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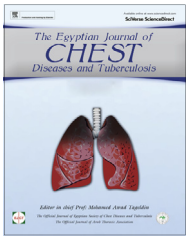

ORIGINAL ARTICLE

Arrhythmias in patients with chronic obstructive pulmonary disease

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KEYWORDS

COPD;
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Electropathy;
QT interval

Abstract *Background:* Supraventricular and ventricular arrhythmias, as well as conduction disturbances are frequently observed in COPD and two major hypotheses for arrhythmogenesis have been proposed: arrhythmias may be a consequence of hypoxaemia, hypercapnia or acid–base disturbances since they increase the electrical heterogeneity within the ventricular wall or arrhythmias may be the result of the autonomic neuropathy that characterizes COPD.

Aim of the work: In this study, we attempted to non-invasively verify these hypotheses in hypoxaemic COPD patients that are not in respiratory failure by examining how PaO_2, $PaCO_2$, pH and HCO_3 correlate with QTd in those patients.

Subjects and methods: 25 COPD patients were subjected for Standard 12-lead ECG for arrhythmia detection and the measurement of QT intervals, chest X-ray, two dimensional echocardiography and myocardial nuclear imaging to exclude IHD.

Results: We found negative significant correlation between O_2 tension and the occurrence of fatal arrhythmias; the same as between O_2 tension and QTd value (P values were <0.0005 in both), with QTd as the dependent variable, and age, pulmonary pressure, duration, Mg, Na, K, Hb PH, CO_2 and O_2 tensions as the independent variables in all subjects, it was shown that only PaO_2 was the predictor of QTd with a P value of 0.02. In stable COPD patients enrolled in our study, new cutoff levels for predicting arrhythmic fatality were proposed for the QTc parameter (395 ms with a sensitivity of 92% and a specificity of 83%) and the QTd parameter (58 ms with a sensitivity of 100% and a specificity of 92%). There is a high positive significant correlation between the age of patients, duration of COPD and Hb level and the occurrence of fatal arrhythmias where P values

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were 0.009, < 0.0005 and < 0.0005 respectively; the same as with QTd value where the P values were 0.015, 0.001 and 0.039. There is a positive significant correlation between pulmonary pressure and QTc where the P value was 0.041 and pulmonary pressure with QTd where the P value was 0.028.

Conclusion: Our results rule out the electropathy hypothesis and underline autonomic neuropathy as the most possible mechanism of arrhythmias in hypoxaemic, non-respiratory failure, and COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) represents an increasing burden worldwide, reported to be the sixth leading cause of death in 1990 and the fourth in 2000. Discouragingly, it is projected to jump to the third place by the year 2020 [1]. Cardiovascular events are the predominant reason for hospitalizations (approximately 50% of all hospitalizations), the second leading cause of mortality in subjects with mild to moderate COPD, and they account for 20–25% of all deaths in COPD [2]. Epidemiological studies have shown that reduced lung function in subjects with COPD is associated with cardiovascular morbidity and mortality, even after taking into account smoking history [3]. The Lung Health Study reported that a 10% decrement in lung function (forced expiratory volume in 1 s, FEV 1) among COPD patients is associated with a ~30% increase in the risk of deaths from cardiovascular diseases that included arrhythmias, heart failure, stroke, and cardiopulmonary disease such as thromboembolic disease (including an increased risk for pulmonary emboli and deep vein thrombosis) and sudden death [4].

Aim of the work

The present work aimed to investigate:

a. The frequency of cardiac arrhythmias in patients with stable COPD.
b. Their relation to QTc, QTd as predictors of cardiac arrhythmia and the severity of hypoxaemia/hypercapnia.

Subjects and methods

All patients were subjected to:

- Complete history taking including smoking index
- clinical examination
- Routine laboratory Arterial blood gases.
- Electrocardiographic Studies
- I Standard 12-lead ECG: for
- Arrhythmia detection.
- Measurement of QT Intervals:
  QT parameters were measured from the 12-lead ECG recording.

ECGs were recorded by means of a 12-channel ECG recorder (model 1709-A; Hewlett–Packard) at a paper speed of 50 mm/s (gain, 10 mm/millivolt). Before the measurement of QT parameters, ECGs were enlarged on the same photocopier by a factor of three.

The QT interval was measured from the onset of QRS complex to the end of the T wave. In the presence of the U wave, the end of the T wave was taken as the lowest point between the T wave and the U wave. If the end of the T wave was unclear, then it was excluded from analysis.

- A minimum of nine leads were studied in each patient. Minimum duration of the QT interval (QTmin), maximum duration of the QT interval (QTmax), and their difference (QTd) were measured. Each QT interval was corrected for patient heart rate according to Bazett (1920) [5]: QTc = QT/$\sqrt{}$RR interval, where QT and R-R interval are expressed in seconds.
- Holter recordings:

Echocardiographic examination:

Nuclear imaging: to exclude patients with ischaemic heart disease.

Statistical analysis and data management

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Mann Whitney *U* test for independent samples. *P* Values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

The present study group includes 25 pts with a mean age of 58.6 ± 6.9 years (ranging from 47 to 72), 19 male (76%) and 6 females (24%) presented with stable chronic obstructive pulmonary disease with a mean disease duration of 5.4 ± 3 years (ranging from 1 to 12 years).

The following parameters were analysed:

Laboratory investigations

The study group was non-anaemic with the Hb level ranging from 12.5 to 16.5 gm/dL (*N* = 13–17 gm/dL in males and 11–16 gm/dL in females) and with normal electrolytes level (Na, K, and Mg) as to exclude anaemia and electrolyte disturbances from being shared in arrhythmogenesis.

As regards the ABG parameters, the study group patients were selected with normal to compensated PH levels ranging from 7.36 to 7.48 (N = 7.35–7.45), normal to compensated HCO_3 levels ranging from 18 to 30 mEq/L (N = 22–26 mEq/L), normal to mild derangements in $PaCO_2$ levels from 30 to 50 mmHg with secondary renal HCO_3 and PH compensation and PaO_2 levels $\geqslant$60 and $<$85 mmHg except in one patient which was 95 mmHg (N = 85–100 mmHg) so as to investigate chronic hypoxaemic patients and not hypoxic ones.

Echocardiographic data

The study group shows normal left atrial diameter values ranging from 3 to 4.3 cm (N = 2–4 cm), normal left ventricular end-diastolic diameter values ranging from 4.3 to 5.5 cm (N = 3.5–5.7 cm), normal left ventricular end-systolic diameter values ranging from 2.7 to 3.9 cm (N = 2–4 cm), normal ejection fraction values ranging from 58 to 65% (N = 53–75%) to exclude heart failure and dilated cadiomyopathic patients and mild to moderately elevated pulmonary artery pressure values ranging from 26 to 55 mmHg (N = 25/10 mmHg) with no right ventricularization of the interventricular septum.

Electrocardiographic data

As shown in Table 1, the study group shows Qt dispersion values ranging from 38 to 80 ms (N = 40–50 ms) with a mean of 60.8 ± 11.4 where the risk for serious ventricular arrhythmias or sudden death was observed in subjects with QT dispersion greater than 65 ms values and corrected Qt interval values ranging from 350 to 480 ms (N is up to 440 ms) with a mean of 401.2 ± 34.

Frequency of arrhythmias

Four pts out of our 25 pts had inappropriate sinus tachycardia (16%), 4 pts presented with arrhythmias in the form of PACs (16%), 3 pts with monomorphic PVCs (12%), 3 pts with polymorphic PVCs (12%), 7 pts with non-sustained VT (28%), one patient with AF(4%) and 3 cases with PVCs in salvoes (12%) (Fig. 1).

Of these arrhythmias 3 types were considered fatal; polymorphic PVCs, PVCs in salvoes and non-sustained VT (13 pts = 52%) while the rest represented the non-fatal ones (12 pts = 48%) (Fig. 2).

Comparison of different parameters between fatal and non-fatal arrhythmias

As shown in Table 2, the mean ± SD of age was 60 ± 7 years in fatal arrhythmias vs. 53 ± 4.9 years in non-fatal arrhythmias, a high significant difference was observed between the two groups. Also, a high significant difference was seen on comparing the mean ± SD of duration of COPD (7.5 ± 2.3 in fatal vs. 2.8 ± 1.3 years in non-fatal), Hb level (15.4 ± 0.95 in fatal vs. 13.8 ± 0.78 gm/dl in non-fatal), O_2 tension (68.7 ± 4.7 in fatal vs. 80.2 ± 5.3 mmHg in non-fatal), left atrium diameter (4.00 ± 0.21 in fatal vs. 3.6 ± 0.41 cm in non-fatal) and pulmonary pressure (43.5 ± 8.3 in fatal vs. 33.5 ± 8.3 mmHg in non-fatal).

Table 1 shows mean and SD of QTd and QT.

	Mean ± SD	Range
Qtd	60.8 ± 11.4	38–80
Qtc	401.2 ± 34	350–480

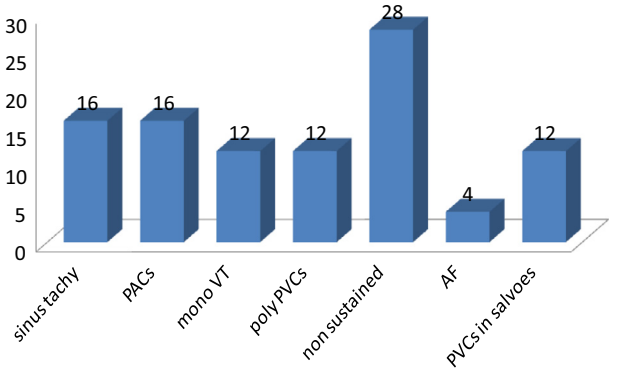

Figure 1 Percentage of each arrythmia in the study group.

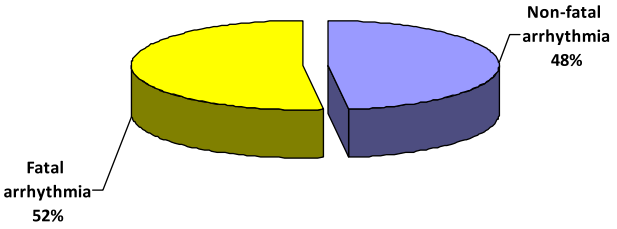

Figure 2 Percentage of fatal to non-fatal arrhythmias.

While no significant difference was observed between the two groups on comparing the mean ± SD of $PaCO_2$ (39.0 ± 5.5 in fatal vs. 38.2 ± 4.0 mmHg in non-fatal), HCO_3 (25.8 ± 2.8 in fatal vs. 24.5 ± 2.15 mEq/L in non-fatal) and PH (7.4 ± 0.02 in fatal vs. 7.4 ± 0.03 in non-fatal).

Also, no significant difference was observed between the two groups on comparing the mean ± SD of LV internal dimensions and EF.

The mean ± SD of QTc was found to be higher in fatal arrhythmias (422.3 ± 29.2) than in non-fatal arrhythmias (378.3 ± 22.5), the mean ± SD of QTd was 69.7 ± 5.9 in fatal vs. 51.25 ± 7.2 in non-fatal with a high statistical difference.

Comparison of different parameters according to QTd

When subjects were divided according to QTd value = 65 ms as a predictor of arrhythmic fatality, 12 cases were found to have QTd >65 ms while 13 cases with QTd <65 ms. On comparing the mean of different parameters between the 2 groups, the mean ± SD of age was 60 ± 7.1 in cases with QTd >65 ms vs. 53 ± 5.2 years in QTd <65 ms, a high significant difference was observed between the two groups. Also, a high significant difference was seen on comparing the mean ± SD of duration of COPD (7.1 ± 3.4 in QTd >65 ms vs. 2.7 ± 2.0 years in QTd <65 ms), Hb level (15.1 ± 1.1 in QTd >65 ms vs. 14.2 ± 1.1 gm/dl in QTd <65 ms), O_2 tension (68.8 ± 4.9 in QTd >65 ms vs. 79.2 ± 6.0 mmHg in QTd <65 ms), left atrium diameter (3.99 ± 0.23 in QTd

Table 2 shows the mean and standard deviation of different parameters in fatal and non-fatal arrhythmias using the student's *t* test.

	Fatal arrhythmias ($n = 13$)	Non-fatal arrhythmias ($n = 12$)	*P* value
Age	60 ± 7	53 ± 4.9	0.009**
Duration	7.5 ± 2.3	2.8 ± 1.3	< 0.0005**
Hb	15.4 ± 0.95	13.8 ± 0.78	< 0.0005**
PaO_2	68.7 ± 4.7	80.2 ± 5.3	< 0.0005**
$PaCO_2$	39.0 ± 5.5	38.2 ± 4.0	0.677
HCO_3	25.8 ± 2.8	24.5 ± 2.15	0.189
PH	7.4 ± 0.02	7.4 ± 0.03	0.371
LA	4.00 ± 0.21	3.6 ± 0.41	0.009**
LVED	4.8 ± 0.45	4.8 ± 0.35	0.981
LVES	3.2 ± 0.38	3.2 ± 0.24	0.814
EF	60.7 ± 2.6	62.4 ± 2.9	0.131
Pulmonary pressure	43.5 ± 8.3	33.5 ± 8.3	0.006**
QTc	422.3 ± 29.2	378.3 ± 22.5	< 0.0005**
QTd	69.7 ± 5.9	51.25 ± 7.2	< 0.0005**

** $P < 0.01$.

> 65 ms vs. 3.6 ± 0.42 cm in QTd < 65 ms) and pulmonary pressure (41.7 ± 9.5 in QTd > 65 ms vs. 35.8 ± 9.1 mmHg in QTd < 65 ms).

While no significant difference was observed between the two groups on comparing the mean ± SD of $PaCO_2$ (38.6 ± 5.9 in QTd > 65 ms vs. 38.7 ± 3.7 mmHg in QTd < 65 ms), HCO_3 (25.3 ± 3.4 in QTd > 65 ms vs. 25.2 ± 1.8 mEq/L in QTd < 65 ms) and PH (7.43 ± 0.025 in QTd > 65 ms vs. 7.42 ± 0.03 in QTd < 65 ms).

Also, no significant difference was observed between the two groups on comparing the mean ± SD of LV internal dimensions and EF.

The mean ± SD of QTc was found to be higher in QTd > 65 ms (428.3 ± 24.4) than in QTd < 65 ms (376 ± 18.9), the mean ± SD of QTd was 69.7 ± 5.9 in QTd > 65 ms vs. 51.25 ± 7.2 in QTd < 65 ms with a high statistical difference.

Comparison of different parameters according to QTc

When subjects were divided according to QTc value = 440 ms as a predictor of arrhythmic fatality, 5 cases were found to have QTc > 440 ms while 20 cases with QTc < 440. On comparing the mean of different parameters between the 2 groups, the mean ± SD of age was 62 ± 9.9 in cases with QTc > 440 ms vs. 55.4 ± 5.5 years in QTc < 440, no significant difference was observed between the two groups. A high significant difference was seen on comparing the mean ± SD of duration of COPD (8.6 ± 2.2 in QTc > 440 ms vs. 4.4 ± 2.6 years in QTc < 440 ms), Hb level (15.7 ± 0.6 in QTc > 440 ms vs. 14.4 ± 1.2 gm/dl in QTc < 440 ms), O_2 tension (64.6 ± 3.4 in QTc > 440 ms vs. 76.7 ± 6.3 mmHg in QTc < 440) (Table 3).

No significant difference was observed between the two groups on comparing the mean ± SD of $PaCO_2$ (38.8 ± 6.6 in QTc > 440 ms vs. 38.6 ± 4.4 mmHg in QTc < 440), HCO_3 (25.2 ± 2.8 in QTc > 440 ms vs. 25.2 ± 2.6 mEq/L in QTc < 440 ms) and PH (7.42 ± 0.035 in QTc > 440 ms vs. 7.42 ± 0.028 in QTc < 440 ms).

Also, no significant difference was observed between two groups on comparing the echocardiographic data (LA, LVED and LVES dimensions, EF and PH).

Table 3 shows the mean and standard deviation of different parameters according to QTd value using the student's *t* test.

	QTd > 65 ms ($n = 12$)	QTd < 65 ms ($n = 13$)	*P* value
Age	60 ± 7.1	53.5 ± 5.2	0.015*
Duration	7.1 ± 2.7	3.4 ± 2.0	0.001**
Hb	15.1 ± 1.1	14.2 ± 1.1	0.039*
PaO_2	68.8 ± 4.9	79.2 ± 6.0	< 0.0005*
$PaCO_2$	38.6 ± 5.9	38.7 ± 3.7	0.983
HCO_3	25.3 ± 3.4	25.2 ± 1.8	0.927
PH	7.43 ± 0.025	7.42 ± 0.03	0.765
LA	3.99 ± 0.23	3.6 ± 0.42	0.017*
LVED	4.8 ± 0.45	4.8 ± 0.35	0.679
LVES	3.2 ± 0.39	3.2 ± 0.24	0.992
EF	60.9 ± 2.6	62.1 ± 3.1	0.313
Pulmonary pressure	41.7 ± 9.5	35.8 ± 9.1	0.126
QTc	428.3 ± 24.4	376 ± 18.9	< 0.0005**
QTd	71 ± 4.8	51.5 ± 6.3	< 0.0005**

** $P < 0.01$.

The mean ± SD of QTc was found to be higher in QTc > 440 ms (452 ± 17.9) than in QTc < 440 ms (388.5 ± 23.5), the mean ± SD of QTd was 74.2 ± 3.6 in QTc > 440 ms vs. 57.5 ± 10.1 in QTc < 440 ms with a high statistical difference.

Predictive values for arrhythmic fatality

a. ROC curve reveals the following: the AUC for QTc was 0.904 at a cutoff level of 395 ms, the sensitivity was 92% and the specificity was 83% (Fig. 3 Table 4).
b. ROC curve reveals the following: the AUC for QTd was 0.962 at a cutoff value of 58 ms, the sensitivity was 100% and the specificity was 92% (Fig. 4).

Correlation between different parameters

A. The correlation between PaO_2 and QT interval parameters:

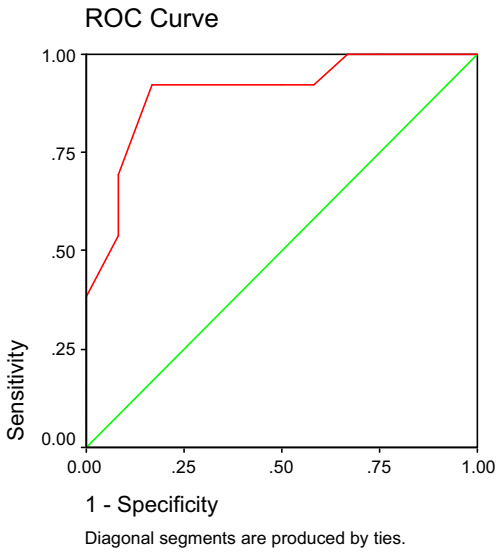

Figure 3 An ROC curve for defining a predictive value for arrhythmic fatality in our patients using QTc parameter.

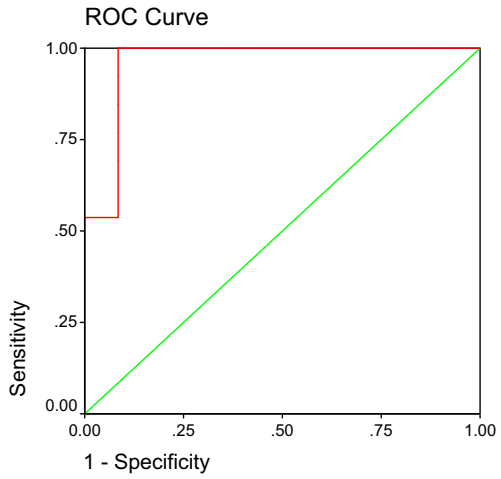

Figure 4 An ROC curve for defining a predictive value for arrhythmic fatality in our patients using the QTd parameter.

Table 4 shows the mean and standard deviation of different parameters according to QTc value using the student's t test.

	QTc >440 ms (n = 5)	QTc <440 ms (n = 20)	P value
Age	62 ± 9.9	55.4 ± 5.5	0.053
Duration	8.6 ± 2.2	4.4 ± 2.6	0.003**
Hb	15.7 ± 0.6	14.4 ± 1.2	0.039*
PaO_2	64.6 ± 3.4	76.7 ± 6.3	<0.0005**
$PaCO_2$	38.8 ± 6.6	38.6 ± 4.4	0.961
HCO_3	25.2 ± 2.8	25.2 ± 2.6	1.000
PH	7.42 ± 0.035	7.42 ± 0.028	0.947
LA	4.00 ± 0.25	3.8 ± 0.39	0.129
LVED	5.2 ± 0.29	4.8 ± 0.39	0.051
LVES	3.4 ± 0.33	3.2 ± 0.31	0.262
EF	60.8 ± 3.0	61.7 ± 2.8	0.534
Pulmonary pressure	42.6 ± 10.7	37.7 ± 9.4	0.317
QTc	452 ± 17.9	388.5 ± 23.5	<0.0005**
QTd	74.2 ± 3.6	57.5 ± 10.1	<0.0005**

** $P < 0.01$.

As regards analysis of the correlations between hypoxaemia and QT interval parameters, a high negative significant correlation was seen between PaO_2 and QTc ($P < 0.0005$, $r = -0.823$) and PaO_2 with QTd ($P < 0.0005$, $r = -0.898$) (Figs. 5 and 6).

A. The correlation between pulmonary pressure and QT interval parameters:

As regards analysis of the correlations between pulmonary pressure and QT interval parameters, a positive significant correlation was seen between pulmonary pr. and QTc ($P = 0.041$, $r = 0.412$) and pulmonary pr. with QTd ($P = 0.028$, $r = 0.438$) (Figs. 7 and 8).

A. The correlation between the duration of COPD and QT interval parameters:

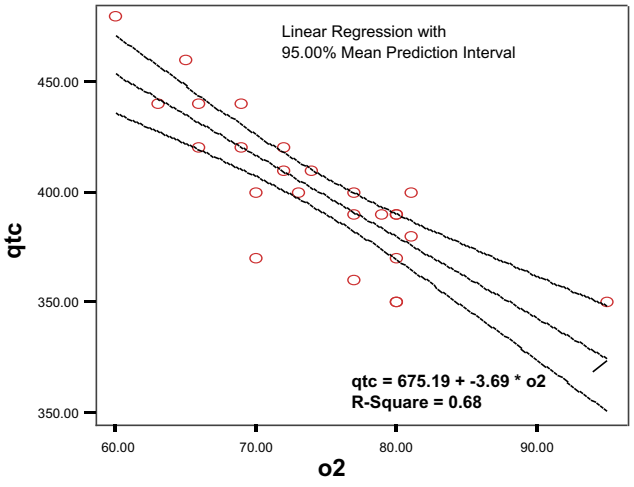

Figure 5 Correlation of O_2 saturation with QTc ($P < 0.0005$, $r = -0.823$).

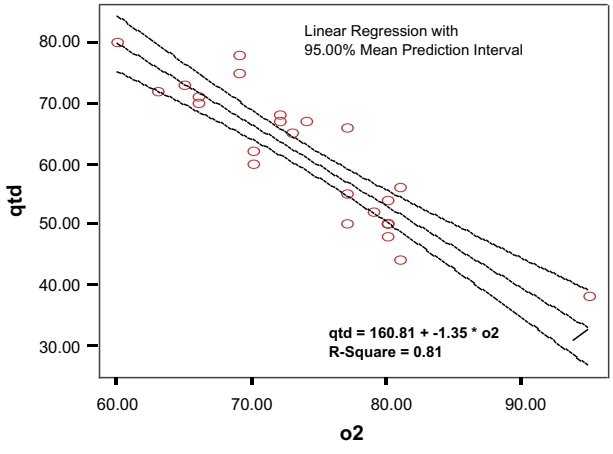

Figure 6 Correlation of O_2 saturation with QTd ($P < 0.0005$, $r = -0.898$).

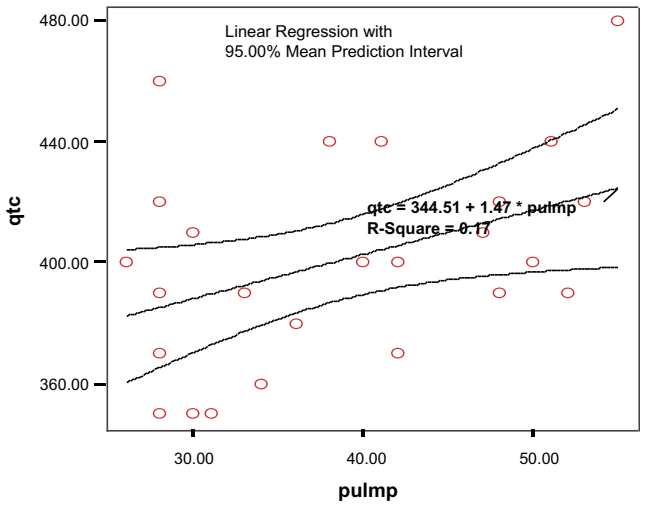

Figure 7 Correlation of pulmonary pressure to QTc ($P = 0.041$, $r = 0.412$).

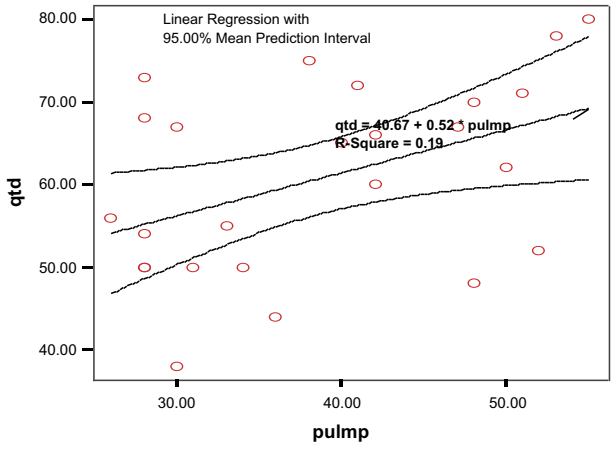

Figure 8 Correlation of pulmonary pressure to QTd ($P = 0.028$, $r = 0.438$).

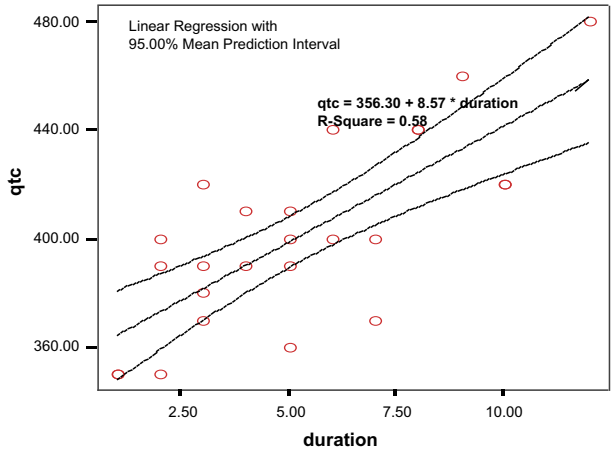

Figure 9 Correlation of the duration of COPD to QTc ($P < 0.0005$, $r = 0.759$).

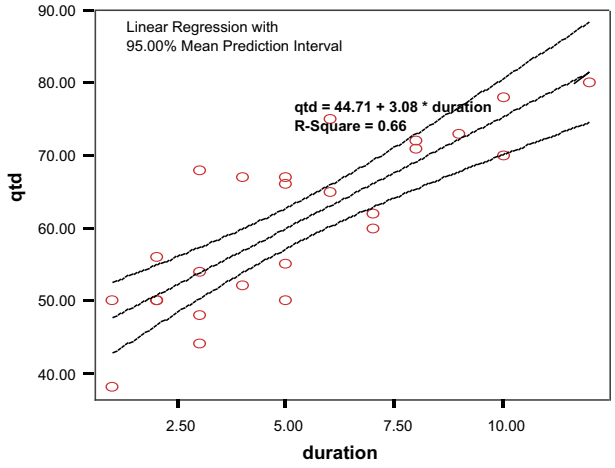

Figure 10 Correlation of duration of COPD to QTd ($P < 0.0005$, $r = 0.815$).

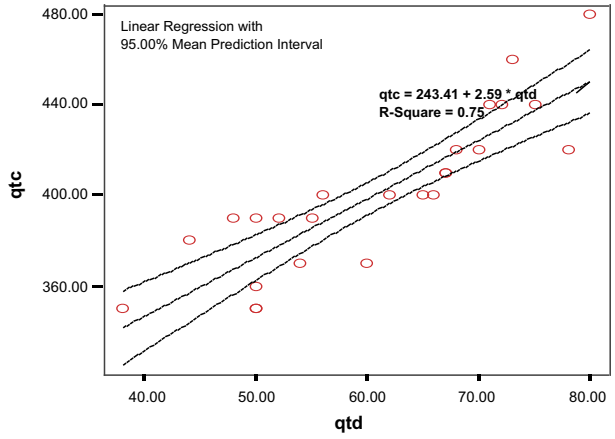

Figure 11 Correlation of QTD to QTc ($P < 0.0005$, $r = 0.867$).

Table 5 The relation between arrhythmic fatality and the QTd cut off value.

	Fatality		Total
	Non-fatal arrhythmias	Fatal arrhythmias	
QTd < 65 ms	11	2	13
QTd > 65 ms	1	11	12
Total	12	13	25

$P < 0.0005$.

As regards analysis of the correlations between the duration of COPD and QT interval parameters, a positive significant correlation was seen between pulmonary pr. and QTc ($P < 0.0005$, $r = 0.759$) and pulmonary pr. with QTd ($P < 0.0005$, $r = 0.815$) (Figs. 9 and 10).

A. The correlation between QTd and QTc:

A high positive significant corelation between QTd and QTc ($P < 0.0005$, $r = 0.867$) (Fig. 11).

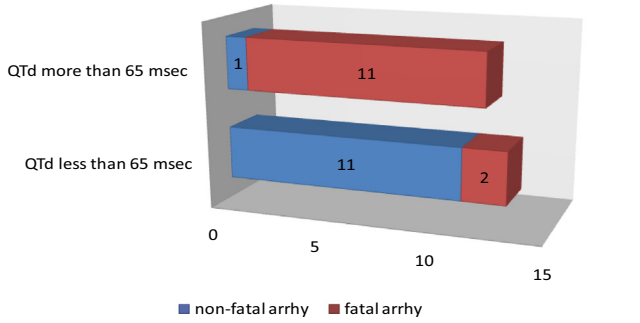

Figure 12 The relation between arrhythmic fatality and the QTd cut off value.

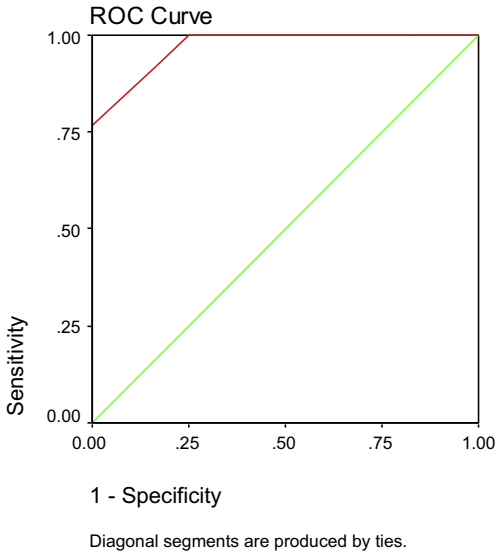

Figure 13 An ROC curve for defining duration.

The relation between fatality and QTd

As shown in Table 5: Out of the 12 cases of non-fatal arrhythmias, 11 cases had a QTd <65 ms and one case had a QTd >65 ms, while of 13 cases of fatal arrhythmias, 2 cases had a QTd <65 ms and 11 cases were with QTd >65 ms Fig. 12.

A high significant agreement between fatality and QTd was observed ($P < 0.0005$) (Fig. 13).

Impact of different parameters on QTd

On analysing the impact of different parameters on QTd, regression analysis showed that only PaO_2 was the predictor of QTd ($P < 0.05$), Overall multiple regression analysis between QTd (dependent variable) and age, pulmonary pressure, duration, Mg, Na, K, PH, Hb, and CO_2 (independent variables) in all subjects.

Multiple stepwise regression analysis was performed with QTd as the dependent variable, and by entering the independent variable with the highest partial correlation coefficient at each step, with a F-value probability for the inclusion of 0.05 and 0.01 for removal.

We performed multiple regression analysis including all the parameters in the statistical model that resulted to be significantly correlated to QTd (age, pulmonary pressure, duration, Mg, Na, K, PH, Hb, and CO_2). The ANOVA inflation factors excluded multicollinearity for these variables.

ROC curve reveals the following: the AUC for QTc was 0.971 at a cutoff level of 4.5, the sensitivity was 92% and the specificity was 8.

Discussion

The cardiac manifestations of chronic obstructive pulmonary disease (COPD) are numerous. Impairments of right ventricular dysfunction and pulmonary vascular disease are well known to complicate the clinical course of COPD and correlate inversely with survival. The coexistence of COPD and coronary artery disease occurs frequently. This association is likely related to shared risk factors as well as similar pathogenic mechanisms, such as systemic inflammation [6].

Arrhythmias occur frequently in patients with COPD. Fatal arrhythmias are a common cause of death in chronic obstructive pulmonary disease (COPD). Two major hypotheses for arrhythmogenesis in COPD have been proposed: The first hypothesis (electropathy) implicates hypoxaemia, hypercapnia and acid–base disturbances as the three main, COPD-related, arrhythmogenic triggers. The second hypothesis proposes autonomic neuropathy as the arrhythmogenic trigger [7].

Autonomic neuropathy has been associated with a prolonged electrocardiograph QTc interval and risk of ventricular arrhythmias and death [8].

QT dispersion reflects in homogenecity of ventricular repolarization. It is calculated using 12-leads standard synchronized ECG or 24-h Holter monitoring. Increased QT dispersion has prognostic value for sustained ventricular tachycardia. Dispersion of repolarization $>$ or $=$ 65 ms is a risk factor for sudden cardiac death [9].

The present study included twenty- five stable COPD patients with a mean age of 58.6 ± 6.9 years (ranging from 47 to 72), 19 male (76%) and 6 females (24%), recruited from the Outpatient Clinic- Chest Department of the Kasr El einy Hospital. They were diagnosed according to criteria of the American Thoracic Society.

A thorough assessment including history taking, physical examination with measurement of lab (haemoglobin, Na, K, Mg, PaO_2, $PaCO_2$, HCO_3 and PH), echocardiographic (LV internal dimensions, global systolic function and pulmonary artery pressure) and electrocardiographic (Qtc and Qtd) parameters were done for each subject.

The present report attempts to examine the frequency of various cardiac arrhythmias in COPD patients as well as focusing on the logical physiological consequences of the two competing theories in order to establish which of the two hypotheses is correct. Indeed, the logical consequence of both theories is that, depending on the effectiveness of the acid–base compensatory mechanisms, all of PaO_2, $PaCO_2$, pH and HCO_3 will be affected in COPD.

On the other hand, if the hypothesis of electropathy is correct, one should expect that factors related to $PaCO_2$, that is pH and HCO_3, will strongly correlate with QT dispersion (QTd), which is a non-invasive index of ventricular repolarisation heterogeneity. Conversely, if autonomic neuropathy is the

basis of COPD arrhythmogenesis, one would expect that only those parameters that directly and strongly influence neuronal excitability, that is PaO_2, will strongly correlate with QTd. In order to discern which of the two hypotheses is correct, we examined how the classical indices of electropathy, such as PaO_2, $PaCO_2$, pH and HCO_3, correlate with QTd in patients with stable COPD.

We used QTd as an index of the electrophysiological response of myocardial cells to hypoxaemia, hypercapnia and acid–base disturbances.

The present study revealed that:

Four pts out of our 25 pts had inappropriate sinus tachycardia (16%), 4 pts presented with arrhythmias in the form of PACs (16%), 3 pts with monomorphic PVCs (12%), 3 pts with polymorphic PVCs (12%), 7 pts with non-sustained VT (28%), one patient with AF(4%) and 3 cases with PVCs in salvoes (12%). Of these arrhythmias 3 types were considered fatal; polymorphic PVCs, PVCs in salvoes and non-sustained VT. (13 pts = 52%) while the rest represented the non-fatal ones (12 pts = 48%).

These results are in agreement with the study of 13 COPD patients reported by Ciobanu et al., who concluded that ventricular premature beats were the most frequent arrhythmias in those patients and stated that there are no current studies showing the precise prevalence of cardiac arrhythmias in COPD patients [10].

There is no significant correlation between $PaCO_2$, HCO_3 and PH and the occurrence of fatal arrhythmias; the same as with QTd and QTc values.

These results are in agreement with the study of 29 stable COPD patients reported by Theofilogiannakos et al., who hypothesised that, if the electropathy theory was correct, a high correlation between QTd and pH or HCO_3 would be found. However, they did not find any statistically significant correlation that would indicate that the hypothesis of electropathy may be correct [7].

There is a high negative significant correlation between O_2 tension and the occurrence of fatal arrhythmias where the P value was <0.0005; the same as between O_2 tension and the QTd value; as a predictor of arrhythmic fatality and the QTc value where the P was <0.0005 value in both.

*In multiple regression analyses, with QTd as the dependent variable, and age, pulmonary pressure, duration, Mg, Na, K, Hb PH, CO_2 and O_2 tensions as the independent variables in all subjects, it was shown that only PaO_2 was the predictor of QTd with a P value of 0.02.

Autonomic neuropathy is the second arrhythmogenic mechanism that has been proposed in COPD. Chronic hypoxaemia is a significant factor in the pathophysiology of autonomic neuropathy and it has been considered to be the underlying cause of COPD autonomic neuropathy.

Scalvini et al. submitted a study aiming to detect if chronically hypoxaemic COPD patients may suffer from abnormal behaviour of the ANS as assessed by a significant reduction in HRV and a markedly abnormal response to vagal and sympathetic stimuli such as controlled breathing and tilting, respectively. This study also showed that correction of hypoxaemia partially reverses these abnormalities [11].

This comes in agreement with evidence suggested by Chhabra and De on their study on 56 patients with mild forms of COPD that autonomic neuropathy can appear even in the very early stages of the disease [12].

This also comes in agreement with the study of 13 COPD patients reported by Ciobanu et al., who concluded that ventricular premature beats were the most frequent arrhythmias in those patients, being recorded at two peaks, one corresponding to the lunchtime (between 1 and 2 pm) due to hypoxaemia occurred while eating, and another one in the early morning (between 2 and 4 am) due to nocturnal hypoxaemia [10].

There is a high positive significant correlation between the age of patients, duration of COPD and Hb level and the occurrence of fatal arrhythmias where the P values were 0.009, <0.0005 and <0.0005 respectively; the same as with the QTd value where *P* values were 0.015, 0.001 and 0.039.

There is a positive significant correlation between pulmonary pr. and QTc where the P value was 0.041 and pulmonary pr. with QTd where the P value was 0.028.

This comes in agreement with the study of 201 patients with pulmonary hypertension reported by Hong-liang et al. who concluded that mean QTc and QTcd are positively correlated to mean pulmonary arterial pressure and are significantly increased in patients with severe pulmonary hypertension [13].

There is a high significant agreement between arrhythmic fatality and QTd value where the P value was <0.0005.

This comes in agreement with the study of 30 patients with COPD reported by Yildiz et al. who found that daily VPB rates were significantly higher in patients with prolonged QTd (>60 ms) as compared to patients with shorter QTd intervals (<60 ms) and that patients with runs of VT had longer QTd compared to patients without VT [8]. These findings; as he stated, suggested that increased QTd was associated with increased risk of malignant cardiac arrhythmia and may be clinically important in patients with COPD. Although patients with COPD with QTd <60 ms had longer QTd compared to control subjects, VPB frequency and runs of VT were not statistically different. This finding implies that the predictive value of QTd may become apparent only after reaching a certain threshold level.

In stable COPD patients enrolled in our study, new cutoff levels for predicting arrhythmic fatality were proposed for the QTc parameter (395 ms with a sensitivity of 92% and a specificity of 83%) and the QTd parameter (58 ms with a sensitivity of 100% and a specificity of 92%).

Summary and conclusion

COPD is characterised by irreversible airflow limitations and symptoms, such as chronic cough, wheezing, expectoration and dyspnoea. Although COPD is an important cause of morbidity and mortality, a large proportion of its mortality is not of pulmonary origin.

Traditionally, it was considered that patients with COPD are at special risk of cardiovascular diseases. COPD increases the risk of cardiovascular disease two- to threefold, and it has been proposed that low-grade systemic inflammation in patients with COPD is strongly associated with their increased risk of cardiovascular injury.

Apart from ischaemic heart disease, supraventricular and ventricular arrhythmias, as well as conduction disturbances are frequently observed in COPD. Many factors have been implicated as potential triggers of COPD-related arrhythmias.

In the present study, we attempted to non-invasively verify these hypotheses in hypoxaemic COPD patients who are not in respiratory failure by examining how PaO_2, $PaCO_2$, pH and HCO_3 correlate with QTd in those patients.

All our 25 patients with chronic obstructive pulmonary disease underwent:

1-Full history, clinical examination and laboratory investigation.

We found negative significant correlation between O_2 tension and the occurrence of fatal arrhythmias where the P value was <0.0005; the same as between O_2 tension and the QTd value; as a predictor of arrhythmic fatality and QTc value where the *P* value was <0.0005 in both.

- In multiple regression analyses, with QTd as the dependent variable, and age, pulmonary pressure, duration, Mg, Na, K, Hb PH, CO_2 and O_2 tensions as the independent variables in all subjects, it was shown that only PaO_2 was the predictor of QTd with a *P* value of 0.02.
- In stable COPD patients enrolled in our study, new cutoff levels for predicting arrhythmic fatality were proposed for the QTc parameter (395 ms with a sensitivity of 92% and a specificity of 83%) and the QTd parameter (58 ms with a sensitivity of 100% and a specificity of 92%).
- Also in this study we found that there is a high positive significant correlation between the age of patients, duration of COPD and Hb level and the occurrence of fatal arrhythmias where *P* values were 0.009, <0.0005 and <0.0005 respectively; the same as with the QTd value where *P* values were 0.015, 0.001 and 0.039.
- There is a positive significant correlation between pulmonary pr. and QTc where the P value was 0.041 and pulmonary pr. with QTd where the P value was 0.028.

In conclusion, our results rule out the electropathy hypothesis and underline autonomic neuropathy as the most possible mechanism of arrhythmias in hypoxaemic, non-respiratory failure, and COPD patients.

Recommendations

- Based on the results of this study, future research is recommended in a larger cohort to confirm that autonomic neuropathy is the most possible arrhythmogenic mechanism in stable COPD patients.
- The addition of Heart Rate Variability study(HRV) to QTd as an index of autonomic nervous system function and as a predictor of future arrhythmic events.
- The new cutoff levels for predicting arrhythmic fatality that were proposed in our study for QTc and QTd parameters deserve further multicenter studies with larger sample sizes to verify their accuracy and applicability.

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