

# Concurrent Exercise-Associated Ventricular Complexes and a Prolonged QT Interval are Associated with Evidence of Myocarditis

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## Abstract

**Background:** Precise myocardial tissue characterization in subjects with exercise-associated ventricular ectopy and prolonged QT interval but no obvious structural heart disease might facilitate further risk stratification. There is no data assessing QT intervals in patients with exercise-associated premature ventricular complexes (PVCs). Cardiovascular magnetic resonance (CMR) enables us to non-invasively assess myocardial scar and oedema. The purpose of our study was to assess the QT intervals in patients with exercise-associated premature ventricular complexes (PVCs).

**Methods:** We analyzed the QT and QTc intervals of the 162 consecutive patients with documented exercise-associated PVCs but no history or evidence of coronary heart disease or cardiomyopathy we previously examined. Findings were compared with those from 182 new controls without exercise-associated PVCs matched for gender and age. Continuous 12-lead ECG during upright bicycle exercise test and ECG-triggered, T2-weighted, fast spin echo triple inversion recovery sequences and late gadolinium enhancement were obtained, as were LV function and dimensions.

**Results:** QT and QTc intervals were significantly prolonged in patients compared to controls ( $396.3 \pm 33.5$  ms vs.  $385.9 \pm 28.4$  ms,  $p=0.002$  and  $431.7 \pm 26.2$  ms vs.  $419.9 \pm 26.6$  ms,  $p=0.0001$ ). Eighty five percent of patients with exercise-associated PVCs and prolonged QT intervals had structural abnormalities in the myocardium suggestive of acute or remote myocarditis or myopericarditis.

**Conclusion:** Patients with exercise-associated PVCs showed prolonged QT intervals compared to controls. As a long QT interval is predictive of increased risk for arrhythmias or sudden cardiac death these findings may supply a potential mechanism for explaining the increased risk of some patients with exercise-associated PVCs.

**Keywords:** QT; QTc; ECG; Cardiovascular magnetic resonance imaging; Myocarditis; Premature ventricular complexes; Late gadolinium enhancement; STIR

**Abbreviations:** CMR: Cardiovascular Magnetic Resonance; ECG: Electrocardiogram; LV-EF: Left Ventricular Ejection Fraction; PVCs: Premature Ventricular Complexes; LV: Left Ventricular, Left Ventricle; LGE: Late Gadolinium Enhancement; STIR: Fast Spin Echo Triple Inversion Recovery Sequence (S)

## Introduction

Exercise-associated premature ventricular complexes (PVCs) may be due to structural heart disease such as myocardial infarction, dilated or hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or ion channel diseases [1-3]. In apparently healthy patients without underlying disease, the etiology of exercise-associated PVCs is often not revealed by basic non-invasive tests such as physical examinations, blood markers, echocardiography and/or treadmill exercise tests [4,5].

During the past two decades, cardiovascular magnetic resonance (CMR) has evolved from a research tool to a clinically validated, safe and comprehensive imaging modality with good reproducibility and diagnostic accuracy superior to other non-invasive approaches [6]. Functional parameters of LV function, dimensions, and flow can be measured accurately [7,8]. Late gadolinium enhancement (LGE) and oedema sequences (STIR) have been performed in patients with acute or remote myocarditis, and oedema and midmyocardial or

subepicardial LGE enhancement has been detected in patients with myocarditis [6,9,10].

Moreover, QT prolongation has been documented in these patients with presumed myocarditis [11] and a greater QT dispersion was found in young patients with carditis [12]. A detailed analysis of QT and QTc intervals in patients with exercise-associated PVCs has not been published to date. We therefore compared the QT and QTc intervals of 162 consecutive patients we examined before and of whom 85% showed evidence of myocardial disease consistent with acute or previous myocarditis or myopericarditis [13] and compared these patients to a control group without PVCs. We hypothesized that exercise-associated PVCs due to remote or acute myocarditis may be associated with QT interval changes.

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## Methods

### Patients

We analyzed retrospectively the 162 consecutive patients referred to our department for palpitations, thoracic pain or dyspnea who developed PVCs during exercise testing as reported before [13], and compared them to 182 age- and sex-matched controls without exercise-induced PVCs.

Patients and controls were excluded if they had a history or findings suggestive of coronary artery disease (history of myocardial infarction, signs of ischemia on stress tests, transmural scar on echocardiography, subendocardial or transmural scars on CMR in patients), dilated or hypertrophic cardiomyopathy, congenital heart disease, pulmonary hypertension, LV hypertrophy, significant valvular regurgitation or valvular stenosis, renal failure (creatinine  $\geq$  1.8 mg/dl, GFR  $<$ 30). Further exclusion factors were: chronic alcohol abuse, use of sympathomimetic drugs, Conn syndrome, chronic loop diuretic treatment, chronic use of laxatives or any other potential causes of hypokalemia.

Informed consent was obtained from each patient and control, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research ethic committee. Our final cohort comprised 162 patients whom we compared to 182 age- and sex-matched controls. Exercise tests and echocardiography was performed in controls and patients. CMR was only performed in patients, not in controls. Echocardiography was used to confirm normal left ventricular function in controls. We did not perform exercise tests in patients with acute heart insufficiency and reduced LVEF (EF $<$ 50%), in line with acute fulminant myocarditis. All patients we examined were outpatients in stable conditions.

Eighty-five patients underwent a follow-up exercise test at a mean of 1.7 years (2 months to 6 years). They had been scheduled for a control visit after myocarditis. We conducted a subgroup analysis of QT intervals in this patient group. QT intervals were measured automatically over 10 heart beats during rest by custo cardio 100 and 200 with CUSTO software using the BAZETT formula (Custo Med GmbH, Ottobrunn, Germany).

To validate the automatic algorithm, we checked the QT measurements visually in 20 randomly chosen patients and observed good comparability. Automatic QT interval measured  $388 \text{ ms} \pm 29 \text{ ms}$  vs. visually  $384 \text{ ms} \pm 26 \text{ ms}$ ,  $p=0.9$ . In 17 out of these 20 patients, the difference was  $<10 \text{ ms}$ , in 15 patients  $<5 \text{ ms}$ .

### Cardiovascular magnetic resonance (CMR)

All images were acquired on a 1.5 Tesla magnetic resonance system (Intera CV 1.5T, Philips Medical Systems, Best, the Netherlands). A specifically designed software (Release 11 using a five-element cardiac phased-array coil combined with a homogeneity correction algorithm (Constant Level Appearance; CLEAR) was used [14]. Data acquisition was ECG-triggered. In addition to 2, 3 and 4-chamber long-axis views, 3-D short-axis volume data was acquired by steady-state free precession imaging to evaluate LV function and dimensions. Phase-contrast velocity images in the ascending aorta were obtained to measure stroke volume and rule out significant aortic insufficiency as described previously [13,15,16]. Functional and morphological data were evaluated using view forum 6.5. (Philips Medical Systems, Best, the Netherlands).

All patients but no controls underwent ECG-triggered, T2-weighted, fast spin echo triple inversion recovery sequences (STIR) in a short axis view covering the whole left ventricle as described in our earlier studies [13,15,16]. Late gadolinium enhancement (LGE) imaging was obtained in all patients 10 minutes after iv administration of 0.2 mmol/kg gadolinium-diethylenetriaminepentaacetate using 3D inversion recovery turbo gradient echo sequences as described previously [13,15,16].

### Statistical analysis

Data are presented as means and standard deviation for quantitative variables and as absolute and relative frequencies for categorical variables. Variables between patients and controls were compared using t-tests for quantitative and Chi-square-tests for categorical variables. Correlations between quantitative patient characteristics were estimated by means of Pearson's correlation coefficient (r). All tests were two-sided and used a significance level of 0.05 to indicate statistical significance. Statistical analysis took place using SAS software (Statistical Analysis System) Version 9 and GraphPad Prism 5.01.

## Results

Baseline characteristics of patients (with exercise-associated PVCs) and controls (without exercise-associated PVCs) are shown in Table 1. Controls did not differ significantly regarding age, sex and blood pressure. There was no significant difference in resting and maximum heart rate between patients and controls. Patients clinical characteristics were dyspnoea in 18%, 31% had thoracic pain, 43% fatigue and 60% palpitations. No patient or control had known long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, early repolarisation syndrome or Brugada syndrome. Seven patients but no control had a history of paroxysmal atrial fibrillation and were in sinus rhythm during investigation; one patient presented permanent atrial fibrillation. As reported, the mean number of PVCs during exercise including the first minute after exercise was 29, range 1-240.

### Cardiovascular magnetic resonance (CMR) findings of patients

As reported patients revealed normal LV function and dimensions (LVEF  $63\% \pm 8\%$ , LV stroke volume  $97 \text{ ml} \pm 17 \text{ ml}$  and LV end-diastolic volume  $155 \text{ ml} \pm 34 \text{ ml}$ ). Sixty out of 162 (37%) patients displayed elevated T2-weighted CMR (STIR) values indicating oedema. Contrast enhancement was present in the myocardium of 110/162 patients (67.9%). Figures 1-3 depict an example of the CMR findings of a 57-year-old female patient. Twenty-seven percent of the patients presented locally-thickened pericardium ( $\geq 4 \text{ mm}$ ) and 17.9% with small pericardial effusion. Overall, structural anomalies had 139 (85.8%) of those patients with exercise-associated PVCs.

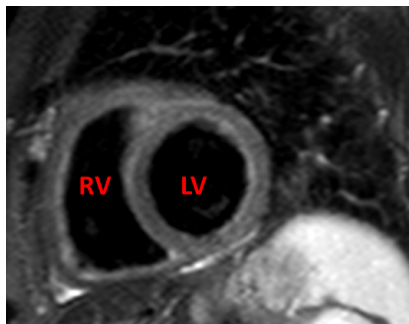
### QT and QTc intervals

QT and QTc intervals were significantly prolonged in patients

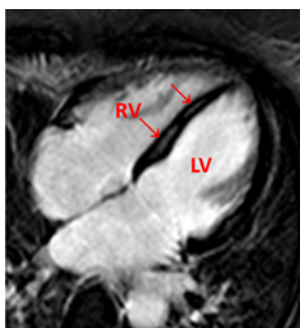
Variable	Patients	Controls	p
Mean age (years)	57.4 $\pm$ 12.8	56.5 $\pm$ 14.3	0.56
Female (%)	54.0 $\pm$ 33.0	78.0 $\pm$ 39.6	0.2
Weight (kg)	80.1 $\pm$ 13.9	80.0 $\pm$ 14.5	0.99
Systolic blood pressure (mmHg)	139.2 $\pm$ 18.8	143.4 $\pm$ 19.0	0.06
Diastolic blood pressure (mmHg)	82.5 $\pm$ 10.1	82.7 $\pm$ 9.7	0.88
Heart rate (beats per min)	75.1 $\pm$ 16.3	74.7 $\pm$ 11.2	0.68
Maximal heart rate (beats per min)	140.2 $\pm$ 24.4	134.6 $\pm$ 19.8	0.59

$\pm$ : Standard Deviation

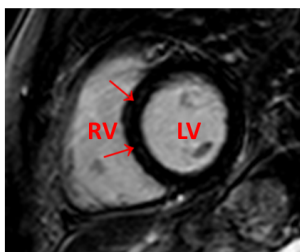
Table 1: Clinical characteristics.



**Figure 1:** Depicts an example of the CMR findings of a 57-year-old female patient with fatigue, palpitations, new documented PVCs after an upper tract respiratory infect three weeks ago. Global STIR+ratio was elevated (2.26). Two-chamber view. LV: Left Ventricle. RV: Right Ventricle. QT 425 ms, QTc 428 ms.



**Figure 2:** Late-enhancement image of the same patient. Note the midmyocardial enhancement in the septal (↑) wall. Four -chamber view. LV: Left Ventricle. RV: Right Ventricle.



**Figure 3:** Two-chamber view of the same patient. the midmyocardial enhancement in the septal (↑) wall. LV: Left Ventricle. RV: Right Ventricle.

Variable	Patients	Controls	p
QT (ms)	396.3 ± 33.5	385.9 ± 28.4	0.002
QTc (ms)	431.7 ± 26.2	419.9 ± 26.6	0.0001
<b>Male patients</b>		<b>Female patients</b>	
QT (ms)	397.3 ± 35.0	392.9 ± 30.3	0.44
QTc (ms)	431.4 ± 27.4	431.9 ± 24.2	0.34
<b>With oedema</b>		<b>No oedema</b>	
QT (ms)	399.5 ± 31.4	393.7 ± 35.4	0.30
QTc (ms)	436.4 ± 24.8	429.6 ± 27.0	0.11

ms: Milliseconds; ±: Standard Deviation; With Edema: Patients with Edema; No Edema: Patients without Edema

**Table 2:** QT and QTc results.

compared to controls (Table 2) (Figure 4). QT and QTc intervals in patients with edema and without edema were not statistically different (Table 2) as were patients with or without scars. We observed no significant correlation between the QT or QTc intervals and the

presence of edema or scar. There was no difference in male and female patients (Table 2). Thirty-three patients had a QTc interval >450 ms, and two patients >500 ms. Although those two patients had no known channelopathies, we excluded them from a separate analysis. The difference in the QT and QTc intervals remained highly significant between patients and controls (QT 395.4 ms ± 32.5 ms and QTc 430.5 ms ± 24.3 ms, p=0.005 and 0.0002).

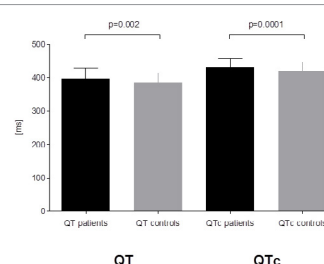
Eighty-five patients took a follow-up exercise test at a mean of 1.7 years (2 months to 6 years). In this patient subgroup, QT and QTc intervals at baseline were 397.9 ms ± 34.5 ms and 428.5 ms ± 25.0 ms, and remained unchanged at follow-up with 399.5 ms ± 42.5 ms and 429.5 ms ± 50.8 ms, (p=0.78 (QT) and p=0.87 (QTc)).

There was no correlation between the amount of PVCs during exercise and QT or QTc in any of the patients (p=0.86) or in those with QTc below 500 ms (p=0.87) or 450 ms (p=0.83). Thus, the automatic QT measurement algorithm was not disturbed by the amount of PVCs.

## Discussion

In the present study patients with exercise-associated PVCs exhibited a prolonged QT interval compared to controls. The vast majority of these patients presented myocardial edema, and midmyocardial or subepicardial scars consistent with acute or remote myocarditis [6,9-13]. A long QT interval is predictive of an increased risk for arrhythmias or sudden cardiac death [17]. Acute and long-term mortality in patients with viral myocarditis is higher in part due to sudden cardiac deaths caused by ventricular arrhythmias [18,19], and there is evidence of QT prolongation in patients with acute myocarditis [11,12]. Some investigations of the prognostic significance of ventricular arrhythmia during exercise have assumed that PVCs are benign [20,21] whereas others detected an association between PVCs and increased risk of cardiovascular or all-cause mortality rates [5,22-24]. In general, those studies examining patients with exercise-associated PVCs did not differentiate between the presence or high probability of coronary artery disease or other underlying cardiac diseases. As reported before [13], the vast majority of our patients with exercise-associated PVCs had structural anomalies consistent with acute or remote myocarditis, i.e. about two-thirds of them revealed subepicardial and/or midmyocardial late contrast-enhancement; about a third exhibited myocardial oedema typical of myocarditis [6,9,10,25-28].

Prolonged QT intervals have been described in patients suffering from acute myocarditis [11,12]. Our novel finding of increased QT and QTc intervals in patients with exercise-associated PVCs compared to controls may supply a potential mechanism for explaining the increased risk of patients with PVCs reported in some studies. In addition, sudden cardiac death in athletes and the general population is not infrequently due to unrecognized myocarditis [17,29]. There is evidence that increased sympathetic nerve activity during physiologic



**Figure 4:** QT and QTc in patients and controls. QT and QTc were significantly increased in patients compared to controls.

stress (e.g., exercise, swimming, emotion, loud noise) has a profound impact on the heart's contractile and electrical functions. In the predisposed heart, these stressors may lead to ventricular arrhythmias and sudden cardiac death [30]. In a case study with 26 patients with Williams-Beuren syndrome, a congenital developmental disorder, Collins et al. [31] reported a correlation between QTc, age, and PVCs at rest. Palatini et al. [32] found in 40 athletes a trend to higher prevalence of PVCs at rest compared to controls as well as prolonged QT and QTc intervals. Thus, there is evidence that patients with prolonged QT intervals and PVCs are at increased risk for lethal arrhythmias. To test the potential mechanisms, we compared the QT and QTc in patients with and without edema, and noted a tendency toward prolonged QT and QTc in the patients with edema.

We found no correlation between the presence of contrast enhancement and QT intervals. Other mechanisms for PVCs such as micro-reentry mechanisms without any detectable structural abnormalities may therefore play an additional role. We found no difference in the QT and QTc intervals between male and female patients. QT intervals were unchanged in patients who came to a follow-up visit. In patients who presented initially with edema and came to a follow-up visit, the QTc interval was modestly but not significantly shortened. These findings are in line with potential contribution of an edema to prolonging the QT interval and to the findings that patients with takotsubo cardiomyopathy present with edema, negative T waves, and QTc prolongation [33].

Structural abnormalities in terms of increased structural heterogeneity often constitute the basis for electrophysiological heterogeneity, e.g., with a prolonged QT interval and/or increased dispersion of repolarisation. In turn, these anomalies promote critical cardiac arrhythmias.

A limitation of our study is that only our patient group underwent CMR. The controls had no PVCs, no structural abnormalities on echocardiographic examination, normal LV function, and normal exercise tests. Therefore, it would not have been ethically justifiable to apply contrast agents to healthy volunteers. Thus, we cannot rule out that some controls might have exhibited areas of late contrast-enhancement.

## Conclusion

In conclusion, QT and QTc intervals were significantly prolonged in patients with exercise-associated premature ventricular beats and evidence of acute or remote myocarditis compared to controls. As a long QT interval is predictive of increased risk for arrhythmias or sudden cardiac death these findings may supply a potential mechanism for explaining the increased risk of some patients with exercise-associated PVCs. These results add important information to what is currently known about the connection between structural and electrophysiological diseases of the heart.

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## Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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