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

B M Pluim, C A Swenne, A H Zwinderman, A C Maan, A van der Laarse, J Doornbos, E E Van der Wall

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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Keywords: heart rate variability; left ventricular mass; hypertrophy; athlete’s heart

The term heart rate variability refers to variations in both instantaneous heart rate and RR interval length.1 Changes in heart rate pri-
Heart rate variability in the athlete’s heart

Tocol was performed as described in vivo spectroscopy (ISIS) protocol was used, and a 10 minute three dimensional image selected in vivo spectroscopy (ISIS) protocol was performed as described previously. 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. 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. 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 using a Marquette 8500 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. 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

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. 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.

MAGNETIC RESONANCE IMAGING ANALYSIS

Multislice multiphase short axis image analysis was performed using the magnetic resonance analytical software system (MASS) 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. 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).

P MAGNETIC RESONANCE SPECTROSCOPY

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.
Table 1  Subject characteristics

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

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; LVMI, left ventricular mass; LVM, 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

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

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 intervals; 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.

Results

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.25

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))
Heart rate variability in the athlete's heart

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)

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

In, 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.

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.13–18 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.19 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; it is a significant predictor of mortality in patients with myocardial infarction1 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 correlation 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.35,37 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.36,39 The correlation between indices of heart rate variability and indices of left ventricular diastolic function

Figure 1 Pearson correlation between SDANN (standard deviation of the average RR intervals during all five minute periods) and PCr/ATP ratio during stress. 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).
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 and without myocardial infarction, mitral valve disease, and chronic heart failure. 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 $^3$P nuclear magnetic resonance spectroscopy, providing data on the energy status of the heart. Our study clearly shows that the relatively high myocardial PCr/ATP ratio during stress, as occurs in well trained athletes, contributes to prediction of high levels of heart rate variability indices.

**Confounders 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. 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, but other reports have failed to show such an increase. 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. 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–Lyons 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.

**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.

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