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Dose-response relationship of endurance training for autonomic circulatory control in healthy seniors

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Okazaki, Kazunobu, Ken-ichi Iwasaki, Anand Prasad, M. Dean Palmer, Emily R. Martini, Qi Fu, Armin Arbab-Zadeh, Rong Zhang, and Benjamin D. Levine. Dose-response relationship of endurance training for autonomic circulatory control in healthy seniors. *J Appl Physiol* 99: 1041–1049, 2005. First published May 12, 2005; doi:10.1152/japplphysiol.00085.2005.—Aging results in marked abnormalities of cardiovascular regulation. Regular exercise can improve many of these age-related abnormalities. However, it remains unclear how much exercise is optimal to achieve this improvement or whether the elderly can ever improve autonomic control by exercise training to a degree similar to that observed in healthy young individuals. Ten healthy sedentary seniors [71 ± 3 (SD) yr] trained for 12 mo; training involved progressive increases in volume and intensity. Static hemodynamics were measured, and R-wave-R-wave interval (RRI), beat-to-beat blood pressure (BP) variability, and transfer function gain between systolic BP and RRI were calculated at baseline and every 3 mo during training. Data were compared with those obtained in 12 Masters athletes (68 ± 3 yr) and 11 healthy sedentary young individuals (29 ± 6 yr) at baseline. Additionally, the adaptation of these variables after completion of identical training loads was compared between the seniors and the young. Indexes of RRI variability and baroreflex gain were decreased in the sedentary seniors but preserved in the Masters athletes compared with the young at baseline. With training in the seniors, baroreflex gain and resting BP showed a peak adaptation after moderate doses of training following 3–6 mo. Indexes of RRI variability continued to improve with increasing doses of training and increased to the same magnitude as the young at baseline after heavy doses of training for 12 mo; however, baroreflex gain never achieved values equivalent to the young at baseline, even after a year of training. The magnitude of the adaptation of these variables to identical training loads was similar (no interaction effects of age × training) between the seniors and the young. Thus RRI variability in seniors improves with increasing "dose" of exercise over 1 yr of training. In contrast, more moderate doses of training for 3–6 mo may optimally improve baroreflex sensitivity, associated with a modest hypotensive effect; however, higher doses of training do not lead to greater enhancement of these changes. Seniors retain a similar degree of "trainability" as young subjects for cardiac autonomic function to dynamic exercise.

aging; autonomic nervous system; blood pressure

THE MORBIDITY AND MORTALITY of cardiovascular disease increase steeply with advancing age (24). The potential mechanisms for the age-related increase in cardiovascular risk may include increased blood pressure (BP) (24, 34) and impaired autonomic control of the circulation with aging (7, 10, 11, 27, 32, 41). There is substantial evidence that elevated BP and impaired cardiac autonomic function, which is manifest by decreased heart rate (HR) variability (HRV) and arterial baroreflex sensitivity, are associated with this increasing cardiovascular risk (17, 24, 34) and are independent predictors of cardiac events and overall mortality in clinically disease-free individuals (15, 48).

Regular physical activity, on the other hand, is known to prevent or even improve the age-related abnormalities of BP (18, 34) and cardiac autonomic function (27, 33, 38, 39, 43) and, thereby, may ameliorate the increasing cardiovascular risk with aging (8, 11, 20). However, the optimal "dose" of exercise required to achieve maximal improvement in these variables is unclear. Recently, our laboratory reported in healthy young subjects that the peak improvement in indexes of cardiovascular variability, along with a modest hypotensive effect due to systemic vasodilation, were observed after moderate doses of training achieved in 3–6 mo, but more intense and prolonged training over 9–12 mo did not lead to greater enhancement of these changes (22). We hypothesized that sedentary senior individuals who begin with depressed HRV and baroreflex sensitivity may have an even greater degree of "trainability" as young individuals for the cardiovascular adaptation to exercise. To test this hypothesis, we quantified the dose-response relationship between exercise duration/intensity and the adaptation of BP and cardiac autonomic function in healthy but initially sedentary seniors. Data were compared with those obtained in healthy sedentary young individuals and Masters athletes who had trained for decades to determine whether and how much exercise training is required to restore the age-related abnormalities. In addition, the adaptation of these variables in sedentary seniors was compared with young subjects after completion of identical training loads.

METHODS

Subjects population. Ten healthy but initially sedentary senior subjects older than 65 yr of age (4 women, 6 men; age, 71 ± 3 yr; mean ± SD; all Caucasian), and 12 age-matched Masters athletes (6 women, 6 men; age, 68 ± 3 yr; all Caucasian) were recruited. Sedentary participants were excluded if they were exercising for >30 min, three times per week. Masters athletes were recruited as previously reported (3). They had participated in regular endurance competitions for 23 ± 8 yr, with a weekly running mileage of 32 ± 10 miles or equivalent swimming or cycling. In addition, 11 healthy sedentary young subjects (5 women, 6 men; age, 29 ± 6 yr; all Caucasian), who were reported previously from our laboratory with regard to cardiovascular adaptation to 1-yr endurance training (22),

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according to the same standards and criteria, were used for comparison. All subjects were carefully screened for comorbidities, including systemic hypertension, obstructive coronary artery disease, or structural heart disease by use of 24-h BP recordings, resting and exercise ECG, and echocardiograms. Exclusion criteria included mean daytime BP >140/90 mmHg, ECG changes suggestive of ischemic heart disease, left bundle branch block, atrial flutter/fibrillation, atrioventricular block greater than first degree, depressed systolic function, baseline or exercise-induced wall motion abnormalities, valvular heart disease other than mild valvular insufficiency, right or left ventricular hypertrophy by ECG or echocardiograms, untreated thyroid disorders, chronic lung disease, regular cigarette smoking within the previous 10 yr, body mass index >30 kg/m^2, cardiovascular medications, and anticoagulation with warfarin. All subjects signed an informed consent form for this study, which was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

Exercise training. The sedentary seniors and the young controls exercised in accordance with a training program prescribed individually for each subject with the goal of increasing duration and intensity over 1 yr. Each quarter (Q) was periodized with gradually increasing stress. Workouts were varied with respect to mode (walk, run, cycle, swim), duration, and intensity to optimize the training response. Table 1 is a template of workouts prescribed over the 1-yr training program for the sedentary seniors. A template of workouts for the young controls was reported previously (22). Because the sedentary seniors had a lower exercise capacity than the young controls at baseline, the workouts prescribed in each month for the sedentary seniors were lower in intensity and less in duration than those for the young controls, to reduce the risk of injury. The training programs for Q2 and Q4 in the sedentary seniors were designed to be identical to those for Q1 and Q2 in the young controls, respectively. On the basis of the HR measured at maximal steady state (MSS) estimated from ventilatory threshold and the maximal HR (HR_{max}) during a maximal exercise test performed before and every 3 mo of training (see *Maximal exercise test* section), five training zones (recovery, base pace, MSS, race pace, and intervals) were determined. The target HR for the MSS was set at ±5 beats/min of the HR at MSS, which was generally equivalent to ~85–90% of HR_{max}. The target HR for the base pace was set within 20 beats/min below the lower limit of the MSS range, which was equivalent to ~75–85% of HR_{max}. The target HR for the intervals was set within 5–10 beats/min below the HR_{max}. The target HR for the race pace was set as the difference between the MSS and the interval range. The majority of training sessions, particularly during the early phase of the program, were prescribed as "base pace." Initially, the sedentary seniors performed at the base pace, 3 times/wk for 25 min/session, by walking. As the subjects became fitter, the duration of the base pace sessions was gradually prolonged, including the addition of one "long-distance" session per week. Subsequently, high-intensity sessions, including "MSS" and "intervals," were added gradually and were always followed by a "recovery" session. Each subject also performed 10 min of light exercise and some stretching exercise before and after the main workout as a warm-up and a cool-down. All of the training sessions were supervised closely by exercise physiologists. Training mode, intensity (zone), and duration for every training session were documented strictly for each subject. Also, HR was monitored and measured during every training session using a HR monitor (Polar Vantage XL, Kempele, Finland). Files from the HR monitor were downloaded, and the training progress was evaluated weekly. To quantify the training stimulus, we used the method of Banister et al. (5) for the calculation of the training impulse (TRIMP) (Fig. 1). This method multiplies the duration of a training session by the average HR achieved during that session, weighted for exercise intensity (5).

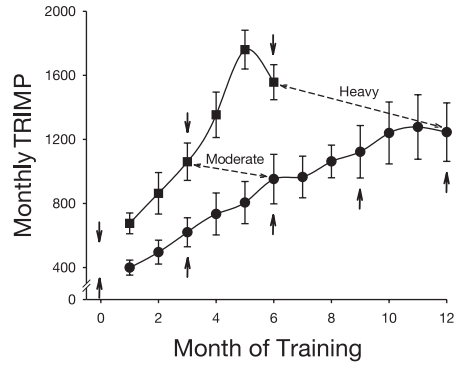

Fig. 1. Intensity and duration of training, as quantified by the monthly training impulse (TRIMP) index during 12 mo of training for sedentary seniors (●). Data (means ± SE) are shown with monthly TRIMP during first 6 mo of 1-yr training for young controls (22). Arrows indicate when experiments were performed (young controls: before and 3 and 6 mo after training; sedentary seniors: before and 3, 6, 9, and 12 mo after training). Dashed arrows indicate when the age effects on cardiovascular adaptation to training were compared between the sedentary seniors and the young controls.

Maximal exercise test. A modified Astrand-Saltin incremental treadmill protocol was used to determine peak exercise capacity (4). Subjects walked or jogged at a constant speed, which was determined based on the individual subjects' fitness to achieve a peak work rate at ~10–12 min; the grade was subsequently increased by 2% every 2

Table 1. *Template of workouts prescribed over a 1-yr training and achieved monthly TRIMP for sedentary seniors*

Month	Long Distance	Base Pace	MSS	Intervals*	Monthly TRIMP
1st		15 @ 25 min			400±148
2nd		15 @ 30 min			496±236
3rd		15 @ 33 min	30 min		621±287
4th		15 @ 35 min	30 min		735±415
5th		15 @ 35 min	2 @ 30 min		806±416
6th		15 @ 40 min	2 @ 30 min		953±489
7th		12 @ 40 min	30 min	3 @ 8 × (30 s "on" 90 s "off")	971±407
8th	4 @ 45 min	3 @ 35 min and 4 @ 40 min	2 @ 30 min	3 @ 8 × (45 s "on" 75 s "off")	1,058±330
9th	4 @ 50 min	4 @ 35 min and 4 @ 40 min	2 @ 30 min	4 @ 8 × (60 s "on" 60 s "off")	1,123±519
10th	4 @ 50 min	5 @ 35 min and 7 @ 40 min	2 @ 30 min	4 @ 8 × (60 s "on" 60 s "off")	1,244±617
11th	4 @ 55 min	12 @ 45 min	2 @ 30 min	4 @ 8 × (60 s "on" 60 s "off")	1,256±619
12th	4 @ 60 min	12 @ 45 min	2 @ 30 min	4 @ 8 × (75 s "on" 45 s "off")	1,265±585

Monthly training impulses (TRIMP) are means ± SD for sedentary seniors, $n = 10$. Target heart rate (HR) for maximal steady state (MSS) is set at ±5 beats/min of the measured HR at MSS during maximal exercise test. Target HR for base pace and long distance is set within 20 beats/min below the lower limit of the MSS range. Target HR for intervals is set within 5–10 beats/min below maximal HR during maximal exercise test. *All interval sessions were followed by a recovery day, usually consisting of 20–30 min of walking. The workouts in the 6th and 12th mo for sedentary seniors are similar to the workouts in 3rd and 6th mo for young controls, who are reported previously (22).

min until exhaustion. Measures of ventilatory gas exchange were made by using the Douglas bag technique. Gas fractions were analyzed by mass spectrometry (Marquette MGA1100), and ventilatory volume was measured using a Tissot spirometer. HR was monitored continuously via ECG. Maximal oxygen uptake ($\dot{V}O_{2\,max}$) was defined as the highest oxygen uptake ($\dot{V}O_2$) measured from at least a 40-s Douglas bag. The criteria to confirm that $\dot{V}O_{2\,max}$ was achieved included an increase in $\dot{V}O_2$ <150 ml, despite increasing work rate of 2% grade; a respiratory exchange ratio > 1.1; and HR within 5 beats/min of age-predicted maximal values. In all cases, at least two of these criteria were achieved.

During the maximal exercise test, breath-by-breath ventilatory gas-exchange variables were calculated from gas fractions measured at the mouth by mass spectrometry (Marquette MGA1100) and minute ventilation ($\dot{V}E$) measured by a turbine flowmeter (VMM, Interface Associates) and were displayed online. The ventilatory threshold for all tests was determined by a single, blinded observer during simultaneous examination of multiple plots of $\dot{V}O_2$ vs. $\dot{V}E$, $\dot{V}O_2$ vs. $\dot{V}E/\dot{V}O_2$, $\dot{V}O_2$ vs. CO_2 production ($\dot{V}CO_2$), and $\dot{V}O_2$ vs. $\dot{V}E/\dot{V}CO_2$ by using commercial software (First Breath, Marquette). The HR at the work rate where the ventilatory threshold was observed was identified as the HR at MSS.

Protocol. Experiments were performed at baseline for all groups, and 3, 6, 9, and 12 mo after the start of training program for the sedentary seniors and the young controls. Studies were performed in the morning at least 2 h after a light breakfast and 12 h after the last caffeinated or alcoholic beverage was consumed, in a quiet environmentally controlled laboratory with an ambient temperature of 25°C, after at least 30 min of quiet rest in the supine position. No high-intensity training sessions were allowed within 72 h of testing, although easy base pace exercise was allowed up to 24 h before the study. An analog ECG was obtained, and beat-by-beat arterial BP was obtained at the finger by photoplethysmography (Finapres, Ohmeda) at heart level. Intermittent BP was measured in the arm by electrosphygmomanometry (Suntech) with a microphone over the brachial artery and the detection of Korotkoff sounds gated to the ECG. Cardiac output (CO) was measured with a modification of the foreign gas rebreathing method by using acetylene as the soluble and helium as the insoluble gas (47). Stroke volume (SV) and total peripheral resistance (TPR) were calculated from CO, HR, and BP (electrosphygmomanometry) measured at the same time. After the establishment of resting hemodynamic steady state (~30 min of repeated measurements until sequential CO measurements were within 500 ml), 6 min of data, including beat-by-beat arterial BP and ECG, were recorded during spontaneous respiration. Respiratory rate and tidal volume were monitored by a turbine flowmeter (VMM, Interface Associates). Subjects were then asked to control their respiratory frequency at a fixed rate of 12 breaths/min (0.2 Hz) by following a graph on a computer. After a 2-min adjustment period, 6 min of data were recorded again for the controlled respiration data collection period. The data from the spontaneous respiration protocol were used to determine mean values for HR, R-wave-R-wave intervals (RRI), systolic BP (SBP), diastolic BP (DBP), and respiratory rate, and the data from both the spontaneous and the fixed respiration protocol were used for spectral and transfer function analysis.

Spectral and transfer function analysis. The analog ECG and arterial BP were sampled simultaneously at 1 kHz, digitized at 12 bits (Metrabyte, DAS-20), and analyzed as previously reported (22, 23). Briefly, the beat-to-beat values of RRI, HR, and SBP were obtained by using a custom program for peak detection and were linearly interpolated and resampled at 2 Hz to create an equidistant time series for spectral and transfer function estimation (1). The time series of RRI, HR, and SBP were first detrended with third-order polynominal fitting and then subdivided into 128-point segments with 50% overlap. Fast-Fourier transforms were implemented within each Hanning-windowed data segment and then averaged to calculate the autospectra of RRI and SBP (Fig. 2). The low-frequency (LF, 0.05–0.15 Hz) and high-frequency (HF, 0.15–0.30 Hz) power of RRI (LFRR and HFRR, respectively) and SBP (LFBP and HFBP, respectively) were calculated from the integration of the autospectra. These values at each specific frequency range were also normalized by dividing by the total spectral power (30). This data acquisition and processing strategy conforms to consensus panel recommendations for the assessment of cardiovascular variability (2). The transfer function gain, phase, and coherence between SBP and RRI were estimated by using the cross-spectral method (23, 37). The LF and HF transfer function gain (GainLF and GainHF, respectively), phase, and coherence were estimated as mean values in the same frequency range as above. The transfer function gain between changes in the SBP and RRI was used to reflect baroreflex sensitivity (37), whereas the estimated phase was used to reflect the time relationship between these two variables (37). The assumption of linearity and reliability of the transfer function estimation was evaluated by the coherence. In addition, standard deviation of RRI (SDRR) was calculated.

Statistics. Numerical data are presented as means ± SD, except for graphics, in which the SE of the mean is used. In the sedentary seniors, the effects of each quarter of training were determined by using one-way repeated-measures ANOVA. The effects of age and identical training loads were determined by using two-way repeated-measures ANOVA. Differences in variables among groups were determined by using one-way ANOVA. Student-Newman-Keuls method was used for multiple comparisons during post hoc testing. To express the dose-response relationship between the exercise stimulus and changes in variables, correlations between the monthly TRIMP and variables at the baseline, 3, 6, 9, and 12 mo were estimated from a second-order regression. A P value of <0.05 was considered statistically significant. All analyses were performed with a personal computer-based analysis system (SigmaStat 3.00, SPSS).

RESULTS

Monthly TRIMP during 1 yr of training for the sedentary seniors is shown in Table 1 and also in Fig. 1 with monthly

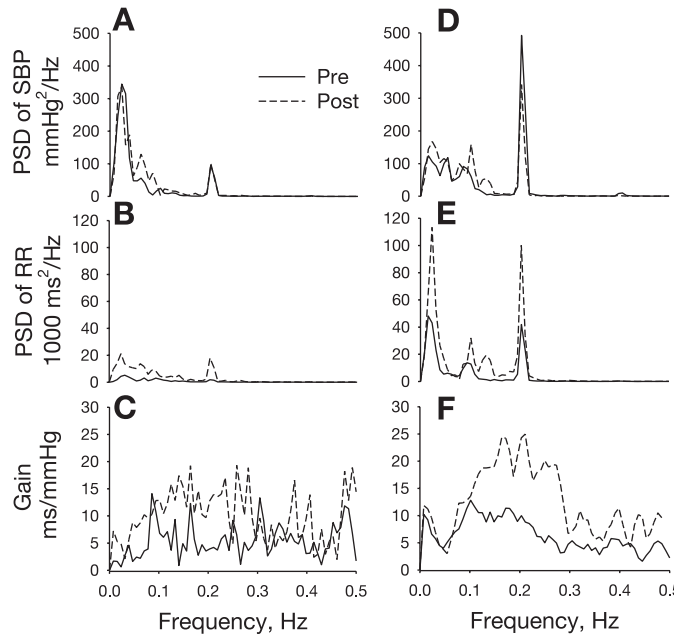

Fig. 2. *A–C*: representative frequency-domain analysis of changes in systolic blood pressure (SBP) and R-wave-R-wave interval (RRI) in a sedentary senior subject before (Pre) and after (Post) 12 mo of training. *D–F*: values obtained from a young individual before and after 6 mo of training. *A* and *D*: power spectral density (PSD) of SBP. *B* and *E*: PSD of RRI. *C* and *F*: transfer function gain between SBP and RRI.

TRIMP during the first 6 mo of 1-yr training for the young controls (22). Monthly TRIMP for both groups steadily increased during the training periods. For the sedentary seniors, monthly TRIMP at 6 mo was above ~930, which is equivalent to the monthly TRIMP typically observed in a traditional cardiac rehabilitation program (~75% HR_{max}, ~140 min/wk). Monthly TRIMP at 12 mo was ~1,300, which was approximately equivalent to training at ~75% HR_{max}, ~200 min/wk. By design, monthly TRIMP at 6 (953 ± 489) and 12 mo (1,265 ± 585) for the sedentary seniors was not different from that at 3 (1,061 ± 388) and 6 mo (1,558 ± 364) for the young controls, respectively ($P = 0.579$ and 0.151). Cumulative TRIMP from 4 to 6 mo (Q2; 2,493 ± 1,294) and 10 to 12 mo (Q4; 3,764 ± 1,762) for the sedentary seniors was not different from that between 1 and 3 mo (Q1; 2,601 ± 938) and 4 and 6 mo (Q2; 4,672 ± 1,015) for the young controls, respectively ($P = 0.829$ and 0.159). Therefore, the age effects on cardiovascular adaptation to training were compared between the sedentary seniors and the young controls after "moderate" (6 mo for the sedentary seniors, 3 mo for the young controls) and "heavy" (12 mo for the sedentary seniors, 6 mo for the young controls) training. For the purposes of this study, moderate training was approximately equivalent to training at ~75% HR_{max}, ~150 min/wk, which is the amount of training currently recommended by national organizations for cardiovascular health and fitness (46); heavy training was ~25% more volume (approximately equivalent to training at ~75% HR_{max}, ~200 min/wk) with the addition of interval sessions and achieves the amount of training associated with the maximal protective mortality benefit of recreational exercise in longitudinal population studies (25).

Steady-state hemodynamics. Table 2 shows physical characteristics during 1 yr of training in the sedentary seniors with those obtained in the Masters athletes and the young controls at baseline. At baseline, there were no significant differences in body weight and height among the groups. $\dot{V}O_{2\,max}$ was significantly lower in the sedentary seniors than the Masters athletes or the young controls. HR was significantly lower in the Masters athletes than the sedentary seniors and the young controls. Peak HR was significantly lower in both senior groups than the young controls. SBP and DBP were significantly higher, CO was lower, and therefore TPR was significantly higher in the sedentary seniors than the Masters athletes and the young controls. SV was significantly lower in the sedentary seniors than the Masters athletes and the young controls.

During 1 yr of training for the sedentary seniors, body weight decreased significantly at 9- and 12-mo time periods. $\dot{V}O_{2\,max}$ increased gradually and achieved statistical significance at 6, 9, and 12 mo; however, it remained significantly decreased compared with the Masters athletes and the young controls throughout training. Resting HR and peak HR decreased gradually throughout training, and resting HR achieved statistical significance at 12 mo compared with the young controls. Respiratory rate remained unchanged throughout training. SBP and DBP measured by cuff decreased significantly at 3 mo; however, more prolonged and intense training did not lead to greater reduction in BP. SBP gradually increased back toward the baseline level during the last 9 mo, whereas DBP remained significantly decreased up to 12 mo. These patterns were similar with BP measured by averaging 6 min of quiet resting beat-by-beat data from finger photoplethysmography. CO and SV increased gradually, and TPR decreased throughout training.

Cardiovascular variability and baroreflex sensitivity. Representative frequency domain analyses of changes in RRI and SBP in a senior subject before and after 1 yr of training are shown compared with those in a young subject before and after 6 mo of training in Fig. 2. Table 3 summarizes the indexes of cardiovascular variability and baroreflex sensitivity. These indexes from controlled respiration are correlated to the doses of exercise with a second-order regression model, as shown in Fig. 3. Data are shown with those obtained from the Masters athletes and the young controls at baseline. At baseline, the indexes of HRV and baroreflex sensitivity were decreased significantly in the sedentary seniors, whereas these indexes were maintained in the Masters athletes compared with the young controls. During 1 yr of training for the sedentary seniors, the indexes of HRV and BP variability increased progressively throughout training with increasing monthly TRIMP, although normalized power in LFRR and HFRR remained unchanged. In contrast, GainLF and GainHF exhibited a "bell-shaped" curve that had a peak adaptation between 3 and 6 mo, equivalent to a monthly TRIMP of 620–950, which was approximately equivalent to training at ~75% HR_{max}, ~95–150 min/wk. However, more prolonged and intense training did not lead to greater improvement for baroreflex gain. Estimated coherence between SBP and RRI both in

Table 2. *Body weight, maximal oxygen uptake, and hemodynamics during quiet, supine rest*

	Sedentary Seniors					Masters Athletes	Young Controls
	Baseline	3 mo	6 mo	9 mo	12 mo		
Body wt, kg	74.2±10.5	73.5±10.6	72.8±10.3	72.2±11.3*	70.8±10.2*	64.6±13.5	70.5±10.9
$\dot{V}O_{2max}$, ml·kg^{-1}·min^{-1}	22.4±3.6†‡	23.5±3.1†‡	24.5±4.3*†‡	25.8±4.9*†‡	26.7±4.4*†‡	38.3±5.9	39.4±4.7
HR, beats/min	63±9‡	63±8‡	62±12‡	62±8‡	59±10†	53±5†	66±7
Peak HR, beats/min	162±13†	160±13†	160±13†	158±12†	159±13†	161±10†	195±10
Respiratory rate, breaths/min	13.6±5.0	14.0±4.2	14.4±3.9	14.1±3.5	13.6±3.6	12.8±3.1	11.9±2.7
SBP, mmHg	140±11†‡	123±8*	128±12*†	127±12*†	137±22†‡	124±20	115±10
DBP, mmHg	79±7†‡	70±5*	70±5*	69±4*	73±4*	68±11	67±7
Stroke volume, ml	75.2±20.1†‡	84.0±20.6	85.1±22.0	85.0±16.9	93.4±17.7*	96.3±20.8	96.5±18.2
Cardiac output, l/min	5.0±0.6†	5.4±0.8†	5.4±0.8†	5.6±0.8	5.5±0.6	5.6±1.1†	6.4±1.0
TPR, dyn·s·cm^{-5}	1,612±255†‡	1,334±209*†	1,360±284*†	1,284±218*†	1,387±170*†	1,280±259†	1,051±179

Values are means ± SD; $n = 10$ for sedentary seniors, 12 for Masters athletes, and 11 for young controls. $\dot{V}O_{2max}$, maximal oxygen uptake; SBP, systolic blood pressure; DBP, diastolic blood pressure; TPR, total peripheral resistance. $P < 0.05$ compared with *baseline, †young controls, and ‡Masters athletes.

Table 3. *Cardiovascular variability*

	Sedentary Seniors					Masters Athletes	Young Controls
	Baseline	3 mo	6 mo	9 mo	12 mo		
				Spontaneous respiration			
SDRR, ms	31±11†‡	32±10†	40±29	40±25	49±29*	51±29	48±17
LFRR, ms^2	326±377	229±232†	565±962	841±1,298	1,280±2,612	1,105±1,496	756±625
HFRR, ms^2	88±107†	111±110†	240±359	297±404	422±744	891±1,697	763±774
NormLFRR	0.26±0.16	0.19±0.12	0.20±0.08	0.28±0.15	0.26±0.19	0.24±0.18	0.26±0.13
NormHFRR	0.08±0.04†‡	0.11±0.09†	0.11±0.06†	0.14±0.08	0.10±0.05†	0.20±0.16	0.25±0.19
LFBP, mmHg^2	6.6±4.7	7.2±7.9	7.4±6.3	5.8±5.7	12.6±11.5*†	4.9±7.9	3.6±2.8
HFBP, mmHg^2	1.2±0.7	1.4±1.5	2.4±3.1	1.7±1.6	1.5±0.9	1.0±1.2	1.8±1.0
GainLF, ms/mmHg	5.2±3.3†‡	6.0±4.5†	7.1±5.9	8.2±6.7	7.9±6.1	10.3±6.2	11.8±4.9
GainHF, ms/mmHg	6.4±3.6†‡	8.8±7.7	10.6±13.0	10.5±9.5	9.6±6.4	20.3±20.0	15.1±7.3
				Controlled respiration			
SDRR, ms	28±13†‡	34±19†	37±26†	43±36	49±39*	47±23	61±30
LFRR, ms^2	124±94†	297±576	287±385	396±654	775±1,757	619±1,003	747±689
HFRR, ms^2	207±396†	378±638†	650±1,068	1,336±2,802	1,378±2,748	2,082±4,707	2,720±3,675
NormLFRR	0.17±0.11	0.15±0.08	0.17±0.09	0.15±0.10	0.16±0.09	0.16±0.11	0.19±0.14
NormHFRR	0.20±0.15†	0.21±0.10†	0.30±0.14	0.27±0.20†	0.28±0.15†	0.24±0.16†	0.45±0.24
LFBP, mmHg^2	3.4±1.9	5.5±4.7	4.5±2.8	10.8±23.7	15.3±27.2	3.8±6.6	2.7±1.7
HFBP, mmHg^2	4.0±2.4	3.3±2.0	4.0±2.6	5.1±5.2	6.8±8.3	4.0±3.9	6.2±5.4
GainLF, ms/mmHg	4.6±2.2†‡	5.5±4.3†	6.7±5.2†	5.5±3.6†	5.3±3.9†	9.7±7.7	12.3±6.4
GainHF, ms/mmHg	5.4±3.1†	6.4±5.1†	8.3±7.8†	6.6±4.1†	6.6±4.4†	12.5±12.9	16.0±9.1

Values are means ± SD; $n = 10$ for sedentary seniors, 12 for Masters athletes, and 11 for young controls. SDRR, standard deviation of R-wave-R-wave intervals (RRI); LFRR and HFRR, power in low and high frequency of RRI, respectively; NormLFRR and NormHFRR, normalized power in low and high frequency of RRI, respectively; LFBP and HFBP, power in low and high frequency of SBP, respectively; GainLF and GainHF, low and high frequency transfer function gain between SBP and RRI, respectively. $P < 0.05$ compared with *baseline, †young controls, and ‡Masters athletes.

LF and HF was near or above 0.5 with a negative phase at baseline and during training; neither coherence nor phase changed during training, confirming the validity of using this technique for the assessment of transfer function gain and phase (37). Most importantly, SDRR, LFRR, and HFRR in the sedentary seniors were not appreciably increased during the first 6 mo of training; however, all of those indexes increased up to similar levels as the young controls after 12 mo of training. On the other hand, GainLF and GainHF in the sedentary seniors remained decreased throughout training compared with those in the young controls, regardless of training intensity.

Effects of age on trainability. Figure 4 shows the adaptation of RRI, indexes of cardiovascular variability, and baroreflex sensitivity after moderate and heavy identical training loads in the sedentary seniors and the young controls, with *P* values by two-way repeated-measures ANOVA. As expected, the age effects were significant in all of the indexes of HRV and baroreflex sensitivity. On the other hand, there were no significant interaction effects in any variable, indicating that the trainability for cardiac autonomic function after the identical training loads was similar between the groups. There were no age, training, or interaction effects in LFBP and HFBP. All of the indexes of HRV and baroreflex sensitivity were significantly lower in the sedentary seniors than the young controls throughout training, except for LFRR and HFRR after heavy training, at which point there were no significant differences between the groups.

DISCUSSION

The major findings from the present study are *1*) autonomic modulation of the heart in sedentary seniors improves with increasing dose of exercise over 1 yr of training; *2*) resting BP and indexes of baroreflex sensitivity in seniors show a peak adaptation after relatively light doses of training for 3–6 mo; however, higher doses of training do not lead to greater enhancement of this effect; *3*) a heavy dose of training for 12 mo reestablishes most of the age-related deterioration in indexes of HRV to youthful levels, but it does not restore the age-related decrease in baroreflex sensitivity; and *4*) seniors retain a similar degree of trainability for indexes of HRV and baroreflex sensitivity compared with young individuals to identical training loads.

HRV. All of the indexes of HRV were significantly attenuated in the sedentary seniors compared with the young controls at baseline in the present study, as reported in previous cross-sectional studies (7, 10, 11, 27, 41). Spectral analysis of HRV quantifies the dynamic, frequency-dependent changes in HR, which reflects autonomic modulation of sinus node activity (1, 30). HF power of RRI variability (>0.15 Hz) appears to be modulated predominantly by respiration-induced changes in vagal activity, whereas LF power of RRI variability (<0.15 Hz) is modulated by both vagal and sympathetic activity (1, 30). The prominent decrease in HFRR and LFRR in the sedentary seniors indicates attenuated autonomic modulation of sinus node activity, mainly because of decreased vagal activity with aging (16, 40, 44). For example, parasympathetic blockade with atropine in humans increases the HR substantially less in elderly than younger subjects (44), suggesting that the HR at rest is under less parasympathetic control with aging. However, an alternative interpretation is that decreases in sinus node function with age make it less sensitive to alterations in vagal or sympathetic neural activity, which could be normal, but still have a more limited ability to modulate phase IV depolarization at the sinus node.

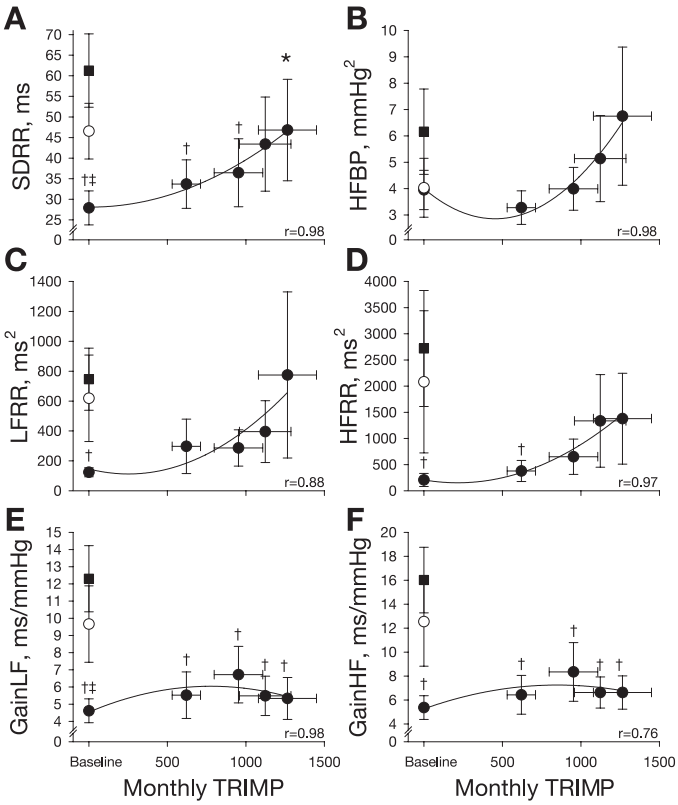

Fig. 3. Dose-response relationship of dynamic cardiovascular indexes to exercise intensity and volume of training (monthly TRIMP) in sedentary seniors (n = 10, ●). Data are shown with values obtained from Masters athletes (n = 12, ○) and young controls (n = 11, ■) at baseline. Means and SE bars are presented. *A*: standard deviation of RRI (SDRR). *B*: power in high frequency of blood pressure (HFBP). *C* and *D*: power in low (LFRR) and high frequency of RRI (HFRR), respectively. *E* and *F*: low- (GainLF) and high-frequency transfer function gain (GainHF), respectively. $P < 0.05$ compared with *pretraining baseline, †young controls, and ‡Masters athletes.

Arguing against an intrinsic defect in sinus node responsiveness with aging alone (10) is the fact that HRV in the Masters athletes was well maintained compared with the young controls in the present study, as well as previous cross-sectional studies (11, 13), suggesting that regular physical activity can prevent the age-related abnormalities of cardiac autonomic function. Conversely, longitudinal studies that investigated the effects of aerobic training on HRV in healthy but initially sedentary elderly subjects have provided inconclusive results: some studies reported increased HRV after training (27, 33, 38, 39, 43), whereas others did not (9, 49). One potential reason for this discrepancy may be differences in exercise loads performed by subjects in the previous studies.

In the present study, we found that the indexes of HRV in the sedentary seniors improved with increasing dose of exercise throughout the year of training. More importantly, these indexes were not appreciably increased after light-moderate doses of training after 3–6 mo, equivalent to a monthly TRIMP of 620–950, ~75% HR_{max}, ~95–150 min/wk, but required heavier doses of training over 12 mo, equivalent to a monthly TRIMP of 1,300, ~75% HR_{max}, ~200 min/wk, to achieve a significant effect. Previous longitudinal studies that reported an increase in indexes of HRV after training in healthy sedentary elderly subjects used relatively higher doses of exercise (27, 33, 38, 39, 43). For example, Levy et al. (27) showed in elderly men (age, 60 to 82 yr) that SDRR measured during 2-min supine rest increased after 6-mo high-intensity training at 50–85% HR reserve for 180–225 min/wk. In contrast, other studies using relatively lower doses of exercise failed to show an increase in indexes of HRV in a similar population (9, 49). Boutcher and Stein (9) reported in middle-aged men (mean age, 46 yr) that time domain parameters of HRV measured during 15-min supine rest remained unchanged after 8-wk light-intensity training, ~60% HR reserve, 60–90 min/wk. More recently, Uusitalo et al. (49) also failed to show an increase in frequency-domain parameters of HRV measured during 5-min supine rest after 5-yr of low-intensity training, 40–60% $\dot{V}O_{2\,max}$, 30–60 min/day, 3–5 days/wk, in middle-aged and older men (age, 53–63 yr). Taken together, these data suggest that indexes of HRV in healthy elderly subjects are beneficially modulated only when training is performed vigorously enough, i.e., heavy doses of training equivalent to exercise at ~75% HR_{max} for ~200 min/wk for at least 6–12 mo.

One previous study by Levy et al. (27) reported effects of similar aerobic training on HRV in healthy young and elderly subjects. They suggested that an increase in SDRR after 6 mo of aerobic training occurred in both age groups. In the present study, we confirmed and extended this observation by carefully

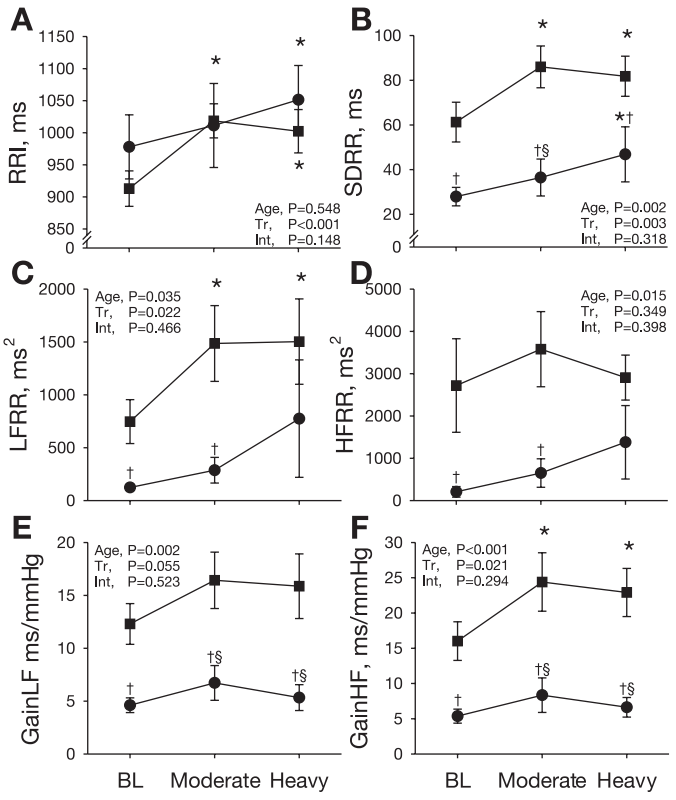

Fig. 4. RRI and indexes of cardiovascular variability at baseline and after moderate and heavy doses of training in sedentary seniors (n = 10, ●) and young controls (n = 11, ■) with P values of the effects of age, training (Tr), and the interaction of age × training (Int) by two-way repeated-measures ANOVA. BL, baseline; moderate, moderate volume of training (6 mo for sedentary seniors, 3 mo for young controls); heavy, heavy volume of training (12 mo for sedentary seniors, 6 mo for young controls). *A*: RRI. *B*: SDRRI. *C* and *D*: power in LFRR and HFRR, respectively. *E* and *F*: GainLF and Gain HF, respectively. $P < 0.05$ compared with *pretraining baseline within group, †young controls at the same points, and §young controls at baseline.

controlling the exercise stimulus in young and older groups of subjects. We showed that there were no significant interaction effects of age and training in any index of HRV and baroreflex sensitivity as well as RRI in the sedentary seniors and the young controls, after identical moderate and heavy loads of training. From these observations, we conclude that senior subjects retain a similar degree of trainability of cardiac autonomic function in response to dynamic exercise as young subjects.

Baroreflex sensitivity and BP variability. Transfer function analysis of spontaneous variations between BP and RRI has been employed for the evaluation of dynamic properties of baroreflex function in humans (22, 23, 50). The assessment of baroreflex function in this analysis reflects a closed-loop relationship between BP and RRI with the basic premise that oscillations in BP lead to baroreflex-mediated oscillations in RRI (14). In contrast, a mathematical simulation of cardiovascular control showed that the feed-forward effects of HR on BP may be more complicated than simple buffering via the baroreflex (6). For example, Taylor and Eckberg (45) showed that oscillations in BP were reduced when the RRI was fixed via cardiac pacing in humans in the supine position and suggested that respiratory sinus arrhythmia can contribute to arterial pressure oscillations. However, Zhang et al. (50) recently reported that, after ganglion blockade, BP variability at high frequencies remained unchanged even though R-R variability was virtually abolished under supine resting conditions. This result provides evidence that BP variability at high-respiratory frequencies is mediated to a large extent by mechanical effects of respiration on intrathoracic pressure and/or cardiac filling and is less influenced by feed-forward effects of changes in RRI on BP variability. In addition, the phase was always negative, both in HF and LF in all groups, and did not change during training in the present study. Finally, transfer function gain correlates significantly with other measures of baroreflex function, including vasoactive drug methods and sequence analysis (31, 35, 36). Therefore, the premise of this study is that the possibility of feed-forward effects of RRI on BP are minimal under the specific conditions of the study and that the technique of transfer function analysis provides a reasonable index of dynamic baroreflex function.

In contrast to the prominent plasticity of HRV, baroreflex sensitivity of the sedentary seniors after training remained considerably lower than that of the young controls at baseline, even at the peak response to training. In addition, contrary to the results of the indexes of HRV, baroreflex sensitivity of the sedentary seniors showed a peak adaptation after more moderate doses of training; more prolonged and intense exercise did not lead to greater enhancement of these changes. These observations appear inconsistent with previous observations from cross-sectional studies that baroreflex sensitivity by the cross-spectral method is decreased along with HRV in sedentary elderly subjects but that both indexes are maintained in physically fit elderly individuals (11, 13, 21). Similarly, in the present study, baroreflex sensitivity in the Masters athletes was preserved along with HRV compared with the young controls.

One potential explanation for this inconsistency between cross-sectional and longitudinal studies may be the effect of circulatory mechanics on cardiovascular variability. Changes in cardiac compliance influence the change in left ventricular filling from the respiratory shift in thoracic blood volume and thereby modulate beat-to-beat SV and BP, influencing the amount of baroreceptor distortion during a pressure pulse (26). Recently, our laboratory demonstrated that lifelong endurance training preserves ventricular compliance, which is decreased prominently with sedentary aging in these same subjects (3). This increased ventricular compliance may augment respiratory fluctuation in SV and thereby BP in lifelong fit compared with unfit individuals.

The fact that BP variability at the respiratory frequency, i.e., HFBP, increased after 9–12 mo of training in the present study suggests that ventricular compliance, or at least respiratory modulation of SV, may well have increased during training in the sedentary seniors. Such increased BP variability should increase the signal to arterial baroreceptors; however, GainHF was not correspondingly enhanced after 9–12 mo of training. This discrepancy suggests that, although cardiac mechanics may have been improved, other components of baroreflex sensitivity (21, 29), i.e., most likely the mechanical transduction of pressure by the baroreceptors, or sensitivity of the baroreceptor-HR reflex arc, remain unchanged, despite 12 mo of training in the sedentary seniors. It has been suggested that the age-related decrease in cardiovagal baroreflex sensitivity is caused mostly by an attenuated mechanical transduction of pressure into baroreceptors due to decreased arterial compliance (29). Conversely, preserved baroreflex sensitivity in fit elderly subjects is associated with a preserved mechanical transduction by an improved arterial compliance (21, 29), as well as a preserved neural transduction (21). It may be that more prolonged training, possibly supplemented by other therapies designed to improve arterial stiffness, is necessary to improve baroreflex sensitivity in chronically sedentary seniors.

Clinical implications. A critical question regarding the effects of exercise on cardiovascular morbidity and mortality is the intensity and duration of exercise training required to achieve a clinically meaningful reduction in cardiovascular risk (19, 22, 25, 34). Decreases in vagal activity, manifested by decreased indexes of HRV and baroreflex sensitivity, known to become manifest with aging (7, 10, 11, 27, 41), may reflect a decrease in fibrillation threshold and predispose to ventricular fibrillation (20). Epidemiological studies have shown an inverse association between indexes of HRV or baroreflex sensitivity and an increased incidence of cardiac events and mortality in clinically disease-free individuals, even after adjusting for other known risk factors (15, 48). In contrast, it has been suggested that increases in cardiac parasympathetic activity with aerobic training may exert a protective effect against life-threatening arrhythmias (8, 20). Therefore, the increased HRV parameters after heavy doses of training for 12 mo in the sedentary seniors may reduce the risk of ventricular fibrillation and may be a key mechanism for the reduction in cardiovascular risk associated with exercise training in this population.

Limitations. Because training increased in dose over the entire study, and there was no control group that did not exercise, we cannot differentiate clearly the effects of time or duration of training per se from the specific doses of training. In addition, because the periods of training to achieve the similar doses of training in the sedentary seniors were twice as long as those in the young controls, we cannot exclude the possibility that the difference in the duration of training between the two groups might affect the results. Hence, our results must be interpreted cautiously. However, we suspect

that continued training over time at any given dose is not likely to change cardiovascular parameters such as those measured here. In addition, these measures of HR and BP variability appear robust and change little over time periods as long as 1 yr without any intervention (23, 39, 43). Moreover, our laboratory previously demonstrated that the cardiovascular adaptation to the same dose of endurance training was comparable between subjects in their late twenties and in their fifties in the same subjects in a long-term longitudinal study, even though the dose of training was achieved over a 6-mo interval later in life compared with 8 wk at a younger age (28).

The subjects examined in the present study were elderly but free from known cardiovascular disease. Thus the present results are more relevant to primary rather than secondary coronary heart disease prevention. Because the presence of cardiovascular disease decreases HRV, regardless of aging (2, 7), the results of this study could be different in patients with manifest cardiovascular disease. It is possible that such patients could have a greater range of responsiveness and thus have a more robust or sustained response to training. Indeed, the effects of aerobic training on HRV and baroreflex sensitivity in chronic heart failure or myocardial infarction patients suggest a considerable and significant improvement in these parameters (12, 42).

In conclusion, indexes of HRV in sedentary seniors improve with increasing dose of exercise over 1 yr of training, with heavy doses of training for 12 mo, equivalent to exercise at ~75% HR_{max} for ~200 min/wk, restoring most of the age-related deterioration in these indexes. Conversely, lower doses of training for 3–6 mo, equivalent to exercise at ~75% HR_{max} for ~95–150 min/wk, achieve a modest hypotensive effect and may improve indexes of baroreflex sensitivity. However, higher doses of training do not lead to greater enhancement of these changes, and the age-related decrease in baroreflex sensitivity is not restored to youthful levels even after 12 mo of heavy training. Finally, healthy sedentary seniors retain a similar but not greater degree of trainability to dynamic exercise as healthy young individuals for autonomic control of the circulation.

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