

# Dose-response relationship of the cardiovascular adaptation to endurance training in healthy adults: how much training for what benefit?

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**Iwasaki, Ken-ichi, Rong Zhang, Julie H. Zuckerman, and Benjamin D. Levine.** Dose-response relationship of the cardiovascular adaptation to endurance training in healthy adults: how much training for what benefit? *J Appl Physiol* 95: 1575–1583, 2003. First published June 27, 2003; 10.1152/jappphysiol.00482.2003.—Occupational or recreational exercise reduces mortality from cardiovascular disease. The potential mechanisms for this reduction may include changes in blood pressure (BP) and autonomic control of the circulation. Therefore, we conducted the present long-term longitudinal study to quantify the dose-response relationship between the volume and intensity of exercise training, and regulation of heart rate (HR) and BP. We measured steady-state hemodynamics and analyzed dynamic cardiovascular regulation by spectral and transfer function analysis of cardiovascular variability in 11 initially sedentary subjects during 1 yr of progressive endurance training sufficient to allow them to complete a marathon. From this, we found that 1) moderate exercise training for 3 mo decreased BP, HR, and total peripheral resistance, and increased cardiovascular variability and arterial baroreflex sensitivity; 2) more prolonged and intense training did not augment these changes further; and 3) most of these changes returned to control values at 12 mo despite markedly increased training duration and intensity equivalent to that routinely observed in competitive athletes. In conclusion, increases in R-wave-R-wave interval and cardiovascular variability indexes are consistent with an augmentation of vagal modulation of HR after exercise training. It appears that moderate doses of training for 3 mo are sufficient to achieve this response as well as a modest hypotensive effect from decreasing vascular resistance. However, more prolonged and intense training does not necessarily lead to greater enhancement of circulatory control and, therefore, may not provide an added protective benefit via autonomic mechanisms against death by cardiovascular disease.

blood pressure; exercise; Fourier analysis; heart rate; nervous system; autonomic

NUMEROUS EPIDEMIOLOGIC STUDIES provide strong evidence that occupational or recreational exercise reduces mortality from cardiovascular disease (13). However, the “dose” of exercise, i.e., the intensity, duration,

and frequency of training required to achieve and optimize this response, remains uncertain. For example, many investigators have argued that moderate-intensity exercise training is sufficient to produce substantial benefits (26). In contrast, others have argued that high-intensity training produces proportionally greater responses (51).

One possible pathway by which exercise reduces cardiovascular mortality may be through modification of conventional risk factors, such as hypertension (11), dyslipidemia (40), or glucose intolerance (19). However, it may take years of sustained exercise training to alter cholesterol levels (23), and these changes are at best only modest (46). Yet the effect of exercise training in patients at highest risk for cardiovascular events is manifest early, i.e., within the first few months after a myocardial infarction (22). Moreover, for such patients, exercise training reduces the risk of sudden death but has a limited impact on recurrent myocardial infarction (34), suggesting a greater effect on dynamic cardiovascular control processes than on slowly developing arteriosclerosis.

Therefore, this long-term longitudinal study of progressive endurance training was conducted to quantify the dose-response relationship between the intensity and amount of exercise training and regulation of heart rate (HR) and blood pressure (BP).

## METHODS

**Subjects.** Eleven initially sedentary men ( $n = 6$ ) and women ( $n = 5$ ), age  $29 \pm 6$  yr, were studied. Subjects were excluded if they exercised for  $>30$  min/day more than once per week. No subject smoked, used recreational drugs, or had significant chronic medical problems. Subjects were screened with a history and physical examination that including ECG and echocardiogram. All subjects signed a consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital. All subjects were experienced and comfortable with all laboratory techniques in this study.

**Exercise training.** HR at maximal steady state (MSS) and peak oxygen uptake ( $\dot{V}O_2$ ) were determined by analysis of gas

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Table 1. Example of 5 training zones

Training Zone	Heart Rate, beats/min
Recovery	<145
Base pace	145–165
MSS	165–175
Race pace	175–185
Intervals	>185

If the maximal steady-state (MSS) heart rate is 170 with a maximum heart rate of 195 beats/min, the zones would look like this table. Thus the MSS heart rate is bracketed by ±5 beats/min to derive the MSS range. Base pace is set at 20 beats/min below the lower limit of the MSS range; interval pace is set within 5–10 beats/min of peak heart rate; and race pace range is the difference between MSS and interval pace.

exchange obtained during incremental treadmill tests performed every 3 mo. MSS was estimated from the ventilatory threshold according to standard criteria (3). On the basis of the MSS HR and peak HR, five training zones were determined (Table 1). Table 2 is a template of workouts prescribed over the 12 mo of the training program. The majority of training sessions, particularly during the early phases of the program, were prescribed as “base training,” with target HRs equivalent to ~75–85% of maximal. Initially subjects trained three to four times per week for 30–45 min/session by either brisk walking or slow jogging. As the subjects became fitter, the duration of the base training sessions was prolonged, including the addition of one “long run” per week. Subsequently, sessions of increased intensity (MSS or interval sessions) were added first once, then twice, and occasionally three times per week, and were always followed by recovery sessions. By the end of the year, subjects were exercising for 7–9 h/wk, including long runs of up to 3 h, plus regular interval sessions on the track and races. This template served as a minimum amount of exercise required of all the subjects and provided a periodized training program (Fig. 1) similar to those routinely used by competitive athletes (50). A sample training schedule over 12 mo is provided in the APPENDIX.

To quantify the training stimulus, we used the method of Banister et al. (4) for the calculation of the training impulse (TRIMP). This method multiplies the duration of a training session by the average HR achieved during that session,

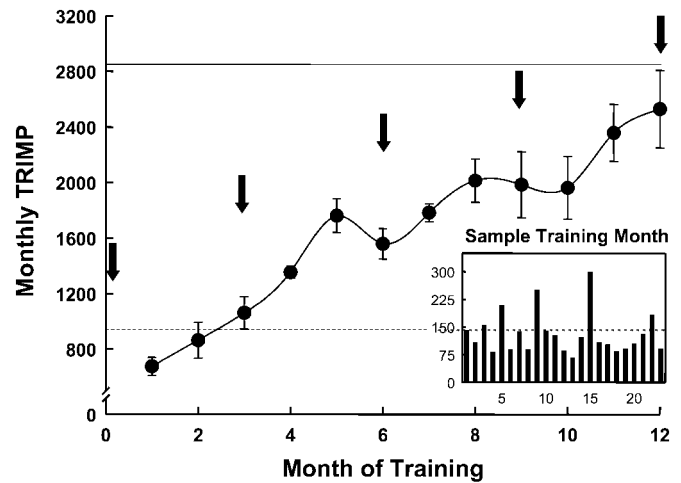


Fig. 1. Intensity and duration of training, as quantified by the training impulse (TRIMP) index during the year of training. The solid horizontal line represents the monthly TRIMP that is equivalent to those observed in competitive athletes [~85% maximal heart rate (HR), 300 min/wk]. The horizontal dashed line represents the monthly TRIMP that is equivalent to a typical cardiac rehabilitation program (~75% maximal HR, 140 min/wk). Arrows indicate when experiments were performed (before training and 3, 6, 9, and 12 mo after the start of training).

weighted for exercise intensity. Thus exercise sessions of longer duration and/or higher intensity, such as interval workouts, are assigned relatively higher TRIMP values than sessions of lower intensity (see APPENDIX).

$\dot{V}O_2$ . An individualized treadmill protocol was used to determine peak exercise capacity. During initial familiarization sessions, a comfortable jogging speed was determined for each subject (generally 5–8 miles/h). This constant speed was used for each subsequent test, with the grade increased by 2% every 2 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 by a dry-gas meter (Collins). Maximal oxygen uptake ( $\dot{V}O_{2\max}$ ) was defined as the highest  $\dot{V}O_2$  measured from at least a 40-s Douglas bag. In nearly all cases, a plateau in  $\dot{V}O_2$  was

Table 2. Template of workouts prescribed over a 1-yr training program

Month	Runs				
	Long run	Base pace runs	MSS	Race pace runs	Intervals*
1	30 min	15 @ 30 min	None	None	None
2	2 @ 40 min	15 @ 35 min	2 @ 25 min	None	None
3	2 @ 60 min	15 @ 40 min	3 @ 30 min	None	None
4	2 @ 70 min	15 @ 40 min / 2 @ 50 min	4 @ 35 min	None	2 sessions of 1 min “on” 2 min “off”
5	2 @ 80 min	15 @ 45 min / 2 @ 60 min	4 @ 40 min	None	3 sessions of 1.5 min “on” 3 min “off”
6	2 @ 90 min	15 @ 45 min / 2 @ 60 min	3 @ 40 min	1 session @ 15 min	3 sessions of 2 min “on” 4 min “off”
7	2 @ 100 min	15 @ 45 min / 2 @ 60 min	2 @ 40 min	2 sessions @ 10 min	4 sessions of 2.5 min “on” 2.5 min “off”
8	2 @ 110 min	15 @ 45 min / 2 @ 60 min	2 @ 45 min	2 sessions @ 30 min	4 sessions of 3 min “on” 3 min “off”
9	2 @ 120 min	15 @ 45 min / 2 @ 60 min	2 @ 45 min	2 sessions @ 40 min	4 sessions of 3 min “on” 3 min “off”
10	1 @ 135 min	15 @ 45 min / 2 @ 60 min	3 @ 40 min	2 sessions @ 1 mile	
	1 @ 150 min	15 @ 45 min / 2 @ 90 min			
11	1 @ 175 min	15 @ 45 min / 2 @ 90 min	3 @ 40 min	None	1 session of 2 min “on” 2 min “off”
	1 @ 195 min	15 @ 45 min / 2 @ 60 min			
12	1 @ 120 min	15 @ 45 min / Taper	1 @ 35 min	None	1 session of 1 min “on” 2 min “off”
	1 @ 90 min				
	1 @ 60 min				

\*All interval sessions were followed by a recovery day, usually consisting of 20–30 min of walking or jogging.

observed with increasing work rate, confirming the identification of  $\dot{V}O_{2\max}$ . In addition, HR was monitored continuously via ECG (Polar).

**MSS.** During the incremental test of  $\dot{V}O_{2\max}$ , breath-by-breath  $\dot{V}O_2$  was calculated and displayed on-line by using gas fractions measured at the mouth by mass spectrometry (Marquette MGA1100), and minute ventilation ( $\dot{V}_E$ ) was measured by a turbine flow meter (VMM, Interface Associates). 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, and  $\dot{V}O_2$  vs.  $\dot{V}_E/CO_2$  production by using commercial software (First Breath, Marquette). The HR at the work rate that elicited the ventilatory threshold was identified and used to determine training zones in Table 1.

**Protocol.** Experiments were performed before and 3, 6, 9, and 12 mo after the start of training, 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 laboratory at 25°C. No high-intensity training sessions were allowed within 48–72 h of testing.

All measurements were made supine, after at least 30 min of quiet rest. An analog ECG was obtained, and beat-by-beat arterial BP was obtained at the finger by photoplethysmography (Finapres, Ohmeda) (38). Intermittent BP was measured in the arm by electrophygmomanometry (Suntech) with a microphone placed over the brachial artery and the detection of Korotkoff sounds gated to the ECG (33). Cardiac output was measured with a modification of the foreign gas rebreathing method by using acetylene as the soluble and helium as the insoluble gas (47). Resting stroke volume and total peripheral resistance (TPR) were then calculated from HR and BP (electrophygmomanometry) measured at the same time. After the establishment of resting, hemodynamic steady state (~30 min of repeated measurements until sequential cardiac output measurements within 500 ml), 6 min of data, including beat-by-beat arterial pressure and ECG, were recorded during spontaneous respiration. Subjects were then asked to control their respiratory frequency at a fixed rate of 12 breaths/min (0.20 Hz) by following a graph on a computer. After a 2-min adjustment period, 6 min of data were recorded again. The data from the spontaneous breathing portion of the protocol were used to determine mean values for HR, R-wave-R-wave (R-R) interval, systolic BP (SBP), and diastolic BP; the data from the fixed breathing protocol were used for spectral and transfer function analysis.

**Spectral and transfer function analysis.** The analog ECG and arterial pressure were analyzed as previously reported (21). High-frequency (0.15 to ~0.30 Hz) and low-frequency (0.05 to ~0.15 Hz) power of R-R interval and SBP were calculated from the integration of the autospectra (Fig. 2). These values at each specified frequency range were also normalized by dividing by the total spectral power (36). This data acquisition and processing strategy conforms to consensus panel recommendations for the assessment of cardiovascular variability (45a).

The transfer function gain, phase, and coherence between SBP and R-R interval were estimated by using the cross-spectral method (21, 41) (Fig. 2). The low- (Gain LF) and high-frequency transfer function gain (Gain HF), phase, and coherence were estimated as mean values in the same frequency ranges as above. The transfer function gain between changes in the SBP and R-R interval was used to reflect baroreflex function (41). The assumption of linearity and reliability of the transfer function estimation was evaluated by the coherence, which ranges between 0 and 1.

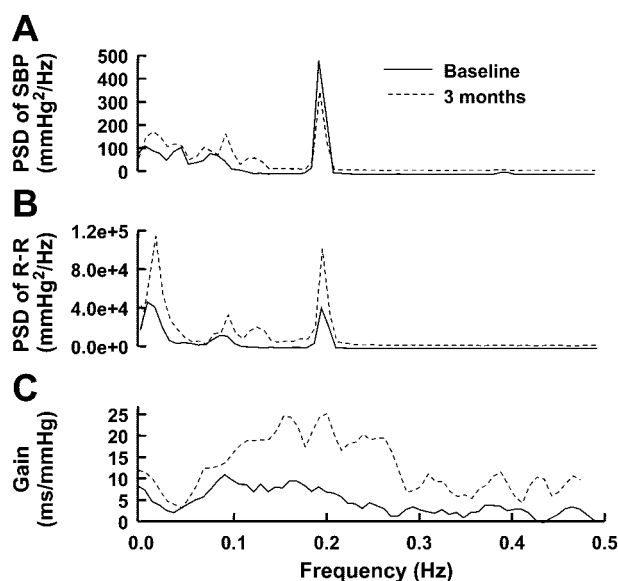


Fig. 2. Representative frequency-domain analysis of changes in R-wave-R-wave (R-R) interval and systolic blood pressure (SBP) in a subject before and after 3 mo exercise training. A: power spectral density (PSD) of SBP. B: PSD of R-R interval. C: transfer-function gain between systolic blood pressure and R-R interval.

**Statistics.** Variables were compared by using one-way ANOVA in conjunction with the Duncan post hoc test for multiple comparisons ( $n = 11$ ). A  $P$  value of  $<0.05$  was considered statistically significant. To express the dose-response relationship between the exercise stimulus and changes in cardiovascular indexes, correlations between the monthly TRIMP and cardiovascular index at baseline, 3, 6, 9, and 12 mo were estimated from a second-order regression (ABstat, Anderson Bell). Data are presented as means  $\pm$  SE.

## RESULTS

All subjects successfully completed a marathon ( $n = 9$ ), triathlon ( $n = 1$ ), or 100-mile endurance cycling race ( $n = 1$ ) as the ultimate performance goal of the training program.  $\dot{V}O_{2\max}$  increased at 3, 6, 9, and 12 mo of training compared with baseline (Table 3). Body weight and respiratory rate did not change during training (Table 3).

**Steady-state hemodynamics.** Compared with baseline, HR decreased significantly (R-R interval increased significantly), and stroke volume increased significantly at 3, 6, 9, and 12 mo of training (Fig. 3). SBP and diastolic BP decreased after 3 mo of training (Fig. 3). This reduction in BP remained unchanged up to 9 mo, despite continued and augmented training. BP returned to pretraining levels at the end of the training program ( $P < 0.05$  compared with 9 mo). This pattern was similar regardless of whether BP was measured by averaging 6 min of quiet resting beat-by-beat data or from automated cuff measurements (Table 3).

Cardiac output increased, and TPR decreased (Fig. 3) significantly at 3, 6, and 9 mo of training. Paralleling the changes in BP, TPR returned to near control levels at 12 mo ( $P < 0.05$  compared with 9 mo).

These indexes were correlated to the dose of exercise with a second-order regression model (Fig. 3). When

Table 3. Subject characteristics and hemodynamics during training

	Baseline	3 mo	6 mo	9 mo	12 mo
Body weight, kg	71 ± 3	70 ± 3	69 ± 3	69 ± 3	70 ± 3
$\dot{V}O_{2max}$ , ml/kg/min <sup>-1</sup>	39.4 ± 1.43	44.4 ± 1.42*	45.9 ± 1.24*	47.6 ± 2.1*	47.4 ± 2.17*
Respiratory rate, breaths/min	11.9 ± 0.8	11.3 ± 0.8	11.5 ± 1.0	11.7 ± 1.2	11.5 ± 1.0
Heart rate, beats/min	66 ± 2	60 ± 2*	61 ± 2*	61 ± 2*	57 ± 2*
Peak heart rate, beats/min	195 ± 3	186 ± 2*	186 ± 2*	185 ± 3*	186 ± 3*
SBP, mmHg	126 ± 4	116 ± 3*	116 ± 4*	113 ± 4*	123 ± 3
DBP, mmHg	74 ± 3	62 ± 2*	60 ± 2*	61 ± 2*	69 ± 2
Stroke volume, ml	96.5 ± 5.5	109 ± 7*	111 ± 5*	116 ± 8*	114 ± 7*
Cardiac output, ml/min	6.4 ± 0.3	7.1 ± 0.3*	7.4 ± 0.3*	7.4 ± 0.5*	6.7 ± 0.4
TPR, dynes · s · cm <sup>-5</sup>	1051 ± 54	915 ± 51*	844 ± 40*	843 ± 54*	1026 ± 51

$\dot{V}O_{2max}$ , maximal oxygen uptake; SBP, systolic blood pressure; DBP, diastolic blood pressure; TPR, total peripheral resistance. \* $P < 0.05$  compared with pretraining baseline.

TRIMP was increased up to ~2,000 (equivalent to exercise at 75% maximal HR for 200 to ~220 min/wk), stroke volume increased progressively and then plateaued with no further increase despite increasing training stimulus. In contrast, TPR, SBP, and diastolic BP exhibited a “U-shaped” curve that centered around a TRIMP of ~1,500, equivalent to exercise at 75% maximal HR for 160 to ~180 min/wk.

*Time domain analysis.* The standard deviation of R-R variability (SDR-R) was increased significantly at 3 and 6 mo of training compared with baseline. However, SDR-R returned to the control levels at 9 and 12 mo (Fig. 3). The change in SDR-R was correlated to the dose of exercise with a second-order regression model and had a “bell-shaped” curve that centered around a TRIMP of 1,000 to ~1,500, approximately equivalent to exercise at 75% maximal HR for 120 to ~180 min/wk (Fig. 3).

*Spectral analysis.* The low-frequency power of R-R interval variability was increased significantly at 3 and 6 mo of training and returned to the control levels at 9 and 12 mo (Fig. 4). The high-frequency power of R-R

interval variability tended to increase at 3 mo, although it was not statistically significant. There were no significant changes in normalized indexes of R-R interval variability. In contrast, the low-frequency power of SBP variability increased significantly at 3, 6, and 9 mo of training compared with baseline, and returned to near control levels at 12 mo (Fig. 4). The high-frequency power of SBP variability tended to decrease, although it was not statistically significant ( $P = 0.06$ ). The low-frequency power in both R-R interval and SBP variabilities was correlated to the dose of exercise with a second-order regression model that resembled a bell-shaped curve, which also centered around a TRIMP of 1,000 to ~1,500 (Fig. 4).

*Baroreflex function.* Compared with baseline, Gain HF was significantly increased at 3 and 6 mo of training and returned to the control levels at 9 and 12 mo (Fig. 4). Furthermore, Gain LF tended to increase at 3 and 6 mo of training and returned to control levels at 9 and 12 mo (Fig. 4). Estimate of coherence was  $0.57 \pm 0.02$  in the high-frequency range and  $0.54 \pm 0.02$  in the low frequency with a negative phase; neither coherence

Table 4. Changes in cardiovascular variability during training

	Baseline	3 mo	6 mo	9 mo	12 mo
Spontaneous respiration					
LFR, ms <sup>2</sup>	756 ± 189	1,963 ± 346*	2,305 ± 374*	1,753 ± 317*	2,412 ± 615*
HFR, ms <sup>2</sup>	763 ± 233	1,318 ± 354	956 ± 218	723 ± 229	1,073 ± 273
LFBP, mmHg <sup>2</sup>	3.6 ± 0.8	7.6 ± 1.4*	7.1 ± 1.2*	9.3 ± 2.2*	5.4 ± 0.7
HFBP, mmHg <sup>2</sup>	1.8 ± 0.3	2.1 ± 1.1	1.0 ± 0.2	0.8 ± 0.2	1.2 ± 0.3
NormLFR	0.26 ± 0.04	0.32 ± 0.04	0.38 ± 0.06	0.42 ± 0.05	0.38 ± 0.13
NormHFR	0.25 ± 0.06	0.23 ± 0.05	0.16 ± 0.03	0.15 ± 0.03	0.18 ± 0.03
GainLF-RR, ms/mmHg	11.8 ± 1.5	15.0 ± 1.6	15.4 ± 2.1	12.3 ± 1.1	15.3 ± 1.8
GainHF-RR, ms/mmHg	15.1 ± 2.2	25.9 ± 4.0*	27.3 ± 4.4*	23.8 ± 3.6	23.0 ± 3.1
Controlled respiration					
LFR, ms <sup>2</sup>	747 ± 208	1,486 ± 358*	1,504 ± 403*	1,064 ± 179	817 ± 158
HFR, ms <sup>2</sup>	2,720 ± 1108	3,581 ± 887	2,909 ± 532	3,075 ± 1105	2,850 ± 953
LFBP, mmHg <sup>2</sup>	2.7 ± 0.5	4.3 ± 0.8*	4.5 ± 0.9*	6.0 ± 1.0*	3.6 ± 0.7
HFBP, mmHg <sup>2</sup>	6.2 ± 1.7	5.4 ± 1.1	4.3 ± 0.7	4.0 ± 0.5	3.5 ± 0.5
NormLFR	0.19 ± 0.04	0.17 ± 0.02	0.2 ± 0.05	0.18 ± 0.03	0.18 ± 0.05
NormHFR	0.45 ± 0.08	0.45 ± 0.06	0.45 ± 0.07	0.46 ± 0.07	0.46 ± 0.05
GainLF-RR, ms/mmHg	12.3 ± 1.9	16.4 ± 2.7	15.9 ± 3.1	10.2 ± 1.0	12.3 ± 1.9
GainHF-RR, ms/mmHg	16 ± 2.7	24.4 ± 4.1*	22.9 ± 3.4*	18.8 ± 3.2	19.4 ± 3.0

Values are mean ± SE;  $n = 11$ . LFR, power in low frequency of R-R variability; HFR, power in high frequency of R-R variability; LFBP, power in low frequency of blood pressure; HFBP, power in high frequency of blood pressure; NormLFR, normalized power in low frequency of R-R variability; NormHFR, normalized power in high frequency of R-R variability; GainLF-RR, low-frequency transfer function gain (ms/mmHg); GainHF-RR, high-frequency transfer function gain (ms/mmHg). \* $P < 0.05$  compared with pretraining baseline.

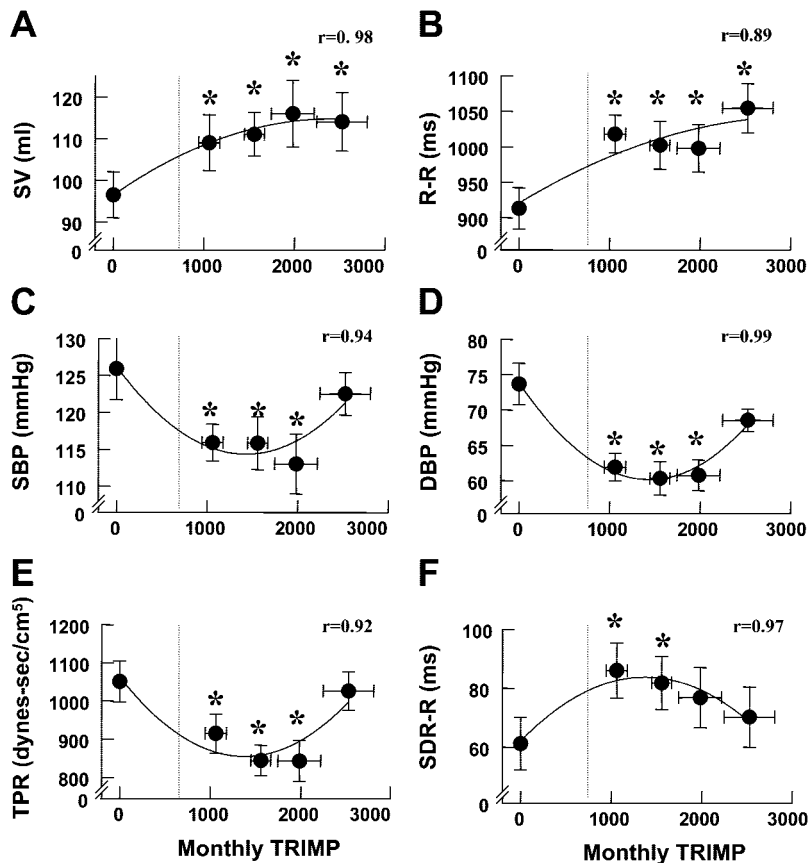


Fig. 3. Dose-response relationship between exercise intensity (monthly TRIMP) and static cardiovascular indexes. The vertical dotted line represents the monthly TRIMP that is equivalent to typical cardiac rehabilitation program. SV, stroke volume (A); DBP, diastolic blood pressure (D); TPR, total peripheral resistance (E); SDR-R, standard deviation of R-R intervals (F). B: R-R; C: SBP. \* $P < 0.05$  compared with pretraining baseline.

nor phase changed during training. Both Gain HF and Gain LF were correlated to the dose of exercise with a second-order regression and had bell-shaped curves that centered around a TRIMP of 1,000 to ~1,500 (Fig. 4).

DISCUSSION

The primary new findings from the present study are threefold. 1) Moderate amounts of exercise training for

3 mo are sufficient to achieve substantial changes in BP and dynamic regulation of HR. 2) More prolonged and intense training does not necessarily lead to greater enhancement of these changes. 3) The relationship between the exercise training stimulus and the responses in BP or reflex control of HR do not follow a simple, linear dose-response relationship and may have a bell-shaped or U-shaped relation with a maximal response at moderate amounts of training.

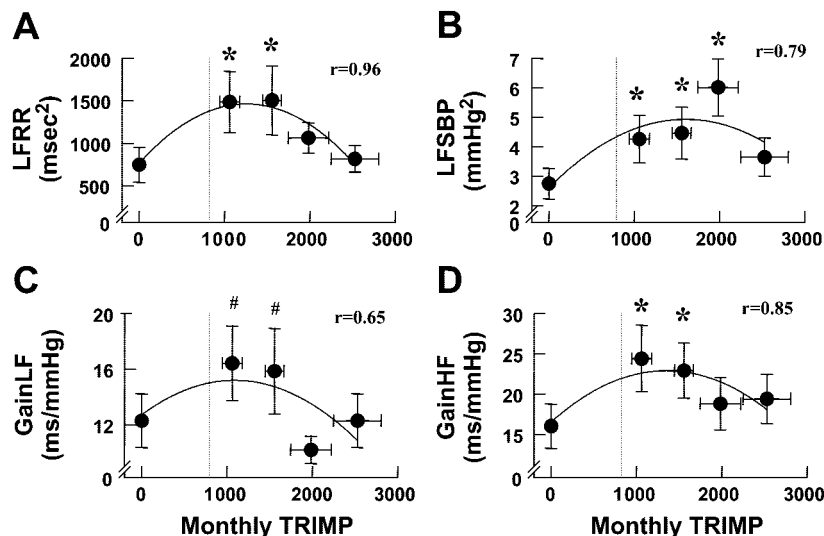


Fig. 4. Dose-response relationship between exercise intensity (monthly TRIMP) and dynamic cardiovascular indexes. The vertical dotted line is the same as in Fig 3. LFR-R, low-frequency power of R-R interval (A); LFSBP, low-frequency power of blood pressure variability (B); Gain LF, transfer function gain in low-frequency range (C); Gain HF, transfer function gain in high-frequency range (D). \* $P < 0.05$  compared with pretraining baseline. # $P < 0.05$  compared with 9 mo.

*Steady-state hemodynamics.* Decreases in BP after 3 mo of training, in association with decreased TPR and increased cardiac output, suggest that the training-induced reduction in BP is mediated primarily by a decrease in peripheral vascular resistance. This initial reduction in BP remained unchanged despite increases in exercise duration and intensity up to 9 mo of additional training. Thus the majority of the hypotensive effect of endurance training was achieved with a moderate dose of exercise that can be achieved by most individuals who engage in an exercise program. One possible mechanism of these changes may be increases in the production of vasoactive factors by the endothelium after training in healthy subjects (24). The fact that BP returned to pretraining levels with high-intensity and long-duration training sessions at the end of training program is consistent with two previous studies (17, 31) that tested different intensities of exercise. Both of these investigations suggested that higher-intensity training may be less effective in decreasing BP than lower-intensity training.

*HR variability.* Spectral analysis of HR variability quantifies the dynamic, frequency-dependent changes in HR, which reflect autonomic modulation of sinus node activity (2, 36). High-frequency power of R-R interval ( $>0.15$  Hz) appears to be mediated predominantly by changes in vagal activity, whereas low-frequency power ( $<0.15$  Hz) is determined by changes in both sympathetic and vagal activity (2, 36).

Most previous longitudinal studies (28, 42, 43) have shown that exercise training increases HR variability. Increases in R-R interval and the variability indexes at 3 and 6 mo in the present study are remarkably consistent with these previous reports. From the present study, it appears that moderate amounts of exercise training for 3 mo are sufficient to achieve the majority of this response.

In contrast, some cross-sectional and more prolonged longitudinal studies showed no difference in HR variability between endurance athletes and untrained subjects (7, 39) or with prolonged endurance training (30). However, these reports are also consistent with our results, which showed that the increased HR variability returned to baseline after high-intensity training for 9 mo. Thus the results from the present study may reconcile these previous apparently contradictory results between longitudinal and cross-sectional studies.

The reduction in HR and increases in HR variability are likely primarily due to augmented parasympathetic activity by training. However, the normalization of HR variability after 9 mo of intensive training, as well as the absence of changes in high-frequency power of R-R interval, are inconsistent with sustained increases in parasympathetic tone. There are three possible explanations for the dissociation between apparent increased parasympathetic tone (i.e., decreased HR) and the changes in HR variability parameters during training. First, increased vagal discharge may give rise to relatively constant or saturated parasympathetic modulation of the sinus node, diminishing the HR variability despite overall increases in vagal tone

(16). Second, it is possible that moderate exercise for 3 mo mainly augments vagal activity but after more prolonged and intense training reductions in resting sympathetic activity (12) may become more prominent. Reduced sympathetic activity may also reduce both HR and HR variability, especially at low frequencies, as observed after 6 mo in this study. Third, cardiac remodeling with training may alter the intrinsic HR, independent of autonomic mechanisms (29). This remodeling may also help explain the reduction in peak HR after training (29).

*BP variability.* Arterial pressure Mayer waves, occurring at  $\sim 0.1$  Hz, are presumed to result from sympathetic vasomotor activity. Therefore, the low-frequency power of BP variability may reflect the magnitude of sympathetic vasomotor variability (37).

However, although BP and TPR decreased, there did not appear to be any decrease in vasomotor activity, as indicated by increases rather than decreases in low-frequency BP variability in the present study. This discrepancy may be explained by vascular remodeling during exercise training, which occurs through adaptation of the endothelium and/or smooth muscle (10, 24). Thus remodeling of peripheral vessels may develop during the time course of exercise training that may modify or counterbalance neural effects on BP variability.

*Baroreflex function.* Previous results of the effects of exercise training on the baroreflex have been conflicting (6, 27, 30, 32, 43, 44). However, the non-linear dose-response relationship between exercise training and dynamic regulation of HR in the present study may explain those previous conflicting reports. Virtually all static (except resting HR) and dynamic circulatory variables in the present study suggested that the relationship between the dose of exercise training and the changes in autonomic control of the circulation has a bell-shaped relation. One explanation may be that, after 12 mo of intensive training, our subjects might have become slightly overtrained (49). A second possibility may be a differential time course of cardiac vs. vascular remodeling with long-term training. Preliminary reports from these subjects suggest that the early stages of exercise training result in concentric, right and left ventricular hypertrophy (15), which would increase right ventricular and/or left ventricular interaction. However, progressive training leads to left ventricular dilation and possibly even reduced pericardial constraint, thereby resetting autonomic control closer to the untrained state. Our findings suggest that different study designs, different levels of fitness, or different training intensities may lead to divergent results (increase, no change, decrease in baroreflex).

*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 dose of training. Therefore, our results must be interpreted cautiously. We suspect, but cannot prove, that continued training over time at any given dose would not change cardiovascular parameters such as

those measured here. We can say, however, that, in previous investigations involving many of these same volunteers, HR and BP variability appear consistently sensitive to physical activity, changing in directionally opposite ways with induced deconditioning compared with exercise training (21). Moreover, these measures of HR and BP variability appear robust and change little over time periods as long as 1 yr without any intervention (21).

In addition, the subjects studied were young and free of known cardiovascular disease. Thus these results are more relevant to primary rather than secondary coronary heart disease prevention. Because both age (1) and the presence of cardiovascular disease both decrease HR variability (8, 9, 14, 45), the results of this study could be different in older individuals or in those with manifest cardiovascular disease. Indeed, it is possible that such patients could have a greater range of responsiveness and thus have a more robust or sustained response to training.

We must also point out that during the last 3 mo of the training program, the increase in exercise dose was accomplished by increasing the duration of base training sessions (particularly long runs) with an actual decrease in the number of high-intensity sessions compared with the previous 3 mo. It is possible that this reduction in intensity could explain at least part of the return of many of the measured cardiovascular variables to baseline. However, the largest improvement in HR, BP, and cardiovascular variability occurred during the first 3 mo of training, when no intervals were performed. Second, the improvements in hemodynamics and cardiovascular variability from 6 to 9 mo were modest and, in the case of many variables, nonexistent (Figs. 1–4) despite the fact that the increase in intensity was most marked during this part of the training program. Third, high-intensity sessions continued to be performed during the last 3 mo of our training program, just at a reduced frequency.

**Clinical implication.** A critical question regarding the effect of exercise on cardiovascular mortality is the intensity and duration of exercise training required to achieve a clinically meaningful reduction in death from cardiovascular disease (18, 26). Previous studies have suggested that increased vagal activity after training, which may reduce the risk of ventricular fibrillation during ischemic exercise, may be a key mechanism for the reduction in sudden death associated with exercise training (20). These experimental observations are supported by epidemiologic studies that have shown an inverse association between HR variability and heart disease risk (25, 48). Although we did not try to elucidate the mechanisms of the reduction in mortality from cardiovascular disease in the present study, our results suggest that moderate exercise training for 3 mo is sufficient to achieve a clinically meaningful increase in vagal modulation of the sinus node. Furthermore, our results also showed that moderate exercise training for 3 mo is sufficient to reduce BP.

These observations extend and provide one potential mechanism for epidemiologic investigations relating

leisure time physical activity to cardiovascular mortality. For example, Paffenbarger et al. (35) suggested that energy expended during recreational activity is inversely related to total mortality, and death rates were significantly lower among the subjects expending  $\geq 2,000$  kcal during exercise per week than among less active men. This level of leisure-time physical activity is remarkably consistent with our results, suggesting that moderate amounts of exercise (from 80–100 kcal/10 min for 180–200 min/wk) is sufficient to achieve substantial changes in BP and dynamic regulation of HR. However, our results also showed that more prolonged and intense training does not necessarily lead to greater enhancement of these changes in BP and autonomic control of the circulation and, therefore, may not provide an added protective benefit against cardiovascular mortality by these mechanisms.

## APPENDIX

Specific calculations for estimation of the TRIMP were derived from Banister et al. (4). The duration of any specific training session is multiplied by the average HR achieved during that session ( $HR_{avg}$ ), as measured by using a HR monitor.  $HR_{avg}$  is then expressed as a fraction of the HR reserve, which is derived from direct measurements of resting HR (quiet, supine rest before arousal from bed in the morning) and maximum HR from a maximal exercise test. The different exponents for males and females are empirically derived from lactate appearance/disappearance curves (4) and provide an additional weighting factor, which increases the TRIMP score for relatively higher exercise intensities.

For males,  $TRIMP = \text{training duration} \times [(HR_{avg} - HR_{rest}) / (HR_{max} - HR_{rest})] \times 0.64 \exp[(HR_{avg} - HR_{rest}) / (HR_{max} - HR_{rest}) \times 1.92]$ , where  $HR_{max}$  is maximal HR and  $HR_{rest}$  is resting HR. For females,  $TRIMP = \text{training duration} \times [(HR_{avg} - HR_{rest}) / (HR_{max} - HR_{rest})] \times 0.86 \exp[(HR_{avg} - HR_{rest}) / (HR_{max} - HR_{rest}) \times 1.67]$ .

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## DISCLOSURES

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