Research Article



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Heart rate variability in chronic obstructive pulmonary disease

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Abstract

Background and purpose: Cardiopulmonary disorders coexist and contribute to the morbidity and mortality of Chronic Obstructive Pulmonary Disease (COPD). There is also a significant contribution of COPD to heart disease. Hypoxemia and respiratory acidosis have been implicated as a major cause of cardiac arrhythmias in patients with COPD through an increase in catecholamines, fluid retention and peripheral edema (electropathy hypothesis). Alternatively, arrhythmias may be the result of autonomic neuropathy. We investigated the relationship between COPD and cardiac arrhythmias and particularly the impact of COPD on heart rate variability (HRV).

Patients and methods: We studied a total of 68 consenting consecutive patients (30 women and 38 men (M = 67.37 years, SD 10.24 years) that met strict inclusion criteria, regarding cardiac or vascular disease, diabetes or medications. Pulmonary function tests, 12-lead ECG and blood gases were performed on all patients. Two different ECG parameters were calculated: Dispersion of QT interval (QTd) and coefficient of variation of the RR interval (CVRR). Analysis was through regression (single or multiple) and cross-correlation methods.

Results: Examination of the cross-correlation of PaO2, PaCO2, pH and HCO3 with QTd and CVRR showed that CVRR correlated best with PaO2 We, therefore, reject the electropathy hypothesis (*i.e.*, that arrhythmia is a result of hypoxia, hypercapnia, or acid-base balance disorders) and conclude that hypoxemia is the likely mechanism of sudden cardiac death in COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, permanent and irreversible lung disease characterized by airway obstruction. In fact, it represents two concomitant diseases: chronic bronchitis (which is characterized by excessive mucus production) and mucosal edema. The coexistence of these two disease entities result in bronchoconstriction, coughing, sputum production, frequent respiratory infections and pulmonary emphysema. Emphysema destroys the walls of alveoli, reduces the ratio between the gas-exchange surface and the volume of air contained in the alveoli and results in inadequate oxygen uptake.

COPD is accompanied by comorbidities. Among them are low intensity diffuse inflammation, cardiovascular disease, metabolic disorders, cachexia and psychological disorders. Of interest are the cardiovascular comorbidities, especially the incidence of COPD in disturbances involving the RR interval of the ECG. The importance of focusing on the impact of COPD on cardiovascular disease is demonstrated in Table 1 which summarizes the relationship between COPD and its co-morbidities.

COPD is emerging as one of the biggest health problems of the 21st century as it is the fourth cause of death and morbidity in the United States [1], where it is predicted that it will become the third cause of morbidity - mortality by 2020 [2] while 24 billion dollars are spent every year, on medicines and COPD related hospitalizations, in the US alone. The prevalence of COPD worldwide is estimated at around 10% of adults over the age of 40 [3] with country-to-country fluctuations impacting significantly on the healthcare costs of the disease which is significantly high [4] and causing significant burdens on the quality

of life of patients [5]. It is characteristic that more than half of COPD sufferers are unaware of it, as the disease is under-diagnosed [6].

The main cause of COPD (80-90%) is smoking [6,7] while biomass burning, car exhaust, dust and volatile chemical emissions are also recognized causative factors.

COPD is a comorbidity of importance for cardiology as supraventricular and abdominal arrhythmias, and conduction disorders are very often encountered in COPD. Despite its obvious significance, however, this phenomenon has not merited attention, and treatment has been symptomatic at best. The basis for the COPD related treatment of arrhythmias is based on the perception that arrhythmias are the result of local deviations from normal myocardiocyte function due to hypoxemia, hypercapnia and associated acid-base disturbances. However, given that the autonomic control of the heart is particularly important for its pacing, and that the sympathetic and parasympathetic inputs are not evenly distributed over the myocardium, it is also possible that the COPD related arrhythmias may be due to the "autonomic neuropathy" that characterizes COPD. Indeed, hypoxemia and respiratory acidosis have been implicated as major causes of cardiac arrhythmias in patients with COPD [8,9]. The putative causative mechanism is apparently the increase of catecholamines which occurs in hypercapnic COPD patients especially when hypercapnia and hypoxia are accompanied by fluid retention and peripheral edema [10]. As COPD cardiac output remains normal, under these circumstances,

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	Hole et al, 1996	Ebi-Kryston, 1988	Schunneman et al, 2000	Persson et al, 1986
Sample size	15411	17717	1195	1492
Duration of observation	15 years	10 years	28 years	12 years
Mean age	15	10	29	12
Pulmonary function	FEV1 73-113%	FEV1<65%	FEV1 80%-114%	PEFR 123-545 l/min
Main conclusion	↑ relative risk X 1.56	Chronic sputum production is connected with increased cardiovascular mortality which can be corrected by improvementh of FEV1	↑ relative risk X 2.11	Inversely related to risk of death from Infarction
Results adjusted for	Age, smoking, serum cholesterol, BMI, social class	Age, smoking, occupation, blood pressure (BP), BP medication, serum cholesterol, diabetes ECG	Age, smoking, BP, BMI, education, ischemia	Age, height, BMI, waist to hips ratio, chest skeletal problems, pulmonary disease, smoking, serum lipids, BP, diabetes, physical activity

while systemic vascular resistances remain low (due to the vasodilatory effect of hypercapnia), it is believed that the resulting drop in arterial pressure triggers neurohormonal mechanisms that result in water and electrolyte retention while they increase the concentration of norepinephrine in the blood. In addition, the (inhaled) β2-stimulants used in COPD treatment may potentially increase the heart rate and induce cardiac arrhythmias through non-selective β-stimulation [11,12]. Salbutamol, which is a drug of choice in the treatment of COPD, reduces the duration of the atrial cycle and the sinoatrial (SA) restoration time, increases the speed of atrioventricular conduction and decreases the duration of the refractory period of the myocardium and of the SA cells. It should be also mentioned that beta-agonists cause arrhythmias, such as atrial tachycardia, atrial fibrillation, syncope, heart failure, arrest and sudden death. It is noteworthy that administering a dose of inhaled β 2-stimulant results in an increase in heart rate of 9 IU / min in cases of asthma, whereas the administration of prolonged β2-stimulatory activity (LABA), such as salmeterol or formoterol, atrial tachycardia but no increase in mean heart rate [13,14].

Patients and methods

We recruited 68 consecutive patients (30 women and 38 men, with mean age of 67.37 years and standard deviation of 10.24 years. All patients were properly informed of the aims and methods of the study following the procedures of the Helsinki Declaration, and they all provided their informed consent. Our patients were selected after a rigorous application of exclusion criteria. We excluded patients with hypertension, heart failure, ischemic heart disease, valvular heart disease, supraventricular and ventricular heart rhythm disorders, atrial fibrillation or flutter, conduction disorders and, finally, diabetes mellitus. Patients on certain medications were also excluded. Thus, patients on medicines that prolong the QT interval - such as antiarrhythmics (quinidine, disopyramide, procainamide, amiodarone, sotalol), certain antibiotics (macrolides, chloroquine, quinine), psychiatric medications (tricyclic antidepressants, phenothiazines, haloperidol) or cholinergic antagonists (cisapride), were excluded. Finally, patients treated with sympathomimetic drugs and/or aminophylline were excluded from the study unless they could discontinue their medication at least 48 hours prior to their examination for the present study. All patients underwent pulmonary function tests and ECG and simultaneous measurement of blood gases. ECG was recorded with patients in the supine position while they displayed a regular, relaxed breathing pattern. Patients were at rest before measurement. ECG recording length was 3 minutes, with each patient completing about 45 respiratory cycles during the recording.

From the data collected, two different ECG parameters were calculated: The dispersion of the QT interval (QTd) which is associated

with ventricular repolarization, [15] and the Coefficient of Variation of the RR interval (CVRR).

The QTd is defined as the difference between the maximum and minimum QT interval in the 12-lead ECGs [16]. The QT interval was measured from the onset of QRS to the end of the T wave. Leads where the T-wave was level (absent) were excluded from the QTd calculation [17]. If U waves appeared in the EEG, then the QT interval was measured from the onset of the QRS to the lowest point of the curve between the T and the U waves [18]. The ECG at each lead was recorded for three consecutive cycles.

For each ECG cycle the corrected QT interval (QTc) was calculated based on the Bazett formula (i.e., $QTc = QT/\sqrt{RR}$). Finally, the QTd was calculated as the difference between the maximum and minimum QTc in the 12-lead pattern, in order to avoid errors from the pulse-to-pulse fluctuations between the leads [19].

The ECG parameter we measured was the instantaneous heart rate, i.e., the inverse of the duration of the RR intervals between two consecutive QRS complexes of physiological morphology and of SA origin. Thus, for each continuous ECG record, the duration of the RR interval between two normal QRS was measured. The simple time domain variables that were calculated include the mean "RR interval between two normal QRS" and the mean heart rate. Following the instructions of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) [20], all electrocardiographic recordings were conducted with patients in supine position and with regular and calm breathing while the patients were rested before the start of the measurement.

Each electrocardiographic recording lasted 3 minutes, and each patient completed about 45 breathing cycles (inhalation - exhalation). The ECG was continuously recorded, covering all inhalation and exhalation cycles during this time, and was therefore not stable with respect to the respiratory cycle, which ensured the normalization of the influence of the vagus nerve on the SA node, which takes place mainly during the exhalation phase and which, is usually week or absent during inhalation.

Data were reviewed of the independence of the measured variables and checked for any correlations between the independent and dependent parameters. Subsequently, correlation matrices were created for each independent parameter and the remaining (dependent) parameters. Patients were then divided according to their respiratory fitness for each studied parameter in two groups: those of better and those of worse fitness and each group was analyzed for its response when FVC, FEV1, pH, PaO2, PaCO2, or CVRR were increased. Only statistically significant (p<0.05) relations were considered. The results were tabulated in five tables (Tables 2-4).

Table 2.	Effect of FEV1	increase on	different	spirometry	and EC	G parameters	of COPD
patients.							

COPD patients with Worse respiratory system fitness		COPD patients with Better respiratory system fitness		
Better respiratory system fitness for PaCO2	↑ pH	Better respiratory system fitness for FEV1	↑ PaO2	
Worse respiratory system fitness for pH	↑ PaO2	Better respiratory system fitness for FVC	↑ PaO2	
Worse respiratory system fitness for pO2	↑ pH	Worse respiratory system fitness for pCO2	↑ PaO2	
Worse respiratory system fitness for FEV1	↓ CVRR	Better respiratory system fitness for CVRR	↓ CVRR	
Worse respiratory system fitness for FVC	↓ CVRR	Better respiratory system fitness for pH	↓ CVRR	
Better respiratory system fitness for PaCO2	↓ PaCO2	Worse respiratory system fitness for PaCO2	↓ CVRR	
Worse respiratory system fitness for PaO2	↓ CVRR	Better respiratory system fitness for pO2	↓ PaCO2	
Worse respiratory system fitness for FEV1	↓ PaCO2	Worse respiratory system fitness for CVRR	↓ PaCO2	
Worse respiratory system fitness for FVC	↓ PaCO2			

Table 3. Effect of pH increase on PaCO₂ or PaO₂ for the different groups of COPD patients.

Worse respiratory system fitness for FVC	↓ PaCO2
Better respiratory system fitness for FVC	↓ PaCO2
Worse respiratory system fitness for FEV1	↓ PaCO2
Better respiratory system fitness for FEV1	↓ PaCO2
Worse respiratory system fitness for pH	↓ PaCO2
Better respiratory system fitness for pH	↓ PaCO2
Worse respiratory system fitness for pO2	↓ PaCO2
Better respiratory system fitness for pCO2	↑ PaO2
Better respiratory system fitness for pCO2	↓ PaCO2
Worse respiratory system fitness for CVRR	↓ PaCO2
Better respiratory system fitness for CVRR	↓ PaCO2

Table 4. Effect of PaO2 increases on the PaCO2 and CVRR of COPD patients.

Better respiratory system fitness for FVC	↑ CVRR
Better respiratory system fitness for FEV1	↑ CVRR
Worse respiratory system fitness for pH	↓ PaCO2
Better respiratory system fitness for pH	↑ PaCO2
Better respiratory system fitness for pH	↑ CVRR
Better respiratory system fitness for PaCO2	↓ PaCO2
Better respiratory system fitness for PaCO2	↑ CVRR

Results

Table 2 describes the effects of FEV1 increases on the different spirometry and ECG parameters we studied.

From Table 2, it is evident that, among the subgroup of patients with worse respiratory system fitness for for the different parameters (i.e., with either hypercapnia, or acidosis, hypoxia, low FVC and reduced FEV1), the increase in FEV1 brought about a corrective action as far as blood PaCO2, PaO2 and pH are concerned. However, despite these corrective actions, the CVRR decreased with the increase of FEV1.

The same behavior was observed among the subgroup of patients with better respiratory fitness (i.e., with reduced hypercapnia or normocapnia, slightly acidic or normal pH, minimal hypoxia or physiological O2 blood values, etc.). In this group of patients, the increase in FEV1 brought about a corrective action as far as blood PaCO2, PaO2 and pH are concerned, and, again, the CVRR decreased with the increase of FEV1.

It is interesting to note that pH increase (alkalosis) was always associated with blood PaCO2 decrease (hypocapnia). This condition was never associated with changes in PaO2, except in the case of patients in the "better respiratory system fitness for PaCO2" subgroup of patients (Table 3) where hypocapnia is apparently related with concomitant increase in O2 uptake due to increase in FEV1.

The increase in blood PaO2 (Table 4) appears to correlate with decrease in blood PaCO2 in both subgroups of "better respiratory system fitness for blood pH" and "worse respiratory system fitness for blood pH" and in the subgroup of patients characterized by "better respiratory system fitness for blood PaCO2". It also correlates with an increase in CVRR in the subgroups of "better respiratory system fitness for" FVC and FV1 as well as in the subgroups of patients in the sample that are characterized by "better respiratory system fitness for blood pH" and "better respiratory system fitness for PaCO2".

Finally, in the case of patients with "better respiratory fitness for pH" the increase in the PaCO2 is correlated with an increase in CVRR.

Discussion

COPD is a manifestation of irreversible airway stenosis accompanied by symptoms of chronic coughing, wheezing (mainly local airway obstruction), inflammation (inflammatory process) and dyspnea due to restriction of flow along the airway tree due to airway obstruction [21]. For the last 30 years, the general impression was (and still is) that patients (especially geriatric patients) with COPD are at increased risk of cardiovascular disease [22]. COPD doubles or triples the risk of inducing or exacerbating cardiovascular disease. At the same time, it appears that low-grade systemic inflammation in patients with COPD is associated with an increased risk of cardiovascular lesions [23]. Besides ischemic heart disease, various supraventricular and ventricular arrhythmias as well as significant conduction disorders often accompany COPD [8,9].

Many factors have been implicated as potential causal factors for cardiovascular disease in patients with COPD. The hypothesis of hypoxemia, hypercapnia and acid-base balance disorders have all been proposed as causes of cardiac arrhythmias [24]. The underlying rationale is that hypoxemia, hypercapnia, and acid-base balance disorders increase the electrical heterogeneity of the ventricular wall's myocardial tissue resulting in the development of potentially fatal episodes of re-entry of myocardial electrical currents during arrhythmias [25].

To non-invasively check the hypothesis of electropathy in patients with COPD, the correlation between each of PaO2, PaCO2, pH and HCO3 with QTd in patients with stable COPD was examined. Given that QTd is the predominantly non-invasive ECG marker of ventricular heterogeneity, it has been proposed as a predictive marker for increasing morbidity and mortality in both cardiovascular and non-cardiovascular disease [26]. The current view wants the cellular heterogeneity of ventricular repolarization to be the result of the presence of M cells in the myocardium. These M cells are characterized by prolonged action potentials compared to the rest of ventricular myocardial cells [27] and despite the fact that M cells do not differ histologically from other myocardial cells, they have distinct electrophysiological characteristics and pharmacological profiles [27]. The rationale of using QTd as an indicator of electrophysiological response of the myocardium to hypoxemia, hypercapnia, and acid-base balance disturbances assumes that the hypothesis of electropathy is correct. In that case one would expect QTd to be highly correlated with pH or HCO3. However, no such (statistically significant) correlation was found.

Autonomous neuropathy is the second arrhythmogenic mechanism that has been proposed to account for the cardiovascular effects of COPD. Chronic hypoxemia is an important factor in the pathophysiology of autonomic neuropathy and is considered as the underlying cause of COPD-associated autonomic neuropathy [28]. Recent evidence suggests that autonomic neuropathy can occur even at the very early stages of the disease [29]. Additional evidence regarding the mechanisms involved in the pathophysiology of autonomic neuropathy is derived from studies in patients with autonomic diabetic neuropathy [30]. There are also strong indications that, in patients with stable COPD, hypoxemia is associated with a disorder of the autonomic nervous system, which can be partially reversed by oxygen administration [31] Finally, it has been observed that among the patients with COPD, those with autonomic neuropathy are at a higher risk of sudden cardiac death [29].

HRV has been used as an indicator of function (and functionality) of the autonomic nervous system. The reason is that it reflects the fluctuation in elapsed time between two heartbeats. These fluctuations are primarily due to the continuously changing activity of, both, the sympathetic and parasympathetic systems, as is evidenced by the acceleration (during inhalation) and deceleration (during exhalation down) of the cardiac rhythm. Current clinical research has shown that high levels of HRV are consistent with low levels of stress [32,33]. HRV has also been investigated as a factor of good physical fitness. Thus, a study published in 2000 by the American Heart Association, shows that low HRV is associated with a higher risk of death in patients with heart disease and in the elderly. HRV is also associated with increased risk of coronary artery disease in the general population [34]. Low HRV has also been associated with other disease states such as hypertension [35], diabetes [36] and, obstructive pulmonary disease [37]. Low HRV has thus been used as a marker of reduced parasympathetic activity while the main reason for determining HRV in the clinical setting is the fact that it predicts survival after myocardial infarction. More precisely, reduced HRV is a "predictor" of sudden death in patients with myocardial infarction [38,39,40]. Another reason for estimating HRV is that its decline is a predictor of future fatal ventricular arrhythmias [41].

Conclusions

We used CVRR, as a best descriptor of HRV and therefore of autonomic nervous system dysfunction to examine all possible correlations between each of PaO2, PaCO2, pH and HCO3, on one hand, and CVRR, on the other, in patients with stable COPD. We found that CVRR correlates with PaO2. Therefore, it is concluded that hypoxemia (a decrease in PaO2) leads to a decrease in CVRR. CVRR, in turn, is strongly associated with autonomic nervous system dysfunction which leads to sudden cardiac death.

We also identified different sets of factors that affect differently COPD patients, depending on whether they are fit (in terms of their respiratory function) with respect to FVC, FEV1, CVRR, PaO2, PaCO2, pH and HCO3. These factors are summarized in Tables 2 -4 and allow for a better pathophysiologic understanding of the diagnosis and treatment of COPD when it co-exists with heart disease.

Finally, our results exclude the hypothesis of electropathy and support that of autonomic neuropathy as the most likely mechanism of instigating arrhythmias in COPD hypoxemia. They also highlight the importance of maintaining high levels of PaO2 during COPD exacerbations. Regarding this last conclusion, it is of interest that the hypoxemia due to residing in high altitudes affects the autonomic nervous system [42-47] and it also has a direct impact on CVRR.

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