Correlation of heart rate variability with cardiac functional and metabolic variables in cyclists with training induced left ventricular hypertrophy

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Abstract

Objective—To examine the correlation between heart rate variability and left ventricular mass in cyclists with an athlete's heart.

Methods—Left ventricular mass and diastolic function were determined at rest and myocardial high energy phosphates were quantified at rest and during atropine–dobutamine stress in 12 male cyclists and 10 control subjects, using magnetic resonance techniques. Ambulatory 24 hour ECG recordings were obtained, and time and frequency domain heart rate variability indices were computed.

Results—In the cyclists, the mean of all RR intervals between normal beats (meanNN), the SD of the RR intervals, and their coefficient of variation were significantly greater than in control subjects ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively). For cyclists and control subjects, only meanNN correlated with left ventricular mass ($r = 0.48$, $p = 0.038$). The heart rate variability indices that correlated with functional or metabolic variables were: meanNN *v* E/A peak (the ratio of peak early and peak atrial filling rate) ($r = 0.48$, $p = 0.039$); the root mean square of successive differences in RR intervals among successive normal beats *v* E/A area (ratio of peak early and peak atrial filling volume) ($r = 0.48$, $p = 0.040$); percentage of successive RR intervals differing by more than 50 ms *v* the phosphocreatine to ATP ratio at rest ($r = 0.54$, $p = 0.017$); and the SD of the average RR intervals during all five minute periods *v* the phosphocreatine to ATP ratio during stress ($r = 0.60$, $p = 0.007$).

Conclusions—Highly trained cyclists have increased heart rate variability indices, reflecting increased cardiac vagal control compared with control subjects. Left ventricular mass has no major influence on heart rate variability, but heart rate variability is significantly correlated with high energy phosphate metabolism and diastolic function.

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The term heart rate variability refers to variations in both instantaneous heart rate and RR interval length.[1] Changes in heart rate primarily result from alterations in autonomic nervous activity in the sinus node. This variable can be measured non-invasively, can be analysed in the time or frequency domain, and can provide general information about the health status of the heart and its autonomic control.[1 2]

The relevance and significance of heart rate variability in various populations has been well established. Attenuation of heart rate variability, indicating either increased sympathetic activity or reduced baroreflex sensitivity,[3] has been shown to be strongly predictive for sudden cardiac death and total cardiovascular mortality in the general population,[4 5] in patients with coronary artery disease,[6–9] and in patients with mitral valve disease.[10] In patients with myocardial infarction, heart rate variability is a better predictor of cardiac events and rhythm or conduction disturbances than left ventricular function and exercise ECG or ambulatory ECG variables.[2 7 11] Increased sympathetic activity can induce cardiac arrhythmias, whereas increased vagal tone is considered to be protective.[2 12]

A significant relation between reduced heart rate variability and the severity of left ventricular hypertrophy secondary to hypertension, diabetes mellitus, or aortic valve disease has recently been demonstrated,[13–16] suggesting that impaired cardiac autonomic function in pathological left ventricular hypertrophy may contribute to the mechanism of sudden cardiac death. Intensive participation in sports may lead to the development of left ventricular hypertrophy, generally called the athlete's heart.[17] To date, there is continuing debate over whether intense participation in competitive sport is associated with an increased risk of sudden cardiac death. Although exercise leads to increased heart rate variability,[18–24] left ventricular hypertrophy may be associated with reduced heart rate variability.[13–16] Accordingly, it would be appropriate to study the impact of exercise induced left ventricular hypertrophy on the modulation of heart rate variability in athletes. With this in mind, we investigated indices of heart rate variability and its physiological correlates in cyclists with exercise induced left ventricular hypertrophy, and these data were compared with those obtained from non-athletic healthy individuals.

Methods

STUDY POPULATION

Twelve highly trained male cyclists (mean (SD) age 41 (10) years) and 10 male control subjects (46 (9) years), matched for height and weight,

volunteered for the study. The athletes cycled at least 12 000 km/year and had been engaged in competitive cycling for 22 (8) years. None of the 10 control subjects was engaged in regular physical activity or competitive sports. All individuals were free from known cardiovascular disease and they were passed as normal on physical examination. The subjects were non-smoking, normotensive, and none was taking any drugs at the time of the study. A standard 12 lead ECG was recorded at rest. All ECGs were normal in the control subjects. In six cyclists the resting ECG met the Sokolow–Lyon voltage criteria for left ventricular hypertrophy (sum of amplitudes in V1 and R wave in V5 or V6 > 3.5 mV). The study was approved by the human research committee at our institution, and all individuals gave informed consent for their participation.

MAGNETIC RESONANCE IMAGING ACQUISITION
Magnetic resonance imaging was performed using a Philips Gyroscan ACS-NT system (Philips Medical Systems, Eindhoven, the Netherlands) operating at 1.5 Tesla, and ECG gating. Magnetic resonance images were acquired with breath hold multi-shot echo planar imaging as described previously.[25] Volume flow was assessed by magnetic resonance velocity mapping of flow across the mitral orifice. Velocity maps were acquired using retrospective gating as described previously.[26]

MAGNETIC RESONANCE IMAGING ANALYSIS
Multislice multiphase short axis image analysis was performed using the magnetic resonance analytical software system (MASS[27]) and a Sun IPX workstation (Sun Microsystems Computer Corporation, Palo Alto, California, USA). End diastolic and end systolic epicardial and endocardial contours of the stack of short axis image sections were traced manually. Papillary muscles were outlined and included in the left ventricular wall. Left ventricular mass was calculated as reported previously by our institution.[28] Volume flow was calculated by tracing a region of interest along the borders of the mitral valve in all time frames of a velocity map series. For each time frame, instantaneous volume flow was calculated using a computer algorithm by multiplying spatial average flow velocity and the area of the region of interest. Summation of all instantaneous volume flow data yielded total flow per cardiac cycle. The following indices of diastolic function were measured or derived: peak early filling rate, peak early filling volume, peak atrial filling rate, peak atrial filling volume, ratio of peak early and peak atrial filling rate (E/A peak), ratio of peak early and peak atrial filling volume (E/A area).[29]

[31]P MAGNETIC RESONANCE SPECTROSCOPY
[31]P Magnetic resonance spectra of the anterior wall of the left ventricle were acquired at rest and during atropine–dobutamine stress. A 1.5 Tesla Gyroscan S15 (Philips Medical Systems) was used, and a 10 minute three dimensional image selected in vivo spectroscopy (ISIS) protocol was performed as described previously.[30][31] Magnetic resonance spectra were transferred to a remote Sun-SPARC workstation to be quantified automatically by model function analysis in the time domain, using a priori spectroscopic knowledge to improve the accuracy of the spectral parameters. The ATP level in the spectra was corrected for the relative contribution of the ATP present in the blood, and the phosphocreatine to adenosine triphosphate (PCr/ATP) ratios were determined. Signal modelling, prior knowledge, and correction for partial saturation effects were applied, according to previously published procedures.[30]

ATROPINE–DOBUTAMINE INFUSION PROTOCOL
After the baseline spectrum was recorded, atropine sulphate (0.03 µg/kg) was given to achieve complete cholinergic blockade. Thereafter, myocardial stress was induced by administration of incremental intravenous doses of dobutamine. Dobutamine infusion was started at a dose of 10 µg/kg/min and was increased every two minutes by 5 µg/kg/min until a steady target heart rate was reached. The maximum infusion rate allowed was 40 µg/kg/min. The target heart rate in beats/min was 85% of the predicted maximum heart rate.[31] Blood pressure was recorded automatically every two minutes at rest, and each minute during dobutamine stress with an automated sphygmomanometer. Acquisition of a spectrum was then carried out during stress.

HOLTER MONITORING
Ambulatory 24 hour ECG monitoring was performed, using a Marquette 8500 three channel Holter recorder (Marquette Electronics, Milwaukee, Wisconsin, USA). The ECGs were analysed according to the guidelines set out by the European Society of Cardiology[1] using a Marquette series 8000 Holter analyser with manual override. Episodes containing beats with normal morphological characteristics were measured. The computed processed Holter ECGs were strategically reviewed by an editor and if necessary, the computer labels applied were modified. The exact point of onset of the QRS complexes was also interactively determined. In particular, episodes with the highest and lowest RR intervals were reviewed. The RR interval series was further analysed using a personal computer.[32] Apart from incidental ectopic beats, all subjects were in sinus rhythm throughout the recording period. RR intervals containing ectopic beats were interpolated by dividing the sum of the intervals of the preceding and successive beat by 2. Data segments in which the Marquette Holter analyser detected dual channel noise were not analysed.

Time domain and frequency domain indices of heart rate variability were computed during six hour sleep periods at night. Sleeping hours were defined as the six consecutive hours immediately before rising. Rising was determined either from an entry in the diary or from the rise in heart rate, or, wherever possible, from both. The analysis was limited to the sleeping period in order to avoid influences of

Table 1 Subject characteristics

	Athletes (n = 12)	Controls (n =10)	p Value*
Age (years)	40.9 (9.5)	46.1 (8.9)	NS
Heart rate (beats/min)	52 (6)	60 (5)	< 0.005
Height (cm)	180.9 (6.7)	181.5 (7.9)	NS
Weight (kg)	76.5 (8.2)	78.1 (10.1)	NS
BSA (m²)	1.96 (0.13)	1.99 (0.17)	NS
LVM (g)	198.7 (25.8)	138.1 (15.2)	< 0.001
LVMI (g/m²)	101.5 (12.0)	69.6 (6.9)	< 0.001
E/A peak	1.9 (0.5)	1.6 (0.2)	NS
E/A area	3.1 (1.0)	2.6 (0.6)	NS
PCr/ATP rest	1.44 (0.18)	1.39 (0.17)	NS
PCr/ATP stress	1.21 (0.11)	1.15 (0.13)	NS

Values are mean (SD). BSA, body surface area; E/A area, ratio of early and atrial filling volume; E/A peak, ratio of peak early and atrial filling; LVM, left ventricular mass; LVMI, left ventricular mass index; PCr, phosphocreatine.
*p value of Student's *t* test or Mann–Whitney test, as appropriate.

Table 2 Time and frequency domain indices of heart rate variability in athletes and control subjects

	Athletes (n = 12)	Controls (n = 10)	p Value*
Time domain			
MeanNN (ms)	1244 (148)	1085 (90)	0.006
SDNN (ms)	101 (28)	70 (18)	0.007
CVNN (%)	8.1 (2.1)	6.5 (1.5)	0.042
SDANN (ms)	68 (12)	61 (18)	NS
RMSSD (ms)	71 (39)	49 (19)	NS
pNN50 (%)	41 (24)	30 (17)	NS
Frequency domain			
ln (LF) (ms²)	7.42 (0.51)	7.08 (0.54)	NS
ln (HF) (ms²)	6.67 (0.93)	6.41 (0.76)	NS
ln (LF/HF)	0.75 (0.63)	0.68 (0.49)	NS

Values are mean (SD). ln, natural logarithm; CVNN, coefficient of variation; HF, high frequency power (>0.15–0.4 Hz); LF, low frequency power (0.04–0.15 Hz); LF/HF, ratio of low frequency and high frequency power; meanNN, mean of all RR intervals between normal beats; pNN50, percentage of successive RR intervals differing more than 50 ms; RMSSD, the root mean square of successive RR differences; SDANN, SD of the mean of RR intervals in all 5 minute segments; SDNN, SD of these RR intervals.
*p Value of Student's *t* test or Mann–Whitney test, as appropriate.

daytime heart rate variability owing to the higher activity level of the cyclists.[33] The analysed part of the Holter ECG was divided into five minute episodes. Heart rate variability analysis was performed on all separate episodes. Spectral heart rate variability indices were computed by integrating the fast Fourier transform generated, interval series power spectrum in the 0.05–0.15 Hz low frequency (LF) band and in the 0.15–0.40 Hz high frequency (HF) band. Preceding the fast Fourier transform, the interval series was detrended by subtracting the linear trend obtained by linear regression, tapered to zero with a cosine function, and padded with zeros to the nearest power of two data points.

The following time domain indices were computed:

- Mean of all RR intervals between normal beats (meanNN)
- SD of the RR intervals (SDNN)
- Coefficient of variation (CVNN) of all RR intervals
- SD of the average RR intervals during all five minute periods (SDANN)
- The root mean square of successive differences in RR intervals among successive normal beats (RMSSD)
- Percentage of successive RR intervals differing more than 50 ms (pNN50).

The following frequency domain indices were computed[34]:

- LF power, that is, the power between 0.05 and 0.15 Hz

- HF power, that is, the power between 0.15 and 0.40 Hz
- The sympathovagal balance, defined by the ratio of low frequency power to high frequency power (LF/HF).

STATISTICAL ANALYSIS

Data are presented as mean (SD). Cyclists and control subjects were compared using Student's *t* test and the Mann–Whitney test. Significance testing of frequency domain parameters was performed after log transformation of the data. The association between variables was quantified with the Pearson correlation coefficient and, where necessary, this association was adjusted for age using the partial correlation coefficient. A p value of 0.05 or less was considered statistically significant.

Results

SUBJECT CHARACTERISTICS

The anthropometric characteristics and magnetic resonance data of the 12 cyclists and 10 control subjects are presented in table 1. There were no significant differences between the following subject characteristics of the two groups: age, height, weight, body surface area, E/A peak, E/A area, and myocardial PCr/ATP concentration ratio measured at rest and during atropine–dobutamine stress (table 1). Heart rate was lower in cyclists than in control subjects (p < 0.005). Left ventricular mass and left ventricular mass index were higher in cyclists than in control subjects (both p < 0.001), which is in agreement with the higher training state of the cyclists.

HEART RATE VARIABILITY IN THE TIME DOMAIN

Time domain analysis of heart rate variability revealed relatively high values for all cyclists compared with control subjects (table 2). In cyclists, the meanNN was higher than in control subjects (p < 0.01), reflecting the lower resting heart rate in cyclists. In addition, SDNN (101 (28) *v* 70 (18) ms, p = 0.007) and CVNN (8.1 (2.1)% *v* 6.5 (1.5)%, p = 0.042) were higher in athletes than in control subjects. SDNN reflects all the cyclic components responsible for variability during the recording period, including short term and long term variations.[1] By analysis of a six hour sleeping period instead of a 24 hour period, variability introduced by different activity levels and differences between day and night time heart rates were eliminated. The higher SDNN in cyclists is therefore a realistic finding, indicative of an intrinsically higher heart rate variability in athletes. This is substantiated by a significantly higher CVNN in cyclists, SD normalised by mean heart rate, which is a highly reproducible and heart rate independent variable.[35]

HEART RATE VARIABILITY IN THE FREQUENCY DOMAIN

There were no significant differences between cyclists and control subjects after log transformation of the data in the following frequency domain indices: LF (7.42 (0.51) *v* 7.08 (0.54)

Table 3 Partial correlation between time and frequency domain parameters of heart rate variability and subject characteristics of athletes and controls pooled, after age correction (n = 22)

	LVM	LVMI	E/A peak	E/A area	Pcr/ATP rest	Pcr/ATP stress
MeanNN	0.48*	0.44	0.48*	0.29	0.29	0.11
SDNN	0.32	0.30	0.28	0.23	0.13	0.15
CVNN	0.21	0.19	0.10	0.11	−0.02	0.13
SDANN	0.20	0.13	−0.22	−0.25	0.44	0.60*
RMSSD	0.07	0.08	0.42	0.48*	0.41	0.12
pNN50	0.27	0.38	0.25	0.19	0.54*	0.11
ln LF	0.00	0.00	0.03	0.07	−0.15	0.00
ln HF	−0.03	−0.04	0.15	0.20	0.21	0.20
ln LF/HF	0.05	0.06	−0.17	−0.20	−0.46	−0.28

ln, natural logarithm; CVNN, coefficient of variation of all RR intervals; E/A area, ratio of early and atrial filling volume; E/A peak, ratio of peak early and atrial filling; HF, high frequency power (>0.15–0.4 Hz); LF, low frequency power (0.05–0.15 Hz); LVM, left ventricular mass; LVMI, left ventricular mass index; meanNN, mean of all RR intervals between normal beats; PCr, phosphocreatine; pNN50, percentage of successive RR intervals differing more than 50 ms; RMSSD, root mean square of successive differences in RR intervals among successive normal beats; SDANN, standard deviation of the average RR intervals during all 5 minute periods; SDNN, standard deviation of the RR intervals.
p Values are nominal; no correction for multiple testing was employed.
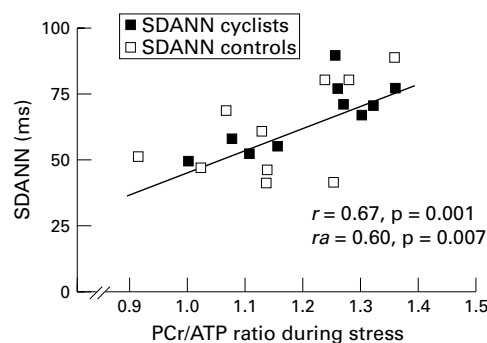*p < 0.05, *p < 0.01.

Figure 1 Pearson correlation between SDANN (standard deviation of the average RR intervals during all five minute periods) and PCr/ATP ratio during atropine–dobutamine stress. ra, partial correlation coefficient adjusted for age. The figure shows the correlation without adjustment.

ms², NS); HF (6.67 (0.93) v 6.41 (0.76) ms², NS); or the ln LF/HF ratio (0.75 (0.63) v 0.68 (0.49), NS).

RELATION BETWEEN HEART RATE VARIABILITY AND SUBJECT CHARACTERISTICS
All time and frequency domain parameters of heart rate variability were negatively and significantly correlated with age. Therefore it was necessary to perform a correction for age when calculating the correlation coefficients between heart rate variability and other subject characteristics. A significant positive relation between meanNN and left ventricular mass was found ($r = 0.48$, $p = 0.038$), reflecting the low resting heart rate of the cyclists. The other indices of heart rate variability were not correlated with left ventricular mass or left ventricular mass index (table 3).

The heart rate variability indices which correlated with left ventricular diastolic function indices were meanNN v E/A peak ($r = 0.48$, $p = 0.039$), and RMSSD v E/A peak ($r = 0.42$, $p = 0.075$) and E/A area ($r = 0.48$, $p = 0.040$).

The heart rate variability indices that correlated with myocardial high energy phosphate metabolism were SDANN v PCr/ATP ratio at rest ($r = 0.44$, $p = 0.059$) and PCr/ATP ratio during stress ($r = 0.60$, $p = 0.007$, fig 1), RMSSD v PCr/ATP ratio at rest ($r = 0.41$,

$p = 0.079$), and pNN50 v PCr/ATP ratio at rest ($r = 0.54$, $p = 0.017$).

Discussion
Our aim in this study was to examine the correlation between heart rate variability and cardiovascular functional and metabolic indices in cyclists with training induced left ventricular hypertrophy. Our study yielded no statistically significant correlation between heart rate variability indices and the extent of left ventricular hypertrophy. This finding suggests that exercise induced increase in left ventricular mass in athletes has no influence on heart rate variability. This is in contrast with findings in left ventricular hypertrophy caused by aortic valve disease, hypertension, or diabetes mellitus, where there is a negative correlation between indices of heart rate variability and left ventricular mass.[13–16] Second, our study shows that meanNN and RMSSD correlated with indices of left ventricular diastolic function. Third, we found a notable correlation between the myocardial PCr/ATP ratio during stress and SDANN, a measure of ultra low frequency heart rate variability. These findings on heart rate variability underscore our previous findings that exercise induced left ventricular hypertrophy in cyclists is a physiological rather than a pathophysiological phenomenon.[26] To the best of our knowledge, this is the first study to evaluate the relation between left ventricular hypertrophy and heart rate variability in highly trained cyclists.

INCREASED HEART RATE VARIABILITY IN CYCLISTS
Time domain analysis of heart rate variability revealed relatively high values for cyclists compared with control subjects. This reached statistical significance with respect to SDNN and CVNN, possibly indicating an increased vagal control in cyclists. Reduced SDNN has been shown to carry an increased risk of sudden cardiac death in a heterogeneous patient population independent of other risk factors[6]; it is a significant predictor of mortality in patients with myocardial infarction[7] and is significantly associated with all cause mortality in the general population.[4 5] Our results therefore might suggest that these cyclists have a decreased risk of sudden cardiac death.

LEFT VENTRICULAR DIASTOLIC FUNCTION
The correlations of meanNN and RMSSD with indices of left ventricular diastolic function are partly explained by a lower resting heart rate in cyclists. An increasing heart rate favours the atrial contribution versus the early phase of diastolic filling. This results in a lower ratio of the early to late peak filling rate and volume.[36 37] This explains the relation between meanNN and E/A ratio, since meanNN is equivalent to heart rate. Part of the relation between RMSSD and E/A ratio can be explained by the fact that RMSSD is an index of vagal tone, and an increased vagal tone and subsequent bradycardia may be held responsible for an increased E/A ratio.[38 39] The correlation between indices of heart rate variability and indices of left ventricular diastolic function

is not very strong. This is to be expected, because both sets of variables are determined by a wide variety of factors. No previous studies appear to have addressed the relation between heart rate variability and left ventricular diastolic function.

MYOCARDIAL HIGH ENERGY PHOSPHATE METABOLISM

Our study showed similar PCr/ATP ratios at rest and during atropine–dobutamine stress in the hypertrophied hearts of the cyclists compared with control subjects at rest and during atropine–dobutamine stress. Second, a moderate, but significant correlation ($r = 0.60$, $p = 0.007$) was found between the myocardial PCr/ATP ratio during stress and SDANN, indicating that high energy phosphate metabolism is associated with heart rate variability. A possible explanation for this correlation might be that both a reduced SDANN and a low stress induced PCr/ATP ratio indicate a decreased energy reserve of the heart. Reduced SDANN may identify individuals at increased risk of dying. This ultra low frequency variable has been found to be a powerful predictor of a poor prognosis in patients with coronary heart disease with[8 9] and without myocardial infarction,[40] mitral valve disease,[10] and chronic heart failure.[41] However, it is unclear whether the reduced heart rate variability plays a causal role or is merely a risk factor.

Myocardial high energy phosphates can be measured non-invasively in man using spatially localised ^{31}P nuclear magnetic resonance spectroscopy, providing data on the energy status of the heart.[42–44] Our study clearly shows that the relatively high myocardial PCr/ATP ratio during stress, as occurs in well trained athletes,[26] contributes to prediction of high levels of heart rate variability indices.

CONFOUNDING FACTORS IN THE USE OF HEART RATE VARIABILITY

It has been shown by Bernardi *et al* that the amount of RR variability and its slower fluctuations largely depend on physical activity, with a very low frequency fluctuation that increases with higher activity levels.[33] Highly trained elite cyclists have, by definition, higher daytime activity levels than sedentary control subjects. To compare ultra low frequency power between these two groups, the higher physical activity level of the cyclists should be corrected. This was accomplished by studying a physiologically comparable period in both groups without any physical activity—that is, sleep.

Studies of heart rate variability in athletes have yielded conflicting results. Most investigations have shown that aerobic training may increase cardiac vagal tone at rest, resulting in increased heart rate variability,[18–24] but other reports have failed to show such an increase.[45–49] Factors that may contribute to the inconsistency of these results are the evaluation of young individuals who already possess high vagal tone and insufficient duration of the training programme to develop left ventricular hypertrophy.[47] We therefore chose to study an older population of elite cyclists with a training history of about 20 years to ensure adequate training stimulus of sufficient duration to develop increased left ventricular mass.

POSSIBLE LIMITATIONS

Only half of the ECGs of the cyclists met the Sokolow–Lyon voltage criteria for left ventricular hypertrophy. However, the sensitivity of ECG left ventricular hypertrophy is very low and we therefore compared the measured left ventricular mass. The increase in left ventricular mass found in cyclists compared with control subjects is substantial (44%) and in agreement with previous magnetic resonance and echocardiographic studies on the athlete's heart.[50]

CONCLUSIONS

Our study shows that cyclists with training induced left ventricular hypertrophy have an increased vagal control that is independent of the extent of left ventricular hypertrophy. Heart rate variability was also significantly correlated with high energy phosphate metabolism and diastolic function. If we take into account that hearts of elite cyclists show normal diastolic function and normal high energy phosphate metabolism, we should classify training induced left ventricular hypertrophy as physiological hypertrophy, without a proven augmented risk of sudden cardiac death. The strong correlation between heart rate variability and myocardial PCr/ATP levels found in our study suggests that a low myocardial PCr/ATP ratio in particular individuals might represent a cardiovascular risk factor.

1 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. *Circulation* 1996;**93**:1043–65.
2 Barron HV, Lesh MD. Autonomic nervous system and sudden cardiac death. *J Am Coll Cardiol* 1996;**27**:1053–60.
3 Coats AJ, Conway J, Sleight P, *et al*. Interdependence of blood pressure and heart period regulation in mild hypertension. *Am J Hypertens* 1991;**4**:234–8.
4 Tsuji H, Venditti FJ, Manders ES, *et al*. Reduced heart rate variability and mortality risk in an elderly cohort. *Circulation* 1994;**90**:878–83.
5 Dekker JM, Schouten EG, Klootwijk P, *et al*. Heart rate variability from short electrocardiographic recordings predict mortality from all causes in middle-aged and elderly men. *Am J Epidemiol* 1997;**145**:899–908.
6 Algra A, Tijssen JGP, Roelandt JRTC, *et al*. Heart rate variability from 24 hour electrocardiography and the 2 year risk for sudden death. *Circulation* 1993;**88**:180–5.
7 Kleiger RE, Miller JP, Bigger JT, *et al*. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;**59**:256–62.
8 Bigger JT, Fleiss JL, Steinman RC, *et al*. Frequency domain measures of heart rate variability and mortality after myocardial infarction. *Circulation* 1992;**85**:164–71.
9 Fei L, Copie X, Malik M, *et al*. Short and long-term assessment of heart rate variability for risk stratification after acute myocardial infarction. *Am J Cardiol* 1996;**77**:681–4.
10 Stein KM, Borer JS, Hochreiter C, *et al*. Prognostic value and physiologic correlates of heart rate variability in chronic severe mitral regurgitation. *Circulation* 1993;**88**:127–35.
11 Odemuyiwa O, Malik M, Farrell T, *et al*. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol* 1991;**68**:434–9.
12 Farrell TG, Bashir Y, Cripps T, *et al*. Risk stratification for arrhythmic events in postinfarction patients based on heart variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;**18**:687–97.

13 Mandawat MK, Wallbridge DR, Pringle SD, *et al.* Heart rate variability in left ventricular hypertrophy. *Br Heart J* 1995;**73**:139–44.

14 Kohara K, Hara-Nakamura N, Hiwada K. Left ventricular mass index negatively correlates with heart rate variability in essential hypertension. *Am J Hypertens* 1995;**8**:183–8.

15 Piccirillo G, Munizzi MR, Fimognari FL, *et al.* Heart rate variability in hypertensive subjects. *Int J Cardiol* 1996;**53**:291–8.

16 Weston PJ, Panerai RB, McCullough A, *et al.* Assessment of baroreceptor-cardiac reflex sensitivity using time domain analysis in patients with IDDM and the relation to left ventricular mass index. *Diabetologia* 1996;**39**:1385–91.

17 Pellicia A, Maron BJ, Spataro A, *et al.* The upper limit of physiological cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;**324**:295–301.

18 De Meersman RE. Heart rate variability and aerobic fitness. *Am Heart J* 1993;**125**:726–31.

19 Seals DR, Chase PB. Influence of physical training on heart rate variability and baroreflex circulatory control. *J Appl Physiol* 1989;**66**:1886–95.

20 Dixon EM, Kamath MV, McCartney N, *et al.* Neural regulation of heart rate variability in endurance athletes and sedentary controls. *Cardiovasc Res* 1992;**26**:713–9.

21 Sacknoff DM, Gleim GW, Stachenfeld N, *et al.* Effect of athletic training on heart rate. *Am Heart J* 1994;**127**:1275–8.

22 Janssen MJA, De Bie J, Swenne CA, *et al.* Supine and standing sympathovagal balance in athletes and controls. *Eur J Appl Physiol* 1993;**67**:164–7.

23 Smith ML, Hudson DL, Graitzer HM, *et al.* Exercise training bradycardia: the role of autonomic balance. *Med Sci Sports Exerc* 1989;**21**:40–4.

24 Goldsmith RL, Bigger T, Steinman RC, *et al.* Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men. *J Am Coll Cardiol* 1992;**20**:552–8.

25 Lamb HJ, Doornbos J, Van der Velde EA, *et al.* Echo planar MRI of the heart on a standard system: validation of measurements of left ventricular function and mass. *J Comput Assist Tomogr* 1996;**20**:942–9.

26 Pluim BM, Lamb HJ, Kayser HWM, *et al.* Functional and metabolic evaluation of the athlete's heart using magnetic resonance imaging and dobutamine stress magnetic resonance spectroscopy. *Circulation* 1998;**97**:666–75.

27 Van der Geest RJ, Buller VGM, Janse E, *et al.* Comparison between manual and semi-automated analysis of left ventricular volume parameters from short-axis MR images. *J Comput Assist Tomogr* 1997;**21**:756–65.

28 Pattynama PMT, Lamb HJ, Van der Velde EA, *et al.* Left ventricular measurements with cine and spinecho MR imaging: a study on reproducibility with variance component analysis. *Radiology* 1993;**187**:261–8.

29 Kayser WM, Stoel BC, Van der Wall EE, *et al.* MR velocity mapping of tricuspid flow: correction for through-plane motion. *J Magn Reson Imag* 1997;**7**:669–73.

30 Lamb HJ, Doornbos J, Den Hollander JA, *et al.* Reproducibility of human cardiac P-31-NMR spectroscopy. *NMR Biomed* 1996;**9**:217–27.

31 Coplan NL, Gleim GW, Stachenfeld N, *et al.* Evaluation of 85% predicted maximal heart rate as an end point for diagnostic exercise testing. *Am Heart J* 1991;**122**:1790–1.

32 Janssen MJA, Swenne CA. Advanced arrhythmia interpretation by batch driven postprocessing of QRS notations and ST values as obtained with a commercial Holter analyzer. In: *Computers in cardiology*. Los Alamitos, California: IEEE Computer Society Press, 1992:449–52.

33 Bernardi L, Valle F, Coco M, *et al.* Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. *Cardiovasc Res* 1996;**32**:234–7.

34 Bootsma M, Swenne CA, Van Bolhuis HH, *et al.* Heart rate and heart rate variability as indexes of sympathovagal balance. *Am J Physiol* 1994;**266**:1565–71.

35 Van Hoogenhuyze D, Weinstein N, Martin GJ, *et al.* Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1991;**68**:1668–76.

36 Van Dam I, Fast J, De Boo T, *et al.* Normal diastolic filling patterns of the left ventricle. *Eur Heart J* 1988;**9**:165–71.

37 Bryg RJ, Williams GA, Labovitz AJ. Effect of aging on left ventricular diastolic filling in normal subjects. *Am J Cardiol* 1987;**59**:971–4.

38 Malik M, Camm AJ. Components of heart rate variability: what they really mean and what we really measure. *Am J Cardiol* 1993;**72**:821–2.

39 Kleiger RE, Stein PK, Bosner MS, *et al.* Time domain measurements of heart rate variability. *Cardiol Clin* 1992;**10**:487–98.

40 Rich MW, Saini JS, Kleiger RE, *et al.* Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. *Am J Cardiol* 1988;**62**:714–17.

41 Ponikowski P, Anker SD, Chua TP, *et al.* Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic cardiomyopathy. *Am J Cardiol* 1997;**79**:1645–50.

42 Beyerbacht HP, Vliegen HW, Lamb HJ, *et al.* Phosphorus magnetic resonance spectroscopy of the human heart: current status and clinical applications. *Eur Heart J* 1996;**17**:1158–66.

43 Neubauer S, Krahe T, Schindler R, *et al.* ³¹P Magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease. *Circulation* 1992;**86**:1810–8.

44 Neubauer S, Horn M, Cramer M, *et al.* Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation* 1997;**96**:2190–6.

45 Boutcher SH, Stein P. Association between heart rate variability and training response in sedentary middle-aged men. *Eur J Appl Physiol* 1995;**70**:75–80.

46 Reiling MJ, Seals DR. Respiratory sinus arrhythmia and carotid baroreflex control of heart rate in endurance athletes and untrained controls. *Clin Physiol* 1988;**8**:511–19.

47 Furlan R, Piazza S, Dell'Orto S, *et al.* Early and late effects of exercise and athletic training on neural mechanisms controlling heart rate. *Cardiovasc Res* 1993;**27**:482–8.

48 Katona PG, McLean M, Dighton DH, *et al.* Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *J Appl Physiol* 1982;**52**:1652–7.

49 Maciel BC, Gallo L, Marin Neto JA, *et al.* Parasympathetic contribution to bradycardia induced by endurance training in man. *Cardiovasc Res* 1985;**19**:642–8.

50 Maron BJ. Structural features of the athlete heart as defined by echocardiography. *J Am Coll Cardiol* 1986;**7**:190–203.