Heart Rate Variability, QT Variability, and Electrodermal Activity during Exercise

SILKE BOETTGER[1], CHRISTIAN PUTA[2], VIKRAM K. YERAGANI[3,4], LARS DONATH[2], HANS-JOSEF MÜLLER[2], HOLGER H. W. GABRIEL[2], and KARL-JÜRGEN BÄR[1,5]

[1]Department of Psychiatry and Psychotherapy, University Hospital, Jena, GERMANY; [2]Department of Sports Medicine, Friedrich-Schiller-University, Jena, GERMANY; [3]Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI; [4]Department of Psychiatry, University of Alberta, Edmonton, CANADA; and [5]Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Ruhr-University, Bochum, GERMANY

ABSTRACT

BOETTGER, S., C. PUTA, V. K. YERAGANI, L. DONATH, H.-J. MÜLLER, H. H. W. GABRIEL, and K.-J. BÄR. Heart Rate Variability, QT Variability, and Electrodermal Activity during Exercise. *Med. Sci. Sports Exerc.*, Vol. 42, No. 3, pp. 443–448, 2010. **Purpose**: Various measures of autonomic function have been developed, and their applicability and significance during exercise are controversial. **Methods**: Physiological data were therefore obtained from 23 sport students before, during, and after exercise. Measures of R-R interval variability, QT variability index (QTvi), and electrodermal activity (EDA) were calculated. We applied an incremental protocol applying 70%, 85%, 100%, and 110% of the individual anaerobic threshold for standardized comparison. **Results**: Although HR increased stepwise, parasympathetic parameters such as the root mean square of successive differences were not different during exercise and do not mirror autonomic function satisfactorily. Similar results were observed with the approximate entropy of R-R intervals ($ApEn_{RR}$). In contrast, the increase in sympathetic activity was well reflected in the EDA, QTvi, and ApEn of the QT interval ($ApEn_{QT}$)/$ApEn_{RR}$ ratio. **Conclusion**: We suggest that linear and nonlinear parameters of R-R variability do not adequately reflect vagal modulation. Sympathetic function can be assessed by EDA, QTvi, or $ApEn_{QT}$/$ApEn_{RR}$ ratio. **Key Words**: SPORT, AUTONOMIC NERVOUS SYSTEM, VAGAL MODULATION, ARRHYTHMIAS

BASIC SCIENCES

Heart rate variability (HRV) has become a widely used tool to describe parasympathetic and sympathetic influence of the autonomic nervous system on the heart. HRV can be described using linear (5) as well as nonlinear parameters (4). Beat-to-beat QT interval variability (QTV), which is a noninvasive measure of cardiac repolarization lability, has received much attention in cardiac diseases and psychiatric conditions (2,3,6,8,17,38). Although changes in HRV mainly reflect the efferent parasympathetic modulation on the heart at the sinus node level (19,40), beat-to-beat QTV depicts the temporal fluctuation in ventricular repolarization and provides information on the phase in which the heart is most susceptible to arrhythmias. There is an association between abnormal QTV

and ventricular arrhythmias and sudden cardiac death in patients after myocardial infarction (10,34). Furthermore, the QT variability index (QTvi) reflects sympathetic activity to some extent (36). This has been shown in experiments applying infusions of the beta receptor stimulant isoproterenol and during changes of posture as we all as due to the application of pemoline and yohimbine (26,36).

Long-term aerobic exercise training increases vagal influence on the heart (30). However, there are inconsistent results about acute changes of autonomic function during exercise. Increasing HR during dynamic exercise is the result of increased sympathetic activity and parasympathetic withdrawal (32). It is, however, not entirely clear how the parasympathetic and sympathetic systems affect HRV and QTV during exercise. Inconsistent results have been reported for classical time and frequency domain measures of HRV during exercise. Above certain levels of exercise, the influence of parasympathetic withdrawal on HR increase may not play a role anymore, and the sympathetic influence prevails (21). Other authors could not differentiate the influence of the sympathetic system in variable experimental conditions (12). Furthermore, discrepant results have been reported for low-frequency (LF) power, which is influenced by both the sympathetic and the parasympathetic nervous system under resting conditions. This might change during

day 1 | day 2

| | 15 min supine | 15 min 70%IAT | 15 min 85%IAT | 15 min 100%IAT | 15 min 110%IAT | 25 min supine |

IAT detection | C1 | exercise | C2

ECG for HRV & QTvi / EDA
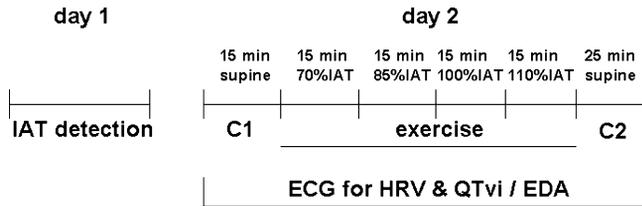
FIGURE 1—Sketch of the study design. C1 and C2 indicate resting conditions before and after exercise, respectively.

exercise (13,20). To better understand changes during exercise, we have added as suggested (29) a novel nonlinear parameter, approximate entropy of R-R intervals ($ApEn_{RR}$), to study the complexity of HR regulation during exercise. Furthermore, we have applied this measure on the QT interval to calculate the ApEn of the QT interval ($ApEn_{QT}$) and the $ApEn_{QT}/ApEn_{RR}$ ratio, which appears to indicate central sympathetic activity (6).

In addition to measures of HRV and QTV, the electrodermal activity (EDA, also called galvanic skin response [16]), has been obtained to assess the influence of the sympathetic nervous system. The sympathetic innervation of sweat glands induces changes in skin resistance to an externally applied current (exosomatic method). The central (28) and the peripheral (9) pathways involved in the generation of EDA are independent of pathways producing vasoconstriction for thermoregulation. However, vasoconstriction is known to alter EDA (11).

Here, we examined the regulation of the autonomic nervous system during steady-state exercise intervals. We hypothesize that the withdrawal of parasympathetic modulation already might be obvious during low exercise intensities, whereas the sympathetic increase is reflected more appropriately in the QTvi and EDA at higher-intensity exercise levels. An incremental protocol with working loads defined as percentage of the individual anaerobic threshold (IAT) was applied to induce comparable physical strain on participants. We calculated measures of parasympathetic function mainly obtained from HRV and sympathetic parameters such as the EDA, the QTvi, and the $ApEn_{QT}/ApEn_{RR}$ ratio to analyze autonomic changes, interrelations, and consequences of physical activity.

METHODS

Twenty-three healthy sport students (9 females, 14 males; age = 23.6 ± 1.6 yr; body mass index = 22.7 ± 2.0 kg·m^{-2};

three smokers (less than three cigarettes per day)) participated in this study. All clinical investigations, including physical examination and 12-lead ECG at rest and during exercise, were completely normal. This study complied with the Declaration of Helsinki, and procedures were approved by the ethics committee of the Faculty of Medicine of the Friedrich-Schiller-University, Jena. All participants gave written informed consent to the approved protocol.

Study design. Subjects were investigated on 2 days (Fig. 1). During the first day, medical history, physical examination, and 12-lead ECG were obtained. Afterwards, the IAT (according to Stegmann et al. (31)) was assessed.

During the second day (72 h after day 1), subjects performed a constant load exercise test on the bicycle ergometer in sitting position with rising intensities, which were calculated according to their IAT (70%, 85%, 100%, and 110% IAT for 15 min per each condition). Two resting records were obtained for 15 min before (condition 1) and 15 min after the exercise (condition 2; Fig. 1). In addition, the Borg scale (starting from 6 = *extremely easy* to 20 = *extremely exhausting*) was used to assess the level of exhaustion at the end of each interval (Table 1).

IAT assessment. Subjects performed a standardized incremental maximal exercise test on a bicycle ergometer (Ergometrics 900®; Ergoline, Bitz, Germany) on the first study day. Starting with 50 W, workload was increased every 3 min by 50 W until exhaustion occurred. Spiroergometry parameters were recorded during this test. Therefore, subjects wore a face mask that was connected to an open spirometric system (MetaLyzer II®; Cortex, Leipzig, Germany). The highest oxygen uptake at the end of the test was regarded as $\dot{V}O_{2peak}$ (Table 1). Capillary blood samples were obtained from the earlobe at baseline, at the end of each level of exercise, and at the end of the 1st, 3rd, 5th, and 10th minute of the recovering period. Lactate concentrations were measured using the EBIO plus system (Eppendorf, Hamburg, Germany).

Using the lactate concentrations of each exercise level, IAT was determined according to the method of Stegmann et al. (31). IAT is assessed by using the blood lactate–performance relationship during incremental graded exercise and immediately after recovery phase within the 1st, 3rd, 5th, and 10th minute. According to a diffusion–elimination model between muscle and blood, Stegmann et al. (31) suggested that IAT should be assessed by making a tangent from a point B (same blood lactate concentration during

TABLE 1. Physiological data and results of participants during exercise.

	Day 1	C1	70% IAT	85% IAT	100% IAT	110% IAT	C2
IAT (W·kg^{-1} body weight)	2.36 ± 0.39	–	–	–	–	–	–
$\dot{V}O_{2peak}$ (mL·min^{-1})	3929.70 ± 838.99	–	–	–	–	–	–
$\dot{V}O_{2peak}$ per kilogram (mL·min^{-1}·kg^{-1})	54.53 ± 7.17	–	–	–	–	–	–
%$\dot{V}O_{2peak}$	–	–	50.9 ± 5.2	61.6 ± 6.8	71.1 ± 7.0	76.3 ± 15.7	–
Borg scale	–	–	11.30 ± 1.96	13.67 ± 1.70	15.60 ± 1.23	17.83 ± 1.64	–
lnHFn	–	−0.92 ± 0.72	−1.71 ± 0.49	−2.21 ± 0.58	−2.17 ± 0.68	−2.21 ± 0.88	−1.38 ± 0.36
lnLFn	–	−0.86 ± 0.51	−0.65 ± 0.32	−0.88 ± 0.39	−1.42 ± 0.49	−2.07 ± 0.77	−0.54 ± 0.35
lnApEn$_{RR}$	–	−0.26 ± 0.15	n. a.	−0.38 ± 0.2	−0.35 ± 0.20	−0.41 ± 0.23	−0.28 ± 0.17

Physiological data and results of participants during exercise assessed on day 1 (IAT, $\dot{V}O_{2peak}$, and $\dot{V}O_{2peak}$ per kilogram of body weight) and on day 2. Data are presented as mean ± SD.

BASIC SCIENCES

recovery phase as at the end of exhaustive exercise). The contact point of the tangent to the blood lactate curve is regarded as IAT. The major advantage compared with other models is the independency of nutrition, medication, and grade of exhaustion. The IAT describes the maximal lactate steady state and represents the upper limit of the aerobic–anaerobic transition, thus reflecting a physiological break-point, and can be considered as an objective individual parameter for physical fitness (14,33).

HR assessment. During the second day, ECG recordings were obtained using the LifeShirt[®] equipment (Vivometrics, Inc., Ventura, CA). This is a device capable of simultaneously monitoring ECG, respiration pattern, and EDA (15). The use of telemetry enabled real-time visualization of the obtained signals (18).

Electrocardiographic records were transferred into the software package (Vivometrics, Inc.). A standardized normal-to-normal interval identification was performed. Ectopic beats were interpolated in a linear fashion for the time series. Subsequently, data were analyzed using the software package Vivologic to estimate standard HRV measures (20,35).

HRV measures. Time domain variables included the mean normal-to-normal interval (ms), the heart rate (HR [beats·min^{-1}]), and the root mean square of successive differences (RMSSD) between normal-to-normal intervals (ms). The frequency domain indices were calculated from the power spectra after fast Fourier transformation. We calculated the power within the LF band (0.04–0.15 Hz), which is linked to both sympathetic and parasympathetic modulation, as well as the high-frequency (HF) band (0.15–0.40 Hz), which is associated with parasympathetic cardiac control (40). LF and HF powers were normalized to total power (LFn and HFn, respectively).

Beat-to-beat QTV. The QT variability algorithm was applied (2,3,6,8,37,38). The R-R and the QT interval data were constructed at 4 Hz for the analyses.

The mean R-R (RRm), detrended R-R variance (RRv), mean QT interval (QTm), and detrended QT variance (QTv) were calculated from the instantaneous R-R and QT interval time series of 256 points (64 s). The average of two 64-s intervals was used. Mean R-R and mean QT intervals are in milliseconds.

A normalized QTvi was calculated (8).

$$\text{QTvi} = \log10[(\text{QTv}/\text{QTm}^2)/(\text{RRv}/\text{RRm}^2)]$$

This index represents the log-ratio between the QT interval and the R-R variabilities (detrended), each normalized for the corresponding mean. We used two sets of 64 s of stationary data in supine posture for the preexercise and postexercise periods and the 85%, 100%, and 110% IAT conditions for the analyses. We were unable to perform the QTV analyses with the 75% IAT ECG data because many recordings showed baseline shifts that precluded the detection of the QT intervals accurately.

Approximate entropy. Because of the irregularity of R-R and QT intervals, classical moment statistics such as means and standard deviations may not explain the nonlinear nature of these complex changes. Thus, we have calculated ApEn for QT and R-R interval durations to better describe the regularity using these nonlinear parameters (23,24,25). Given N data points $u(1)$, $u(2)$,…, $u(N)$, two input parameters should be set before the computation of ApEn. These are the run length m and the filter level r. A value of 2 for m and 0.2 times the standard deviation of the time series for the value of r reveals reliable results. First, we obtained vector sequences from the consecutive data points, which represent m consecutive u values, beginning with the ith point. Consecutively, the distance between vectors $x(i)$ and $x(j)$ is defined as the maximum difference in their respective scalar components. Then the sequence $x(1)$, $x(2)$,…, $x(N - m + 1)$ is used to construct $\ln C_i^m(r) = $ {number of $x(j)$ such that $d[x(i),x(j)] \leq r$} / $(N - m + 1)$ for each $i \leq N - m + 1$.

The $C_i^m(r)$ values measure, within a tolerance r, the regularity or frequency of patterns similar to a given pattern of window length, m.

Here, ApEn is defined as

$$\text{ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r)$$

In this equation, $\Phi^m(r)$ is the average value of $\ln C_i^m(r)$, ln being the natural logarithm.

The value of N is fixed, typically between 100 and 5000 points, but it has been shown that one can get a reliable estimate of ApEn even with a data length of <50 points, especially in studies related to endocrinology. ApEn measures the logarithmic likelihood that runs of patterns, which are close, because m observations remain close on next incremental comparisons. If there is greater likelihood of remaining close and being regular, ApEn values will be smaller.

Electrodermal activity. Skin conductance was recorded using the SC-Flex/Pro[®] of the LifeShirt-System. Here, a tiny electrical voltage is applied to two finger pads of the right hand. The real-time variation in conductance (in microsiemens) was calculated. EDA was measured with a sampling rate of 25 Hz. Raw traces were filtered with low- and high-pass filter with a cutoff frequency of 0.03 Hz.

Statistical analyses. Parameters were log transformed to achieve normal distribution after performing the Kolmogorov–Smirnov test. A repeated-measures MANOVA was performed using the within-subject factor time (rest vs 70% IAT) to demonstrate differences between rest and initial exercise step condition. A second repeated-measures MANOVA was applied using the factor IAT to reveal changes between different exercise intensities (70%, 85%, 100%, and 110%). Both MANOVA were followed-up by univariate ANOVA for each parameter (HR, RMSSD, HFn, LFn, ApEn$_{RR}$, EDA, QTvi, ApEn$_{QT}$, and ApEn$_{QT}$/ApEn$_{RR}$ ratio). All F values were adjusted according to the

Greenhouse–Geisser correction. Finally, *post hoc t*-tests were computed to compare parameters between different time intervals (70% vs 85%, 85% vs 100%, and 100% vs 110%; see Fig. 2 and Table 1).

RESULTS

A difference for time (rest vs 70% IAT) was observed ($F_{10,8} = 250.0$, $P < 0.001$) in the repeated-measures MANOVA, indicating changes after subjects started
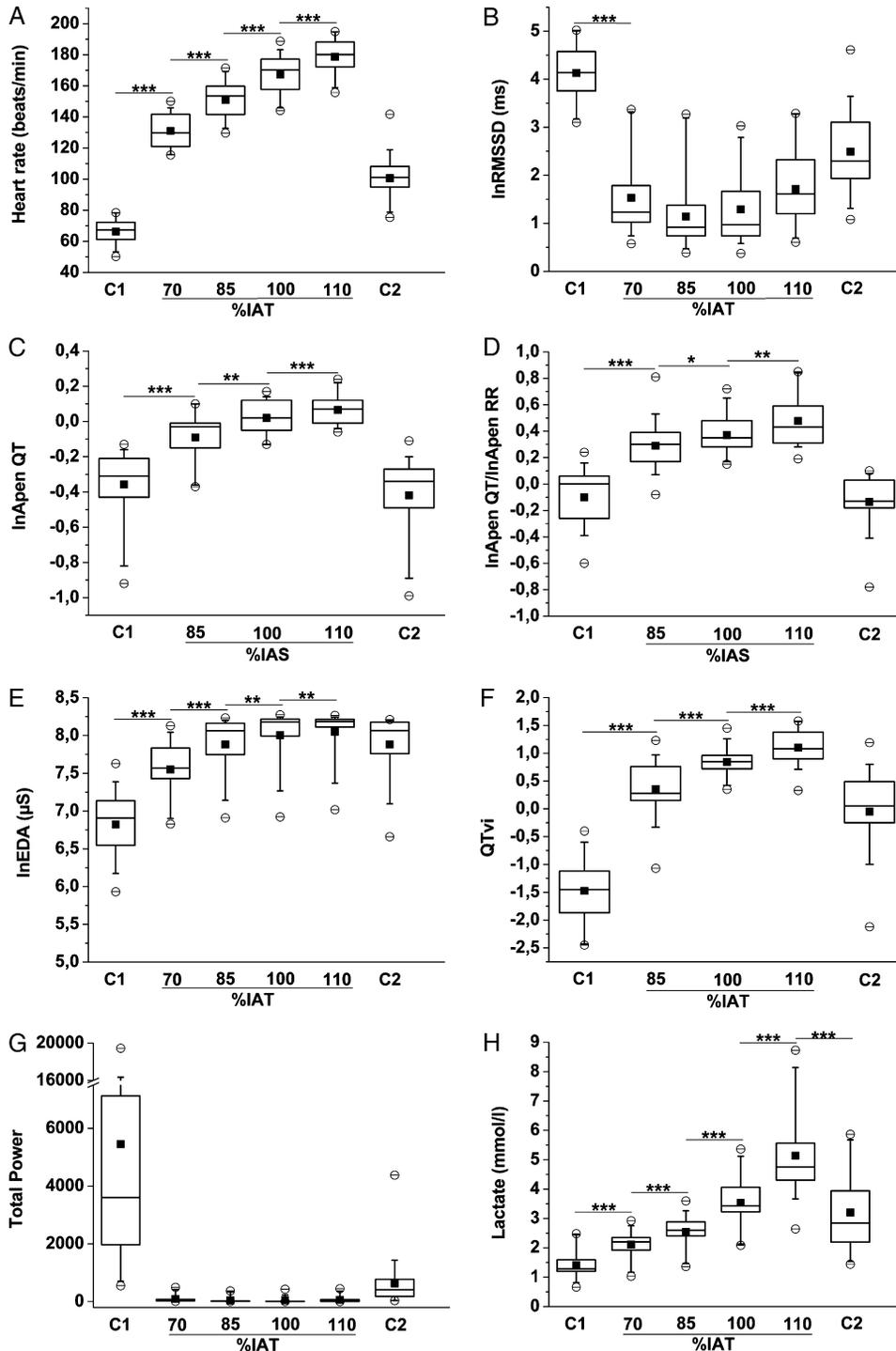
FIGURE 2—Condition 1 (C1) is the resting period before exercise, followed by increasing exercise intensities during 70%–110% IAT followed again by a resting condition (C2). HR (A) increased with exercise intensity and was accompanied by changes of RMSSD (B). ApEn_{QT} (C) increased reflecting sympathetic activity. The increase of the ApEn_{QT}/ApEn_{RR} ratio indicates sympathetic modulation (D). Changes of the sympathetic measures EDA and QTvi are depicted in panels E and F. Variations of total power and lactate are illustrated in panels G and H. Boxes indicate data between the 25th and the 75th percentile with the supine bar reflecting the median (■, mean; o, 1st and 99th percentile; −, minimum and maximum of data; *$P < 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$).

exercising. Similarly, we observed a difference for IAT (parameters obtained from 70% to 110% IAT; $F_{7,11} = 122.2$, $P < 0.001$).

We found differences over time (rest vs 70%) for lnHR ($P < 0.001$) and the parasympathetic parameters lnRMSSD ($P < 0.001$) and lnHFn ($P < 0.017$). The sympathetic parameters lnEDA ($P < 0.001$), QTvi ($P < 0.001$), and $ApEn_{QT}/ApEn_{RR}$ ratio ($P < 0.001$) were also different. Similarly, a change was observed in complexity parameters $ApEn_{RR}$ ($P < 0.003$) and $ApEn_{QT}$ ($P < 0.001$). No difference was observed for lnLFn. Means of single values are displayed in Figure 2 and Table 1.

Analyzing changes for IAT (70%–110%) for single parameters, we found a difference for lnHR ($P < 0.001$) and the parasympathetic measure lnHFn ($P < 0.001$). Sympathetic measures lnEDA ($P < 0.001$), QTvi ($P < 0.001$), and $ApEn_{QT}/ApEn_{RR}$ ratio ($P < 0.001$) were also different. The complexity of the QT interval changed as well ($ApEn_{QT}$; $P < 0.001$). No difference was observed for $lnApEn_{RR}$ ($P < 0.447$) and lnRMSSD ($P < 0.94$).

Correlations. The time domain measure, RMSSD representing vagal activity, negatively correlated with HR at rest before exercise ($r = -0.49$, $P < 0.05$) as well as during the lowest investigated activity of 70% IAT ($r = -0.44$, $P < 0.05$). There were correlations of sympathetic measures EDA at 100% and QTvi at 100% of IAT ($r = 0.48$, $P < 0.04$). Similarly, a correlation was observed for the sympathetic parameters $ApEn_{QT}/ApEn_{RR}$ ratio at 85% IAT with EDA at 70% ($r = 0.604$, $P < 0.008$) and a trend for the former with EDA at 85% IAT ($r = 0.44$, $P < 0.06$).

DISCUSSION

Our findings indicate that the RMSSD or the nonlinear parameter $ApEn_{RR}$ are not suitable measures during higher exercise intensities because of low vagal modulation. This is in agreement with studies showing a decrease of time domain measures already at very low exercise intensities (22). This might indicate that the parasympathetic system has very little influence on HR regulation during exercise (22). This assumption is supported by the dramatic breakdown of the power spectrum (Fig. 2G). There are very few frequency bands left pointing to reduced HR regulation. Although the LFn under resting conditions is thought to represent sympathetic activity to some extent (1), this measure further decreased during the four-step exercise protocol (Table 1). Similar results of LFn power have been shown under steady-state exercise conditions (12,27). Thus, the analysis of time and frequency domain measures of HRV may not yield adequate information during exercise tests. Because complexity of HR regulation is only insufficiently reflected in measures of classical moment statistics, we have applied $ApEn_{RR}$ (23). The complexity of HR regulation was reduced in the comparison between the resting condition and the initial exercise step. However, no further

changes were observed within the exercise protocol, indicating that the regularity of HR did not increase any further, supporting the linear results of very low vagal modulation as indicated by HFn. The measure HFn did not add additional information, and this mirrors previous results of a close correlation between $ApEn_{RR}$ and HF (39).

To monitor the sympathetic activity in parallel to HRV, we have assessed the QT variability, the $ApEn_{QT}/ApEn_{RR}$ ratio, and the EDA in this study. The variability of the QT interval indicated by the parameter QTvi increased during higher intensities of exercise, possibly reflecting sympathetic activity in this specific physiological condition. This is in agreement with findings at rest (36). In addition, this new finding might be of great importance for the occurrence of exercise test-induced arrhythmias (7). QTvi reflects cardiac repolarization lability and provides information on the phase in which the heart is most susceptible to arrhythmias.

Changes of skin conductance represent the level of central sympathetic activity (16). Our results suggest incremental changes over time with increasing exercise levels (Fig. 2E). Although studies have shown that pathways involved in the generation of EDA are independent from pathways producing vasoconstriction (16), this might be more complex during exercise. However, the correlation between EDA and QTvi at the lowest exercise intensity and the correlation with the $ApEn_{QT}/ApEn_{RR}$ ratio indicate the possibility that all three measures reflect sympathetic modulation during exercise. However, these correlations are modest and there may not be a one to one relationship between EDA and QTV.

This protocol has several advantages such as obtaining relatively stationary measures of HRV and QTV over periods of 15 minutes. In addition, the use of the IAT as a reference for the exercise intensities ensures that the physical fitness of participants was adjusted to a certain degree.

Finally, there are several limitations that we need to point out. One of the main limitations is that the measure QTvi needs stationary ECG segments, and thus we were unable to determine this measure from the entire data segment available. This may have caused some difficulty as far as the accuracy of the results is concerned, although a correlation to EDA was observed. Furthermore, it is clear that the QT interval depends on many mechanisms and is not solely under sympathetic control as other factors such as the potassium channels also play a role. In addition, we have investigated a relatively small number of sport students used to regular physical activity. Future studies need to tackle the question whether our results are applicable to casually exercising people.

In conclusion, applied parasympathetic linear and nonlinear measures of HRV are not conclusive during exercise. The pronounced withdrawal of vagal modulation on the heart might account for this result. In contrast, we would suggest that the QT variability, the EDA, and the $ApEn_{QT}/ApEn_{RR}$ ratio are useful to monitor sympathetic modulation and cardiac health during exercise.

REFERENCES

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science*. 1981;213:220–2.

2. Atiga WL, Calkins H, Lawrence JH, Tomaselli GF, Smith JM, Berger RD. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. *J Cardiovasc Electrophysiol*. 1998;9:899–908.

3. Bär KJ, Boettger MK, Koschke M, et al. Increased QT interval variability index in acute alcohol withdrawal. *Drug Alcohol Depend*. 2007;89:259–66.

4. Bär KJ, Boettger MK, Koschke M, et al. Non-linear complexity measures of heart rate variability in acute schizophrenia. *Clin Neurophysiol*. 2007;118:2009–15.

5. Bär KJ, Greiner W, Jochum T, Friedrich M, Wagner G, Sauer H. The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. *J Affect Disord*. 2004;82:245–52.

6. Bär KJ, Koschke M, Boettger MK, et al. Acute psychosis leads to increased QT variability in patients suffering from schizophrenia. *Schizophr Res*. 2007;95:115–23.

7. Beckerman J, Wu T, Jones S, Froelicher VF. Exercise test-induced arrhythmias. *Prog Cardiovasc Dis*. 2005;47:285–305.

8. Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation*. 1997;96:1557–65.

9. Bini G, Hagbarth KE, Hynninen P, Wallin BG. Regional similarities and differences in thermoregulatory vaso- and sudomotor tone. *J Physiol*. 1980;306:553–65.

10. Bonnemeier H, Wiegand UK, Bode F, et al. Impact of infarct-related artery flow on QT dynamicity in patients undergoing direct percutaneous coronary intervention for acute myocardial infarction. *Circulation*. 2003;108:2979–86.

11. Casale R, Glynn CJ, Buonocore M. Investigation on the effect of 30-min tourniquet ischemia on the so-called sympathetic skin response. *J Auton Nerv Syst*. 1990;30(suppl):S39–41.

12. De Vito G, Galloway SD, Nimmo MA, Maas P, McMurray JJ. Effects of central sympathetic inhibition on heart rate variability during steady-state exercise in healthy humans. *Clin Physiol Funct Imaging*. 2002;22:32–8.

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

14. Gabriel H, Kindermann W. The acute immune response to exercise: what does it mean? *Int J Sports Med*. 1997;18(suppl 1):S28–45.

15. Grossman P, Wilhelm FH, Spoerle M. Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. *Am J Physiol Heart Circ Physiol*. 2004;287:H728–34.

16. Gutrecht JA. Sympathetic skin response. *J Clin Neurophysiol*. 1994;11:519–24.

17. Haigney MC, Zareba W, Gentlesk PJ, et al. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol*. 2004;44:1481–7.

18. Heilman KJ, Porges SW. Accuracy of the LifeShirt (Vivometrics) in the detection of cardiac rhythms. *Biol Psychol*. 2007;75:300–5.

19. Low PA, Pfeifer MA. Standardization of autonomic function. In: Low PA, editor. *Clinical Autonomic Disorders*. Philadelphia: Lippincott-Raven Publishers; 1997. p. 287–95.

20. Novak V, Novak P, Low PA. Time-frequency analysis of cardiovascular function and its clinical applications. In: Low PA, editor. *Clinical Autonomic Disorders*. 2nd ed. Philadelphia: Lippincott-Raven; 1997. p. 323–47.

21. Perini R, Orizio C, Baselli G, Cerutti S, Veicsteinas A. The influence of exercise intensity on the power spectrum of heart rate variability. *Eur J Appl Physiol Occup Physiol*. 1990;61:143–8.

22. Perini R, Veicsteinas A. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. *Eur J Appl Physiol*. 2003;90:317–25.

23. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A*. 1991;88:2297–301.

24. Pincus SM. Assessing serial irregularity and its implications for health. *Ann N Y Acad Sci*. 2001;954:245–67.

25. Pincus SM. Approximate entropy as a measure of irregularity for psychiatric serial metrics. *Bipolar Disord*. 2006;8:430–40.

26. Pohl R, Balon R, Jayaraman A, Doll RG, Yeragani V. Effect of fluoxetine, pemoline and placebo on heart period and QT variability in normal humans. *J Psychosom Res*. 2003;55:247–51.

27. Polanczyk CA, Rohde LE, Moraes RS, Ferlin EL, Leite C, Ribeiro JP. Sympathetic nervous system representation in time and frequency domain indices of heart rate variability. *Eur J Appl Physiol Occup Physiol*. 1998;79:69–73.

28. Prout BJ. Independence of the galvanic skin reflex from the vasoconstrictor reflex in man. *J Neurol Neurosurg Psychiatry*. 1967;30:319–24.

29. Sandercock GR, Brodie DA. The use of heart rate variability measures to assess autonomic control during exercise. *Scand J Med Sci Sports*. 2006;16:302–13.

30. Sandercock GR, Bromley PD, Brodie DA. Effects of exercise on heart rate variability: inferences from meta-analysis. *Med Sci Sports Exerc*. 2005;37(3):433–9.

31. Stegmann H, Kindermann W, Schnabel A. Lactate kinetics and individual anaerobic threshold. *Int J Sports Med*. 1981;2:160–5.

32. Tulppo MP, Makikallio TH, Seppanen T, Laukkanen RT, Huikuri HV. Vagal modulation of heart rate during exercise: effects of age and physical fitness. *Am J Physiol*. 1998;274:H424–9.

33. Urhausen A, Weiler B, Coen B, Kindermann W. Plasma catecholamines during endurance exercise of different intensities as related to the individual anaerobic threshold. *Eur J Appl Physiol Occup Physiol*. 1994;69:16–20.

34. Vrtovec B, Starc V, Starc R. Beat-to-beat QT interval variability in coronary patients. *J Electrocardiol*. 2000;33:119–25.

35. Wilhelm FH, Grossman P, Coyle MA. Improving estimation of cardiac vagal tone during spontaneous breathing using a paced breathing calibration. *Biomed Sci Instrum*. 2004;40:317–24.

36. Yeragani VK, Pohl R, Jampala VC, Balon R, Kay J, Igel G. Effect of posture and isoproterenol on beat-to-beat heart rate and QT variability. *Neuropsychobiology*. 2000;41:113–23.

37. Yeragani VK, Pohl R, Jampala VC, Balon R, Ramesh C. Effect of age on QT variability. *Pediatr Cardiol*. 2000;21:411–5.

38. Yeragani VK, Pohl R, Jampala VC, Balon R, Ramesh C, Srinivasan K. Increased QT variability in patients with panic disorder and depression. *Psychiatry Res*. 2000;93:225–35.

39. Yeragani VK, Srinivasan K, Vempati S, Pohl R, Balon R. Fractal dimension of heart rate time series: an effective measure of autonomic function. *J Appl Physiol*. 1993;75:2429–38.

40. Malik M, Bigger JT, Cumm J, et al. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93:1043–65.

BASIC SCIENCES