Premature ventricular complex is more prevalent during acute exacerbated than stable state of chronic obstructive pulmonary disease, and related to cardiac troponin T

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Abstract

During acute exacerbation of chronic obstructive pulmonary disease (AECOPD), myocardial stress may be aggravated. Sparse data exist concerning the prevalence and correlates of cardiac arrhythmias in the stable and exacerbated state of COPD. We hypothesized that AECOPD is associated with increased prevalence of cardiac arrhythmias independent of COPD-severity and co-morbidity, and explored possible mechanisms.

A 24h Holter registration was collected in 74 patients with stable COPD and 45 patients with AECOPD (mean age 54y, 56% women). Any supraventricular tachycardia (SVT), frequent premature ventricular complex (PVC, >30/h) and complex ventricular ectopy (bigeminy, trigeminy or non-sustained ventricular tachycardia) were recorded and compared between the two groups. Adjustments were made for by stable disease-related co-variables (demography, co-morbidity, COPD-severity) and by acute disease-related co-variables (heart rate, cardiac troponin T (cTnT), P_{O_2} , P_{CO_2} and C-reactive protein (CRP)) in explorative analyses.

The prevalence of SVT, frequent PVC or complex ventricular ectopy were 40%, 27% and 33% in AECOPD, and 31%, 31% and 12% in stable COPD, respectively. Only frequent PVC was significantly increased in AECOPD compared to stable COPD, odds ratio 3.03 (1.03-10.5, $p=0.039$) when adjusted for stable disease-related co-variables. Higher heart rate, cTnT and CRP attenuate the association between AECOPD and frequent PVC to non-significant, while heart rate remains associated with frequent PVC.

In conclusion, frequent PVC is more prevalent in an exacerbated than in the stable state of COPD. Attenuation effects by cTnT, tachycardia and CRP suggest that cardiac stress or inflammation may be involved in the mechanisms for frequent PVC in AECOPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is the third most common cause of mortality in Western countries [1, 2]. Medical co-morbidities, such as cardiovascular diseases, contribute to the overall morbidity and mortality in patients with COPD [3, 4]. The patient phenotype characterized by frequent acute exacerbations of COPD (AECOPD) has recently received attention, as it may be associated with rapid progression of COPD as well as increased short-term mortality [5]. Cardiovascular co-morbidity may be of particular importance during AECOPD, and circulating biomarkers of cardiac disease such as cardiac troponins (cTn) have been reported to peak during AECOPD [6-9]. Still, the direct causes for cTn release are not fully understood [10].

Non-fatal cardiac tachyarrhythmia is another biomarker which in some, but not all, studies has been linked to increased risk of sudden cardiac death and death from cardiovascular causes [11-14]. Patients with COPD are often exposed to pro-arrhythmic factors such as hypoxemia, inflammation and drugs with chronotropic and pro-arrhythmic effects, particularly during AECOPD. Previously, the prevalence of atrial fibrillation/flutter and non-sustained ventricular tachycardia (NSVT) have been reported higher in patients with stable COPD compared to patients without COPD [15]. However, to our knowledge there are no studies comparing the prevalence of cardiac arrhythmias between AECOPD and stable COPD.

Accordingly, the primary aim of the present study was to test the hypothesis that the prevalence of cardiac arrhythmia is higher in patients during AECOPD than in patients with COPD in a stable state. Secondly, we sought to explore potential mechanisms associated with acute disease that may mediate any increased risk for arrhythmias.

Material and methods

Design and population

This was a cross-sectional study of patients with COPD (Figure 1). The patients were between 40 – 74 years of age, they had smoked at least 10 pack years, and they should have had spirometry at a stable state to verify airway obstruction within the last year. The index group consisted of 47 patients hospitalized at Akershus University Hospital due to AECOPD. On a daily basis between January and September 2010, one of the authors (VS) consecutively screened patients admitted to the bed ward at the Pulmonary Department for presence of AECOPD. According to the recommendations [2], patients with established COPD, ≥ 2 days of increase in either two of the symptoms dyspnea, cough, volume or colour of sputum and assessed by the clinician and VS as having AECOPD, were invited to participate in the study between the 3rd and 5th day of the admission. Exclusion criteria were reduced mental functioning or other psychiatric or somatic disease hindering obtainment of an informed consent.

The reference group consisted of 123 patients admitted to a pulmonary rehabilitation clinic (Glittre), further details have been reported previously [16]. The first 37 consecutive patients admitted to Glittre were not included in the current analysis due to technical problems (Figure 1).

Data collection

Cardiac arrhythmias: A 5-channel Holter recording (MedilogAR12, Oxford instruments Medical Ltd., Surrey, United Kingdom) was performed in 133 patients. The recordings were started in the evening, and had a mean recording length of 23.7h (standard deviation (SD) 3.3h). The digital recordings were interpreted by an automatic software engine (Medilog Darwin, ScanMed Medical, Gloucestershire, United Kingdom), and manually reviewed by

two researchers (GE and RB) blinded for participant data. Recordings with more than 30% artifacts (n=2 in index group, n=12 in the reference group) were excluded from further analyses (Figure 1). Episodes of atrial fibrillation, atrial flutter, atrial tachycardia or other supraventricular tachycardias with >3 complexes and $> 140 \text{ min}^{-1}$ were defined as supraventricular tachyarrhythmia. A single ventricular extrasystole (VES) was defined as any QRS-complex $>0.12\text{ms}$ with normal (N) QRS-complex before and after. In patients with known bundle branch block, a change in QRS-morphology and length was also considered of ventricular origin. Bigeminies and trigeminies were defined as ≥ 3 consecutive V-N or V-N-N couples, respectively. Ventricular tachycardia (VT) was defined as three or more consecutive V $>110\text{min}^{-1}$, NSVT if shorter than 30 seconds. All arrhythmias were coded as dichotomous outcomes (present or absent) according to previously used cutoffs (11).

Medical history, clinical examination and laboratory analyses: Age, sex, medical comorbidities body mass index and current medication (use of short and long-acting inhaled beta-adrenergic agonists, inhaled anticholinergic agents, inhaled corticosteroids, betablockers and oxygen) were recorded from patient interviews and medical records. History of hypertension and diabetes mellitus were self-reported diagnoses, while coronary heart disease (CHD) was defined as an established diagnosis of myocardial infarction, stable angina or previous coronary revascularization. Cumulative tobacco-exposure was noted as number of pack years. A standard spirometry was performed in the stable COPD group, and noted from a recent (<1 year) out-of-hospital visit in a stable state in the exacerbated group. Post-bronchodilatory forced vital capacity (FVC) and forced expiratory volume during 1st second (FEV_1) was registered, and the FEV_1/FVC -ratio was calculated. Left ventricular hypertrophy was assessed by the Sokolow-Lyon criteria on a standard 12-lead electrocardiography [17].

Regarding factors associated with acute disease, variables associated with cardiac stress, hypoxemia and systemic inflammation were recorded. Mean heart rate was calculated based

on the whole Holter-recording. High sensitivity (hs) cTnT was analyzed consecutively in the index group, while in the reference group, venous blood was sampled in the morning after the 24h Holter registration and the serum samples were frozen at -80 °C pending analysis. Hs-cTnT was analyzed at the Cobas Integra 400 with an enzymelinked immunoassay (Elecsys Troponin T hs STAT, Roche Diagnostics, Basel, Switzerland). The lower limit of normal is 5 ng/L, the lowest value with 10% variability and the upper 99% percentile in adult population is 14 ng/L. Arterial blood was obtained from a puncture of the radial artery at admission for both groups, and standard analyses of pO₂ and pCO₂ performed. Systemic inflammation was assessed by a high-sensitive assay of the venous concentration of C-reactive protein (CRP).

Statistical analyses

Prior to the study start, the sample size calculation assumed the expected median rate of VES/h is 5 in patients with TnT <0.04ug/L (old assay), and 10 in patients with TnT >0.04ug/L. With a 1:3 allocation of patients above and below these cut offs, $\alpha = 0.05$ and $1-\beta = 0.9$ is achievable for a total of 100 patients. Continuous and categorical data are reported as mean (SD) and number (%). Continuous data were tested for normality distribution by the Kolmogorov-Smirnov test, and log-transformed if not normally distributed. Comparisons between two groups were performed by t-tests, Mann-Whitney U-tests or Chi-Square tests, as appropriate.

Co-variates were separated into stable and acute disease-related. Only stable disease-related co-variates (age, sex, pack years, lung function, co-morbidity, body mass index, medication, left ventricular hypertrophy, oxygen treatment) were considered regarding the primary aim of the study, while acute disease-related co-variates (cTnT, heart rate, arterial blood gases and CRP) were considered in the explorative secondary aim of the study.

The primary aim was evaluated in three steps. First, we compared the prevalence of each type of arrhythmia between the stable COPD and the AECOPD group. Secondly, we compared the stable disease-related co-variables between the stable COPD and AECOPD group, and the co-variables that were associated with AECOPD having p-value ≤ 0.2 were then analyzed for univariate association with each of the arrhythmias. In the third step, multivariate logistic models adjusted for covariates that were associated with both AECOPD and arrhythmias were made for the arrhythmias that deviated significantly between the stable COPD and AECOPD groups.

For the purpose of assessing the second aim of the study, we used the Mantel-Haenszel test in stratified analyses by the acute disease-related co-variables that were associated ($p \leq 0.2$) with AECOPD. This was performed to assess possible confounding and effect modification of the association between AECOPD and arrhythmia by the acute disease-related co-variables, and to assess whether these co-variables caused meaningful changes in the association between AECOPD and arrhythmia. Finally, we made a second explorative multivariate model to assess the associations between arrhythmias and AECOPD *per se*, adjusted for the acute disease-related co-variables.

If not otherwise mentioned, a p-value < 0.05 in two-way analyses was regarded statistically significant. The statistical analyses were performed with the Statistical Package for Social Sciences (SPSS), version 20.0 (IBM, Chicago, IL) and Stata version 14.1 (StataCorp LP, TX77845).

Ethical considerations

The studies were approved by the regional ethical committee and signed consent was obtained from all participants before inclusion. The studies were conducted in accordance with the Declaration of Helsinki.

Results

Characteristics of the index group (n=45) and the reference group (n=74) are shown in Table 1. The AECOPD group was characterized by more prevalent CHD, more often use of beta-blocker and less use of long-acting beta-agonists than stable COPD patients. The patients with AECOPD also tended to have higher age, lower body mass index and lung function, less hypertension and were more often male sex than were stable COPD patients.

The number of patients with any supraventricular arrhythmia, frequent PVC or any complex ventricular ectopy were 41 (35 %), 21 (18 %) and 38 (32 %), respectively. Paroxysmal short supraventricular tachycardia (n=37) was more common than persistent atrial fibrillation or flutter (n=4). There were no VT's registered in any patients, while the overall prevalence of NSVT, bigeminies and trigeminies were 11 (12%), 12 (12%) and 18 (19%), respectively. The prevalence of supraventricular arrhythmias and ventricular ectopy according to COPD-state are shown in Figure 2. AECOPD was associated with frequent PVC (odds ratio (OR) 2.63, 95% confidence interval (CI) 1.01 – 6.86, p=0.049), while there were no associations between AECOPD and the presence of supraventricular arrhythmia or complex ventricular ectopy (OR (95% CI) 1.11 (0.50, 2.45) and 1.45 (0.68, 3.20) respectively).

The associations between stable co-variables and presence of frequent PVC are shown in Table 2. Subsequently, adjustments were made for sex, age, history of hypertension, history of CHD, body mass index, FVC, FEV₁ and use of beta-blockers or inhaled long-acting beta agonists in multivariate analyses (Table 2). Presence of AECOPD was still statistically significant associated with increased prevalence of frequent PVC.

Regarding acute disease-related variables, there were expectedly higher heart rate, higher concentrations of hs-cTnT, lower partial pressure of arterial oxygen and higher levels of systemic inflammation in the AECOPD-group than in the stable COPD group (Table 1). We

found no evidence of effect modification of the relationship between frequent PVC and AECOPD in any of these strata (p-value for test of homogeneity range: 0.332 to 0.429). However, the crude association between frequent PVC and AECOPD attenuated close to the zero effect after stratification by hs-cTnT (Table 3). A modest attenuation of the relationship between PVC and AECOPD was also found by heart rate and CRP, but not by hypercapnia or hypoxemia. Thus, the multivariate adjusted model containing acute-related co-variables expectantly shows no statistically significant association between frequent PVC and AECOPD (Table 4). This model showed a consistent association between the prevalence of frequent PVC and increasing heart rate, whereas the dose-response slope between the prevalence of frequent PVC and hs-cTnT as well as CRP attenuated to non-significant relationships.

Discussion

In the present study supraventricular and asymptomatic ventricular arrhythmias were commonly identified among COPD-patients. While frequent PVC was the only type of arrhythmia that was more prevalent during AECOPD than in stable COPD, this association attenuated to the zero effect after adjustment for heart rate, hs-cTnT and CRP.

As we were not aware of previous studies considering cardiac arrhythmias in the setting of AECOPD, we tested the hypothesis that supraventricular and ventricular arrhythmias were more prevalent in the exacerbated than in the stable state of COPD. The most direct clinical relevance of recording cardiac arrhythmias in AECOPD may be to diagnose arrhythmias causing symptoms or circulatory collapse, such as persistent rapid atrial fibrillation or sustained VT. This was not reported in our study.

Another rationale for performing the current study, was to assess the prevalence of cardiac arrhythmia as a cardiac biomarker in COPD patients, and to explore potential mechanisms related to the arrhythmia during acute disease. Although still debated in patients with established heart disease, a recent population-based study suggest that ventricular ectopy is associated with increased mortality and incidence of heart failure [14]. In the current study both supraventricular tachyarrhythmia and complex ventricular ectopic activity were observed in more than 1/3 of patients with COPD during a 24 h Holter-registration. This is a higher prevalence than in general population-based studies and more similar with patients at high cardiovascular risk, i.e. post-myocardial infarction patients [12, 18, 19].

Furthermore, we found that frequent PVC, but not supraventricular tachyarrhythmia or complex ventricular arrhythmia, were more prevalent in AECOPD than in stable COPD, adjusted for medical history, medication and COPD-severity. The preferred design for

comparing cardiac arrhythmias during acute and stable phases would be longitudinal studies with repeated measurements. In the current cross-sectional design, we cannot exclude that patients in the AECOPD represent another phenotype of COPD than patients in the stable group. However, statistical adjustment by demographic factors and COPD-severity in the stable phase in both groups was made. Thus, the pathophysiologic effects by acute disease are the main difference between the groups.

In contrast to our previous analysis of the effect by AECOPD on the cardiac biomarker cTnT [8], AECOPD was not associated with frequent PVC when adjusted for indicators of the acute disease. Foremost, serum concentrations of hs-cTnT, but also higher average heart rate during 24h observation and CRP attenuated the effect by AECOPD on frequent PVC to non-significant. These factors indicate various pathophysiological mechanisms such as myocardial damage, higher sympathetic activity and inflammation, respectively, in which all may aggravate ventricular ectopy. Interestingly, in a different cohort of patients hospitalized for AECOPD, we found that the combination of tachycardia and cTnT elevation was associated with increased mortality [5]. Thus, prospective analyses of ventricular ectopy during AECOPD as biomarker for future cardiovascular events and mortality may be merited.

Besides the cross-sectional design, another limitation is the moderate sample size, which increases the risk for type II errors, particularly with the use of dichotomous variables. Other factors not accounted for in the present analyses could have influenced the prevalence of arrhythmias. Particularly, an indicator of myocardial function, such as N-terminal pro-B-type natriuretic peptide or ejection fraction would be relevant. There might also be random effects by day-to-day variability in physical activity and psychological stress during the Holter registrations.

In conclusion, we found that patients with COPD have a higher prevalence of frequent PVC during the exacerbated state than in the stable phase. Attenuation effects of this association by cTnT, tachycardia and CRP indicate that subclinical myocardial damage, sympathetic activity and systemic inflammation are involved in pro-arrhythmic effects during AECOPD.

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Declaration of interest:

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Figure legends

Figure 1. Study flow and patient recruitment.

Figure 2. Prevalence in % of cardiac arrhythmias in patients with stable COPD (n=75) and patients with acute exacerbation of COPD (n=45).

Table 1. Comparisons of demographic, clinical and biochemical variables between stable COPD patients and patients hospitalized for AECOPD.

	Stable COPD (n=74)	AECOPD (n=45)	p-value*
Stable disease-related co-variates			
Age, years (SD)	64 (7)	66 (7)	0.076
Female, n (%)	46 (62)	21 (47)	0.098
History of coronary heart disease, n (%)	5 (7)	11 (24)	0.011
History of hypertension, n (%)	31 (42)	13 (29)	0.154
History of diabetes mellitus, n (%)	3 (4)	3 (7)	0.672
Tobacco packyears (SD)	42 (10)	41 (16)	0.658
Long-term oxygen treatment, n (%)	9 (12)	7 (16)	0.599
Use of beta-blocker, n (%)	7 (10)	18 (40)	<0.001
Use of LABA, n (%)	67 (92)	33 (73)	0.007
Use of inhaled anticholinergic, n (%)	13 (19)	41 (91)	<0.001
Use of inhaled corticosteroid, n (%)	56 (80)	33 (73)	0.404
FVC, L (SD)	2.5 (1.1)	2.1 (0.7)	0.078
FEV ₁ , L (SD)	1.1 (0.5)	0.9 (0.4)	0.045
FEV ₁ /FVC, % (SD)	45 (11)	41 (12)	0.126
Body mass index, kg/m ² (SD)	25.0 (5.9)	23.2 (5.6)	0.128
Left ventricular hypertrophy, n (%)	2 (3)	0 (0)	0.523
Acute disease-related co-variates			
Average heart rate, min ⁻¹ (SD)	84 (10)	90 (13)	0.004
Cardiac troponin T, n (%)			< 0.001
<5 ng/L	48 (65)	4 (9)	
5-14 ng/L	13 (18)	6 (13)	
>14 ng/L	13 (18)	35 (78)	
pO ₂ , kPa (SD)	8.9 (1.3)	8.1 (1.8)	0.012
pCO ₂ , kPa (SD)	5.6 (5.1-6.4)	5.9 (5.2-7.2)	0.058
C-reactive protein, mg/L (SD)	2.5 (1.4-5.1)	40 (14-100)	<0.001

*p-values from t-tests or chi-square-tests, as appropriate. AE, acute exacerbation; COPD, chronic obstructive pulmonary disorder; FEV₁, forced expiratory volume during 1st second; FVC, forced vital capacity; LABA, long-acting betaagonists; SD, standard deviation.

Table 2. Univariate* and multivariate adjusted OR for frequent PVC during 24h Holter registration (n=119).

	Descriptive data		Univariate analyses		Multivariate analyses	
	PVC >30/h	PVC <30/h	OR (95% CI)	p	OR (95% CI)	p
AECOPD	12 (57)	33 (34)	2.63 (1.01-6.86)	0.049	3.28 (1.04-10.4)	0.043
Age, years (SD)	65 (8)	64 (7)	1.01 (0.95-1.08)	0.746	1.00 (0.93-1.08)	0.964
Female, n (%)	13 (62)	54 (55)	1.32 (0.50-3.48)	0.569	1.66 (0.56-4.96)	0.361
History of CHD, n (%)	1 (5)	15 (15)	0.28 (0.03-2.22)	0.226	0.16 (0.02-1.46)	0.104
History of hypertension, n (%)	6 (29)	38 (39)	0.63 (0.23-1.77)	0.382	0.54 (0.16-1.80)	0.316
Use of betablocker, n (%)	5 (24)	20 (21)	1.20 (0.39-3.68)	0.746	1.30 (0.34-4.98)	0.704
Use of inhaled LABA, n (%)	17 (81)	83 (86)	0.72 (0.21-2.45)	0.595	1.03 (0.27-3.91)	0.968
FVC, L (SD)	2.3 (0.7)	2.3 (1.0)	0.90 (0.54-1.52)	0.702	0.97 (0.39-2.42)	0.952
FEV ₁ , L (SD)	1.0 (0.5)	1.0 (0.5)	0.79 (0.29-2.15)	0.646	1.30 (0.19-8.89)	0.787
FEV ₁ /FVC, % (SD)	43 (11)	44 (11)	0.99 (0.95-1.04)	0.756	Not included	
Body mass index (SD)	24.0 (5.3)	24.3 (6.0)	0.99 (0.91-1.08)	0.822	1.00 (0.90-1.11)	0.981

* Stable disease-related co-variables associated (p-value <0.2) with AECOPD are shown.

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CHD, coronary heart disease; CI, confidence interval; FEV₁, forced expiratory volume during 1st second; FVC, forced vital capacity; LABA, long-acting betaagonist; OR, odds ratio; PVC, premature ventricular complex; SD, standard deviation.

Table 3. Bivariate analysis of the prevalence (%) of frequent PVC among COPD patients in their stable state compared with COPD patients during exacerbation, stratified by covariates of exacerbation severity.

Covariate	PVC $\geq$ 30 /h		Prevalence ratio (95% CI)	
	Stable	AECOPD	Crude	Adjusted
None	9 (13)	12 (27)	2.2 (1.0 – 4.8)	-
hs-cTnT, ng/L				1.1 (0.45 – 2.8)
< 5	3 (6)	1 (25)	4.2 (0.6 – 31.4)	-
5 – 13	3 (23)	0 (0)	0.0 (0.0 – 1.1)	-
$\geq$ 14	3 (23)	11 (31)	1.4 (0.5 – 4.1)	-
Heart rate, 1/min				1.7 (0.72 – 4.2)
< 80	1 (4)	1 (9)	2.2 (0.2 – 31.8)	-
80 - 99	7 (15)	5 (23)	1.4 (0.5 – 4.2)	-
$\geq$ 100	1 (25)	6 (50)	2.0 (0.3– 12.0)	-
pO ₂ , kPa				2.2 (1.1 – 4.6)
> 8.0	6 (11)	8 (31)	2.2 (1.2 – 6.6)	-
< 8.0	3 (17)	4 (22)	1.4 (0.4 – 5.4)	-
pCO ₂ , kPa				2.1 (0.98 – 4.6)
< 6.3	5 (10)	4 (15)	1.5 (0.4 – 5.1)	-
$\geq$ 6.3	4 (17)	8 (53)	2.8 (1.0 – 7.9)	-
C-reactive protein, mg/L				1.6 (0.64 – 4.1)
< 5	6 (11)	2 (40)	3.7 (0.99 – 13.6)	-
5 – 19	2 (13)	1 (14)	1.1 (0.12 – 10.6)	-
$\geq$ 20	1 (33)	9 (27)	.82 (0.15 – 4.5)	-

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; PVC, premature ventricular complex; cTnT, cardiac troponin T.

Table 4. Unadjusted and adjusted* odds ratio of frequent PVC by AECOPD using logistic regression.

Covariate	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
AECOPD, yes vs. no	2.6 (1.0 – 6.7)	1.0 (0.21 – 5.01)
p-value	0.049	0.966
Hs-cTnT, ng/L		
< 5		1
5 – 13		3.6 (0.6 – 20.7)
≥ 14		2.6 (0.6 – 12.0)
p- trend		0.194
Heart rate, min ⁻¹		
< 80		1
80 – 99		3.1 (0.6 – 15.9)
≥ 100		8.6 (1.3 – 59.1)
p- trend		0.036
pCO ₂ ≥ 6.3 kPa, yes vs. no		3.0 (0.9 – 9.9)
p-value		0.071
Hs-C-reactive protein, mg/L		
< 5		1
5 – 19		0.6 (0.1 – 3.0)
≥ 20		1.6 (0.3 – 8.8)
p- trend		0.635

* Acute disease-related co-variables associated (p-value <0.2) with AECOPD are shown.

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; Hs, high-sensitivity; PVC, premature ventricular complex; cTnT, cardiac troponin T.