Atrial and Ventricular Arrhythmia-Associated Factors in Stable Patients with Chronic Obstructive Pulmonary Disease

Yuji Kusunoki^{a, b} Toshie Nakamura^b Kumiko Hattori^{a, b} Takashi Motegi^{a, b}
Takeo Ishii^{a, b} Akihiko Gemma^a Kozui Kida^{a, b}

^aRespiratory Care Clinic, and ^bDepartment of Pulmonary Medicine, Infection, and Oncology, Nippon Medical School, Tokyo, Japan

Key Words

Chronic obstructive pulmonary disease · Arrhythmia · Bronchodilator · Multidimensional assessments

Abstract

Background: Supraventricular and ventricular premature complexes (SVPC and VPC, respectively) are associated with chronic obstructive pulmonary disease (COPD) and with increased mortality in COPD patients. However, there are few reports on the causes of arrhythmia in COPD patients. **Objectives:** This study explores the associations between cardio-pulmonary dysfunction and COPD by comparing patients with defined arrhythmias (>100 beats per 24 h) and those without, based on 24-hour electrocardiogram (ECG) recordings. **Methods:** Patients with arrhythmia underwent a 24-hour ECG and subsequent pulmonary function tests, computed tomography, ECG, 6-min walk test (6MWT), and BODE (body mass index, airflow obstruction, modified Medical Research Council Dyspnoea Scale, exercise capacity) index calculation. **Results:** Of 103 study patients (71 COPD patients and 32 at-risk patients), 36 had VPC, 45 had SVPC, 20 had both, and 42 had neither. The predicted post-bronchodilator forced expiratory volume in 1 s, the proportion of low-atten-

uation area on computed tomography, and BODE index values were significantly worse in the SVPC and VPC groups compared with the corresponding reference groups. Patients in the VPC group showed significantly increased right ventricular pressure and increased desaturation in the 6MWT compared with the reference group. In the multivariate analyses, bronchodilator use was a significant risk factor in the SVPC group, whereas in the VPC group, all parameters of the BODE index except for the dyspnoea score were identified as risk factors. **Conclusions:** Increased SVPC might be caused by bronchodilator use, whereas increased VPC is likely related to the peculiar pathophysiology of COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in both developed and developing countries [1]. Large studies have shown that cardiovascular events are a leading cause of COPD-related mortality [2, 3], and there is limited evidence suggesting that some of these events may be partly caused by arrhythmias [4]. Multifocal arterial tachycar-

dia, arterial fibrillation, or ventricular arrhythmias are common comorbidities in patients with COPD [5], and atrial or ventricular rhythm disorders can occur in patients with both stable [5] or exacerbated COPD [6, 7] and may increase the incidence of sudden death in such patients [6, 7].

The estimated prevalence of arrhythmias in COPD patients is 12–14% [8, 9]. COPD and arrhythmias have common risk factors, such as older age and smoking, and arrhythmias may be caused by other comorbidities, including coronary heart disease, hypertensive heart disease, right and/or left ventricular failure, hypokalaemia and hypomagnesaemia, digoxin, or macrolide antibiotics [10]. Despite reports of ischaemic heart disease during bronchodilation, and smoking interaction in COPD, there have been no reports on arrhythmias [11]. Especially, arrhythmias caused by bronchodilators have received considerable attention; recently, to avoid fatal arrhythmia, critical warnings have been made when administering bronchodilators to patients with bronchial asthma and COPD [12–14]. Theophylline is a commonly prescribed methylxanthine bronchodilator that has a variety of effects on the cardiac rate and rhythm at therapeutic or toxic concentrations [15], and inhalation of salbutamol results in significant spontaneous arrhythmias [16]. Furthermore, a recent study indicated that newly prescribed long-acting inhaled β -agonists (LABAs) and anticholinergics (long-acting muscarinic antagonists; LAMAs) are associated with cardiovascular events [14], and, indeed, both LABAs and LAMAs are known causal factors for arrhythmias [17–19]. Particularly, LABAs have been associated with serious adverse outcomes in asthma patients, such as hospitalization, need for intubation, and even death [12]. With this background information, in 2010, the US Food and Drug Administration (FDA) sought to improve the safety of LABAs by issuing a requirement for manufactures of products containing LABAs [12]. On the other hand, several researchers have disputed the adverse effects of LAMAs. Dong et al. [20] reported that the tiotropium Respimat Soft Mist inhaler was associated with a higher risk of mortality than the tiotropium HandiHaler, and should hence be used with caution; however, this finding has been disputed [21]. Another study found that tiotropium Respimat has a safety profile and exacerbation efficacy similar to that of the tiotropium HandiHaler [22]. Taken together, these previous findings suggest that arrhythmias in patients with COPD are complex and require more detailed investigation.

In this study, we hypothesized that most clinically significant arrhythmias, both supraventricular and ventric-

ular premature complexes (SVPC and VPC), can be monitored using a 24-hour Holter electrocardiogram (ECG) in stable patients with COPD, and aimed to study the effects of bronchodilators and the pathophysiology of COPD, both at rest and during exercise.

Preliminary results have previously been reported in abstract form at the annual congress of the European Respiratory Society in 2014.

Materials and Methods

Patients

In this prospective cohort study, we recruited patients between February 2010 and March 2013 at the Respiratory Care Clinic, which is a secondary referral facility affiliated with the Nippon Medical School in Tokyo, Japan.

We recruited patients with a lifelong history of smoking and current symptoms of dyspnoea during exertion, prolonged coughing, and/or sputum. Subjects were diagnosed with COPD according to a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <0.70 , as indicated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [23]. Subjects not meeting the COPD criteria were classified into the ‘at-risk’ group. All patients were stable for at least the 3 previous months, without episodes of exacerbations. As a screening test, all patients underwent ECG, and those with any type of arrhythmia on a single ECG or those experiencing any symptoms suggestive of arrhythmias at the initial visits received 24-hour ECG Holter monitoring (see below). The exclusion criteria are provided in detail in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000442447).

This study was approved by the Ethics Committee of the Nippon Medical School (approval No.: 18-11-31), and informed consent was obtained from all participants before enrolment.

Study Design

Comorbidities

Major comorbidities were studied, including hypertension, dyslipidaemia, diabetes mellitus, and medications for pulmonary disease and the comorbidity itself. Patients with congestive heart failure were excluded.

Multidimensional Assessments

The BODE index (body mass index, airflow obstruction, modified Medical Research Council Dyspnoea Scale, exercise capacity) was assessed using the appropriate parameters [24].

Examinations

Detailed information is provided in the online supplementary material.

Twenty-Four-Hour ECG

Holter ECG was performed using the RAC-3103 (NIHON KODEN, Japan) system. ECG data were recorded during normal activities in the daily life setting of each patient. Holter Soft (DSC3300, NIHON KODEN, Japan) was used to automatically analyse the collected ECG data. The VPC and SVPC groups in-

Table 1. Baseline characteristics of the study patients

Age, years	68.8 ± 10.7
Male sex, n (%)	90 (87.4)
Body mass index	23.4 ± 3.52
Smoking history	
Current smoker, n (%)	21 (20.4)
Pack-year (n = 81)	61.6 ± 34.6
mMRC	0.91 ± 1.03
BODE index	1.59 ± 1.67
Comorbidities, n (%)	
Hypertension	54 (52.4)
Hyperlipidaemia	34 (33.3)
Diabetes mellitus	8 (7.7)
PFT	
FVC, liters	3.23 ± 0.89
FEV ₁ , liters	2.01 ± 0.87
Ratio of FEV ₁ to FVC, %	61.0 ± 16.1
FEV ₁ , % predicted	72.0 ± 24.0
%DLCO/VA	71.7 ± 26.1
6MWT	
Distance, m	478.6 ± 107.2
Minimum SpO ₂ , %	90.6 ± 5.41
Borg scale	3.11 ± 2.14
Chest computed tomography	
LAA%	23.4 ± 14.6
Echocardiography	
RVP, mm Hg	35.5 ± 7.93
Blood sampling data	
hs-CRP, mg/dl	0.367 ± 1.23
BNP, pg/ml	30.63 ± 43.4

Data are presented as mean ± standard deviation, unless otherwise stated. mMRC = Modified Medical Research Council dyspnoea scale; PFT = pulmonary function test; DLCO = carbon monoxide diffusing capacity of the lung; VA = alveolar volume; RVP = right ventricular pressure; hs-CRP = high-sensitive C-reactive protein; BNP = brain natriuretic peptide.

cluded subjects with over 100 beats recorded per 24 h, and the remaining patients were assigned to the reference group.

Pulmonary Function Tests

The tests were performed according to the American Thoracic Society guidelines [25], and the standards of the Japanese Respiratory Society [26] were used as the reference values for post-bronchodilator FEV₁ and FVC. The diagnosis and classification of COPD was based on the GOLD criteria [23].

Arterial Blood Gas Analysis

Arterial blood gas measurements were obtained while the patients were in a neutral spine position breathing room air, within 10 min after blood sampling.

High-Resolution Computed Tomography Parameters

The proportion of low-attenuation area (LAA%) for the overall mean values obtained from the upper, middle, and lower lungs on both the right and left sides was calculated as previously reported [27].

Six-Minute Walk Test

The 6-min walk test (6MWT) was performed in accordance with the American Thoracic Society guidelines [28], and the reduction in oxygen saturation between at rest and the minimum value was measured during the test.

Echocardiography

Echocardiography was performed using a diagnostic ultrasound system (Aplio SSA-770A; Toshiba Medical Systems Co., Japan) with a 2.5-MHz transducer while the patients were in a left lateral recumbent position.

Blood Chemistry

Measurements including high-sensitive C-reactive protein and brain natriuretic peptide were performed.

Statistical Analysis

Categorical variables are described as frequencies and percentages and continuous variables as mean ± standard deviation. Analysis of variance and the χ^2 test were used to compare each variable between the groups. Logistic regression was performed to determine cross-sectional associations between patients with SVPC or VPC and each reference group. We tested the significance of the interaction between SVPC or VPC and each variable at the time of the examinations by adding the interaction term to a model containing both main effects and compared the number of patients with SVPC or VPC with a model containing only the main effect. In the absence of significant interactions, each variable of interest was examined using univariate analysis (see online suppl. material), and variables that were significant at the 0.05 level were included in a multivariable model. All analyses were conducted using JMP9 software (SAS Institute Inc., Cary, N.C., USA). All p values are two-sided, and a p value of <0.05 was considered statistically significant.

Results

A total of 103 patients were studied. The basic characteristics of the patients are shown in table 1. Seventy-one patients had COPD, and 32 were deemed at risk of COPD. The patients in the former group were classified as GOLD stage (2004) I (n = 18; 17.5%), II (n = 29; 28.2%), III (n = 20; 19.4%), and IV (n = 4; 3.9%). The study patients had an overall mean age of 68.8 ± 10.7 years and were predominantly male (87.4%). The number of patients with VPC, SVPC, and both was 36 (35.0%), 45 (43.7%), and 20 (19.4%), respectively. Forty-two patients showed no sign of SVPC or VPC. The major comorbidities were hypertension (52.4%), hyperlipidaemia (33.3%), and diabetes

Fig. 1. Prevalence of VPC (left) and SVPC (right) at various stages (**a**) and grades (**b**) of COPD. The prevalence of VPC increased in parallel with increasing COPD severity. Note that stage IV showed the highest prevalence of both SVPC and PVC.

mellitus (7.7%) (see online suppl. material for more detailed information). The overall number of patients prescribed LAMAs, LABAs, and theophylline was 56 (54.3%), 66 (64%), and 19 (18.4%), respectively (see the online suppl. material for more detailed information). The BODE index was significantly increased in both the VPC and SVPC groups compared with those of each reference group [VPC group: odds ratio (OR) 1.57, 95% confidence interval (CI) 1.20–2.13, $p < 0.0006$; SVPC group: OR 1.72, 95% CI 1.28–2.42, $p < 0.0001$]. Both the SVPC and VPC groups showed a significantly increased prevalence of

COPD with advancing GOLD stages (fig. 1). The correlation coefficients of various factors with the VPC and non-VPC groups, and with the SVPC and non-SVPC groups are shown in tables 2 and 3, respectively. There were significant negative correlations between reduced FEV₁/FVC predicted values and both VPC (OR 0.96, 95% CI 0.95–0.98, $p < 0.0001$; table 2) and SVPC (OR 0.97, 95% CI 0.95–0.99, $p < 0.0006$; table 3). Increased LAA% showed a significant positive correlation with both VPC (OR 1.04, 95% CI 1.01–1.08, $p < 0.003$) and SVPC (OR 1.03, 95% CI 1.00–1.06, $p < 0.03$). Increased right ven-

Table 2. Factors associated with PVC

	PVC group	Non-PVC group	OR	95% CI	p value
Age, years	73.8±9.95	66.2±10.18	1.08	1.04–1.15	0.0003
Body mass index	21.9±3.08	24.2±3.50	0.80	0.70–0.91	0.0009
mMRC	1.08±1.02	0.82±1.03	1.28	0.86–1.90	0.2
BODE index	2.36±1.85	1.18±1.41	1.57	1.20–2.13	0.0006
Comorbidities					
Hypertension, %	38.9	59.7	0.42	0.18–0.97	0.04
PFT					
FVC, liters	2.84±0.78	3.44±0.87	0.38	0.20–0.67	0.0005
FEV ₁ , liters	1.58±0.78	2.25±0.83	0.32	0.16–0.57	0.0001
Ratio of FEV ₁ to FVC, %	53.7±17.4	64.8±14.0	0.96	0.93–0.98	0.0007
FEV ₁ , % predicted	59.8±24.8	78.6±21.0	0.96	0.95–0.98	0.0001
%DLCO/VA	60.2±28.9	77.9±22.4	0.97	0.95–0.99	0.0007
6MWT					
Distance, m	412.6±103.5	514.2±91.9	0.99	0.98–0.99	0.0001
Minimum SpO ₂ , %	88.6±6.45	91.8±4.40	0.90	0.82–0.97	0.005
Borg scale	3.69±2.12	2.80±2.10	1.22	1.01–1.49	0.04
Chest computed tomography					
LAA%	29.3±16.5	20.3±12.6	1.04	1.01–1.08	0.003
Echocardiography					
RVP, mm Hg	38.7±9.68	33.8±6.23	1.09	1.03–1.17	0.003
ABG					
PaCO ₂ , mm Hg	40.6±5.10	40.6±3.32	1.002	0.90–1.12	0.9
PaO ₂ , mm Hg	80.8±11.82	83.2±9.37	0.98	0.93–1.02	0.3
Pulmonary medications					
Bronchodilator use, %	77.8	65.7	1.83	0.25–1.35	0.2
LAMA, %	61.1	50.7	1.53	0.67–3.52	0.3
LABA, %	75.0	58.2	2.15	0.90–5.50	0.08
Theophylline, %	22.2	16.4	1.45	0.51–4.01	0.5

mMRC = Modified Medical Research Council dyspnoea scale; PFT = pulmonary function test; DLCO = carbon monoxide diffusing capacity of the lung; VA = alveolar volume; RVP = right ventricular pressure; ABG = arterial blood gases; PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension.

tricular pressure significantly correlated with VPC (OR 1.09, 95% CI 1.03–1.17, $p < 0.003$), and the degree of desaturation in the 6MWT negatively correlated with VPC (OR 0.90, 95% CI 0.82–0.97, $p < 0.005$).

Figure 2 shows the prevalence of VPC and SVPC according to the use of 3 different bronchodilators. Significant correlations between the use of the 3 different bronchodilators and SVPC were observed (LAMA: OR 3.49, 95% CI 1.55–8.20, $p < 0.002$; LABA: OR 3.73, 95% CI 1.57–9.53, $p < 0.003$, and theophylline: OR 4.79, 95% CI 1.66–16.00, $p < 0.003$); on the other hand, no correlation was observed for VPC. In the multivariate analyses, in the SVPC group, bronchodilator use was found to be a signif-

icant independent risk factor (OR 3.472, 95% CI 1.17–11.50, $p = 0.02$), whereas significant risk factors in the VPC group included decreased body mass index (OR 0.737, 95% CI 0.59–0.90, $p = 0.002$), FEV₁/FVC predicted (OR 0.963, 95% CI 0.93–0.999, $p = 0.04$), and 6MWT distance (OR 0.991, 95% CI 0.98–0.999, $p = 0.03$; online suppl. material).

Discussion

Interpretation of the Findings

In this study, we found that COPD, SVPC, and VPC were caused by different mechanisms in patients with or

Table 3. Factors associated with SVPC

	SVPC group	Non-SVPC group	OR	95% CI	p value
Age, years	73.4±9.06	65.3±10.56	1.09	1.04–1.15	0.0001
Body mass index	22.9±3.46	23.8±3.56	0.93	0.83–1.04	0.2
mMRC	1.18±1.11	0.71±0.92	1.59	1.07–2.43	0.02
BODE index	2.29±1.95	1.05±1.18	1.72	1.28–2.42	<0.0001
Comorbidities					
Hypertension, %	46.7	56.9	0.66	0.30–1.45	0.3
PFT					
FVC, liters	2.90±0.69	3.49±0.94	0.40	0.22–0.68	0.0004
FEV ₁ , liters	1.62±0.67	2.32±0.90	0.31	0.16–0.55	0.0001
Ratio of FEV ₁ to FVC, %	55.5±17.4	65.2±13.7	0.96	0.93–0.99	0.002
FEV ₁ , % predicted	63.0±24.0	79.1±21.8	0.97	0.95–0.99	0.0006
%DLCO/VA	67.2±28.2	75.2±24.1	0.99	0.972–1.003	0.1
6MWT					
Distance, m	437.1±109.1	511.0±94.8	0.99	0.988–0.997	0.0003
Minimum SpO ₂ , %	89.8±5.38	91.3±5.39	0.95	0.88–1.02	0.2
Borg scale	3.32±2.15	2.95±2.14	1.09	0.90–1.31	0.4
Chest computed tomography					
LAA%	26.9±15.9	20.8±13.2	1.03	1.00–1.06	0.03
Echocardiography					
RVP, mm Hg	36.7±8.54	34.5±7.34	1.04	0.98–1.10	0.2
ABG					
PaCO ₂ , mm Hg	40.2±4.60	40.9±3.41	0.96	0.86–1.07	0.4
PaO ₂ , mm Hg	80.7±12.1	83.8±8.30	0.97	0.93–1.01	0.2
Pulmonary medications					
Bronchodilator use, %	86.7	56.9	4.92	1.90–14.57	0.0007
LAMA, %	71.1	41.4	3.49	1.55–8.20	0.002
LABA, %	80.0	51.7	3.73	1.57–9.53	0.003
Theophylline, %	31.1	8.6	4.79	1.66–16.00	0.003

mMRC = Modified Medical Research Council dyspnoea scale; PFT = pulmonary function test; DLCO = carbon monoxide diffusing capacity of the lung; VA = alveolar volume; RVP = right ventricular pressure; ABG = arterial blood gases; PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension.

those at risk of these conditions. VPC was associated with pathophysiological variables, such as airflow obstruction, hypoxaemia, severity of emphysema, right atrial or ventricular pressure overload, and prescribed bronchodilators, whereas bronchodilator appeared to be associated with SVPC.

To our knowledge, this is the first study primarily designed to investigate the close association between VPC or SVPC and the pathophysiology of COPD.

Parameters Associated with VPC

Shih et al. [6] reported that VPC and non-sustained ventricular tachycardia were present in 83 and 22% of the

hypoxaemic patients with severe but stable COPD who underwent continuous ECG recordings, respectively. In our study, the prevalence of VPC in patients with COPD was consistent with those of previous observations, despite our use of a different study design. The present study included patients with arrhythmias on a 12-lead ECG or with chest symptoms such as palpitations, who were subsequently studied using 24-hour ECG. However, our finding that the prevalence of VPC increased in parallel with deteriorating COPD pathophysiology, including worsening of airflow obstruction, increased LAA%, and increased hypoxaemia during 6MWT, has not been reported previously. Hypoxaemia at rest or during exercise

Fig. 2. Prevalence of VPC (left) and SVPC (right) among three bronchodilators. No significant differences were observed in the VPC group; however, significant differences were observed in SVPC prevalence between patients who used bronchodilators and those who did not.

was suspected to cause these arrhythmias. We hypothesize that increased accumulation of hypoxaemic cardiac tissue, which cannot be measured by arterial blood gas analysis, is a causal factor for VPC or SVPC. In this regard, whether long-term oxygen therapy might reduce the prevalence of VPC in COPD patients with higher or mild hypoxaemia and can be used as a therapeutic option in clinical practice needs further study. Interestingly, the BODE index was closely associated with VPC, a finding that was further supported by the multivariate analysis (except for the dyspnoea score). The BODE index has been shown to be a better predictor of survival than the degree of airway obstruction [24], and this index predicts hospitalization [29], response to interventions such as lung volume reduction surgery [30] and pulmonary rehabilitation [31], and reflects well on health status [29]. Our observation might further illustrate the value of multidimensional assessment using the BODE index in terms of risk analysis for VPC, which is likely associated with fatal arrhythmias in patients with severe COPD.

Parameters Associated with SVPC

In a previous cohort of 1,429 patients with COPD who had undergone Holter ECG, up to 40% of the patients had atrial tachycardias in the absence of on-going treatment with LABAs [17]. More recently, Konecny et al. [5], in an epidemiological study, evaluated atrial and ventricular arrhythmias in COPD patients using 24-hour ECG mon-

itoring in a large cohort. They clarified the independent association between the presence and severity of COPD and arrhythmias; however, their study design differed from that of the present study, as our study was based on detailed examinations of patients with COPD who used prescribed bronchodilators. In our study, SVPC increased along with increasing COPD severity. Moreover, multivariate analysis suggested that the administration of bronchodilators, including LABAs and/or LAMAs, might cause SVPC. While we were unable to determine whether bronchodilator(s), LABAs, or LAMAs might be the stronger causal factor in this case, the results suggest a close association between the severity of COPD and the prevalence of SVPC and VPC. Randomized controlled trials for LABAs and LAMAs were initiated by the US FDA in 2011, and the results (which are expected in 2017) will help to clarify this issue [12]. Studies of each LAMA- and LABA-containing product will also be needed.

There are several limitations to our study. The number of patients enrolled was small, and most patients were referred to our clinic. Moreover, the cohort mainly consisted of patients with mild or moderate airflow obstruction. The population was selected based on ECG alterations or symptoms suggesting the presence of arrhythmias. Therefore, there is the possibility of a bias. Clearly, additional studies using larger samples of patients with various disease severities are required. Lastly, our study focused on two major arrhythmias, i.e. VPC and SVPC;

however, various other types of arrhythmias may occur in patients with COPD, and therefore, further studies are needed.

Clinical Application

The present study suggests that the occurrence of frequent VPC or SVPC increases as the severity of COPD progresses, and it has been demonstrated that the use of LABAs or LAMAs increases the risk of fatal arrhythmias, even in mild COPD. Thus, unless there are obvious indications for the use of these drugs in these patients, the administration of LABAs and LAMAs should be carefully considered in terms of both their advantages and disadvantages.

Finally, 24-hour Holter ECG is a useful tool, which is superior for detecting arrhythmias occurring during the

activities of daily living (including sleep), and the frequency of VPC might reflect the specific pathophysiology of COPD. Thus, using 24-hour Holter ECG for COPD patients is highly recommended, as previously suggested by Bousquet et al. [32] in patients with asthma, despite its cost and troublesome applications in daily practice.

In conclusion, our findings reveal that increased SVPC might be caused by bronchodilator use, whereas increased VPC is likely caused by the particular pathophysiology of COPD.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest to declare in connection with this work.

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