# Effect of exercise induced hypoxaemia on myocardial repolarisation in severe chronic obstructive pulmonary disease

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**Abstract**

***Background*—Exercise training is being promoted increasingly for patients with chronic obstructive pulmonary disease (COPD). Many of these patients experience exercise related arterial desaturation but the clinical importance of these hypoxaemic episodes is not known. QTc dispersion is a marker of myocardial repolarisation abnormalities and there has been much interest in its role as a non-invasive predictor of cardiac arrhythmias and sudden death. However, little is known about the dynamic effects that exercise and hypoxaemia have on QTc dispersion in patients with COPD.**

***Methods*—20 patients with severe COPD ($FEV_1$ <40% predicted) undertook two 15 minute treadmill tests at a speed calculated to produce a constant workload of 50% maximum oxygen consumption ($Vo_2max$) during which they were blindly given either air or 35% oxygen in random order. Physiological measurements taken throughout exercise included 12 lead electrocardiograms from which QTc dispersion values were calculated according to standard criteria. Nine of the patients who desaturated with exercise were studied further. A similar degree of hypoxaemia was induced at rest by giving them a titrated mixture of air and oxygen and the changes in QTc dispersion were recorded.**

***Results*—11 of the 20 patients developed significant hypoxaemia (desaturation by ⩾5% to <90%) with exercise breathing air. There were no significant changes in QTc dispersion with either exercise or hypoxaemia. There were no significant changes in QTc dispersion when comparing those who did and did not desaturate, and those with and without a high baseline QTc dispersion values (60 ms). Induced hypoxaemia without exercise also failed to worsen QTc dispersion.**

***Conclusions*—No evidence was found to suggest that exercise, even when associated with hypoxaemia, causes myocardial repolarisation abnormalities in patients with COPD.**

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Keywords: chronic obstructive pulmonary disease, exercise, hypoxaemia, QT dispersion

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The hypoxaemia associated with severe chronic obstructive pulmonary disease (COPD) may result in cor pulmonale, polycythaemia and premature death. Oxygen treatment has been shown to be of benefit to those patients with COPD who have significant arterial hypoxaemia at rest.[1 2] However, a group of COPD patients only develop significant hypoxaemia on exercise and there is much uncertainty as to how they should be managed. These patients tend to suffer more from dyspnoea and some may be prescribed oxygen to alleviate symptoms, but the clinical importance of these recurrent hypoxaemic events both acutely, in terms of arrhythmias and sudden death, and chronically, in terms of hypoxic end organ damage, is not known. With exercise training increasingly being recommended as part of pulmonary rehabilitation programmes, it is important that the safety of exercising patients with COPD who develop arterial desaturation is established.

Patients with COPD are at increased risk of ventricular arrhythmias and sudden death.[3–5] QTc dispersion is a simple, non-invasive measure that can be calculated from a surface 12 lead electrocardiogram (ECG) and is thought to represent regional differences in cardiac repolarisation.[6] It has been identified as an independent risk factor for sudden cardiac death in patients with myocardial infarction,[7] hypertrophic cardiomyopathy,[8] congestive cardiac failure,[9] and peripheral vascular disease.[10] Dynamic changes in QTc dispersion have been demonstrated with acute myocardial ischaemia,[11] and with profound hypoxia induced in normal volunteers.[12] In this latter study high doses of fenoterol, a potent $\beta_2$ agonist, was also shown to increase QTc dispersion. These findings raise the concern that exercise, which may induce arterial desaturation, is exposing COPD patients, many of whom are taking $\beta_2$ agonists, to a major risk of ventricular arrhythmia or sudden cardiac death.

Our study examines the effect of exercise, at a level comparable with that encountered in pulmonary rehabilitation programmes, on QTc dispersion in patients with severe COPD. The effect of supplemental oxygen given with exercise was also examined.

## Methods

### SUBJECTS

Twenty subjects (17 men; mean age 66 years), randomly selected from our pulmonary rehabilitation programme, were studied (table 1).

*Table 1 Demographic data for group as a whole*

| | *Mean (SD)* | *Range* |
|---|---|---|
| Age (years) | 65.4 (6.9) | 49–76 |
| $FEV_1$ (litres) | 0.76 (0.28) | 0.32–1.40 |
| Vital capacity (litres) | 2.27 (0.84) | 1.10–4.60 |
| Shuttle distance (m) | 328 (94) | 200–470 |
| Treadmill speed (km/h) | 2.55 (0.37) | 2.0–3.0 |

All had severe COPD as defined by a forced expiratory volume in one second ($FEV_1$) less than 40% predicted, and had resting oxygen saturations of greater than 92% breathing room air. All patients were in a clinically stable state. Three were taking regular nebulised salbutamol and ipratropium bromide, 13 were on regular or as required inhaler treatment (salbutamol, ipratropium, or both) and four were on no inhaled treatment. None had unstable symptoms or resting ECG evidence of ischaemic heart disease and none was taking antiarrhythmic drugs known to affect the QTc interval.

PROTOCOL

Local ethics committee approval was obtained to undertake the study. Each patient's maximal exercise performance was assessed by the incremental shuttle walking test[13] and they then attended for three consecutive days. No measurements were taken on the first day but patients were given the opportunity to familiarise themselves with the treadmill to minimise any subsequent learning effect. On both the second and third days they undertook a 15 minute treadmill test. The treadmill speed was set at a level that was estimated to produce a constant workload of 50% maximum oxygen consumption ($V_{O_2}max$), which could be compared with activities of daily living or with rehabilitation exercises. This treadmill speed was calculated for each individual using a conversion derived from their shuttle walking test performance.[14] Arterial blood samples were taken for blood gas, potassium, and lactic acid estimation before and immediately after exercise. Continuous pulse oximetry and 12 lead ECGs were also recorded and Borg dyspnoea scores were noted every three minutes. Patients were blindly given either air or 35% oxygen to breathe during the first exercise test and were given the other for the second test. The order in which the air and oxygen was given was randomised.

Of the 11 patients who demonstrated arterial desaturation to below 90% during the treadmill test, nine were studied further. In an attempt to study the effects of hypoxaemia without the compounding effects of exercise and its associated tachycardia, each patient was rendered hypoxaemic for a period of 15 minutes by breathing a variable mixture of air and nitrogen. This mixture was delivered via a 25 litre Douglas bag and a series of one way valves, which connected to a mouthpiece through which the patient breathed while wearing an occlusive nose clip. The air and nitrogen mixture was titrated to a concentration sufficient to produce the same degree of oxygen desaturation experienced while performing the 15 minute treadmill test breathing air. Twelve lead ECGs were recorded before and at the end of this 15 minute period.

QTC DISPERSION

The 12 lead ECGs recorded before and at the end of each study period were analysed. The QTc dispersion measurements were made by an experienced observer who was blinded to the source of each ECG. The QT intervals were measured according to standard criteria[6]—that is, from the start of the QRS complex to the end of the T wave. If U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. A computer linked digitising pad and customised software were used to improve accuracy and the average value of three cycles was taken from each lead. QT intervals were corrected for heart rate using Bazett's formula ($QTc = QT/RR$).[15] Where possible measurements were taken from all 12 leads but, as recommended,[6] if there was doubt about the boundaries of a QT interval, the observer omitted that lead rather than force a measurement that might ultimately have resulted in a spurious QTc dispersion value. In our patients QT measurements were possible from all or 11 of the 12 leads in 65% of the ECGs, from 10 of the 12 leads in 25%, and from nine of the 12 leads in 10% of the ECGs. The QTc dispersion was defined as the difference between the minimum and maximum QTc intervals measured for a given ECG. No correction was made for unmeasured leads.

To assess reproducibility, 50% of the ECGs in our study were randomly selected to be analysed for QTc dispersion by a second blinded observer. An interobserver variation in QTc dispersion of 11 ms with a repeatability coefficient[16] of 31 ms was observed; this is similar to that achieved by other investigators looking at dynamic changes[11] or by those specifically assessing the reproducibility of

*Table 2 Mean (SD) values and mean differences of measurements recorded before and immediately after the exercise test while breathing room air*

| | *Patients who desaturated (n = 11)* | | | *Patients who did not desaturate (n = 9)* | | |
|---|---|---|---|---|---|---|
| | *Pre-exercise* | *Postexercise* | *Mean difference (CI)* | *Pre-exercise* | *Postexercise* | *Mean difference (CI)* |
| Oxygen saturation (%) | 93.4 (2.0) | 84.6 (6.4) | −8.7 (−12.8, −6.5)* | 95.8 (0.8) | 94.0 (2.2) | −1.8 (−0.4, −3.2) |
| $P_{O_2}$ (kPa) | 9.3 (1.1) | 7.8 (1.4) | −1.5 (−2.1, −0.9)* | 10.4 (0.8) | 10.6 (1.2) | 0.2 (1.6, −1.0) |
| $P_{CO_2}$ (kPa) | 6.3 (1.0) | 6.7 (1.1) | 0.4 (0.2, 0.6)* | 5.5 (0.4) | 5.6 (0.5) | 0.1 (−0.2, 0.3) |
| Potassium (mg/l) | 4.39 (0.3) | 4.54 (0.3) | 0.15 (−0.2, 0.31) | 4.2 (0.2) | 4.4 (0.3) | 0.2 (0, 0.3) |
| Lactate (mg/l) | 1.33 (0.3) | 1.66 (0.5) | 0.34 (−0.04, 0.72) | 1.34 (0.3) | 1.58 (0.4) | 0.23 (−0.04, 0.51) |
| Borg dyspnoea score | 0 (0) | 3.3 (1.9) | 3.3 (2.1, 4.6)* | 0 (0) | 3.1 (1.8) | 3.1 (2.2, 4.1)* |
| QTc dispersion (ms) | 43.2 (17) | 38.8 (19) | −4.36 (−17.4, 8.7) | 48.2 (18) | 49.9 (32) | 1.7 (−10.9, 14.2) |

*$p < 0.05$.
CI, 95% confidence intervals.

*Table 3 Means (SD) of data for the exercise tests with and without supplemental oxygen*

| | *Air (n = 20)* | | | *Oxygen (n = 20)* | | |
|---|---|---|---|---|---|---|
| | *Pre-exercise* | *Postexercise* | *Mean difference (CI)* | *Pre-exercise* | *Postexercise* | *Mean difference (CI)* |
| Oxygen saturation (%) | 94.4 (2.0) | 88.8 (6.8) | −5.6 (−8.3,−2.9)* | 97.8 (1.5) | 96.0 (2.5) | −1.8 (−2.6,−0.9) |
| $P_{O_2}$ (kPa) | 9.8 (1.1) | 9.0 (1.9) | −0.8 (−1.4,−0.1)* | 15.7 (3.1) | 14.8 (2.9) | −0.9 (−1.9,0.1) |
| $P_{CO_2}$ (kPa) | 5.9 (0.9) | 6.2 (1.0) | 0.3 (0.1,0.4)* | 6.1 (0.9) | 6.4 (1.2) | 0.3 (0.1,0.6)* |
| QTc dispersion (ms) (all patients) | 45.4 (17) | 43.8 (26) | −1.6 (−12.2,8.9) | 52.6 (29) | 45.0 (17) | −7.6 (−18.8,3.6) |
| QTc dispersion (ms) | | | | | | |
| Desaturator (n = 11) | 43.2 (17) | 38.8 (19) | −4.4 (−17.4,8.7) | 46.9 (29) | 45.2 (18) | −1.7 (−16.5,13.0) |
| Non-desaturator (n = 9) | 48.2 (18) | 49.9 (32) | 1.7 (−10.9,14.2) | 59.6 (31) | 44.8 (16) | −14.8 (−29.4,1.5) |

Mean differences (95% confidence intervals (CI) for these differences) refer to the comparison of measurements taken before and immediately after exercise.
*$p < 0.05$.
CI, 95% confidence intervals.

QTc dispersion measurements.[17] We did not calculate intrasubject variability as only one ECG for each patient was performed at each stage of the study.

### STATISTICS

The data were stored and analysed using the Statistical Package for Social Science (SPSS). The Wilcoxon rank test was used to compare paired measurements before and after exercise and with and without supplemental oxygen. Differences between those who desaturated with exercise and those who did not were determined using the two tailed Mann-Whitney U test; $p<0.05$ (two tailed) was considered significant.

## Results

### PATIENT PERFORMANCE

The level of dyspnoea experienced by the patients during exercise varied widely with Borg scores ranging from 0.5 to 6 at the end of exercise breathing air (table 2). Eleven of the 20 patients developed significant hypoxaemia (desaturation by at least 5% from baseline and to below 90%) exercising at 50% $V_{O_2}$max, but there was no significant correlation between the degree of this hypoxaemia and the dyspnoea score. No patients exhibited any ECG changes indicative of myocardial ischaemia. Administration of 35% oxygen prevented this arterial desaturation in all cases and limited the lactic acid rise (air 1.62 mg/l, oxygen 1.42 mg/l; $p<0.05$); however, it did not significantly improve the level of dyspnoea experienced by the end of the 15 minute exercise test (mean Borg score: air 3.23, oxygen 3.18).

### MYOCARDIAL REPOLARISATION

In the group as a whole there was no significant difference between mean (SD) QTc dispersion recorded before (45.4 (17) ms) and after (43.8 (26) ms) exercise ($p = 0.75$). Administration of oxygen did not influence the QTc dispersion values (before 52.6 (29) ms; after 45.0 (17) ms; $p = 0.171$). Reassuringly, in those patients who experienced arterial desaturation, there was no significant difference between QTc dispersion values before and after exercise, following exercise with or without supplemental oxygen, or when compared with those who did not desaturate with exercise (table 3).

Seven patients had a baseline QTc dispersion greater than 60 ms (65 (5.5) ms), a threshold that one study suggests has a high sensitivity and specificity for predicting sudden death.[10] When these patients were analysed separately no significant change in QTc dispersion occurred following exercise while breathing air (61 (34) ms; $p = 0.79$); there was, however, a trend towards a reduction in QTc dispersion (51 (21) ms; $p = 0.12$) when oxygen was administered with exercise, though this did not reach significance.

Inducing hypoxaemia with a titrated air and nitrogen mixture (mean (SD) oxygen saturation at baseline 94.0(2.1)%; breathing air and nitrogen mixture 84.6(6.4)%), without the compounding effects of exercise and tachycardia, produced a small increase in QTc dispersion (baseline 56.7 (23) ms, air and nitrogen mixture 59.9 (17) ms; $p = 0.89$). This change was neither clinically important nor significant.

## Discussion

There has been considerable interest recently in QTc dispersion as an inexpensive, non-invasive predictor of ventricular arrhythmias and of sudden death. A role has been proposed for QTc dispersion in risk stratification of patients with a number of conditions associated with sudden cardiac death.[7–10] COPD is also associated with an increased risk of cardiac arrhythmias presumably as a consequence of the high concurrent incidence of ischaemic heart disease with which it shares a major aetiological factor—smoking. In patients with COPD, QTc dispersion has been correlated with numbers of ventricular extrasystoles,[18] and an association between a prolonged QTc interval and sudden death has been proposed.[19] These studies based their QTc measurements on ECGs taken at rest, but few data are available on the dynamic effect of stimuli such as exercise and hypoxaemia on QTc dispersion in patients with COPD. Frequent and profound hypoxaemic episodes occur in patients with COPD while conducting activities of daily living[20] or even low grade exercise.[21] Exercise training is recommended as part of pulmonary rehabilitation programmes,[22 23] but the issue of how safe this exercise is remains unresolved.

It is common practice to give oxygen to desaturators during pulmonary rehabilitation exercise sessions and oxygen is commonly prescribed to palliate the dyspnoea and anxiety associated with COPD. However, if arterial desaturation during exercise was shown to carry a significant acute cardiovascular risk to this group of patients, it would have major

implications in terms of oxygen prescription beyond the currently recommended criteria for oxygen treatment. The results of our study are therefore reassuring. We found no evidence that exercise induced hypoxaemia increased QTc dispersion or that it worsened it in individuals who had high levels (greater than 60 ms) at baseline. In addition, no increases in QTc dispersion were observed with the hypoxaemia induced by breathing an air and nitrogen mixture when the compounding effects of exercise, with its attendant tachycardia and circulating catecholamines, were removed.

Our findings conflict with those of Keily *et al* who found that induced hypoxaemia significantly increased QTc dispersion in normal volunteers.[12] Admittedly the hypoxaemia they exposed their subjects to (oxygen saturation 75 to 80%) was more extreme than in our study (mean 83%), which was designed to reproduce levels encountered in activities of daily living or during rehabilitation exercises. However, their observations are difficult to explain from a pathophysiological view point. QTc dispersion is thought to represent regional myocardial variations in repolarisation and is characteristically associated with coronary artery disease[7 10 11] or structural myocardial abnormalities.[8 9] It is therefore surprising that a sample of young volunteers (21 to 37 years), with presumably normal hearts, should develop significant QTc dispersion when challenged with hypoxaemia. Although we excluded patients from our study if they had symptoms or evidence on ECG of ischaemic heart disease, it is likely that, being an older age group with a history of smoking, a proportion will have had asymptomatic coronary disease. Indeed, seven of our 20 patients had a notably raised QTc dispersion (greater than 30 ms) at baseline, although there was no dynamic worsening with exercise or hypoxaemia.

An alternative explanation for why no adverse change in QTc dispersion was observed in our patients is that they may have become resistant to the effects of ischaemia. Resistance to ischaemic conduction failure in peripheral nerves has been shown to occur in hypoxaemic COPD patients,[24 25] and this is thought to occur as a consequence of adaptive metabolic and vascular changes. It is plausible that exposure to recurrent hypoxaemia might produce similar changes in the myocardial conducting system, giving a degree of protection against the effects of ischaemia and thus limiting the observed QTc dispersion occurring with acute hypoxaemia.

Calculation of QTc dispersion is simple to perform but inaccuracies can arise when the end of the T wave is indistinct. For this reason it is recommended practice that the ECG leads in which the boundaries of the QT interval cannot easily be defined are excluded from the calculation. Even with strict adherence to this methodology it is generally accepted that a degree of error occurs. The mean interobserver error for QTc dispersion measurement in our hands was 11 ms, which is similar to that reported by others,[11 17] and the intrasubject variability has been estimated by others to be 6 ms.[26] We therefore accept that our study may not have been sensitive enough to detect small changes in QTc dispersion with exercise. We also accept that, owing to small numbers, the comparison of desaturators and non-desaturators may not have been powerful enough to rule out firmly differences in myocardial repolarisation between these two groups. It is unlikely, however, that our study missed clinically important changes in QTc dispersion of a magnitude (greater than 30 ms) that have been demonstrated elsewhere to stratify risk of cardiac events or sudden death.[7–10]

Our study therefore provides no evidence to suggest that exercise in patients with severe COPD, even when associated with arterial oxygen desaturation, confers an increased cardiovascular risk. Clearly our findings cannot be extrapolated to those patients with concomitant unstable cardiac disease, nor do they give an indication of the long term risk of cor pulmonale and polycythaemia arising from recurring exercise induced hypoxaemic episodes. However, these results do give some reassurance to clinicians actively promoting exercise training which has been proven to be of so much benefit to these patients.

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