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ORIGINAL RESEARCH

Electrocardiographic Characteristics of Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular disease. Electrocardiography (ECG) carries information about cardiac disease and prognosis, but studies comparing ECG characteristics between patients with and without COPD are lacking. We related ECG characteristics of patients with COPD, to ECG characteristics of patients without COPD, and determined whether ECG abnormalities are related to COPD severity. A cross-sectional study was conducted within a cohort of 243 COPD patients, aged 65 years or older. All patients underwent extensive examinations, including resting 12-lead ECG and pulmonary function tests. The reference group (n = 293) was a sample from the general population, also aged 65 or older, without COPD. Abnormal ECGs were more prevalent in COPD patients (50%) than in patients without COPD (36%, p = 0.054). Conduction abnormalities were the most common ECG abnormality in COPD patients (28%) being significantly more prevalent than in patients without COPD (11%, p < 0.001). The mean heart rate was higher in COPD patients (72 bpm (SD 14)) compared to controls (65 bpm (SD 13), p < 0.001), and QTc prolongation was less frequent in COPD patients (9% versus 14%, p = 0.01). The prevalence of ECG abnormalities increased with severity of pulmonary obstruction. ECG abnormalities, especially conduction abnormalities are common in COPD patients, and the prevalence of ECG abnormalities increases with severity of COPD. This underlines the importance of an integrated-care approach for COPD patients, paying attention to early detection of unrecognized coexisting cardiac disorders.

Keywords: Cardiac arrhythmia, Cardiovascular diseases, Clinical epidemiology, Conduction abnormalities, Cross-Sectional Study, Electrocardiography, Ischemic heart disease, Pulmonary disease

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Introduction

Patients suffering from chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular morbidity and mortality (1–3). Compared to people without COPD, they are more prone to develop ischemic heart disease, cardiac arrhythmias, and heart failure (2). Moreover, most hospitalizations and deaths in COPD patients are caused by cardiovascular disease (3). High co-existence of COPD and cardiovascular diseases (CVD) is partly attributable to high prevalence of both diseases. In addition, they share important risk factors: cigarette smoking, advanced age, inactive lifestyle, and low socio-economic status (2,4,5). Importantly, however, after adjusting for risk factors for CVD, including the aforementioned, COPD remains a strong independent predictor for cardiovascular events and death (2,6,7). Large population-based studies also showed a strong association between lung function impairment

and cardiovascular morbidity and mortality, independent of age and smoking habits (7–9).

Schneider et al. recently showed that the relative risk of developing arrhythmia was comparable for patients with and without COPD, and independent of COPD severity (10). In contrast, Finkelstein et al. demonstrated that COPD patients had a higher risk of myocardial infarction [OR 2.0 (1.5–2.5)] and arrhythmia [OR 2.4 (2.0–2.8)] than non-COPD controls (2). Many previous studies also reported that COPD patients are at increased risk of cardiac arrhythmias (3,6).

Although an increasing body of evidence is available on the elevated risk of cardiovascular events in COPD patients, information on ECG characteristics of these patients is scarce and comparisons with patients without COPD are lacking. In addition, studies of ECG characteristics in COPD patients focus on ECG abnormalities related to pulmonary hypertension and cor pulmonale, i.e. right atrial enlargement, right ventricular hypertrophy, P-pulmonale, right axis deviation and right bundle branch block, while less than 1% of the COPD patients develop pulmonary hypertension (11). Electrocardiography is the standard method for diagnosing cardiac arrhythmias (12). In addition, it can provide useful information about cardiac disease or end-organ damage, e.g., detection of prior myocardial infarction, ischemia, chamber enlargements, conduction abnormalities, left ventricular hypertrophy, etc., and it is helpful for indicating which additional cardiac investigations should be considered (12). Finally, the ECG carries prognostic information, and it can offer clues for targeted preventive therapy.

We determined the prevalence of various ECG characteristics among COPD patients and focused on abnormalities related to cardiac disease, classified according to the Minnesota coding criteria (13). Secondary objectives were to determine whether COPD patients are at higher risk for ECG abnormalities than patients without COPD, and to assess if the prevalence of various ECG characteristics is related to severity of pulmonary obstruction.

Materials and Methods

Setting and study design

We performed a cross-sectional study within a cohort of 404 COPD patients from the vicinity of Utrecht, The Netherlands, aged 65 years or older, with a general practitioners diagnosis of COPD (International Classification of Primary Care (ICPC) code R91 (chronic bronchitis) or R95 (COPD or emphysema)). Patients were investigated between April 2001 and June 2003. The cohort is described in detail elsewhere (14). In short, all patients underwent extensive examinations in an outpatient clinic, including history taking, physical examination, ECG, chest radiography, blood tests, pulmonary function tests, and echocardiography. All patients with COPD were included, including those (co-)treated by a pulmonologist, because in the Netherlands all individuals, except nursing residents, are registered with one general practice.

Patients with a cardiologist-confirmed diagnosis of heart failure were excluded, because the aim of the original study was to assess the prevalence of unrecognised heart failure. This cohort is a representative sample of the COPD patients in the general practice population. From this cohort we selected all patients (n = 243) that fulfilled the GOLD criteria for COPD diagnosis: i.e., post-dilatory FEV_1/FVC was < 70%, either with or without complaints (15). GOLD stages were defined according to current guidelines: stage I (mild): FEV_1 > 80% of predicted; stage II (moderate): FEV_1 ≤ 80% of predicted and FEV_1 > 50% of predicted; stage III and IV ((very) severe): FEV_1 ≤ 50% of predicted (Figure 1). The Medical

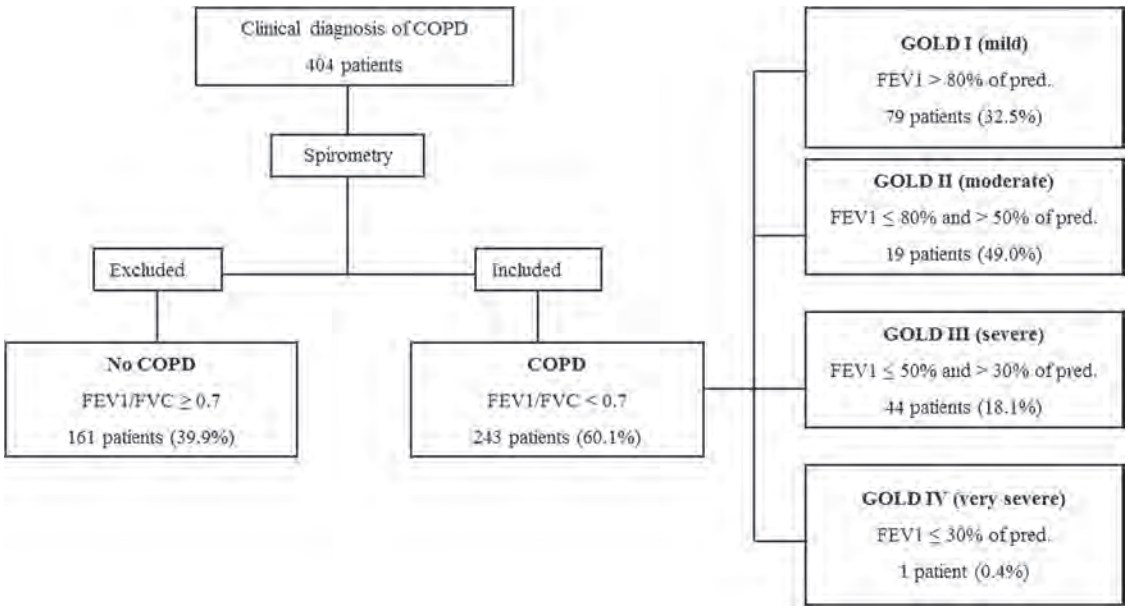

Figure 1. Inclusion of participants and severity of COPD according to the GOLD criteria in the study population (15).

Ethics Committee of the University Medical Center Utrecht, the Netherlands, approved the study and all participants gave written informed consent.

Electrocardiography

A standard resting 12-lead ECG was recorded at a paper speed of 25 mm per second (GE electronics, San Diego, California). ECG characteristics and abnormalities studied included heart rate, arrhythmias (pacemaker rhythm, sinus tachycardia, bradycardia (sinus bradycardia or bradyarrhythmia), premature ventricular contractions (PVC), atrial fibrillation), conduction abnormalities (left bundle branch block (complete left bundle branch block, left anterior fascicular block, or left posterior fascicular block) right bundle branch block (complete or incomplete right bundle branch block), atrioventricular (AV) block), right atrial and left ventricular enlargement, left and right ventricular hypertrophy, ischemic heart disease ((prior) myocardial infarction (inferior or anterior Q-wave myocardial infarction), ST and/or T-wave abnormalities (ST segment elevation or depression, other repolarization abnormalities or T-wave abnormalities)), and characteristics of arrhythmogenecity, that is, ventricular repolarisation abnormalities (QTc, QTc dispersion) and autonomic activity (heart rate variability (HRV)).

Each ECG was visually analyzed for recording errors and classified according to the Minnesota coding criteria by a single cardiologist to detect arrhythmias, conduction abnormalities and ischemic heart diseases (13). The hard-copy ECGs were also scanned and converted to digital ECG files (ECGScan Version 3.0, AMPSLLC, New York) (16). Subsequently, the ECGs were processed by a digital caliper software system (CalECG, Version 1.0, AMPSLLC, New York) to obtain the following ECG measurements: mean corrected QT (QTc) interval, QTc dispersion, mean RR interval and standard deviation of the RR interval (17).

The QT interval was corrected for heart rate according to Bazett's formula: $QTc=QT/\sqrt{RR}$ (18). A normal QTc interval was defined as <430 ms for males and <450 ms for females, a borderline QTc interval as 430-450 ms for males and 450-470 for females, and a prolonged QTc interval as >450 ms for males and >470 ms for females (19). QTc dispersion was defined as the difference between the maximum and minimum QT across the 12-lead ECG, and was calculated in ECGs in which at least 5 leads were measurable and corrected for heart rate according to Bazett's formula.[18] To compute mean RR interval and HRV, only intervals between two adjacent 'normal' dominant beats were used (both premature atrial and ventricular complexes were considered abnormal). HRV was defined as the standard deviation of the RR intervals (SDNN).

Reference group without COPD

Participants aged 65 or older from the population-based Utrecht Health Project (UHP) and without COPD or an established diagnosis of heart failure, were included in the reference group. The UHP is an ongoing longitudinal primary care based study among all inhabitants of "Leidsche Rijn," a newly developed residential area of Utrecht, The Netherlands. The UHP started recruitment in 2000 and for this study data were available of 6542 unselected adult participants. The cohort is described in detail elsewhere (20). In short, baseline assessments included physical examination, ECG, blood tests, pulmonary function tests and an interview assisted questionnaires, including information about smoking habits, demographic factors and current health status. More than 50% of the invited residents of "Leidsche Rijn" participated in the UHP cohort and gave informed consent.

Standard 12-lead resting ECGs were obtained from all participants of the UHP older than 18 years old recruited from April 2000 to January 2007, and stored digitally. Each ECG was manually classified according to the Minnesota coding criteria, and analyzed by the Modular ECG Analysis System (MEANS) as described previously in detail (13,21). ECG characteristics and abnormalities studied included heart rate, arrhythmias (sinus tachycardia, bradycardia, premature ventricular contractions (PVC), atrial fibrillation), conduction abnormalities (left bundle branch block, right bundle branch block, atrioventricular (AV) block), ischemic heart disease ((prior) myocardial infarction, ST and/or T-wave abnormalities), QTc, QTc dispersion and heart rate variability). Pharmacy records were used to obtain medication use at baseline.

Only patients 65 or older of age, with an available ECG and a spirometry result not compatible with COPD (pre-dilatory $FEV_1/FVC > 70$), and without an ICPC code R91 (chronic bronchitis) or R95 (COPD or emphysema) were included in the reference group. Of the 824 patients with a pre-dilatory $FEV_1/FVC>70$, 306 patients were 65 years or older. Eleven patients were excluded because they had a ICPC code R95 and 2 patient were excluded because of an ICPC code R91. In total, 293 participants of the UHP were included in the present study. The Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands, approved the UHP.

Data analysis

Continuous variables were described as means and standard deviations and categorical variables as absolute numbers and percentages. Differences in baseline characteristics were examined with chi-square tests or t-tests, when appropriate. Dichotomous outcome variables were analyzed with multivariate logistic regression to compute odds ratios (OR). Linear regression analysis was used for analyzing continuous outcome variables. We corrected for differences in age and sex distribution between the COPD group and the control group using multivariate analysis. As this is a non-etiological prevalence study, we do not correct for confounding factors.

To test the robustness of the association, several sensitivity analyses were performed. All data were analyzed using the statistical software package of SPSS (SPSS for Windows, version 16.0, SPSS Inc.).

Results

The characteristics of the participants with and without COPD are presented in Table 1. The mean age of the 243 COPD patients was 73 years, and 69% were male (reference group: 71 years and 51% male, respectively). Of the COPD patients, 33% had stage GOLD I, 49% stage GOLD II and 18% stage GOLD III (Figure 1). Only one patient (0.4%) had stage GOLD IV COPD and was included in the GOLD III COPD group. Patients with GOLD III COPD were more often male and current or previous smokers compared to GOLD I and II patients. Table 2 presents the occurrence of all possible ECG diagnosis in the COPD patient population. Left anterior fascicular block (14%), premature ventricular contraction (11%), ST segment depression (10%) and intraventricular block (10%) were most present.

ECG characteristics of patients with and without COPD

COPD patients, had significantly more abnormal ECGs compared to patients without COPD (50% vs. 36%, adjusted OR 1.5 (1.0–2.1), Table 3). In COPD patients, conduction abnormalities were most frequently observed (28%); and conduction abnormalities, especially left bundle branch block, were significantly more common in COPD patients (28% and 16%, respectively) than in patients without COPD (11%, $p < 0.001$ and 2%, $p < 0.001$, respectively). Sensitivity analyses showed that even after excluding all patients with known heart disease (n = 98 patients with COPD, 27 people without COPD),

Table 2. Frequency of all ECG abnormalities, classified according to the Minnesota coding criteria, in 243 patients with COPD (13)

Electrocardiographic abnormality	N	%
Pacemaker rhythm	0	0%
Sinus tachycardia (>100/minute)	4	2%
Sinus bradycardia (<50/minute)	2	1%
Bradyarrhythmia	1	0.4%
Premature ventricular contraction	27	11%
Premature atrial contraction	10	4%
Atrial fibrillation	16	7%
Complete left bundle branch block	5	2%
Left anterior fascicular block	34	14%
Left posterior fascicular block	1	0.4%
Complete right bundle branch block	17	7%
Incomplete right bundle branch block	9	4%
Intra-ventricular block	23	10%
Atrio-ventricular block	19	8%
Right atrial enlargement	3	1%
Left ventricular enlargement	15	6%
Left ventricular hypertrophy	17	7%
Right ventricular hypertrophy	3	1%
Inferior Q-wave myocardial infarction	18	7%
Anterior Q-wave myocardial infarction	9	4%
ST segment elevation	3	1%
ST segment depression	25	10%
Other repolarization abnormalities	31	13%
T-wave abnormalities	0	0%
Prolonged QTc interval	21	9%

More than one electrocardiographic diagnosis per patient is possible. Values are numbers and percentages.

Table 1. Baseline characteristics of the study population stratified by severity of COPD according to the GOLD criteria (15)

	Participants without COPD n = 293	Participants with COPD				P-value COPD vs. no COPD
		All n = 243	GOLD I n = 79, 33%	GOLD II n = 119, 49%	GOLD III n = 45, 19%	
Male	148 (51%)	167 (69%)	44 (56%)	82 (69%)	41 (91%)	<0.001
Age (years, SD)	71 (5)	73 (5)	73 (5)	74 (5)	73 (5)	<0.001
Current or past smoker	191 (65%)	206 (85%)	64 (81%)	99 (83%)	43 (96%)	<0.001
Signs and symptoms						
FEV_1(%pred., SD)	–	71 (20)	94 (10)	66 (8)	42 (6)	–
FEV_1/FVC (SD)	0.85 (0.08)	0.55 (0.11)	0.63 (0.05)	0.56 (0.09)	0.42 (0.09)	<0.001
History of						
Cardiac arrhythmias[a]	7 (2%)	24 (10%)	8 (10%)	12 (10%)	4 (9%)	<0.001
Ischemic heart disease[b]	22 (8%)	82 (34%)	25 (32%)	41 (35%)	16 (36%)	<0.001
Medication use at baseline						
Cardiovascular drugs[c]	145 (50%)	145 (60%)	38 (48%)	76 (64%)	31 (69%)	0.02
QT prolonging drugs[d]	4 (1%)	12 (5%)	4 (5%)	7 (6%)	1 (2%)	0.02
ß-blockers	70 (24%)	25 (10 %)	12 (15%)	12 (10%)	1 (2%)	<0.001
Respiratory drugs use[e]	22 (8%)	215 (89%)	64 (81%)	106 (89%)	45 (100%)	<0.001
Inhaled corticosteroids	17 (6%)	160 (66%)	47 (60%)	79 (66%)	34 (76%)	<0.001
Inhaled anticholinergics	4 (1%)	134 (55%)	34 (43%)	64 (54%)	36 (80%)	<0.001
Inhaled beta-agonists	13 (4%)	170 (70%)	48 (61%)	81 (68%)	41 (91%)	<0.001

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables.
COPD = chronic obstructive pulmonary disease, GOLD = global initiative for chronic obstructive lung disease. FEV_1 = forced expiratory volume in 1 second, %pred = percentage of predicted, FVC = forced vital capacity, SD = standard deviation, n = number.
[a] Including atrial fibrillation, supra ventricular tachycardia, ventricle fibrillation, ventricular tachycardia, and other cardiac arrhythmias.
[b] Including prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention.
[c] Including diuretics, β-blockers, dioxin, calcium-antagonists, anti-arrhythmics, platelet aggregation inhibitors, ACE-inhibitors, ATII receptor blockers, nitrates, and statins.
[d] Drug with (possible) risk of QTc prolongation according to the internet based registry of QTc prolonging drugs (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm) (28) (Appendix 1).
[e] Including beta-agonists, anticholinergics, and inhaled corticosteroids.

Table 3. ECG characteristics of participants with or without COPD

	COPD n = 243	No COPD n = 293	Crude		Adjusted[1]	
			OR (95%CI)	p-value	OR (95%CI)	p-value
Abnormal ECG[2]	122 (50%)	104 (36%)	1.8 (1.3–2.6)	<0.001	1.5 (1.0–2.1)	0.04
Arrhythmias	47 (19%)	41 (14%)	1.5 (0.9–2.3)	0.10	1.2 (0.8–2.0)	0.39
Tachycardia (>100/min)	4 (2%)	5 (2%)	1.0 (0.3–3.6)	0.96	1.1 (0.3–4.3)	0.94
Bradycardia (<50/min)	3 (1%)	15 (5%)	0.2 (0.1–0.8)	0.02	0.2 (0.1–0.7)	0.01
PVC	27 (11%)	18 (6%)	1.9 (1.0–3.6)	0.04	1.7 (0.9–3.3)	0.10
Atrial fibrillation	16 (7%)	7 (2%)	3.4 (1.3–8.8)	0.01	2.7 (1.0–7.2)	0.05
Conduction abnormalities	67 (28%)	31 (11%)	3.2 (2.0–5.1)	<0.001	2.8 (1.7–4.5)	<0.001
LBBB	38 (16%)	6 (2%)	8.9 (3.7–21.4)	<0.001	7.7 (3.1–18.9)	<0.001
RBBB	26 (11%)	6 (2%)	5.7 (2.3–14.2)	<0.001	4.6 (1.8–11.5)	0.001
AV block	19 (8%)	19 (7%)	1.2 (0.6–2.4)	0.55	1.1 (0.5–2.1)	0.89
Ischemic heart disease	45 (19%)	63 (22%)	0.8 (0.5–1.3)	0.39	0.7 (0.4–1.1)	0.09
Myocardial infarction	25 (10%)	30 (10%)	1.0 (0.6–1.8)	0.99	0.8 (0.5–1.5)	0.52
ST and/or T–wave changes	27 (11%)	41 (14%)	0.8 (0.5–1.3)	0.32	0.6 (0.4–1.1)	0.11
Heart rate (bpm)	72 (14)	65 (13)	–	<0.001	–	<0.001
Mean QRS length	100 (20)	102 (18)	–	0.37	–	0.04
Mean RR (ms)[3]	863 (161)	952 (164)	–	<0.001	–	<0.001
Median SDNN (ms)[3] 25–75 percentile	24 (14–49)	20 (12–33)	–	0.04	–	0.15
Mean QTc length (ms)[3,4]	421 (25)	427 (29)	–	0.02	–	0.06
normal[4]	184 (76%)	211 (72%)				
borderline[4]	38 (16%)	42 (14%)				
prolonged[4]	21 (9%)	40 (14%)	0.6 (0.3–1.0)	0.07	0.5 (0.3–0.8)	0.01

Values are means (SD) for continuous variables and absolute numbers (percentages) for dichotomous variables. Differences in ECG abnormalities between participants with or without COPD were determined by multivariate logistic regression (dichotomous variables) or linear regression analysis (continuous variables).
AV block = atrioventricular block, CI = confidence interval, COPD = chronic obstructive pulmonary disease, LBBB = left bundle branch block, PVC = premature ventricular contraction, OR=odds ratio, QTc = corrected QT time, RBBB = right bundle branch block, SDNN = standard deviation of all normal to normal RR-intervals.
[1]Adjusted for age and sex.
[2] Including arrhythmia, conduction abnormality, and ischemic heart disease. More than one electrocardiographic diagnosis per patient is possible.
[3] Mean RR, median SDNN: n = 292 participants without COPD, n = 239 COPD patients; heart rate, mean QTc length: n = 242 COPD patients; mean QRS length: n = 240 COPD patients.
[4] Normal QTc interval: QTc < 430 ms for males, QTc < 450 ms for females.
Borderline QTc interval: QTc = 430-450 ms for males, QTc = 450-470 ms for females.
Prolonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

conduction abnormalities, especially left bundle branch block, were significantly more common in COPD patients (27% and 15%, respectively) than in patients without COPD (9%, p < 0.001 and 2%, p < 0.001, respectively).

In patients without COPD signs of ischemic heart disease was the most common ECG abnormality (22%). The mean heart rate was significantly higher in COPD patients (72 bpm (14)) compared to controls (65 bpm (13), p < 0.001). Bradycardia was significantly less frequently observed in patients with COPD (1%) than in patients without COPD (5%, adjusted OR 0.2 (0.1–0.7), p = 0.01). Overall, 9% of the COPD patients and 14% of the participants without COPD had a prolonged QTc interval (adjusted OR 0.5 (0.3-0.8)). In addition, the mean QTc length was lower in COPD patients (421 ms (25)) compared to controls (427 ms (29), p = 0.06).

ECG characteristics in COPD patients according to disease severity

The prevalence of ECG abnormalities increased, although not statistically significantly, with increasing severity of obstruction (GOLD I: 46%, GOLD II: 50%, GOLD III: 58%, adjusted OR III vs. I: 1.5 (0.7-3.3), Table 4. The prevalence of conduction abnormalities, ECG changes suggestive of ischemic heart disease, and QTc prolongation increased with increasing GOLD stage. Heart rate significantly increased from 69 bpm (11) in stage GOLD I to 76 bpm (14) in GOLD III (p = 0.002) (Table 4). QTc dispersion increased with increasing disease severity from 42 ms in GOLD I to 48 ms in GOLD III (p = 0.50). With the exception of heart rate (p = 0.05) none of the differences in ECG characteristics between stage GOLD II and I were statistically significant.

Discussion

To our knowledge, this is the first study that compares differences in cardiac-disease-related ECG characteristics of COPD patients with persons without COPD. In our study among 243 COPD patients and 295 men and women without COPD, ECG abnormalities known to be related to cardiovascular disease, were more prevalent in COPD patients (the majority being conduction abnormalities) than in those without COPD. Heart rate was higher and QTc prolongation less common in COPD patients.

The prevalence of ECG abnormalities, in general, increased with GOLD stage. Recently, Holtzman et al. reported the prevalences of some ECG abnormalities associated with COPD in patients with mild or moderate COPD versus severe COPD. In concordance with our results, they reported high prevalences of ECG abnormalities in COPD patients, which increased with severity of the disease (22).

Table 4. ECG characteristics of COPD patients, stratified by disease severity according to the GOLD criteria (15)

				GOLD III vs. I	
	GOLD I 79 (33%)	GOLD II 119 (49%)	GOLD III 45 (19%)	Adjusted[1] OR (95%CI)	Adjusted[1] p-value
Abnormal ECG[2]	36 (46%)	60 (50%)	26 (58%)	1.5 (0.7–3.3)	0.30
Arrhythmias	12 (15%)	26 (22%)	9 (20%)	1.3 (0.5–3.5)	0.63
Tachycardia (>100/min)	1 (1%)	1 (1%)	2 (4%)	3.8 (0.3–50.6)	0.32
Bradycardia (<50/min)	1 (1%)	2 (2%)	0 (0%)	–	–
PVC	8 (10%)	14 (12%)	5 (11%)	1.0 (0.3–3.4)	0.99
Atrial fibrillation	3 (4%)	11 (9%)	2 (4%)	1.3 (0.2–9.5)	0.77
Conduction abnormalities	20 (25%)	31 (26%)	16 (36%)	1.4 (0.6–3.2)	0.44
LBBB	6 (8%)	17 (14%)	15 (33%)	4.7 (1.6–13.5)	0.005
RBBB	10 (13%)	12 (10%)	4 (9%)	0.6 (0.2–2.1)	0.41
AV block	7 (9%)	8 (7%)	4 (9%)	0.8 (0.2–3.0)	0.72
Ischemic heart disease	12 (15%)	21 (18%)	12 (27%)	1.9 (0.7–4.9)	0.18
Myocardial infarction	7 (9%)	11 (9%)	7 (16%)	1.3 (0.4–4.2)	0.62
ST/T-wave changes	7 (9%)	12 (10%)	8 (18%)	2.7 (0.8–8.8)	0.09
Heart rate	69 (12)	72 (14)	76 (14)	–	0.002
Mean QRS length	98 (19)	101 (22)	103 (18)	–	0.63
Mean RR (ms)[3]	897 (151)	857 (168)	819 (150)	–	0.003
Median SDNN (ms)[3]	22 (12–47)	24 (15–52)	24 (14–47)	–	0.57
25-75 percentile					
Mean QTc length (ms)[3,4]	422 (21)	421 (27)	419 (26)	–	0.93
normal	61 (77%)	88 (75%)	34 (76%)		
borderline	13 (17%)	20 (17%)	5 (11%)		
prolonged	5 (6%)	10 (8%)	6 (13%)	1.7 (0.5–6.2)	0.41
QTc dispersion (ms) [∞]	42 (33)	46 (42)	48 (34)	–	0.50

AV block = atrioventricular block, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GOLD = global initiative for chronic obstructive lung disease, LBBB = left bundle branch block, PVC = premature ventricular contraction, OR = odds ratio, QTc = corrected QT time, RBBB = right bundle branch block, SDNN = standard deviation of all normal to normal RR-intervals.

[1]Adjusted for age and sex.

[2] Including arrhythmia, conduction abnormality, and ischemic heart disease. More than one electrocardiographic diagnosis per patient is possible.

[3] Mean RR, median SDNN: n = 239 COPD patients; heart rate, mean QTc length, mean QTc dispersion: n = 242 COPD patients; mean QRS length: n = 240 COPD patients.

[4] Normal QTc interval: QTc < 430 ms for males, QTc < 450 ms for females.
Borderline QTc interval: QTc = 430-450 ms for males, QTc = 450-470 ms for females.
Prolonged QTc interval: QTc > 450 ms for males, QTc > 470 ms for females.

Values are absolute numbers (percentages) for dichotomous variables and means (SD) for continuous variables. Odds ratios (OR) and p-values were calculated by multivariate logistic regression (dichotomous variables) or linear regression analysis (continuous variables) and adjusted for age and sex.

Consistent with large population-based studies, we demonstrated that COPD is associated with an excess of cardiac arrhythmias, particularly atrial fibrillation (2,3,8). As arrhythmias are often intermittently present and ECGs are a snap-shot of the cardiac situation, our results could underestimate the actual prevalence of arrhythmias. Nevertheless, bradycardia (heart rate < 50 bpm) was significantly less prevalent in our patients with COPD than in patients without COPD. This could be partly attributable to the higher prevalence of beta-blocking agent use in patients without COPD (24%) compared to COPD patients (10%, p < 0.001). However, exclusion of patients receiving beta-blockers revealed similar results (bradycardia: COPD: 1.4%, no COPD: 4.0%, OR adjusted for age and sex: 0.2 (0.1–0.9), p = 0.04).

In analogy with other studies, we showed that patients with COPD had a relatively high heart rate and that heart rate significantly increased with increasing GOLD stage (23,24). Exclusion of patients receiving beta-blocking agents did not change these findings (e.g., mean heart rate: COPD 72 bpm, no COPD: 66 bpm, p-value adjusted for age and sex: < 0.001). An elevated heart rate is associated with an increased risk of cardiac mortality in population based studies (25), and a recent observational study from our group suggested that beta-blocking agents may improve prognosis in COPD patients (26).

Next, tachyarrhythmia is a well-recognised side effect of beta-mimetic and anticholinergic agents. As inhaled beta-mimetic as well as anticholinergic agents are central to symptom management in COPD, this could be another explanation of the increased heart rate of COPD patients. However, as 84% of the COPD patients used at least one of these medications (41% of the COPD patients used both) we were not able to determine the effect of these drugs on heart rate. Finally, another potential cause of the increased heart rate could be lung hyperinflation. Hyperinflation in COPD may lead to decrease of the ventricular size and function, with decreased stroke volume and cardiac output. As a result, this may cause an increase in heart rate and tachycardia (27).

Although COPD patients are prone to cardiac arrhythmias, this seems not to be related to QTc prolongation, because the mean corrected QT interval was lower in COPD patients than in controls. This, although patients with COPD more often received QT-prolonging medication [according to the internet based registry of QTc prolonging drugs, appendix 1 (28)] than patients without COPD. The QT interval in both groups was corrected

for heart rate according to Bazett's formula. This correction is necessary as the QT interval varies with RR interval: the shorter the RR interval (or the faster the heart rate), the shorter the QT interval. However, QT corrections are prone to under- or overestimation of the true QT interval (29). As the mean RR interval is significantly shorter in COPD patients than in controls, it is questionable if heart rate correction was optimal. The QTc interval of the COPD patients could be underestimated due to the shorter RR interval. However, different techniques were used to determine the QT-interval in COPD patients and controls, and the effect of this is difficult to predict, but may partly account for the differences in QTc length between both groups.

In agreement with our results, Lange et al. found that COPD patients, particularly with stage GOLD III and IV, frequently have conduction defects (36%) (8). COPD is one of the main causes of right bundle branch block, due to chronically increased right ventricular pressure, and 11% of the COPD patients in this study showed right bundle branch block. However, left bundle branch block, which usually indicates underlying cardiac pathology, is even more common in our COPD patients. This further underlines that COPD is an important risk factor of cardiac disease (1).

Several limitations of the current study should be discussed: the number of COPD patients was limited, and consequently, because of limited power, none of the trends in the association of cardiovascular disease with COPD severity were statistically significant, although some interesting trends of increased prevalences with increasing COPD severity were observed. Many trends shown are not statistically significant. However, although not statistically significant, we think we should mention that ECG abnormalities have a trend to increase with GOLD class, and thus severity of pulmonary obstruction, which may be clinically relevant. Furthermore, in the reference group only pre-dilatory measurements of the pulmonary function were available.

For establishing a diagnosis of COPD according to GOLD criteria, post-dilatory measurements should be used. However, for excluding COPD, pre-dilatory measurements are sufficient. Next, we measured heart rate variability for periods shorter than 10 seconds. Heart rate variability, when measured on continuous ECG registrations, is an indication of autonomic nervous system functioning. Short-term variability mainly reflects sinus arrhythmia, and autonomic nerve system functioning is less represented (30).

Previous studies showed that COPD, as well as a decreased FEV1 value, are independently associated with cardiovascular events and death (2,6,7); an association that persists after adjusting for multiple risk factors of cardiovascular disease, including cigarette smoking, age, inactive lifestyle, and low socioeconomic status (2,4,5). However, residual confounding cannot be completely excluded in these studies, and thus, could explain part of the observed association. Importantly, this finding does not preclude that both diseases have important common pathophysiological pathways, including cigarette smoking and systemic inflammation.

Different mechanisms have been proposed to explain why COPD patients have a higher risk of cardiovascular events. One potential mechanism may relate to systemic inflammation. The increased cardiovascular risk is not only shown in COPD, but also in other systemic diseases characterized by chronic inflammation, such as rheumatic arthritis or chronic renal impairment. Epidemiologic data strongly associate systemic inflammation to atherosclerosis and ischemic heart disease (7).

Furthermore, there is evidence that COPD patients have autonomic dysfunction, most likely due to chronic hypoxemia, which contributes to the development of CVD: increased resting heart rate, as well as an increased risk of arrhythmias, abnormal conduction and ectopic beats (31). Heart rate variability, being the beat-to-beat alteration in heart rate, is an indication of autonomic nervous system functioning, and when reduced, this indicates autonomic dysfunction. In contrast with our results, several studies showed that heart rate variability is reduced in COPD patients (23,24), and heart rate invariability is associated with a higher risk of cardiovascular mortality the elderly (32). However, the fact that we did not find a reduced HRV could be due to the fact that we measured heart rate variability for periods shorter than 10 seconds, while in the former studies HRV, which did show a reduced HRV in COPD patients, was measured for longer periods.

Finally, there is a growing concern that the pulmonary medications used for COPD increases morbidity and mortality, although the currently available studies and meta-analysis yield conflicting results (33–35). Lee et al. as well as the Lung Health Study showed that the use of ipratropium was associated with an increased risk of cardiovascular death (33,35), and a meta-analysis of Salpeter et al. showed that use of beta-mimetics in COPD patients increases the risk of cardiovascular events (34). In contrast with these trials, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial did not show an increased risk of cardiovascular morbidity and mortality in COPD patients using tiotropium (36) and a review of Wood-Baker et al. conclude that there is no evidence of increased mortality associated with the use of betamimetics in patients with COPD (37). Currently, much uncertainty remains about the association of pulmonary medication with mortality.

Although the available evidence strongly suggests that COPD patients are at increased risk of cardiovascular morbidity and mortality, the care provided seems to be focused mainly on the lungs. The NICE guideline on COPD does not point out the high risk of cardiovascular morbidity and mortality at all (38), and the GOLD guideline only mentions it briefly (15). An integrated-care approach for COPD patients with special attention for investigating of previously unrecognized cardiovascular

disease is desirable, as is a more integrated pulmonary and cardiovascular care.

Conclusion

We conclude that electrocardiographic abnormalities, particularly conduction abnormalities, are common in patients with chronic obstructive pulmonary disease, and more prevalent than in patients without COPD. The prevalence of ECG abnormalities related to cardiac diseases, in general, is higher in those with more severe pulmonary obstruction. Previous studies suggest that COPD is related with cardiovascular morbidity and mortality. Our results show that COPD patients more often have ECG abnormalities, including abnormalities that have been shown to increase the risk of future cardiovascular events and mortality (39–41). Therefore, special attention in the diagnostic work-up of these patients is needed, including ECG and in selected cases echocardiography, coming to a more integrated pulmonary and cardiovascular care.

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Declaration of Interests

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Appendix

Drugs with (possible) risk of QTc prolongation according to the Internet-based registry of QTc prolonging drugs (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm, accessed on 25 August 2010) (28).

Drugs with estabilised Possible Risk of Torsades de Pointes

Alfuzosin
Amantadine
Atanavir
Azithromycin
Chloral hydrate
Clozapine
Dolasetron
Dronedarone
Felbamate
Flecinide
Foscarnet
Fosphenytoin
Gatifloxacin
Gemifloxacin
Granisetron
Indapamide
Isradipine
Lapatinib
Levofloxacin
Lithium
Moexipril/HCTZ
Moxifloxacin
Nicardipine
Nilotinib
Octreotide
Ofloxacin
Ondansetron
Oxytocin
Paliperidone
Quetiapine
Ranolazine
Risperidone
Roxithromycin
Sertindole

Sunitinib
Tacrolimus
Tamoxifem
Telithromycin
Tizanidine
Vardenafaxine
Voriconazole
Ziprasidone

Drugs with Establised Risk of Torsade de Pointes
Amiodarone
Arsenic trioxide
Astemizole
Bepridil
Chloroquine
Chlorpromazine
Cisapride
Clarithromycin
Disopyramide
Dofetilide
Domperidone
Droperidol
Erythromycin
Halofantrine
Haloperidol
Ibutilide
Levomethadyl
Mesoridazine
Methodone
Pentamidine
Pimozide
Probucol
Procainamide
Quinide
Sotalol
Sparfloxacin
Terfenadine
Thioridazine