age Ageing.* 2002; 31:359–364. [PubMed: 12242198]
- Chapleau MW, Cunningham JT, Sullivan MJ, Wachtel RE, Abboud FM. Structural versus functional modulation of the arterial baroreflex. *Hypertension.* 1995; 26:341–347. [PubMed: 7543454]
- Colombo R, Mazzuero G, Spinatonda G, Lanfranchi P, Giannuzzi P, Ponikowski P, Coats AJ, Minuco G. Comparison between spectral analysis and the phenylephrine method for the assessment of baroreflex sensitivity in chronic heart failure. *Clin Sci (Lond).* 1999; 97:503–513. [PubMed: 10491351]
- Diaz T, Taylor JA. Probing the arterial baroreflex: is there a ‘spontaneous’ baroreflex? *Clin Auton Res.* 2006; 16:256–261. [PubMed: 16732466]
- Dietrich A, Riese H, van Roon AM, van Engelen K, Ormel J, Neeleman J, Rosmalen JG. Spontaneous baroreflex sensitivity in (pre)adolescents. *J Hypertens.* 2006; 24:345–352. [PubMed: 16508583]
- Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol.* 2006; 59:1087–1091. [PubMed: 16980149]
- Ebert TJ, Morgan BJ, Barney JA, Denahan T, Smith JJ. Effects of aging on baroreflex regulation of sympathetic activity in humans. *Am J Physiol.* 1992; 263:H798–803. [PubMed: 1415605]
- Eckberg DL, Kifle YT, Roberts VL. Phase relationship between normal human respiration and baroreflex responsiveness. *J Physiol.* 1980; 304:489–502. [PubMed: 7441548]
- Fadel PJ, Ogoh S, Keller DM, Raven PB. Recent insights into carotid baroreflex function in humans using the variable pressure neck chamber. *Exp Physiol.* 2003; 88:671–680. [PubMed: 14603365]
- Fadel PJ, Ogoh S, Watenpaugh DE, Wasmund W, Olivencia-Yurvati A, Smith ML, Raven PB. Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol.* 2001; 280:H1383–1390. [PubMed: 11179088]

- 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*. 2007; 293:H777–783. [PubMed: 17449546]
- Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Pina IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001; 104:1694–1740. [PubMed: 11581152]
- Gribbin B, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res*. 1971; 29:424–431. [PubMed: 5110922]
- Grundey SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999; 100:1134–1146. [PubMed: 10477542]
- Hunt BE, Farquhar WB, Taylor JA. Does reduced vascular stiffening fully explain preserved cardiovagal baroreflex function in older, physically active men? *Circulation*. 2001; 103:2424–2427. [PubMed: 11369680]
- Iellamo F. Neural mechanisms of cardiovascular regulation during exercise. *Auton Neurosci*. 2001; 90:66–75. [PubMed: 11485294]
- Iellamo F, Galante A, Legramante JM, Lippi ME, Condoluci C, Albertini G, Volterrani M. Altered autonomic cardiac regulation in individuals with Down syndrome. *Am J Physiol Heart Circ Physiol*. 2005; 289:H2387–2391. [PubMed: 16024564]
- Iellamo F, Legramante JM, Raimondi G, Peruzzi G. Baroreflex control of sinus node during dynamic exercise in humans: effects of central command and muscle reflexes. *Am J Physiol*. 1997; 272:H1157–1164. [PubMed: 9087588]
- Iwasaki K, Zhang R, Perhonen MA, Zuckerman JH, Levine BD. Reduced baroreflex control of heart period after bed rest is normalized by acute plasma volume restoration. *Am J Physiol Regul Integr Comp Physiol*. 2004; 287:R1256–1262. [PubMed: 15242830]
- Kent BB, Drane JW, Blumenstein B, Manning JW. A mathematical model to assess changes in the baroreceptor reflex. *Cardiology*. 1972; 57:295–310. [PubMed: 4651782]
- La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet*. 1998; 351:478–484. [PubMed: 9482439]
- La Rovere MT, Pinna GD, Hohnloser SH, Marcus FI, Mortara A, Nohara R, Bigger JT Jr, Camm AJ, Schwartz PJ. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation*. 2001; 103:2072–2077. [PubMed: 11319197]
- La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. *Ann Noninvasive Electrocardiol*. 2008; 13:191–207. [PubMed: 18426445]
- Lipman RD, Salisbury JK, Taylor JA. Spontaneous indices are inconsistent with arterial baroreflex gain. *Hypertension*. 2003; 42:481–487. [PubMed: 12975383]
- Lucini D, Cerchiello M, Pagani M. Selective reductions of cardiac autonomic responses to light bicycle exercise with aging in healthy humans. *Auton Neurosci*. 2004; 110:55–63. [PubMed: 14766326]
- Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation*. 1991; 84:482–492. [PubMed: 1860193]
- Matsukawa T, Sugiyama Y, Mano T. Age-related changes in baroreflex control of heart rate and sympathetic nerve activity in healthy humans. *J Auton Nerv Syst*. 1996; 60:209–212. [PubMed: 8912273]
- Mazzeo R, Cavanagh P, Evans WJ, Fiatarone M, Hagberg J, McAuley E, Startzell J. American College of Sports Medicine Position Stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc*. 1998; 30:992–1008. [PubMed: 9624662]
- McDowall LM, Dampney RA. Calculation of threshold and saturation points of sigmoidal baroreflex function curves. *Am J Physiol Heart Circ Physiol*. 2006; 291:H2003–2007. [PubMed: 16714364]

- Monahan KD, Dinunno FA, Seals DR, Clevenger CM, Desouza CA, Tanaka H. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. *Am J Physiol Heart Circ Physiol*. 2001; 281:H284–289. [PubMed: 11406495]
- Mortara A, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O, Pozzoli M, Opasich C, Tavazzi L. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation*. 1997; 96:3450–3458. [PubMed: 9396441]
- O’Leary DS. Heart rate control during exercise by baroreceptors and skeletal muscle afferents. *Med Sci Sports Exerc*. 1996; 28:210–217. [PubMed: 8775156]
- Ogoh S, Fadel PJ, Monteiro F, Wasmund WL, Raven PB. Haemodynamic changes during neck pressure and suction in seated and supine positions. *J Physiol*. 2002; 540:707–716. [PubMed: 11956357]
- Ogoh S, Fadel PJ, Nissen P, Jans O, Selmer C, Secher NH, Raven PB. Baroreflex-mediated changes in cardiac output and vascular conductance in response to alterations in carotid sinus pressure during exercise in humans. *J Physiol*. 2003; 550:317–324. [PubMed: 12730341]
- Ogoh S, Fisher JP, Dawson EA, White MJ, Secher NH, Raven PB. Autonomic nervous system influence on arterial baroreflex control of heart rate during exercise in humans. *J Physiol*. 2005; 566:599–611. [PubMed: 15890708]
- Pagani M, Malfatto G, Pierini S, Casati R, Masu AM, Poli M, Guzzetti S, Lombardi F, Cerutti S, Malliani A. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. *J Auton Nerv Syst*. 1988; 23:143–153. [PubMed: 3049759]
- Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens*. 2000; 18:7–19. [PubMed: 10678538]
- Parati G, Di Rienzo M, Mancia G. Dynamic modulation of baroreflex sensitivity in health and disease. *Ann N Y Acad Sci*. 2001; 940:469–487. [PubMed: 11458702]
- Parati G, Frattola A, Di Rienzo M, Castiglioni P, Pedotti A, Mancia G. Effects of aging on 24-h dynamic baroreceptor control of heart rate in ambulant subjects. *Am J Physiol*. 1995; 268:H1606–1612. [PubMed: 7733361]
- Parati G, Mancia G, Di Rienzo M, Castiglioni P. Point: cardiovascular variability is/is not an index of autonomic control of circulation. *J Appl Physiol*. 2006; 101:676–678. discussion 681–672. [PubMed: 16645191]
- Parker P, Celler BG, Potter EK, McCloskey DI. Vagal stimulation and cardiac slowing. *J Auton Nerv Syst*. 1984; 11:226–231. [PubMed: 6491162]
- Parlow J, Viale JP, Annat G, Hughson R, Quintin L. Spontaneous cardiac baroreflex in humans. Comparison with drug-induced responses. *Hypertension*. 1995; 25:1058–1068. [PubMed: 7737717]
- Pitzalis MV, Mastropasqua F, Passantino A, Massari F, Ligurgo L, Forleo C, Balducci C, Lombardi F, Rizzon P. Comparison between noninvasive indices of baroreceptor sensitivity and the phenylephrine method in post-myocardial infarction patients. *Circulation*. 1998; 97:1362–1367. [PubMed: 9577947]
- Potts JT, Shi XR, Raven PB. Carotid baroreflex responsiveness during dynamic exercise in humans. *Am J Physiol*. 1993; 265:H1928–1938. [PubMed: 8285231]
- Raven PB, Fadel PJ, Ogoh S. Arterial baroreflex resetting during exercise: a current perspective. *Exp Physiol*. 2006; 91:37–49. [PubMed: 16210446]
- Rimoldi O, Furlan R, Pagani MR, Piazza S, Guazzi M, Pagani M, Malliani A. Analysis of neural mechanisms accompanying different intensities of dynamic exercise. *Chest*. 1992; 101:226S–230S. [PubMed: 1576840]
- Robbe HW, Mulder LJ, Ruddel H, Langewitz WA, Veldman JB, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension*. 1987; 10:538–543. [PubMed: 3666866]
- Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. *Am J Physiol*. 1991; 261:H1231–1245. [PubMed: 1928405]

- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*. 1996; 93:1043–1065. [PubMed: 8598068]
- Taylor JA, Studinger P. Counterpoint: cardiovascular variability is not an index of autonomic control of the circulation. *J Appl Physiol*. 2006; 101:678–681. discussion 681. [PubMed: 16892500]
- Whipp BJ. The slow component of O₂ uptake kinetics during heavy exercise. *Med Sci Sports Exerc*. 1994; 26:1319–1326. [PubMed: 7741865]
- Zhang R, Iwasaki K, Zuckerman JH, Behbehani K, Crandall CG, Levine BD. Mechanism of blood pressure and R-R variability: insights from ganglion blockade in humans. *J Physiol*. 2002; 543:337–348. [PubMed: 12181304]

Figure 1.

Summary data showing indices of cardiac baroreflex sensitivity obtained from analysis of spontaneous fluctuations in systolic blood pressure (SBP) and heart rate (HR), or SBP and RR interval (RRI) using the sequence technique (panel A; G_{SEQ}) and low frequency transfer function gain (panel B; G_{TF}) for younger and older subjects at rest and during low, moderate and high intensity cycling. * represents $P < 0.05$ vs. rest, † represents $P < 0.05$ vs. young, \$ represents $P = 0.05$ vs. rest.

Figure 2.

Modeled carotid-cardiac baroreflex function curves (panel A) and measures of cardiac baroreflex sensitivity (panels B–E) in younger and older subjects at rest. In panel A the lines and symbols denote actual group data for all subjects. Filled symbols represent young subjects and open symbols denote older subjects. Squares indicate the centering points, triangles indicate the operating points, circles indicate the carotid sinus pressure thresholds, and upside-down triangles represent the carotid sinus pressure saturations. Panel B represents the sequence analysis measure of cardiac baroreflex sensitivity (G_{SEQ}); panel C represents the low frequency transfer function analysis measure of cardiac baroreflex sensitivity (G_{TF}); panel D represents the operating point gain of the carotid-cardiac baroreflex function curve (G_{OP}); and panel E represents the maximal gain of the carotid-cardiac baroreflex function curve (G_{MAX}). † represents $P < 0.05$ vs. young.

Figure 3. Modeled carotid-cardiac baroreflex function curves (panel A) and measures of cardiac baroreflex sensitivity (panels B–E) in younger and older subjects during moderate intensity exercise. Abbreviations and symbols are identical to Figure 3. † represents $P < 0.05$ vs. young.

Figure 4.

Relationship between the sequence technique gain (G_{SEQ}) and the operating point gain (G_{OP} ; panel A) or the maximal gain (G_{MAX} ; panel B) of the modeled carotid-cardiac baroreflex function curve at rest and during exercise in young and older subjects. Filled symbols denote individual data for young subjects, and open symbols represent individual data for older subjects.

Table 1

Selected cardiovascular parameters at rest and during low, moderate and high intensity cycling in younger and older subjects.

	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)	Pulse Pressure (mmHg)	Heart Rate (bpm)
Rest					
Young	122 ± 2	70 ± 2	87 ± 2	53 ± 3	64 ± 3
Older	119 ± 2	77 ± 2 [†]	91 ± 2	42 ± 2	59 ± 2
Low Ex					
Young	138 ± 3 [*]	71 ± 3	94 ± 3 [*]	67 ± 3	95 ± 1 [*]
Older	151 ± 3 ^{*†}	83 ± 3 ^{*†}	106 ± 2 ^{*†}	68 ± 5	88 ± 2 ^{*†}
Moderate Ex					
Young	162 ± 4 [*]	68 ± 3	99 ± 2 [*]	94 ± 5	123 ± 2 [*]
Older	183 ± 4 ^{*†}	86 ± 3 ^{*†}	118 ± 2 ^{*†}	98 ± 5	109 ± 2 ^{*†}
High Ex					
Young	181 ± 5 [*]	65 ± 3	104 ± 3 [*]	116 ± 7	152 ± 2 [*]
Older	201 ± 4 ^{*†}	84 ± 4 ^{*†}	123 ± 3 ^{*†}	117 ± 6	130 ± 2 ^{*†}
P value					
Group	0.003	<0.001	<0.001	0.796	<0.001
Condition	<0.001	0.082	<0.001	<0.001	<0.001
Interaction	<0.001	0.002	<0.001	0.074	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; Ex, exercise. *P* values indicate ANOVA results. Values are means ± SEM.

^{*} represents *P* < 0.05 vs. rest;

[†] represents *P* < 0.05 vs. young.

Table 2

Time and frequency domain measures of heart rate variability at rest and during low, moderate and high intensity cycling in younger and older subjects.

	RMSSD (ms)	SDNN (ms)	HF PSD (ms ²)	LF PSD (ms ²)
Rest				
Young	67 ± 12	70 ± 8	1327 ± 466	1821 ± 444
Older	25 ± 3 [†]	41 ± 4 [†]	133 ± 25 [†]	508 ± 117 [†]
Low Ex				
Young	11 ± 1 [*]	19 ± 1 [*]	26 ± 5 [*]	95 ± 20 [*]
Older	12 ± 3 [*]	16 ± 1 [*]	31 ± 13	69 ± 8
Moderate Ex				
Young	4 ± 1 [*]	10 ± 1 [*]	3 ± 1 [*]	24 ± 4 [*]
Older	5 ± 0.3 [*]	11 ± 1 [*]	3 ± 1	15 ± 5
High Ex				
Young	2.2 ± 0.2 [*]	6 ± 1 [*]	0.3 ± 0.04 [*]	4 ± 1 [*]
Older	3.0 ± 0.2 [*]	7 ± 1 [*]	1.1 ± 0.5	3 ± 1
P value				
Group	0.033	0.015	0.020	0.011
Condition	<0.001	<0.001	<0.001	<0.001
Interaction	0.006	<0.001	0.002	<0.001

RMSSD, square root of the mean successive differences; SDNN, standard deviation of normal to normal R-R intervals; HF PSD, high frequency (0.15–0.4Hz) power spectral density expressed in absolute units; LF PSD, low frequency (0.04–0.15Hz) power spectral density expressed in absolute units; Ex, exercise. *P* values indicate ANOVA results. Values are means ± SEM.

* represents *P* < 0.05 vs. rest.

[†] represents *P* < 0.05 vs. young.

Table 3

Logistic model parameters and derived variables describing carotid baroreflex control of HR at rest and during moderate intensity cycling in younger and older subjects.

	A1 (bpm)	A2	A3 (mmHg)	A4 (bpm)	Threshold (mmHg)	Saturation (mmHg)	HR _{OP} (bpm)	ECSP _{OP} (mmHg)
Rest								
Young	16 ± 1	0.11 ± 0.01	89 ± 3	52 ± 2	57 ± 3	120 ± 5	62 ± 2	83 ± 1
Older	7 ± 1	0.10 ± 0.01	99 ± 4	54 ± 2	65 ± 6	133 ± 7	60 ± 3	89 ± 3
Exercise								
Young	16 ± 3	0.13 ± 0.02	113 ± 1	112 ± 3 [*]	80 ± 6	147 ± 7	126 ± 2 [*]	94 ± 2 [*]
Older	9 ± 1	0.12 ± 0.02	128 ± 2	102 ± 4 [†]	95 ± 7	161 ± 7	109 ± 3 [†]	110 ± 3 [†]
P value								
Group	<0.001	0.631	0.002	0.248	0.044	0.070	0.005	<0.001
Condition	0.577	0.306	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Interaction	0.748	0.835	0.398	0.006	0.509	0.966	<0.001	0.016

A1, response range; A2, gain coefficient; A3, centering point; A4, minimum response; HR_{OP}, heart rate at the operating point which is the pre-stimulus heart rate; ECSP_{OP}, estimated carotid sinus pressure at the operating point which is the pre-stimulus mean blood pressure; Ex, exercise. *P* values indicate ANOVA results. Values are means ± SEM.

^{*} represents *P* < 0.05 vs. rest.

[†] represents *P* < 0.05 vs. young.