Long-Term Exercise-Training Improves QT Dispersion in the Metabolic Syndrome

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SUMMARY

Increased QT dispersion (QTd) is a marker of myocardial electrical instability and predicts ventricular arrhythmias and sudden cardiac death. Exercise training (ET) has been shown to reduce both QTd and cardiovascular mortality in various populations. Patients with metabolic syndrome (MS) have been shown to have increased QTd. The effect of ET on QTd in MS patients however is unknown. We sought to assess the effect of a long-term (≥6 months) ET program on QTd parameters in MS patients with and without coronary heart disease (CHD). Fifteen CHD and 31 non-CHD patients with MS (mean age, 64 ± 7 and 57 ± 9 years, respectively) were identified at entry into identical ET programs. MS was defined using modified National Cholesterol Education Program criteria. A control group consisted of 8 MS patients with CHD (mean age, 65 ± 6 years). Ventricular repolarization (QT dispersion = QTd, standard deviation of QT = SDQT, relative dispersion of QT = RDQT, QT corrected dispersion = QTc) were measured before and after ET. Program duration was over 9 months (312 ± 100 versus 284 ± 101 days in CHD and non-CHD cohorts, P = NS). QTd decreased in both ET groups (QTd pre versus post = 66 versus 56 ms in CHD, P < 0.01; 58 versus 51 ms in non-CHD, P ≤ 0.01). Other ventricular repolarization parameters also improved significantly in both MS groups following ET, but remained unchanged in the control group. A long-term ET program improves QTd in patients with MS with and without CHD. (Int Heart J 2010; 51: 41-46)

Key words: Ventricular repolarisation, Cardiac rehabilitation program, Cardiometabolic risk factors, Coronary heart disease

Q T dispersion (QTd) is defined as the difference between the longest and the shortest QT intervals on a standard 12-lead electrocardiogram (EGC). QTd is a noninvasive method to assess the inhomogeneity of myocardial repolarization. Originally proposed as an index of the spatial dispersion of ventricular recovery times, in reality, QTd is a marker of myocardial electrical instability and a predictor of arrhythmic events. QTd is thought to reflect the autonomic regulation of cardiovascular function, with increased QTd reflecting higher sympathetic and lower parasympathetic inputs to the heart. In patients with a history of acute myocardial infarction, increased QTd is associated with a higher risk of ventricular fibrillation and sudden cardiac death. The metabolic syndrome (MS), a constellation of cardiovascular risk factors including abdominal obesity, dysglycemia, hypertension, and hypertriglyceridemia, is associated with hyperactivation of the sympathetic nervous system. A recent study also demonstrated that MS is associated with increased QTd. Exercise training (ET), which generally results in increased parasympathetic tone and decreased sympathetic tone, has been shown to reduce QTd in various populations including individuals with chronic coronary heart disease (CHD), congestive heart failure, and following myocardial infarction. No studies have evaluated the effect of exercise training on QTd in patients with MS. The objectives of this study were to 1) evaluate baseline QTd on the resting 12-lead ECG in a sample of MS patients with and without CHD, 2) evaluate the effect of a long-term ET program (≥6 months duration) on QTd parameters in subjects with MS, and 3) study potential associations between changes in QTd parameters and changes in metabolic and exercise parameters after ET.

METHODS

This retrospective chart review study was conducted at the Cardiovascular Prevention Center of the Montreal Heart Institute and was approved by the local ethics committee. Data were examined from a cohort of MS patients without CHD (group 1; n = 31) and with CHD (group 2; n = 15) enrolled into identical ET and cardiac rehabilitation (CR) programs. The control group for the present study consisted of 8 MS patients with CHD (group 3) who were followed at our centre but who decided not to undertake CR. All patients included in our study had a diagnosis of MS at entry into ET and CR programs. All subjects underwent...
baseline physical examination with measurement of height and weight, an initial symptom-limited exercise stress test, and measurement of fasting blood glucose and lipid profile. Long-term ET was defined as all subjects in the ET and CR programs who regularly exercised for ≥ 6 months. The duration of cardiac rehabilitation was 284 ± 101 days in group 1 and 312 ± 100 days in group 2 (P = NS). Consecutive attendees of the program fitting the study criteria and with complete data were identified from our center’s database from 2003 to 2006. Their data are included in the present study. Coronary heart disease was defined as the presence of documented prior myocardial infarction, prior coronary revascularization, or documented myocardial ischemia on myocardial scintigraphy. Hypertension was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive therapy. Presence of dyslipidemia was defined as a medical history of dyslipidemia, use of lipid-lowering therapy, or an LDL-cholesterol > 2.5 mmol/L and total/HDL-cholesterol ratio > 4 mmol/L in patients not receiving statins.\(^\text{10}\)

**Left ventricular repolarization parameters:** All subjects underwent a routine standard 12-lead surface ECG recorded at a paper speed of 25 mm/s and gain of 10 mm/mV (MAC 5000, rest system ECG, GE Healthcare, Marquette, USA) in the supine position and were breathing freely but not allowed to speak during the ECG recording. The ECGs were recorded at baseline and at the end of follow-up. ECGs were transferred to a personal computer via scanner (Hewlett-Packard Scanjet 4370, USA), magnified, and QT measurement was performed manually using a commercial software package (Adobe Photoshop CS2, Adobe Systems Incorporated, USA, 2005). The QT interval was measured from the beginning of the QRS complex to the end of the T wave at the level of the TP isoelectric baseline. If U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves.\(^\text{6,16}\) QTd was assessed via 4 recognized and validated QTd parameters: \(^\text{7,18}\)

1. QT dispersion (QTd), defined as the difference between the maximal and the minimal QT interval across the 12-lead ECG, with at least 8 interpretable leads; 2. standard deviation of QT (sdQT) is the standard deviation of all QT measurements for each patient; 3. relative dispersion of QT (rdQT), defined as sdQT/mean QT X 100; and 4. correction of QTd using Bazett’s formula (QTc), defined as QTc = QTd / \sqrt{RR}\). All ECG analyses were performed by one individual (TG), blinded to time and group.

**Metabolic syndrome definition:** Metabolic syndrome was defined according to recently modified National Cholesterol Education Program Adult Treatment Panel III criteria,\(^\text{19}\) requiring the presence of ≥ 3 of 5 criteria, namely abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), triglycerides ≥ 1.70 mmol/L, decreased HDL-cholesterol (< 1.0 mmol/L in men and < 1.3 mmol/L in women), systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, and fasting plasma glucose (FPG) ≥ 5.6 mmol/L. Because waist circumference was not systematically available for all patients, a body-mass index (BMI) > 27 kg/m\(^2\) cut-point was chosen as our criterion for abdominal obesity.\(^\text{20,21}\) Patients receiving pharmacological therapy for either diabetes or hypertension were not excluded from our analyses.

**Cardiac rehabilitation, exercise training, and risk factor intervention:** All subjects underwent the same aerobic training program at an exercise intensity corresponding to 65-90% of their maximal heart rate (Borg scale level 11-14) based upon the initial and subsequent symptom-limited exercise tests.\(^\text{20}\) Exercise prescription and intensity were gradually increased through the training program according to each patient’s progress. Supervised exercise training according to recent recommendations\(^\text{22}\) was performed two times per week for 40 minutes per session (5-minute warm-up, 30-minute aerobic exercise and 5-minute cool down) and included different activities such as walking, stationary cycling, and rowing. In addition, subjects were advised to perform 1 to 2 additional aerobic exercise sessions such as walking and/or cycling (30-45 minute duration) outside the center on a weekly basis. Physicians and/or nurses provided patients with recommendations regarding a low-fat, low-cholesterol diet and smoking cessation, generally on a yearly basis. In addition, formal dietary and psychological counseling, and a smoking cessation program were available for subjects if deemed necessary.\(^\text{20}\)

**Patient follow-up, exercise stress testing, and risk factor analysis:** During the follow-up period, patients were reevaluated every 6-12 months by a physician with repeat measurement of weight and height, FPG and lipid profile, and completion of an exercise stress test. Treadmill exercise testing was performed using a symptom-limited ramp protocol with a 5-minute passive recovery period.\(^\text{20}\) During the tests, the subject’s ECG and blood pressure were monitored continuously. The ECG was recorded at 30-second intervals. Maximal exercise tolerance was defined as the highest level of metabolic equivalent units (METs) achieved, and was estimated from maximal treadmill speed and grade during the treadmill. All patients were instructed to take their usual medications prior to exercise testing.

**Program attendance:** Data on program attendance was obtained from medical charts. In addition, data was obtained from an electronic entry system which automatically records patient entry into the center.\(^\text{20}\) The median program attendance was 3.5 ± 1 sessions per week in group 1 and 3.3 ± 1 sessions per week in group 2.

**Statistical analysis:** All group data are expressed as the mean value ± standard deviation and/or in number and percentage. For continuous variables, statistical differences between groups and time were evaluated by repeated measures ANOVA. Differences in the prevalence of metabolic syndrome and medication prescription before and after training were tested using chi-square analysis. Associations between changes in QTd parameters and changes in metabolic and exercise parameters were correlated using Fisher’s exact test. All analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NC, USA) and Statview 5.0 (SAS Institute Inc., Cary, NC, USA). A P ≤ 0.05 was considered statistically significant.

**RESULTS**

The mean duration of exercise training was 284 ± 101 versus 312 ± 100 days in groups 1 and 2, respectively (P = NS). Table I describes the clinical characteristics of
significantly lower in group 2 at baseline relative to group

Approximately 80% of patients at baseline suffered from abdominal obesity as defined by a BMI > 27 kg/m². Metabolic coronary risk factors of the three MS groups.

Table II describes the metabolic risk factors of the three MS groups. Approximately 80% of patients at baseline suffered from abdominal obesity as defined by a BMI > 27 kg/m².

The prevalence of hypertension, abdominal obesity, and abnormal glucose metabolism were not significantly different among the groups. Beta-blocker use was more common in group 2 relative to groups 1 and 3, respectively (data not shown).

Metabolic coronary risk factors: Table II describes the metabolic coronary risk factors of the three MS groups. Approximately 80% of patients at baseline suffered from abdominal obesity as defined by a BMI > 27 kg/m².

Exercise stress testing data: Exercise tolerance increased significantly over time in groups 1 and 2 while HDL-cholesterol increased in both groups. Metabolic parameters remained unchanged after one year in the control group (group 3). The prevalence of MS was reduced by 22% and 25% in groups 1 and 2, respectively (data not shown).
1 relative to group 2 patients at baseline and decreased significantly in both groups at follow-up (P < 0.05). Maximum rate-pressure product was significantly higher in group 1 relative to group 2 at baseline and did not change significantly in either group at follow-up (262 ± 57 in group 1 versus 197 ± 65 in group 2 at baseline, P < 0.01). Heart rate recovery at 1 minute was higher in group 2 relative to group 1 at baseline and did not change in either group following ET/CR programs (18 ± 6 bpm in group 1 versus 23 ± 11 bpm in group 2 at baseline, P < 0.05). Again, the use of beta-blockers was higher in group 2 relative to groups 1 and 3 (Table I).

**Modifications of QTd parameters:** Myocardial repolarization parameters are shown in Table III. At baseline, no differences between groups 1, 2, and 3 were noted. After exercise training, all QTd parameters decreased significantly in groups 1 and 2. In contrast, QTd parameters remained unchanged in group 3 (control group).

**Associations between QTd and metabolic and exercise parameters:** We also evaluated the relationship between changes in QTd parameters over time and changes in metabolic (weight, BMI, systolic and diastolic blood pressure, triglycerides, HDL-cholesterol, FPG) and exercise (functional capacity) parameters following ET/CR programs. No significant associations were identified.

### Discussion

The main findings of our study are: 1) although not grossly abnormal, QTd was at the upper limit of normal in patients with MS, particularly in the CHD cohort (group 2); 2) long-term ET/CR programs were associated with significant improvements in QTd parameters; and 3) the improvement in QTd observed with ET/CR did not appear to be related to improvements in metabolic parameters or functional capacity, suggesting a direct beneficial effect of ET on myocardial repolarization.

Our results demonstrate that long-term (>6 months) ET/CR programs can be effective in reducing myocardial repolarization parameters in subjects with MS. QTd decreased by 12 and 16% in groups 1 and 2, respectively. In contrast, patients in group 3 (control group) showed no change in QTd parameters after a one-year period, despite being provided with the same degree of medical care and risk factor management. Our results agree with previous training studies in other populations. Kalapura, *et al*\(^{14}\) found that a 12-week CR program reduced QTd parameters by approximately 30% following acute myocardial infarction (AMI). Similarly, Fujimoto, *et al*\(^{13}\) showed that a 4-week CR program decreased QTd parameters by 25% following AMI. In CHF patients, a 12-week CR program decreased QTd parameters by approximately 16%.\(^{13}\) Despite the fact that our ET and CR programs were significantly longer than other ET programs reported here, we did not witness greater reductions in QTd parameters. Possible explanations include the lack of a significant training stimulus to provide incremental reductions in QTd. Importantly however, QTd values at the end of the ET and CR programs (51 ms and 56 ms in groups 1 and 2, respectively) are similar to the values observed in prior training studies.\(^{12,13}\)

While improvements in several metabolic and exercise parameters were observed with ET/CR including weight, BMI, diastolic blood pressure, triglycerides, HDL-cholesterol, and functional capacity, none were associated with the improvements in QTd witnessed. These findings would suggest that in our study, ET directly contributed to improving myocardial repolarization. Influences of the autonomic nervous system on QTd are well known.\(^{32}\) Bonnar, *et al*\(^{33}\) reported a correlation between QTd and autonomic imbalance in conditions of heart failure and acute myocardial infarction. This finding was indirectly confirmed by a reduction in QTd during treatment with β-blocking agents.\(^{24}\)

Exercise training induces a resting bradycardia and a reduction in baroreflex-mediated tachycardia in animals and humans, the consequence of increased vagal and decreased sympathetic tone.\(^{25}\) Aerobic exercise has also been shown to result in significant improvements in cardiovascular autonomic function in patients following acute myocardial infarction\(^{26}\) and in overweight Type 2 diabetic patients.\(^{27}\) Physical training might therefore improve QTd parameters directly via beneficial effects on the autonomic regulation of cardiovascular function. Other potential mechanisms whereby ET might improve QTd are through improvements in risk factor control including weight loss. Weight loss in obese subjects has been shown to significantly decrease QTd, with the amount of improvement in QTd being proportional to the degree of weight loss.\(^{28}\) As mentioned previously, weight loss was not associated with improvements in QTd in our study. Studies evaluating the impact of glucose, blood pressure, or lipid control interventions on QTd parameters have yet to be performed.
Soydinc, et al\(^1\) showed that uncomplicated MS is associated with significantly higher QTd relative to healthy nonobese subjects. Indeed, among our group 1 subjects with MS but without CHD, baseline QTd was very similar to the mean QTd reported by Soydinc, et al (58 ms versus 55 ms, respectively). In contrast, QTd values in healthy nonobese individuals are commonly between 35-40 ms.\(^{29}\) Patients with diabetes mellitus may also have increased QTd.\(^{30}\) In our study, group 2 patients (possessing CHD) had the highest values of QTd. This is consistent with previous data showing that CHD per se is associated with higher QTd.\(^{11}\) Therefore, the association of CHD and MS would appear to increase QTd, which could have greater prognostic implications.

**Study limitations:** There are limitations inherent with the study design. Firstly, this was a nonrandomized, observational, and retrospective study. Secondly, our sample size was small, particularly for the control group. Nevertheless, we were able to identify significant improvements in QTd parameters with long-term ET and CR programs in groups 1 and 2. Thirdly, most of our subjects were men, the effects of ET on QTd parameters perhaps being different in women with MS. Finally, our measurements were made manually but we took great care to use consistent criteria to define the end of the QT interval by a single experienced observer who was unaware of the clinical data.

**Conclusions:** We conclude that in MS patients with and without CHD, long-term ET/CR programs improve QTd parameters. Although concomitant improvements in exercise tolerance, resting heart rate, and metabolic parameters were observed, the improvements in QTd parameters observed appeared to be related primarily to the effects of physical training rather than secondarily via an improvement in the metabolic profile. Prospective studies are now required to address this question, especially in women.

**REFERENCES**