

## Relationship between electrocardiographic RR and QT interval variabilities and indices of ventricular function in healthy subjects

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### Abstract

To date there has been no simultaneous characterization of the influence of physical exercise on cardiac ventricular function and cardiac electrical variability. Consequently, little is known about the relationship between the ventricular function and either heart rate (RR) or repolarization (QT) variability. In particular, the relationship between the QT variability index (QTVI) and ventricular function would be of clinical interest. Eight males of similar age ( $20.7 \pm 0.4$  years (mean  $\pm$  SD)), mass ( $78.4 \pm 7.7$  kg) and aerobic fitness ( $50.7 \pm 4.9$  ml kg<sup>-1</sup> min<sup>-1</sup>) undertook progressive bicycle exercise. A three-lead Holter ECG was recorded continuously during pre-exercise, exercise and recovery, and mean values of RR and QT, their variabilities (RMSSD and SDNN) and their relative variability (QTVI) were determined. Traditional indices of ventricular function were determined beat to beat via impedance cardiography, and beat-to-beat blood pressure was recorded via photoplethysmography. Multiple linear regression analysis using the stepwise method resulted in significant models for each of the dependent variables (RR, QT, RR and QT variabilities, QTVI), using indices of the ventricular function as predictor variables. Notably, the QTVI reflected both the stroke volume index (SVI) and the acceleration index (ACI), which are measures of cardiac 'output' per contraction and the force of contraction, respectively. This relationship was largely unperturbed by physical exercise, in contrast with the results for all other dependent variables. We conclude that the QTVI is a reasonably consistent measure of the cardiac ventricular function, and as such is a more useful index than other parameters based on RR or QT interval alone.

Keywords: ventricular function, QTVI, electrocardiogram, heart rate variability, ventricular repolarisation, impedance cardiography

## 1. Introduction

The QT variability index (QTVI) was introduced by Berger *et al* (1997); it is expressed as the base-10 logarithm of the ratio of the squared coefficients of variance of the electrocardiographic repolarization (QT) and heart rate (RR) intervals. The QTVI therefore compares the magnitude of temporal variability in electrocardiographic depolarization and repolarization intervals. Several previous studies have indicated an association between changes in the QTVI and altered autonomic nervous system (ANS) activity. For example, the QTVI is decreased after postural tilt in healthy subjects (Piccirillo *et al* 2001) and is increased in patients with chronic renal failure (Johansson *et al* 2004). Moreover, an increased QTVI is a risk factor for sudden cardiac death (Atiga *et al* 1998, 2000), indicates a greater susceptibility for malignant ventricular arrhythmias (Berger *et al* 1997, Atiga *et al* 1998, 2000) and is associated with an independent risk for ventricular tachycardia or ventricular fibrillation (Haigney *et al* 2004). Recently, Piccirillo *et al* (2007) found that an elevated QTVI was a strong predictor of sudden cardiac death in chronic heart failure patients, who were asymptomatic and had only a slightly depressed ejection fraction (EF).

Despite its increasing use in clinical research, to our knowledge our previous study (Lewis *et al* 2006) has been the only investigation of the QTVI during physical exercise, a physiological condition during which there are marked changes in both ANS activity and cardiac functional performance. In that work we observed a substantial and rapid increase in the QTVI during exercise, and the QTVI remained elevated for an extended recovery period. It is worthy of note that Atiga *et al* (1998) suggested a non-exercise QTVI value of 0.1 or greater to be a discriminator for an elevated risk of arrhythmic events. In our previous study, the QTVI exceeded this value even at relatively low work rates ( $42 \pm 7\%$  and  $32 \pm 8\%$  of maximal work rate in males and females, respectively). We speculated that this might be interpreted as indicating an elevated risk of arrhythmia during physical exercise at intensities greater than these values. We also now postulate that the QTVI is an index of cardiac functional 'demand', and that it might be more sensitive in this regard compared with other measures of RR and QT variabilities. In particular, it would be of great clinical interest to investigate the relationship between the QTVI and the various standard measures of cardiac (ventricular) function, in an attempt to establish those aspects of cardiac performance that have the greatest association with the QTVI.

However, to date there has been no investigation of the relationship between the QTVI and traditional indices of cardiac functional performance. Moreover, there appears to have been no previous study in which the range of cardiac ventricular performance indices have been characterized and compared during conditions of rest, exercise and subsequent recovery. Our first aim in the present study was therefore to quantify indices of the cardiac ventricular function, non-invasively and simultaneously with the measurement of the electrocardiogram (ECG). The ECG would be used to determine the RR and QT intervals and their variabilities in the time domain, and their relative variabilities would be quantified via the QTVI index. The specific objectives of this study were therefore (1) to characterize measures of the cardiac ventricular function during rest, progressive (maximal) physical exercise and post-exercise recovery; (2) to examine and compare the relationships between ventricular function indices and standard measures of RR and QT interval variabilities (including the QTVI) using multiple regression analysis and (3) to examine whether the relationship between these parameters is altered following the performance of high-intensity physical exercise.

## 2. Materials and methods

### 2.1. Subjects

Eight males (age  $20.7 \pm 0.4$  years, mass  $78.4 \pm 7.7$  kg (mean  $\pm$  SD)) volunteered to take part in the investigation, which was approved by a University ethics committee. Individual maximal oxygen uptake ( $\dot{V}O_{2\max}$ ) values confirmed the homogeneity of aerobic fitness within the group ( $50.7 \pm 4.9$  ml kg<sup>-1</sup> min<sup>-1</sup> (mean  $\pm$  SD)). Subject health screening was undertaken using the American Heart Association/American College of Sports Medicine pre-participation screening questionnaire (Balady *et al* 1998). All subjects were apparently healthy non-smokers and were physically active to a similar level. The subjects were free of cardiovascular and chronic respiratory problems (including asthma), had no history of sleep apnoea, central or peripheral nervous system disorder and were not taking any medication at the time of the study. All subjects were informed in writing about the demands of the study, and subsequently gave their written informed consent for participation prior to commencing the study. Subjects were not permitted to consume tea, coffee, alcohol or heavy meal within 2 h prior to physiological assessment, and no physical exercise was permitted within the 24 h period prior to assessment.

### 2.2. Exercise testing protocol

All measurements were carried out between 9.00 am and 10.00 am in the Exercise Physiology Laboratory at the Department of Sports Science, University of Wales Swansea. The subjects were initially at rest and were asked to breathe in accordance with a metronome set to a rate of 15 breaths per minute (0.25 Hz) for a period of 6 min. At the end of this period, they were instructed to breathe spontaneously for a further 6 min at rest. The subjects then immediately performed a progressive exercise test on an electromagnetically braked cycle ergometer (Lode Excalibur Sport; Lode, Holland). The subjects were instructed to pedal at a constant cadence of 60 rpm. The exercise work rate began at 60 W for a period of 5 min and thereafter increased in 30 W increments every 3 min until volitional fatigue. Breath-by-breath oxygen uptake ( $\dot{V}O_2$ ) data were recorded throughout using an Oxycon Pro respiratory gas analysis system (Jaeger, Germany) to enable estimation of subjects' aerobic capacity.

### 2.3. Physiological measurement

A Reynolds Lifecard CF digital Holter recorder (Del Mar Reynolds Medical Ltd, UK) was used to record a three-lead ECG continuously throughout the pre-exercise, exercise and post-exercise periods. The ECG leads were positioned in the 'modified V5, CC5, modified V5R' electrode configuration. This system provided ECG data with a sample accuracy of  $2.5 \mu\text{V}$  (magnitude of least significant bit; 12 bit resolution) and 128 Hz sampling frequency. We have previously quantified the between-lead differences in RR and QT data using this ECG system (Lewis and Short 2006), and we therefore considered that there would be no benefit from quantifying QT and RR in each lead. All analyses in this investigation were therefore performed using data from a single ECG lead (lead 1 for each subject). The ECG recordings were analysed using a Reynolds Pathfinder digital analyser (Del Mar Reynolds Medical Ltd, UK). All ECG data used for subsequent analysis in this study were free of any form of morphologically abnormal beat, and this was verified by both the Holter system and by human observation. Beat-to-beat cardiac interval (RR) and QT interval data were automatically measured for each sinus beat and exported for further analysis using the Reynolds Research Tools software (Del Mar Reynolds Medical Ltd, UK). The QT and RR data also underwent

human visual examination in order to verify the accuracy of the data prior to subsequent analysis. When either the RR or QT interval was considered to be anomalous, both the RR and QT data points were removed from the data set. This occurred infrequently (and mainly during exercise), overall resulting in fewer than 1% of the data being removed. All QT analysis in this investigation was based on the  $QT_e$  interval (Q wave onset to T wave end), as we have previously observed that it provides a reliable estimate of the duration of the ventricular depolarization–repolarization phase (Lewis and Short 2006).

The Task Force Haemodynamic monitor (CNSystems Medizintechnik GMBH, Austria) was used to record beat-to-beat cardiac ventricular performance parameters (via impedance cardiography) and beat-to-beat blood pressure (via photoplethysmography, employing the vascular unloading technique at the finger). Using these methods, the following parameters were determined: stroke volume index (SVI), cardiac output index (CI), left ventricular ejection time (LVET), end diastolic volume index (EDVI), ejection fraction (EF), index of contractility and acceleration index (IC and ACI, both of which are measures of the inotropic state of the myocardium), total peripheral resistance (TPRI), left ventricular work index (LVWI), systolic and diastolic blood pressure (BP) and pulse pressure (PP). The term ‘index’ in several of these definitions indicates that the original parameter values were normalized by dividing the individual values by the subject’s body surface area (mean  $\pm$  SEM body surface area =  $1.97 \pm 0.03 \text{ m}^2$ ).

#### 2.4. Data analysis

Subsets of the QT and RR data sets were defined that represented these data within specified intervals during exercise and during the pre- and post-exercise phases: (i) consecutive 1 min intervals during the 6 min period of metronomic breathing, (ii) consecutive 1 min intervals during the 6 min period of spontaneous breathing, (iii) the final 1 min period of each exercise stage (in order to represent physiologically steady-state conditions), (iv) consecutive 1 min intervals during the post-exercise resting phase, which lasted for 15 min. Prior to further data processing, the QT and RR data were linearly detrended within consecutive 1 min segments (corresponding to the subsets defined above) in order to remove any time-dependent trends in the data.

Variability of the RR interval was quantified in the time domain (RMSSDNN: square root of the mean of the sum of the squares of differences between adjacent RR intervals, and SDNN: standard deviation of all RR intervals) according to the Task Force guidelines on HRV (Task Force 1996). (In these definitions, ‘NN’ indicates that the RR intervals are measured from normal beats of sinus origin.) RMSSDNN and SDNN represent the high-frequency variability and the total variability of the RR interval data, respectively (Task Force 1996). Equivalent time-domain parameters were calculated to describe the variability of the QT interval (RMSSDQT and SDQT). The QTVI was calculated according to the equation described by Berger *et al* (1997):  $QTVI = \log_{10}\{[QT_v/(QT_m)^2]/[RR_v/(RR_m)^2]\}$ , where  $QT_v$  and  $RR_v$  are the variabilities of QT and RR, respectively, and  $QT_m$  and  $RR_m$  are the mean values of these parameters for each defined period.

Each of the measured parameters was separately averaged to provide single representative values for the discrete physiological states during pre-exercise (metronomic breathing and spontaneous breathing states) and during post-exercise (0–5, 5–10 and 10–15 min post-exercise recovery periods). (Exercise values for each parameter were already defined for representative 1 min stages.) All data quoted in the text represent mean  $\pm$  SD. The error bars in the figures represent the SEM (standard error in the mean) for the plotted parameters.

**Table 1.** Pearson correlation coefficient matrix for the selected predictor variables.

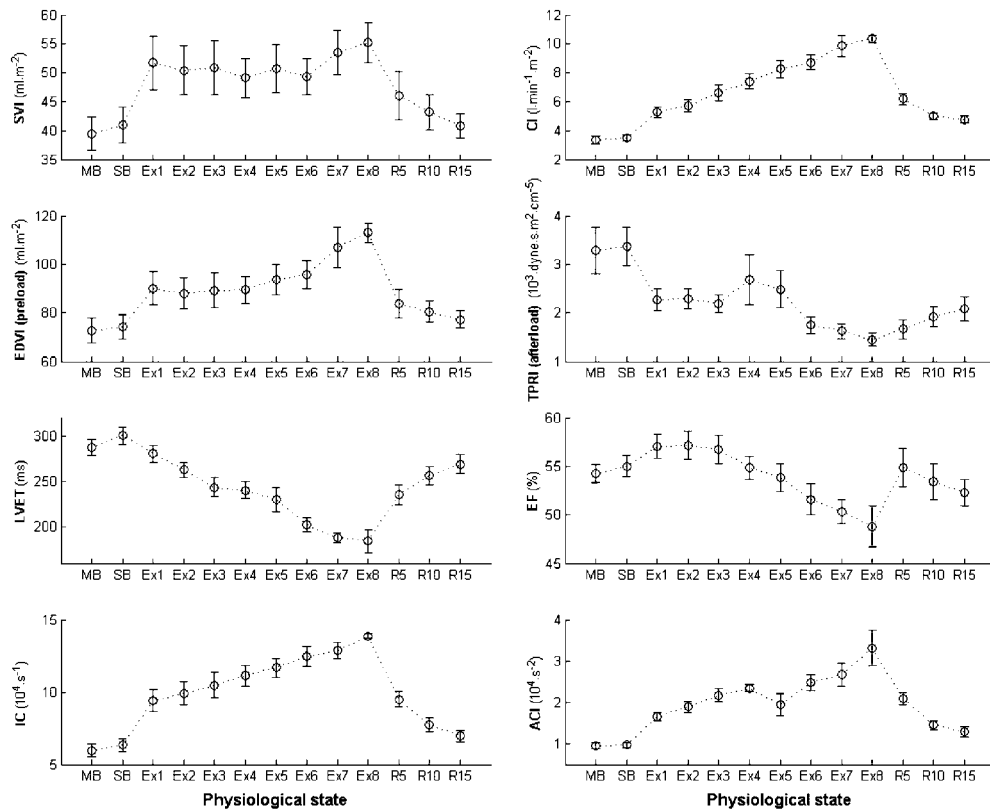
Predictor variable	SVI	LVET	EDVI	IC	ACI	TPRI	LVWI	PP
SVI	1.00	0.65	0.97	0.88	0.34	-0.30	0.61	0.66
LVET		1.00	0.49	0.48	-0.18	0.36	0.33	0.34
EDVI			1.00	0.88	0.44	-0.46	0.59	0.68
IC				1.00	0.45	-0.40	0.66	0.63
ACI					1.00	-0.51	0.20	0.16
TPRI						1.00	-0.01	-0.20
LVWI							1.00	0.73
PP								1.00

### 2.5. Statistical analysis

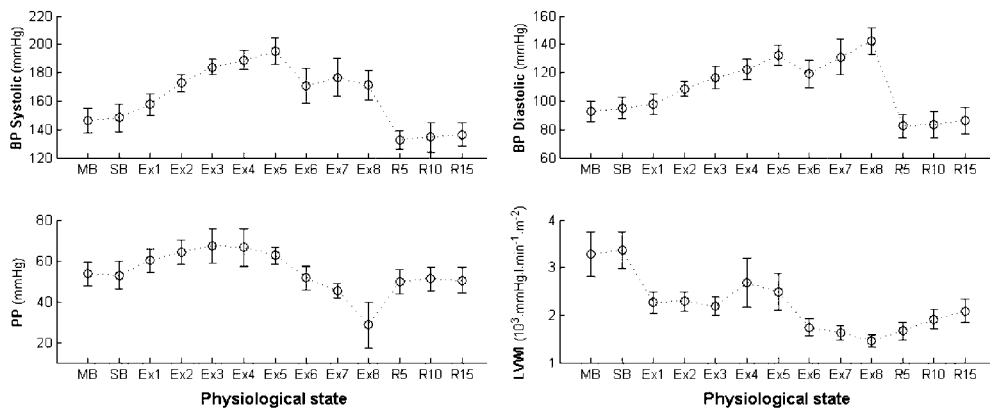
The stepwise method of multiple linear regression was used to establish whether a significant predictor model could be obtained for the following dependent variables: RR, QT<sub>e</sub>, RMSSDNN, SDNN, RMSSDQT, SDQT and QTVI. Each of the independent (predictor) variables was first visually checked for the presence of outliers and to assess linearity using scatterplots. Each of the predictor variables obeyed these assumptions and so each was standardized (giving its  $z$  score) prior to subsequent regression analysis. Parameter inclusion was carefully considered with regard to underlying physiology; any parameter that was a direct linear product of other (included) fundamental parameters was excluded from subsequent analysis to avoid singularity. Multicollinearity was minimised by the judicious selection of predictor variables, examination of the predictor variable correlation matrix (table 1) and manual examination of the influence of variable inclusion on the resulting  $R^2$  values (proportion of explained dependent parameter variance for the models). These procedures resulted in our selection of the following subset of predictor variables: SVI, LVET, EDVI, IC, ACI, TPRI, LVWI, PP. Standardized (beta) coefficients were used to report the contribution of each predictor variable to the multiple regression models. Adjusted  $R^2$  (adj  $R^2$ ) values were reported as this was considered to be the most appropriate measure of  $R^2$  for small samples. A value of  $p < 0.05$  for a predictor variable indicated its statistically significant unique contribution to the model. The standard assumptions of multiple regression (normality, linearity and homoscedasticity) were verified via scatterplots of the residuals (differences between the observed values of the dependent variable and those predicted by the regression model) and using normal probability plots, separately for pre- and post-exercise states.

## 3. Results

Figure 1 presents the characterization plots of cardiac ventricular function indices during pre-exercise, exercise and post-exercise recoveries. The blood pressure response and associated functional indices are shown in figure 2. The plots show substantial differences in parameter values during exercise compared with pre- and post-exercise periods, with parameters exhibiting gradual returns to pre-exercise values within the observation period. The magnitude and trends in the response of each variable were consistent for all subjects. For the same periods, figure 3 presents the absolute values of RR and QT together with indices of their variability and a measure of their relative variability (QTVI). RR variability parameters (RMSSDNN and SDNN) demonstrated the expected exponential-type decline with increasing exercise work rates (Lewis *et al* 2007). Conversely, the QT variability (RMSSDQT and SDQT) increased at the onset of exercise with a gradual reduction prior to a second increase at



**Figure 1.** Cardiac ventricular performance indices (MB = Metronomic breathing; SB = Spontaneous breathing; Ex1–Ex5 = Exercise stages; R5, R10, R15 = Recovery periods (0–5, 5–10 and 10–15 min post-exercise, respectively).



**Figure 2.** Blood pressure response and related performance indices.

the higher exercise work rates. It was not possible to determine the QT variability during the highest exercise work rates owing to acknowledged difficulties in accurate QT determination at very high heart rates. For consistency, we have therefore not reported values of QT or

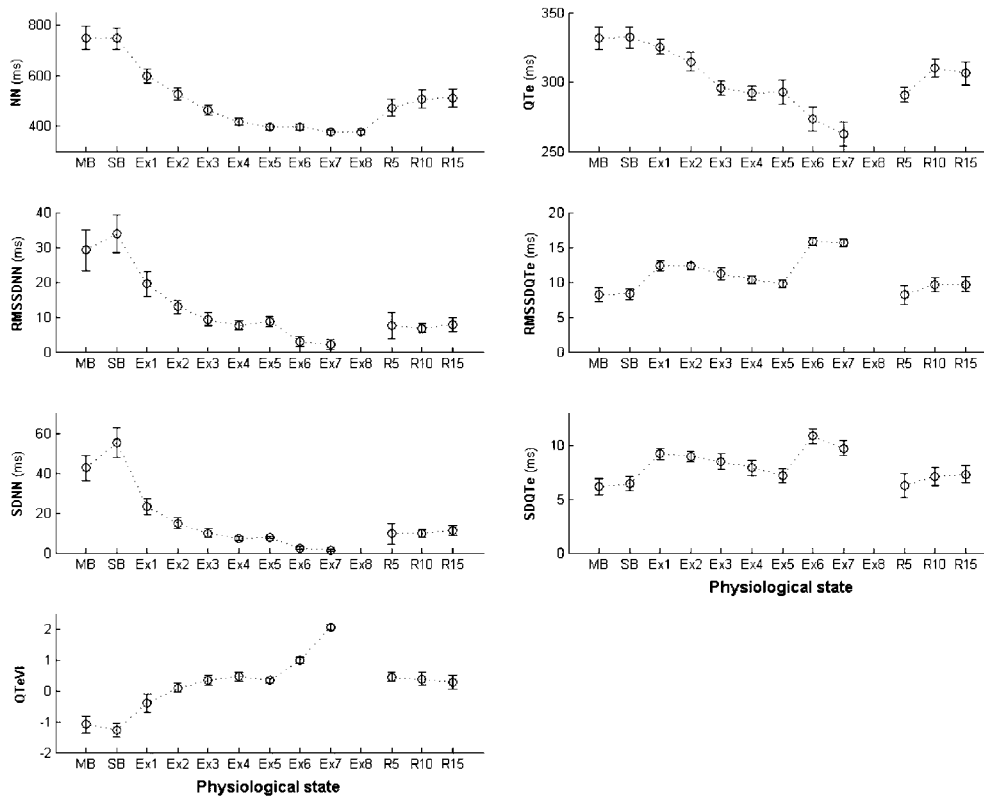


Figure 3. RR (NN) and QT variability indices, together with the QTnVI.

RR variability (or QTnVI) during exercise stage ‘Ex8’. The QTnVI demonstrated the rapid and substantial increase in magnitude that we have reported previously (Lewis *et al* 2006). Reflecting to a degree the observation for QT variability, the QTnVI was further substantially increased during the highest exercise work rates. Again, as we have previously observed, the QTnVI was substantially elevated in comparison with pre-exercise values throughout the post-exercise period.

Multiple linear regression analysis using the stepwise method resulted in significant models for the dependent variables. These models are reported in tables 2–9, which also quantify the strength of the model (ANOVA  $F$  statistic and  $p$  value, together with the adj  $R^2$  value), separately for the pre- and post-exercise states. For comparison between pre- and post-exercise states, each table lists those predictor variables (cardiac performance parameters) that made a significant unique contribution to either the pre- or the post-exercise model. Significant predictor variables are highlighted in bold and have associated  $p$  values less than 0.05. Where a predictor variable is listed but did not make a significant unique contribution to the model, the specified beta coefficient is that which would have resulted from adding that term to the model.

The regression models for both RR and QT included significant unique contributions from a large number of the predictor variables, and consequently accounted for a large proportion of the variance in these parameters (91% and 86% during pre-exercise and 84% and 57% during post-exercise for RR and QT, respectively). However, whereas the predictor variables

**Table 2.** Multiple linear regression model for RR.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.912, F_{5,90} = 200.5, p < 10^{-4}$			$\text{adj } R^2 = 0.839, F_{5,114} = 125.9, p < 10^{-4}$		
Dependent variable = RR	Predictor variable	Beta	$p$	Predictor variable	Beta	$p$
	<b>SVI</b>	0.65	0.0003	<b>SVI</b>	1.51	0.0000
	<b>EDVI</b>	0.61	0.0011	<b>EDVI</b>	-0.50	0.0000
	<b>IC</b>	-0.18	0.0176	<b>IC</b>	-0.82	0.0000
	<b>TPRI</b>	0.93	0.0000	<b>TPRI</b>	-0.20	0.0004
	<b>LVWI</b>	0.56	0.0000	<b>LVWI</b>	-0.16	0.0173

**Table 3.** Multiple linear regression model for QT.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.856, F_{6,89} = 96.4, p < 10^{-4}$			$\text{adj } R^2 = 0.570, F_{3,116} = 32.9, p < 10^{-4}$		
Dependent variable = QT	Predictor variable	Beta	$p$	Predictor variable	Beta	$p$
	<b>SVI</b>	1.32	0.0000	<b>SVI</b>	0.29	0.1838
	<b>EDVI</b>	0.45	0.0636	<b>EDVI</b>	0.68	0.0000
	<b>IC</b>	-0.20	0.0416	<b>IC</b>	-0.28	0.0680
	<b>ACI</b>	0.21	0.0000	<b>ACI</b>	-0.45	0.0001
	<b>TPRI</b>	0.65	0.0000	<b>TPRI</b>	-0.25	0.0005
	<b>LVWI</b>	-0.59	0.0000	<b>LVWI</b>	-0.04	0.6889
	<b>PP</b>	-0.20	0.0025	<b>PP</b>	-0.05	0.7067

**Table 4.** Multiple linear regression model for RMSSDNN.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.654, F_{2,93} = 92.0, p < 10^{-4}$			$\text{adj } R^2 = 0.099, F_{1,118} = 15.2, p = 0.0001$		
Dependent variable = RMSSDNN	Predictor variable	Beta	$p$	Predictor variable	Beta	$p$
	<b>SVI</b>	0.14	0.2662	<b>SVI</b>	0.34	0.0002
	<b>LVET</b>	0.69	0.0000	<b>LVET</b>	-0.07	0.5060
	<b>TPRI</b>	0.25	0.0002	<b>TPRI</b>	0.14	0.1491

**Table 5.** Multiple linear regression model for SDNN.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.602, F_{1,94} = 147.3, p < 10^{-4}$			$\text{adj } R^2 = 0.297, F_{2,117} = 18.2, p < 10^{-4}$		
Dependent variable = SDNN	Predictor variable	Beta	$p$	Predictor variable	Beta	$p$
	<b>SVI</b>	0.07	0.3838	<b>SVI</b>	0.71	0.0000
	<b>LVET</b>	0.78	0.0000	<b>LVET</b>	-0.16	0.2844
	<b>IC</b>	0.09	0.2139	<b>IC</b>	-0.28	0.0218

**Table 6.** Multiple linear regression model for RMSSDQT.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.253, F_{2,94} = 17.8, p < 10^{-4}$			$\text{adj } R^2 = 0.183, F_{3,116} = 10.3, p < 10^{-4}$		
Dependent variable = RMSSDQT	Predictor variable	Beta	<i>p</i>	Predictor variable	Beta	<i>p</i>
	<b>SVI</b>	-0.98	0.0000	<b>SVI</b>	0.24	0.3435
	<b>EDVI</b>	-0.32	0.3686	<b>EDVI</b>	0.39	0.0044
	<b>IC</b>	0.62	0.0010	<b>IC</b>	-1.02	0.0000
	<b>ACI</b>	0.14	0.1735	<b>ACI</b>	0.51	0.0005

**Table 7.** Multiple linear regression model for SDQT.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.248, F_{2,93} = 17.3, p < 10^{-4}$			$\text{adj } R^2 = 0.220, F_{3,116} = 12.6, p < 10^{-4}$		
Dependent variable = SDQT	Predictor variable	Beta	<i>p</i>	Predictor variable	Beta	<i>p</i>
	<b>SVI</b>	0.98	0.0000	<b>SVI</b>	-0.24	0.3725
	<b>EDVI</b>	-0.45	0.2116	<b>EDVI</b>	0.40	0.0017
	<b>IC</b>	0.64	0.0008	<b>IC</b>	-1.21	0.0000
	<b>ACI</b>	0.12	0.2132	<b>ACI</b>	0.68	0.0000

**Table 8.** Multiple linear regression model for QTVI.

Stage	Pre-exercise			Post-exercise		
Model	$\text{adj } R^2 = 0.411, F_{2,93} = 35.0, p < 10^{-4}$			$\text{adj } R^2 = 0.270, F_{2,117} = 23.6, p < 10^{-4}$		
Dependent variable = QTVI	Predictor variable	Beta	<i>p</i>	Predictor variable	Beta	<i>p</i>
	<b>SVI</b>	-0.68	0.0000	<b>SVI</b>	-0.43	0.0000
	<b>ACI</b>	0.38	0.0000	<b>ACI</b>	0.51	0.0000

**Table 9.** Multiple linear regression model for EF.

Stage	Pre-exercise			Post-Exercise		
Model	$\text{adj } R^2 = 0.975, F_{2,93} = 1885.2, p < 10^{-4}$			$\text{adj } R^2 = 0.967, F_{2,117} = 1741.3, p < 10^{-4}$		
Dependent variable = EF	Predictor variable	Beta	<i>p</i>	Predictor variable	Beta	<i>p</i>
	<b>SVI</b>	3.88	0.0000	<b>SVI</b>	2.33	0.0000
	<b>EDVI</b>	-3.65	0.0000	<b>EDVI</b>	-1.91	0.0000

included in the model for RR were consistent for pre- and post-exercise, fewer predictor variables contributed to the post-exercise QT model compared with those during pre-exercise.

The ability of the regression model to describe the variability of RR (RMSSDNN and SDNN) was substantially reduced post-exercise (accounting for 65% and 10% of variability in RMSSDNN and 60% and 30% of variability in SDNN, pre- and post-exercise respectively).

Moreover, the predictor variables making a unique contribution to the model were different (and mutually exclusive) for the pre- and post-exercise models for both RMSSDNN and SDNN.

The predictive abilities of the regression models for RMSSDQT and SDQT were low to moderate but were very similar to one another, and also did not differ greatly for pre- and post-exercise states (25% and 25% during pre-exercise and 18% and 22% during post-exercise for RMSSDQT and SDQT, respectively). The predictor variables included in the models for RMSSDQT and SDQT were identical when compared for either the pre- or the post-exercise state. There was partial consistency between the predictor variables included in the pre- and post-exercise models for RMSSDQT and SDQT, with IC providing a significant unique contribution in both.

The predictive abilities of the regression models for the QTVI were moderately good (41% and 27% for pre- and post-exercise, respectively) and there was good consistency between the predictor variables included in the pre- and post-exercise models, with SVI and ACI providing significant unique contributions in both.

In order to test and validate our methods of multiple regression modelling, we also performed an additional multiple regression analysis with the EF as the dependent variable. All possible predictor variables were as previously stated. The predictive abilities of the regression models for the EF were very high (98% and 97% for pre- and post-exercise, respectively), and there was good consistency between the predictor variables included in the pre- and post-exercise models, with SVI and EDVI providing significant unique contributions in both. The magnitude of the beta coefficients for SVI and EDVI were large, indicating a strong contribution to the model, and were appropriately signed in accordance with the theoretical relationship between these parameters ( $EF = SVI/EDVI$ ).

## 4. Discussion

### 4.1. Characterization of cardiac ventricular performance indices

Cardiac performance indices were measured reliably and continuously during rest, exercise and recovery using the Task Force monitor. These indices provided a comprehensive characterization of the cardiac and haemodynamic responses to the progressive exercise protocol. Variability in electrocardiographic RR and QT intervals was reliably quantified throughout the protocol apart from during the final stage of exercise, during which time the substantially elevated heart rates made it impossible to measure the QT interval.

### 4.2. Quantification and interpretation of ventricular repolarization variability

The QT interval of the ECG represents the period of ventricular depolarization–repolarization, and is known to vary in part as a function of the heart rate or RR interval (Porta *et al* 1998). However, Almeida *et al* (2006) found that the RR-independent contribution to QT variability in healthy subjects was substantial (greater than 40%). Previous studies had also observed that QT shortening during exercise has a substantial component that is not controlled by the heart rate (Rickards and Norman 1981, Milne *et al* 1982). A complete understanding of the temporal variability of electrical activity in the ventricular myocardium, therefore, requires consideration of both RR and QT variabilities.

*4.2.1. QT variability.* The temporal variability of the QT interval of the ECG is caused by transmural dispersion of myocardial repolarization (Piccirillo *et al* 2007); the duration of

repolarization varies between subendocardial, subepicardial and intermediate layer (M) cells, being delayed in the M cells owing to ion channel population differences (Rosen and Cohen 2006). Temporal myocardial repolarization inhomogeneity might be accentuated owing to pathological structural changes or as a result of sympathetic hyperactivity or reduced vagal activity (Tomaselli and Zipes 2004, Piccirillo *et al* 2007). In fact, the ANS has a direct influence on the ventricular myocardium and could influence ventricular repolarization independently of SA node modulation (Magnano *et al* 2002). The magnitude of QT variability is of great clinical significance as it is related to the risk of sudden cardiac death, caused by sustained ventricular tachycardia or fibrillation (Antzelevitch and Oliva 2006, Piccirillo *et al* 2007). Nevertheless, despite this understanding of the mechanistic origins and the diagnostic and prognostic utility of QT variability measures, we are not aware of any previous study that has assessed the relationship between QT variability and standard measures of ventricular performance.

*4.2.2. The QT variability index.* The QTVI is a marker of temporal inhomogeneity in myocardial repolarization (Piccirillo *et al* 2007). Several studies have demonstrated that the QTVI, in preference to other indices of either RR or QT variability, has utility as a risk factor or discriminator for cardiac pathologies related to a diminished or abnormal ventricular function. Also, we have previously reported that the QTVI is highly sensitive to changes in physiological states including rest, exercise and recovery. For example, we noted a substantial and rapid increase in the QTVI within the first minute of exercise at relatively low work rates. Subsequently, elevated QTVI values were observed throughout a progressive exercise protocol and during an extended period of recovery, indicating a sustained shift towards the dominance of QT variability over RR variability.

The potential clinical utility of the QTVI, yet the lack of a clear functional interpretation of this index, led to the rationale for the present study. We suggested that it would be of great interest to determine the relationship between the QTVI and standard measures of cardiac ventricular performance, and to compare this relationship with that for other indices of cardiac (QT and RR) temporal variability. Since we had previously observed substantial differences in the QTVI during exercise and recovery compared with those during pre-exercise rest, we also sought to investigate whether exercise alters these relationships.

#### *4.3. Relationship between cardiac performance indices and RR and QT variabilities*

We observed differences between the subsets of included predictor variables, and differences in their magnitudes, in several of the pre- and post-exercise models. This suggests that exercise had a substantial influence on the relationship between measures of RR and QT variabilities and these indices of cardiac ventricular performance.

On the basis of the reported regression models, RMSSDNN appears to reflect LVET and TPRI during rest and reflect SVI following exercise. SDNN appears to reflect LVET during rest and both SVI and IC following exercise. The results suggest that RMSSDQT and SDQT are equivalent with regard to their relationships with the indices of the cardiac ventricular performance: RMSSDQT and SDQT reflect SVI and IC during rest and reflect EDVI, IC and ACI following exercise. SVI and ACI (measures of cardiac 'output' per contraction and the force of contraction, respectively) are the strongest predictors of the QTVI, and notably the relationship between the QTVI and these indices of the cardiac ventricular performance is not altered following high-intensity exercise.

#### 4.4. Limitations

We did not try to quantify the relationship between cardiac ventricular performance parameters and RR and QT variables during exercise because the relatively short periods during which we could have assumed physiological steady states would have been an insufficient basis for performing meaningful regression analysis. Future work might attempt to evaluate such relationships by employing longer, single periods of exercise at uniform work rates.

It is also worthy of note that the majority of variables considered in this study remained substantially altered at the end of the recovery period (15 min post-exercise) compared with those at rest; future studies should therefore employ longer recovery periods to analyse the complete recovery behaviour of these variables.

In our previous work (Lewis *et al* 2006), we observed gender differences in both the magnitude and dynamic properties of the QTVI index during conditions of rest and exercise. The QTVI was lower (more negative) in males compared with females during pre-exercise rest and during moderate intensity exercise, indicating a more marked dominance of RR variability over QT variability in males compared with females. Only males were considered in the present study and a comparison of these results for females would be a useful future addition to this work.

Finally, we wish to emphasize that the data reported in this study were obtained from young, physically active, healthy subjects. The direct applicability of this work to clinical populations (such as those with cardiac pathology), and the influence of age and physical fitness thereon, remains questionable; in this context, the results of our study should be interpreted with caution.

#### 4.5. Concluding remark

In quantifying the relative variability of RR and QT intervals, the QTVI index appears to be strongly influenced by both SVI and ACI and this relationship is maintained following a period of high-intensity physical exercise. Each of the other regression models of electrocardiographic RR and QT interval magnitudes and variabilities was altered following the performance of physical exercise. We conclude that the QTVI is a reasonably consistent measure of cardiac ventricular performance during pre- and post-exercise physiological conditions, and as such is a more useful index than other parameters based on the RR or QT interval alone.

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