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Comparison of 24-Hour Parasympathetic Activity in Endurance-Trained and Untrained Young Men

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Objectives. **This study compares 24-h parasympathetic activity in aerobically trained and untrained healthy young men.**

Background. **Higher values of parasympathetic nervous system activity are associated with a low mortality rate in patients after myocardial infarction, but it remains uncertain what therapeutic interventions can be used to increase parasympathetic activity. Although it is thought that exercise training can increase parasympathetic activity, studies have reported conflicting results, perhaps because this variable was measured for only brief intervals and usually inferred from changes in reflex responses induced by pharmacologic blockade.**

Methods. **Parasympathetic activity was assessed noninvasively from 24-h ECG recordings by calculating high frequency (0.15 to 0.40 Hz) beat to beat heart period variability in eight endurance-trained men (maximal oxygen consumption ≥55 ml/kg per min) and eight age-matched (mean = 29 yr) untrained men (maximal oxygen consumption ≤40 ml/kg per min). The data were analyzed separately for sleeping hours when parasympathetic activity is dominant and also for waking hours.**

Results. **The geometric mean of high frequency power was greater in the trained than in the untrained men during the day (852 vs. 177 ms^2, $p < 0.005$), during the night (1,874 vs. 427 ms^2, $p < 0.005$) and over the entire 24 h (1,165 vs. 276 ms^2, $p < 0.001$).**

Conclusions. **Parasympathetic activity is substantially greater in trained than in untrained men, and this effect is present during both waking and sleeping hours. These data suggest that exercise training may increase parasympathetic activity over the entire day and may therefore prove to be a useful adjunct or alternative to drug therapy in lessening the derangements of autonomic balance found in many cardiovascular diseases.**

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Enhancement of parasympathetic nervous system activity may be of therapeutic benefit in cardiac disease. Mortality risk after myocardial infarction has been reported to be lower in patients with greater parasympathetic nervous system activity (1). Exercise training may be an intervention that increases such activity. However, the data to support this hypothesis are inconclusive (2–5) primarily because efferent vagal outflow to the heart cannot be measured directly in conscious humans or laboratory animals. Recently a variety of approaches have been proposed to evaluate parasympathetic nervous system activity in humans by examining beat to beat variations in normal RR (NN) intervals. These techniques are especially appealing because they are noninvasive, allow for continuous long-term measurements and avoid the use of drugs. Power spectral analysis of heart period variability can reveal peaks in the spectrum that quantify cyclic changes in NN intervals. For example, a high frequency peak (0.15 to 0.40 Hz) that corresponds to the respiratory frequency reflects modulation solely by the parasympathetic nervous system (6–8), and a low frequency peak (0.04 to 0.15 Hz) reflects NN modulation by both the parasympathetic and sympathetic nervous systems (6–9). Although short-term measures of low frequency power have been reported to be strongly influenced by sympathetic activity, Kleiger et al. (10) recently reported that low frequency power calculated over 24 h in normal young subjects is predominantly influenced by parasympathetic tone.

The aim of the present study was to compare parasympathetic modulation of normal RR (NN) intervals in athletes with a high level of endurance training and untrained subjects by analyzing the spectral components of heart period variability. We hypothesized that athletes would exhibit greater high and low frequency power during 24-h continuous electrocardiographic (ECG) recordings. A separate examination of heart period variability during sleep permitted us to observe the differences in parasympathetic tone between endurance-trained and untrained men when vagus nerve activity is high and sympathetic nerve activity is low.

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Methods

Study subjects. Eight untrained and eight endurance-trained healthy men 24 to 38 years old who were nonsmokers, were not taking any drugs, consumed no more than 300 mg/day of caffeine, had a body mass index between 19 and 25 kg/m^2 and had maintained a stable body weight (<2 kg gain or loss during the 6 months before the study) were recruited for this study. The objective of these inclusion criteria was to eliminate the possible confounding influences of disease, drugs, caffeine, obesity, weight changes and erratic dietary habits on autonomic function. Men who trained in aerobic activities such as running, cycling and swimming and who achieved a maximal oxygen consumption (VO_2 max) of ≥55 ml/kg per min were classified as endurance trained. Men who had not participated in any regular exercise in the last year and who achieved a VO_2 max of ≤40 ml/kg per min were classified as untrained. To clearly separate trained and untrained groups, candidates who achieved a VO_2 max between 41 and 54 ml/kg per min were excluded from participation in this study.

Experimental treatments. After a graded exercise test and on acceptance into the study, the subjects were asked to return on another morning between the hours of 6 and 10 AM to begin a 24-h continuous ECG recording. The subjects were instructed to avoid caffeinated and alcoholic beverages and to refrain from moderate, heavy or sustained exercise on the morning before the application of the Holter recorder, as well as during the next 24 h. They were also asked to record the time they went to sleep and the time they woke up. The protocol was approved by the Institutional Committee on Human Research of the Columbia Presbyterian Medical Center. Before participation in this study, subjects gave their informed consent.

Procedures

Graded exercise test. Maximal oxygen consumption was assessed by an incremental exercise test on an electronically braked bicycle ergometer. During the test the work rate increased continuously as a ramp function. The increment size, that is, the slope of the ramp function, selected for each subject was based on the subject's age, height, weight (11) and training status.

Expired gas analysis was performed continuously during the test with a commercially available Medical Graphics 2001 unit. Subjects breathed through a Hans Rudolph nonrebreathing valve with a dead space of 95 ml. Expired air flow was measured with a pneumotachograph equipped with a differential pressure transducer. Volume calibration was performed with a 3L calibration syringe before each test. Oxygen and carbon dioxide were measured continuously from the mouthpiece. Oxygen content was measured by a solid state zirconium cell, accurate to within 0.05%. Carbon dioxide content was measured by an infrared absorption analyzer accurate to within 0.2%. The gas analyzers were calibrated before each test with commercially prepared gas mixtures of known concentration certified to within 0.02%. The signals underwent analog to digital conversion for on-line breath by breath computations.

Holter ECG recordings. Dual-lead ECG recordings (leads CM_5 and CM_5) were made on Marquette 8500 recorders, which contain a digital clock to provide a time signal that is continuously recorded on the tape. The Holter tapes were digitized on a Marquette series 8000 scanner and the signal was sampled at 128 Hz. Sampling was triggered by the timing track on the tape to correct for flutter and wow of the recording or playback tape transport. QRS recognition and arrhythmia detection were done automatically by template matching. This system generates a beat by beat annotation of the ECG with a consistent and accurate time stamp for each QRS complex and classifies each complex as normal sinus, atrial or ventricular premature complex or noise. The decisions made automatically by the computer were reviewed and corrected by an experienced technician and then by a cardiologist. The digitized ECG, QRS trigger list and report data were then transferred over a high speed direct memory access link to a Sun Microsystems 4/75 computer where additional editing on the sorted intervals and further analysis including time and frequency domain analysis of heart period variability were performed. Each completed analysis, comprising 50 Mbytes of digitized ECG and a QRS trigger list, was stored on a laser disk.

Analyses

Twenty-four-hour heart period variability. The 24-h heart period power spectrum was computed with use of a fast Fourier transform on data for the entire 24-h period (12,13). The following frequency domain measures were computed by integrating over their frequency intervals: total (1.15×10^{-5} to 0.40 Hz), low frequency (0.04 to 0.15 Hz) and high frequency (0.15 to 0.40 Hz) power. In addition to the frequency domain variables, the SD of all NN intervals (SDNN) was computed in the time domain.

Day and night heart period variability. Heart period variability was computed for daytime (awake) and nighttime (asleep) hours. The hours that comprised sleep were determined from the patient diaries. Because the number of hours that each subject slept varied, a 5-h segment ending 1 h before the subject's awakening was designated as "asleep." The clock hours that were designated as sleep were similar in the two groups. The hours between 11 AM and 9 PM were selected to be representative of "awake." This interval was chosen to allow monitoring of a continuous and uninterrupted block of time in all subjects because the Holter recorder was applied between 7 and 10 AM. The 24-h data consisted of the waking and sleeping hours, as well as the transition times not included in either.

The sleeping and waking power spectra were obtained with use of the algorithm described by Rottman et al. (13). The sleeping and waking periods were each divided into consecutive, nonoverlapping 5-min segments. At least 80%

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of the RR intervals in a 5-min segment were required to be normal intervals, that is, bounded by two normal QRS complexes; otherwise, the segment was excluded from further processing. Segments containing substantial periods of noise or very frequent atrial or ventricular premature complexes would thereby be excluded from analysis. Then, the mean NN interval was subtracted from the sampled night and day heart period data, a Hanning window was applied and a fast Fourier transform was computed. The resulting 5-min periodograms were corrected for attenuation caused by the sampling and the Hanning window. The spectra of all usable 5-min segments were averaged to obtain low (0.04 to 0.15 Hz) and high (0.15 to 0.40 Hz) frequency bands for the daytime and nighttime periods.

The correlation between the 24-h in toto method and the 5-min segmental method just described has been shown to be excellent for low ($r = 0.999$) and high ($r = 0.997$) frequency power (14). The in toto method was used to compute the 24-h spectra because it allowed for the computation of frequencies <0.0033 Hz that contribute to the total power over 24 h and cannot be computed by the 5-min method.

Statistical analysis. Unpaired *t* tests were performed to compare the two groups on mean heart period variability during the entire 24 h and on the fractions of the total power accounted for by low frequency and high frequency power. The night and day heart periods and heart period variability data were analyzed with use of a 2 × 2 analysis of variance where the factors were fitness group (trained vs. untrained) and time of day (day vs. night).

Because the distributions of the heart period measures were positively skewed, these data were transformed to their natural logarithms. The logarithmic transformations succeeded in producing approximately symmetric distributions and thus allowed use of parametric statistics that require near normal distributions. The means of the logarithmic data were transformed back into the original units by computing their antilogarithms along with their associated 95% confidence intervals. The means calculated this way are known as geometric means. They are validly compared with each other in terms of their ratios (15).

Table 1. Characteristics of 16 Study Subjects

	Untrained Men (n = 8)	Trained Men (n = 8)	p Value
Age (yr)	29.3 ± 2.8	28.5 ± 4.1	NS
Height (cm)	177.6 ± 7.1	179.4 ± 11.2	NS
Weight (kg)	73.6 ± 5.7	73.3 ± 9.5	NS
Body mass index (kg/m²)	23.4 ± 1.0	27.7 ± 0.8	NS
VO_2max (liters/min)	2,623 ± 479	4,879 ± 617	*
VO_2max (ml/kg per min)	35.5 ± 4.6	66.6 ± 3.7	*
Maximal work load (W)	227 ± 32	381 ± 44	*

*Because fitness level was used to qualify subjects and assign them to the untrained and trained groups, we did not perform statistical tests on these variables. Values are expressed as mean value ± SD for each group. VO_2max = maximal oxygen consumption.

Results

Descriptive data. Demographic and physical characteristics of the trained and untrained subjects are shown in Table 1. The mean age, height, weight and body mass index were similar for the two groups. The mean maximal oxygen consumption expressed in absolute terms (2,623 vs. 4,878 $ml \cdot min^{-1}$) and relative to total body weight (35.5 vs. 66.6 $ml \cdot kg^{-1} \cdot min^{-1}$) were substantially higher in the trained group.

Twenty-four-hour heart period variability. The 24-h normal RR (NN) intervals and the time and frequency domain measures of heart period variability are presented in Table 2. Noise on the average accounted for <4% and ectopic activity for <1% of any recording. As expected, the trained subjects demonstrated significantly longer average NN intervals. All the measures of heart period variability were significantly greater in the trained compared with the untrained subjects. The NN intervals during a random 10-min period at night are presented graphically for an untrained and an endurance-trained subject in Figure 1. Although the mean heart period for each subject remains essentially unchanged during the designated time period, the trained subject clearly exhibits greater beat to beat variability.

Table 2. Comparison of 24-Hour Normal RR (NN) Intervals and Heart Period Variability in 16 Study Subjects

	Untrained Men (n = 8)	Trained Men (n = 8)	p Value
Average NN interval (ms)	747 ± 61	1,101 ± 146	
Ln NN intervals (Ln ms)	6.61 ± 0.08	7.00 ± 0.13	< 0.0005
SD of NN intervals (SDNN) (ms)	146 ± 19	218 ± 59	
Ln SDNN (Ln ms)	4.98 ± 0.13	5.36 ± 0.25	< 0.005
Total power (<0.40 Hz) (ms^2)	23,050 ± 6,320	50,449 ± 29,288	
Ln total power (Ln ms^2)	10.02 ± 0.25	10.71 ± 0.49	< 0.005
Low frequency power (0.04 to 0.15 Hz) (ms^2)	1,169 ± 389	3,240 ± 1,288	
Ln low frequency power (Ln ms^2)	7.00 ± 0.39	8.01 ± 0.43	< 0.0005
High frequency power (0.15 to 0.40 Hz) (ms^2)	318 ± 193	1,399 ± 776	
Ln high frequency power (Ln ms^2)	5.62 ± 0.57	7.06 ± 0.72	< 0.001

Values are expressed as mean value ± SD for each group. Ln = natural logarithm; NN = normal RR.

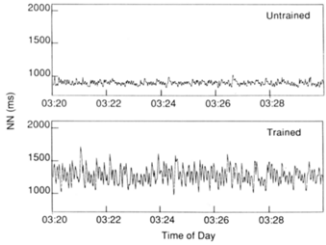

Figure 1. Normal RR (NN) intervals of an untrained (**top panel**) and endurance-trained (**bottom panel**) subject during a 10-min interval during the night. Note the longer NN intervals and greater amplitude of high frequency fluctuations in the endurance-trained subject.

The trained subjects displayed significantly greater total power in their 24-h heart period power spectrums than did the untrained subjects (Table 2). In the time domain SDNN calculated over 24 h is equivalent to the square root of total power calculated over the same interval; accordingly, SDNN is also significantly greater in the trained subjects.

High frequency power, a pure index of vagal tone, was 4.2 times greater ($p < 0.005$) in the trained men than in the untrained men over 24 h (geometric means = 1165 and 276 ms^2, respectively). Low frequency power was 2.8 times greater ($p < 0.001$) in the trained men, a finding consistent with the notion that 24-h low frequency power is strongly influenced by the vagus. When the content of each frequency band was expressed as a percent of total power (Fig. 2), high frequency power accounted for a significantly ($p < 0.02$) greater proportion of total power in the trained than in the untrained group, whereas low frequency power contributed a similar amount to the total power in the trained and untrained groups. In both groups the combined power in the high and low frequency ranges constitutes a small percentage of the total 24-h heart period variability, whereas the majority of the heart period power over 24 h is <0.04 Hz.

Night and day heart period variability. The mean NN interval was significantly ($p < 0.005$) longer in the trained than in the untrained subjects during the day and during the night (Fig. 3). The mean NN interval increased in both groups from day to night ($p < 0.005$). The magnitude of the relative increase in the average NN interval from night to day was similar in the trained and untrained groups (31% vs. 38%).

High frequency power increased during sleep in both groups ($p < 0.005$) (Fig. 3) and was maintained at a higher level in the trained subjects during the day (852 vs. 177 ms^2) and during the night (1,874 vs. 427 ms^2) ($p < 0.005$). The absence of a significant group by time interaction indicated that the relative magnitudes of the changes in this variable between night and day were not significantly different in the two groups. Low frequency power was also higher in the trained than in the untrained subjects ($p < 0.005$) and was higher during the night than during the day ($p < 0.05$), suggesting that low frequency power has a substantial parasympathetic component. However, the magnitude of the increase in low frequency power from day to night averaged across groups was significantly ($p < 0.005$) less than the increase in high frequency power; that is, low frequency power during the night was 1.4 times as great during the night as during the day, whereas high frequency power was 2.4 times as great. This latter finding is the result of high frequency power being solely influenced by parasympathetic activity, whereas low frequency power is influenced by both sympathetic and parasympathetic activity.

Discussion

Role of parasympathetic activity in the bradycardia of endurance-trained athletes. The relative bradycardia exhibited by endurance-trained individuals is thought to be mediated in part by greater parasympathetic activity. However, studies (2–5,16,17) that have examined differences in para-

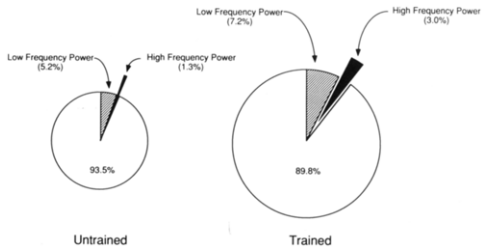

Figure 2. Relative contribution of low frequency (0.04 to 0.15 Hz) and high frequency (0.15 to 0.40 Hz) power to the 24-h total power. The area of the circles is proportional to the total power. Note that the majority of the 24-h total power is derived from frequencies <0.04 Hz in both groups and the proportional contribution of high frequency power to the total power is significantly ($p < 0.02$) greater in the trained group.

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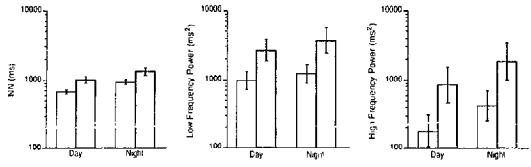

Figure 3. Normal RR (NN) (**left**), low frequency power (**middle**) and high frequency power (**right**) during the day and during the night in untrained (**white bars**) and trained (**gray bars**) subjects. The bars represent geometric means along with their corresponding 95% confidence intervals. A logarithmic scale was used so that equal differences would represent equal ratios. NN, low frequency power and high frequency power were significantly greater ($p < 0.05$) during the night than during the day and significantly greater ($p < 0.001$) in trained than in untrained subjects during both the day and the night.

sympathetic activity between endurance-trained and untrained subjects have yielded conflicting findings. Factors other than parasympathetic activity that may determine heart rate at rest in humans include intrinsic heart rate and sympathetic tone. Previous studies have uniformly found that a decline in the intrinsic heart rate contributes to rest bradycardia in athletes (3,4,5,17), whereas a reduction in sympathetic tone probably makes little (3) or no contribution (5,18) because sympathetic activity is very low under conditions at rest in normal persons. The uncertain contribution of the parasympathetic nervous system to the athlete's bradycardia relates in large part to the use of pharmacologic blockade techniques in many investigations and the problems inherent in this methodology. For example, the landmark studies (2,16) in this area did not perform dose-response curves. In the absence of this information, differing interpretations could be applied to experimental observations. Furthermore, in more recent studies (3,5) in which complete blockade was demonstrated, the results remain conflicting.

Parasympathetic activity and beat to beat variation in heart period. In this study we assessed parasympathetic activity by measuring the beat to beat variation in heart period. Specifically, we used spectral analysis to quantify the component of heart period variability generated by respiration, that is, high frequency power. This technique may provide the best available indirect estimate of vagal cardiac efferent activity and has been validated in a number of studies (6–8,19,20). In anesthetized animals the magnitude of the respiratory sinus arrhythmia correlates well with total cardiac vagal efferent traffic (19), and changes in the magnitude of the respiratory sinus arrhythmia occur in parallel with vagal traffic (19,20). Whereas previous studies have only examined vagal activity during short-term laboratory experiments, we compared continuous long-term measurements of parasympathetic activity in trained and untrained men.

The present findings provide strong evidence for the hypothesis that endurance-trained men exhibit greater parasympathetic activity than do untrained men during sleep (when vagal tone is high) and while awake. These data suggest an upward resetting of vagal tone in the trained subjects over the entire 24-h period. Our findings are consistent with those reported by Molgaard et al. (21), who classified healthy subjects according to their leisure time physical activity. Even though fitness level was defined less rigorously than in our study, there was still a significant influence on parasympathetic indexes of day and night heart rate variability independent of age, gender and smoking habits.

Twenty-four-hour low frequency power (0.04 to 0.15 Hz). The greater low frequency power demonstrated by the trained subjects supports the finding of Kleiger et al. (10) that low frequency power in normal young subjects calculated over 24 h is predominantly influenced by parasympathetic rather than sympathetic activity. If low frequency power was mostly sympathetic in origin, one would expect that low frequency power would be greater in untrained than in trained subjects because sympathetic activity is known to be higher in untrained subjects during exercise (22), and at rest it is either slightly higher (3) or not different (5,18) from that in trained subjects. However, we found the opposite to be true; that is, low frequency power was higher in the trained subjects, indicating that 24-h low frequency power is primarily parasympathetically and not sympathetically mediated.

Clinical implications. Disturbances in the autonomic control of the heart are often associated with cardiac disease. Eckberg et al. (23) demonstrated that patients with the most advanced disease exhibit the greatest impairment in parasympathetic activity. Heart period variability techniques have been used to advance knowledge in this area. For example, 24-h high frequency power is significantly associated with survival 2 to 4 years after acute myocardial infarction (1). In addition, high frequency power was found (24) to be reduced in patients with heart disease known to be at increased risk of sudden cardiac death when compared with the level in those not at increased risk. This finding provides additional evidence that cardiac paraysmpathetic

function is depressed in patients prone to development of sudden death, and that altered autonomic function contributes to the development of electrical instability in such individuals. Conversely, numerous studies have shown that increased vagal activity decreases vulnerability to ventricular fibrillation during experimental myocardial ischemia in animals (25–27), as well as in patients with severe coronary artery disease (28). Therefore, because loss of cardiac vagal activity appears to be associated with cardiac electrophysiologic instability, the findings in the current investigation suggest that endurance training promotes vagal activity and hence could emerge as an effective, nonpharmacologic cardioprotective therapy.

Preliminary evidence to support the preceding hypothesis already exists. Billman et al. (29) demonstrated that chronic exercise increased the sensitivity of the baroreflex, which is mediated primarily by the parasympathetic nervous system, and prevented ventricular fibrillation during acute myocardial ischemia in a subgroup of dogs identified as susceptible to sudden cardiac death. La Rovere et al. (30) demonstrated a similar effect of exercise training on baroreflex sensitivity in postmyocardial infarction patients. Somers et al. (31) also found that patients with borderline hypertension had increased baroreflex sensitivity and vagal modulation of RR intervals after an endurance training program.

Our results may help explain the improved survival demonstrated by a recent meta-analysis (32) of exercise rehabilitation studies in postmyocardial infarction patients. Perhaps an exercise-mediated increase in parasympathetic activity contributes to this mortality benefit.

Limitations. Although the findings of the present study suggest that exercise training may indeed serve as a nonpharmacologic approach to modifying vagal activity, the study design was cross sectional, and therefore causal inferences can only be tentative. It is conceivable that genetic differences may somehow have contributed to the differences in both vagal activity and fitness in our two groups. It is also possible that those subjects who were endurance-trained athletes may have become so because of their inherently high vagal activity. However, experimental studies with animals (29) and several preliminary training studies involving patients with heart failure (33), postmyocardial infarction patients (30) and patients with borderline hypertension (31) support the hypothesis of a cause and effect relation between training and vagal tone.

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