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Review

Electrocardiographic abnormalities and cardiac arrhythmias in chronic obstructive pulmonary disease

Christos A. Goudis [a], Athanasios K. Konstantinidis [b], Ioannis V. Ntalas [c], Panagiotis Korantzopoulos [c,*]

[a] Department of Cardiology, Grevena General Hospital, Grevena, Greece
[b] Department of Pulmonary Medicine, University of Ioannina Medical School, Greece
[c] First Department of Cardiology, University of Ioannina Medical School, Greece

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is independently associated with an increased burden of cardiovascular disease. Besides coronary artery disease (CAD) and congestive heart failure (CHF), specific electrocardiographic (ECG) abnormalities and cardiac arrhythmias seem to have a significant impact on cardiovascular prognosis of COPD patients. Disturbances of heart rhythm include premature atrial contractions (PACs), premature ventricular contractions (PVCs), atrial fibrillation (AF), atrial flutter (AFL), multifocal atrial tachycardia (MAT), and ventricular tachycardia (VT). Of note, the identification of ECG abnormalities and the evaluation of the arrhythmic risk may have significant implications in the management and outcome of patients with COPD. This article provides a concise overview of the available data regarding ECG abnormalities and arrhythmias in these patients, including an elaborated description of the underlying arrhythmogenic mechanisms. The clinical impact and prognostic significance of ECG abnormalities and arrhythmias in COPD as well as the appropriate antiarrhythmic therapy and interventions in this setting are also discussed.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem [1]. Indeed, the worldwide prevalence of COPD of Global Initiative on Obstructive Lung Disease (GOLD) stage 2 or higher in adults aged 40 years and older is 9–10% [2]. In the United States, COPD ranks as the fourth leading cause of mortality, second leading cause of morbidity, and it remains the only common mortality etiology that continues to rise [3]. COPD is associated with cardiovascular disease while it is characterized by specific electrocardiographic (ECG) abnormalities [4]. An increased burden of cardiac arrhythmias has also been recently recognized [4]. Cardiac arrhythmias represent a major contributor to population morbidity and mortality. The American Heart Association estimates that AF and AFL are present in 2.7–6.1 million Americans (expected to increase to approximately 5.6–12 million in 2050), and sudden cardiac death (SCD) occurs in >400,000 Americans annually [5]. The identification of ECG risk markers and the understanding of the relationship between COPD and certain arrhythmias seem to be of particular importance given the alarming rise in COPD related cardiovascular mortality. The present article provides a concise overview of the ECG abnormalities and arrhythmias observed in COPD patients, and critically discuss the arrhythmogenic mechanisms as well as their clinical impact and prognostic significance in this setting. Data on the appropriate drug therapy and interventions, as well as novel therapies and future directions are also discussed. Sources included MEDLINE and EMBASE (last search update performed on 30 May 2015). The search strategy was based on the combination of the following terms: chronic obstructive pulmonary disease; smoking; nicotine; ECG abnormalities; cardiac arrhythmias; multifocal atrial tachycardia; atrial fibrillation; atrial flutter; ventricular tachycardia; bronchodilators; β agonists; anticholinergics; corticosteroids; β blockers; and prognosis. References of the retrieved articles were also screened.

2. COPD: definition, risk factors, and comorbidities

COPD represents a common preventable and treatable disease that is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases [1]. Smoking cigarettes is the main cause, but other causes might increase the risk and lead to the disease in non-smokers. In specific, maternal smoking, childhood asthma, and childhood respiratory infections are significantly associated with reduced forced expiratory volume in the first second (FEV1), while previous tuberculosis, outdoor air pollution, occupational exposure to dusts and smoke inhalation have been particularly associated with the development of airflow obstruction and chronic respiratory symptoms [1,5]. Genetics, lung development abnormalities, accelerated

* Corresponding author at: 1st Department of Cardiology, University of Ioannina Medical School, 45110 Ioannina, Greece.
E-mail addresses: p.korantzopoulos@yahoo.gr, pkorantz@cc.uoi.gr (P. Korantzopoulos).

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aging, bronchial hyper-reactivity, and socioeconomic status have also been associated with the development and progression of COPD [1]. Comorbidities including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer, occur frequently in COPD patients [1].

3. COPD and cardiovascular diseases

Cardiovascular diseases are major comorbidities in COPD and probably represent the most frequent and clinically important coexisting conditions. An accumulating body of evidence indicates that COPD is associated with CAD, CHF, hypertension, and cardiac arrhythmias, independently of shared risk factors [6–18]. In fact, the presence of COPD has been associated with angina (odds ratio: 1.61), CHF (odds ratio: 3.84), and arrhythmia (odds ratio: 1.76) after adjusting for known risk factors [6]. Apart from the common risk factors (advanced age, smoking, environmental pollutants, gender, and diet), it appears that multiple pathophysiologic abnormalities contribute to the development and progression of both COPD and CAD. However, it should be acknowledged that the evidence supporting these common pathways is weak while a cause–effect relationship cannot be easily established [4]. Roughly 30% of patients with stable COPD have some degree of HF [11], while worsening of HF is a significant cause of COPD exacerbations. The multivariable adjusted incidence of HF was higher in those with FEV1/forced vital capacity <70% vs. ≥70%: HR 1.44 (95% CI 1.20–1.74) among men and 1.40 (1.13–1.72) among women [12]. The pathophysiological mechanisms implicated in CHF development in COPD patients include CAD, lung hyperinflation, and cor pulmonale, with CAD being the most prominent cause [4]. On the other hand, hypertension seems to be the most prevalent comorbidity in COPD and may have significant prognostic implications [13]. It has also been shown that the prevalence of cardiac arrhythmias is increased in COPD [14]. MAT is almost exclusively associated with COPD [18] whereas other arrhythmias that have been associated with higher morbidity and mortality risk often occur in these patients. These include PACs, PVCs, AF, AFL, and VT [4]. In the ARIC study, after multivariable adjustment for traditional cardiovascular disease risk factors and height, hazard ratios of AF comparing the lowest with the highest quartile of FEV1 were 1.37 (95% CI, 1.02–1.83) for white women, 1.49 (95% CI, 1.16–1.91) for white men, 1.63 (95% CI, 1.00–2.66) for black women, and 2.36 (95% CI, 1.30–4.29) for black men [16]. In a recent study, Konency et al. reported that COPD was associated with increased likelihood of AF/AFL (23.3% vs 11.0%, respectively, $p < 0.0001$), nonsustained ventricular tachycardia (NSVT) (13.0% vs 5.9%, respectively, $p < 0.0001$), and sustained VT (1.6% vs 0.9%, respectively, $p < 0.0001$) compared to patients without COPD [19].

Of note, COPD patients seem to have a different burden of arrhythmia compared to CAD. The prevalence of AF in patients with stable CAD does not seem to be substantially higher than in populations without CAD (0.6%) [20], but in COPD patients the AF incidence reaches 11% [16]. For sustained VT, the overall incidence following MI is about 3% to 5% [21], while in COPD this incidence is 1.6% [19].

Cigarette smoking has also been implicated in the development of cardiac arrhythmias [22–25]. Chamberlain et al. assessed the risk of incident AF in relation to smoking status and amount in the ARIC study and reported that compared to never smokers, the multivariable-adjusted hazard ratios for AF were 1.32 (95% CI, 1.10–1.57) in former smokers and 2.05 (95% CI, 1.71–2.47) in current smokers [22]. Smoking was also found to be an independent predictor of AF or AFL recurrence after cardioversion in women, while an increased mortality risk, but not arrhythmia recurrence risk, was seen in men [26].

4. ECG abnormalities and arrhythmias in COPD

Numerous studies have reported ECG abnormalities and cardiac arrhythmias in COPD patients [6,14–17,19,27–43]. The ECG abnormalities associated with COPD include right atrial enlargement (P wave ≥0.25 mV in extremity leads or >0.15 mV in V1), vertical P-wave axis (P-axis >60°), right ventricular hypertrophy (R wave in lead V1 > 0.5 mV or R/S ratio in lead V1 > 1), marked clockwise rotation with poor R-wave progression, right bundle branch block (RBBB), left bundle branch block (LBBB), low voltage in limb leads (overall QRS ≤0.5 mV in all limb leads), S1S2S3 pattern (S waves in leads I, II, and III ≥0.15 mV in each lead), right axis deviation, left axis deviation [44], as well as ischemic changes (Q or QS pattern, ST junction and segment depression, and T-wave inversions) [36]. These abnormalities result mainly from the combination of 2 factors; namely pulmonary hypertension and anatomic changes. Pulmonary hypertension develops early in the course of the disease and causes hypertrophy and altered electrical conduction in the right ventricle. Also, hyperinflation causes a shift of the position of the heart in the thorax. Of note, conduction abnormalities occur late in COPD, after the right ventricle has hypertrophied to such an extent that its electrical forces overcome those of the left ventricle. When this abnormality ensues the QRS axis shifts rightward along with a vertical descent and clockwise rotation of the heart [44]. A vertical P-wave axis can be easily identified by an entirely inverted or dominantly negative P-wave in lead aVL or alternatively by a P-wave in lead III larger than the P-wave in lead II [45]. Interestingly, Baljepally et al. investigated vertical P-wave axis as a single criterion to screen for COPD in an adult hospital population and concluded that vertical P-wave axis can detect COPD with 89% sensitivity and 96% specificity [46]. It was recently indicated that a combination of vertical P-wave axis and narrow QRS (duration <75 ms) is associated with 100% specificity, but decreased sensitivity (33%) for COPD detection [45]. A recent cross-sectional study compared the differences in ECG characteristics between patients with and without COPD and demonstrated that conduction abnormalities were the most common ECG abnormalities in COPD patients [42]. It was also shown that mean heart rate was higher, and QTc prolongation was less prevalent in COPD patients [42].

MAT is a common heart rhythm disturbance in patients with COPD [47,48] while an exacerbation of COPD seems to be the most common triggering factor (18). With regard to AF, it has been consistently shown that FEV1 and FVC are inversely related with the arrhythmia independently of other factors such as age, gender, smoking, blood pressure, and body mass index [15–17]. In this context, it has recently been indicated that impaired pulmonary function, hypercapnia, and high values of pulmonary artery systolic pressure are independent predictors of incident AF [49]. The presence and severity of COPD are associated with increased likelihood of AF/AFL, NSVT, and sustained VT [19]. Remarkably, COPD remained a significant predictor of AF/AFL and NSVT after adjusting for age, gender, tobacco use, obesity, hypertension, CAD, HF, diabetes mellitus, anemia, cancer, chronic kidney disease, and rate/rhythm control medications [19]. It has also been reported that 21% of COPD patients have ischemic ECG changes while the prevalence of these changes in patients without self-reported cardiovascular comorbidities was 14% [36]. The markers that have been associated with COPD are summarized in Table 1. Also, a summary of the published studies reporting ECG abnormalities and cardiac arrhythmias in COPD is provided in the online Table 1.

Table 1
ECG markers associated with chronic obstructive lung disease.

1. S1S2S3 syndrome with R/S ratio <1 in limb leads I, II, and III
2. "P pulmonale" with P waves ≥2.5 mm in limb leads II, III, or aVF
3. Mean P wave axis ≥60° in the frontal plane
4. "Lead I sign" with an isoelectric P wave, QRS amplitude <1.5 mm, and T wave amplitude <0.5 mm
5. Mean QRS axis ≥90° in the frontal plane
6. Low voltage: QRS amplitude in limb leads ≤5 mm
7. QRS amplitude ≤5 mm in leads V5 and/or V6, or an R-wave ≤7 mm in lead V5, or ≤5 mm in lead V6
8. R/S ratio <1 in leads V5 and/or V6