Factors Associated with the Development of Atrial Fibrillation in COPD Patients: The Role of P-Wave Dispersion

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Background: Supraventricular tachyarrhythmia is a common problem in chronic obstructive pulmonary disease (COPD) patients. The purpose of this study is to analyze the factors associated with paroxysmal atrial fibrillation (AF) in COPD patients.

Methods: Forty COPD patients (38 male, 2 female, mean age 60 ± 9 years) and 33 healthy controls (29 male, 4 female, mean age: 58 ± 10 years) were included in this study. Echocardiography, 24-hour ambulatory and 12-lead ECG, pulmonary function tests, arterial blood gases, and serum electrolytes were measured. On ECG, maximum (P_{max}) and minimum (P_{min}) duration of P wave and its difference, P-wave dispersion (PWd), were measured.

Results: On echocardiography, diastolic dysfunction was found in 14 of the 40 (35%) COPD patients. Heart rate variability analysis revealed that COPD patients had decreased SDANN, SDNN, SDNNIDX in time-domain, and decreased LF in frequency domain parameters. Fourteen of the 40 COPD patients (35%) had AF. Patients with AF were older (57 ± 10 vs 64 ± 5 years, $P = 0.03$) and had lower SDANN, SDNN, and LF/HF ratio as compared to patients without AF in univariate analysis. All P-wave intervals (P_{max} , P_{min} , and PWd) were increased in COPD patients compared to controls. P-wave dispersion was significantly increased in COPD patients with AF, as compared to patients without AF (57 ± 11 vs 44 ± 7 ms, $P = 0.001$). In logistic regression analysis PWd was found to be the only factor associated with the development of AF ($P = 0.04$).

Conclusions: The presence of AF was significantly related to the prolongation of PWd, but not with pulmonary function, arterial blood gasses, and left and right atrial function.

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COPD; heart rate variability; paroxysmal atrial fibrillation, P-wave dispersion

Cardiac arrhythmias including supraventricular rhythm disorders are common and can cause mortality in patients with chronic obstructive pulmonary disease (COPD).¹⁻³ Multiple factors such as hypoxemia or hypercapnia, acid-base disorders, right-sided heart failure, and medications such as

digital glycosides and xanthine derivatives have been implicated for this disorder.^{2,3,4-7}

In recent studies, P-wave dispersion (PWd), which reflects inhomogeneous and fractionated propagation of sinus impulse, has been reported to predict development of atrial fibrillation,⁸⁻¹⁰ in hy-

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pertensive patients,¹¹ and after coronary artery surgery.¹²

The aim of this study was to investigate PWD in COPD patients and its effect on development of paroxysmal atrial fibrillation (AF) in this group of patients.

PATIENTS AND METHODS

Patients

In this study, 40 patients with COPD (38 male, 2 female, mean age: 60 ± 9 years) and 33 healthy controls (29 male, 4 female, mean age: 58 ± 10 years) were included. There was no difference in age and sex distribution between patients and controls. Patients with hypertension, valvular, congenital heart disease, systolic left ventricular dysfunction (ejection fraction [EF] < 50% and/or fractional shortening [FS] < 25%), pre-excitation syndrome, sick sinus syndrome, bundle branch blocks, and chronic AF were excluded. Patients were evaluated by history, physical examination, ECG, echocardiography and 24 hour-Holter ST segment analysis for ischemic heart disease; if detected, the patients were also excluded. Cardioactive drugs such as beta 2-mimetics and xanthine derivatives were stopped 48 hours before the study. None of the patients were receiving antiarrhythmic drugs. The diagnosis of paroxysmal AF was made if patient had a history of documented AF, or if AF was present in the Holter recording.

Echocardiography, 12-lead ECG, 24-hour rhythm Holter, pulmonary function tests, arterial blood gas analysis, and serum electrolytes were analyzed (Table 1).

Electrocardiographic Data Collection

Twelve leads ECG of patients in supine position was recorded with a paper speed of 50 mm/s and the gain calibrated to 0.5 cm/mV. P-wave duration was measured manually under magnifying glass by one observer from the beginning of the P-wave deflection from the isoelectric line to the end of the deflection returning to isoelectric line as described previously.^{9, 13, 14} If the beginning or the end of the deflection could not be satisfactorily defined, that lead was not used. At least 10 leads were available in the assessment of PWD. Maximum ($P_{\max}$) and minimum ($P_{\min}$) P-wave durations were measured and the PWD, the difference $P_{\max} - P_{\min}$, was

Table 1. Demographic and Baseline Characteristics of COPD Patients

Demographic Features	
Age (years)	60 ± 9
Sex (male/female)	38/2
Duration of COPD (years)	12 ± 7
Smoking (pack-year)	51 ± 29
Arterial Blood Gases	
pO ₂ (mmHg)	67 ± 15
PCO ₂ (mmHg)	46 ± 9
HCO ₃ (mEq/L)	26 ± 3
pH	7.39 ± 0.04
Electrolytes	
Na (mEq/L)	143 ± 3
K (mEq/L)	4.2 ± 0.4
Mg (mEq/L)	1.95 ± 0.23
Pulmonary Function Test	
VC (L)	2.35 ± 0.73
FVC (L)	2.14 ± 0.69
FEV ₁ (L)	1.19 ± 0.56
FEV ₁ /FVC (%)	55 ± 13

Abbreviations as in text.

calculated.¹⁴ The heart rate, QRS duration, and PR duration were also recorded.

Echocardiographic Examination

Echocardiographic examination was carried out with Hewlett-Packard Sonos 1000 echocardiographic system equipped with 2.5 MHZ "phased-array" transducer. M-Mode and 2D measurements were done in accordance to methods recommended by the American Society of Echocardiography.^{15, 16} Criteria for left ventricular hypertrophy was left ventricular mass index (LVMI) > 134 g/m² for males and > 110 g/m² for females.¹⁷ The cardiac mass was calculated by the formula derived by Reichek and Devereux:¹⁸

Left ventricle mass (gr) = 1.04

$$\times ((LVID_d + IVS_d + LVPW_d)^3 - (LVID_s)^3)$$

$$- 13.6$$

where LVID = left ventricular diastolic diameter; IVS = interventricular septum thickness; and LVPW = left ventricular posterior wall thickness. Cardiac mass was standardized by dividing it to body surface area, which was calculated using Du Bois formula:

Body surface area

$$= (\text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184).$$

Left atrial diastolic and systolic diameters were recorded. On apical four chamber view, planimetric left atrial dimensions were measured to calculate left atrial volumes at the beginning of the mitral valve opening and closures were measured to calculate maximum ($V_{\max}$), minimum ($V_{\min}$) atrial volumes. Atrial ejection fraction (AEF) was calculated with the formula: $(V_{\max} - V_{\min}) / V_{\max}$. Mitral E/A ratio and isovolumetric relaxation time (IVRT) were measured for the assessment of diastolic function.

Rhythm Holter Recordings and Heart Rate Variability Analysis

Twenty-four hour ambulatory ECG recordings were taken with a Marquette SEER solid-state recorder. The recordings were downloaded to Marquette Laser SXP Holter system (Marquette Electronics, Inc., Milwaukee, WI, USA). The recordings were reviewed to confirm 18 hours of clear recording and the beat classifications were manually checked and corrected.

Time-domain and long term frequency-domain heart rate variability (HRV) were calculated using the software present in the system (Marquette Electronics Series 8000 Holter Analysis System Version 5.8, 1-Sept-92). The software used a fast-Fourier transform algorithm for the calculations and spectral smoothing function was the Hamming window.

In time-domain analysis: SDNN (standard deviation of all the RR intervals); SDANN (standard deviation of the 5-minute RR interval means); SDNNIDX (mean of the 5-minute RR interval standard deviations); rMSSD (square root of the mean of the squared differences of two consecutive RR intervals); and pNN50 (percentage of the beats with consecutive RR interval difference of more than 50 milliseconds) were calculated. In frequency-domain analysis: total power (TP) (area under the spectral curve from 0.01 to 1.0 Hz); low-frequency power (LF) (area under the spectral curve from 0.04 to 0.15 Hz); high-frequency power (HF) (area under the spectral curve from 0.15 to 0.40 Hz); and the ratio LF/HF were calculated.

In time-domain analysis SDNN and SDNNIDX were accepted as equivalent to TP, SDANN to ultra-low frequency not measured by our system, and rMSSD and pNN50 to HF. In frequency-domain analysis, LF was accepted as equivalent to the sympathetic plus parasympathetic components of

autonomic function, HF was accepted as representing the parasympathetic component of autonomic function, and LF/HF as depicting the sympathovagal balance of the autonomic function.¹⁹

Pulmonary Function Tests

Pulmonary function tests were performed with Sensor Medics 2400, Holland. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1 /FVC ratio, forced expiratory flow at 25 to 75% of FVC ($FEF_{25-75\%}$), and peak expiratory flow rate (PEFR) were measured and compared to predicted values. Arterial blood gases were also obtained simultaneously.

All patients were examined with good medical and laboratory practice according to the recommendations set forth by the Declaration of Helsinki on Biomedical Research involving Human Subjects.²⁰ Informed consent was obtained from all patients.

Statistical Analysis

Statistical analysis was carried out with Statistical Package for Social Sciences for Windows version 10.0 (SPSS Inc, Chicago, IL, USA). All non-numeric variables are reported as frequency and percentage, and all numeric variables are reported as mean $\pm$ SD. The comparison of the means of two numerical parameters was done with Student's *t*-test and Wilcoxon rank when appropriate. Correlation between two numerical variables with non-normal distribution was done with Spearman's bivariate nonparametric correlation test. Multivariate analysis of the factors on the presence or absence of paroxysmal AF was analyzed with logistic regression test with backward elimination. Age, LVMI, and PWd were taken as independent variables. $P < 0.05$ was accepted as significant.

RESULTS

On echocardiographic analysis, COPD patients had increased interventricular wall thickness, lower EF, and fractional shortening compared to controls. However, none of the COPD patients had systolic dysfunction ($EF < 50\%$ and/or $FS < 25\%$). Left ventricular posterior wall thickness, internal diameter (diastolic), mass index, left atrial diameter, and EF were similar between COPD patients and controls. Decreased mitral E/A ratio and increased IVRT were found in COPD patients as

compared to controls. Diastolic dysfunction (E/A ratio < 1 and IVRT > 100 ms) was found in 14 (35%) of 40 COPD patients (Table 2).

Heart rate variability analysis revealed that COPD patients had decreased SDANN, SDNN, SDNNIDX in time-domain, and decreased LF in frequency domain parameters. However, no significant difference in RMSSd, pNN50, total power, and HF was found between study groups (Table 3).

Fourteen (35%) of 40 COPD patients had AF on rhythm Holter analysis according to criteria described in the Methods section. Patients with AF were older (57 ± 10 vs 64 ± 5 years, $P = 0.03$) and had lower SDANN, SDNN, and LF as compared to patients without AF in univariate analysis. However, all echocardiographic, pulmonary function tests parameters, arterial blood gases, and electrolytes were similar (Table 4).

On ECG analysis, all P-wave intervals ($P_{\max}$, $P_{\min}$, and PWd) were increased in both groups of COPD patients with and without AF as compared to controls. In addition, P-wave dispersion was significantly increased in COPD patients with AF, as compared to patients without AF (Table 5). P-wave dispersion was not correlated with pulmonary function test and arterial blood gas parameters.

In logistic regression analysis (model $r^2: 0.71$, $P = 0.002$), age, LVMI, and PWd have been included into the model as independent variables for the development of AF. Only PWd was found significant in the regression equation $\text{ExpB}: 1.358$ (1.009-1.827; %95 CI, $P = 0.04$).

Table 2. Echocardiographic Results of the Study Groups

	COPD N: 40	Control N: 33	Statistics
LAD (cm)	3.87 ± 0.4	3.95 ± 0.4	NS
LVMI (g/m ²)	123 ± 27	118 ± 25	NS
IVS (cm)	1.13 ± 0.17	0.98 ± 0.01	0.008
IVRT (msec)	94 ± 13	80 ± 15	0.004
Mitral E/A ratio	0.83 ± 0.22	1.09 ± 0.31	0.004
EF (%)	62 ± 8	71 ± 4	< 0.001
FS (%)	34 ± 6	41 ± 3	0.001
LVID (cm)	4.7 ± 0.5	4.6 ± 0.4	NS
LVPW (cm)	1.03 ± 0.13	1.06 ± 0.19	NS

Abbreviations as in text.

Table 3. Time and Frequency-Domain Analysis of Heart Rate Variability in COPD Patients and Controls

	COPD N: 40	Controls N: 33	Statistics
Time-domain			
SDANN (ms)	83 ± 32	112 ± 29	0.008
SDNN (ms)	94 ± 32	123 ± 31	0.004
SDNNIDX (ms)	37 ± 14	47 ± 15	0.02
RMSSD (ms)	26 ± 10	26 ± 7	NS
PNN50 (%)	6.5 ± 5.8	5.7 ± 4.2	NS
Frequency Domain			
Total power (ms)	24.8 ± 10.4	30.8 ± 9.2	0.07
HF (ms)	8.8 ± 4.0	10.0 ± 3.4	NS
LF (ms)	14.3 ± 8.1	19.9 ± 6.5	0.01
LF/HF	1.66 ± 0.60	2.02 ± 0.37	0.03

Abbreviations as in text.

DISCUSSION

Supraventricular tachyarrhythmias including AF are common in patients with COPD. Several factors such as hypoxemia, hypercapnia, acid-base disturbances, autonomic dysfunction, and medications may contribute to the development of arrhythmias in these patients.²⁻⁷ In addition, structural changes in myocardium may be implicated for the development of AF in COPD groups. In our study, increased interventricular septum thickness and decreased left ventricular EF in COPD patients were found. However, none of the patients had systolic left ventricular dysfunction. These findings were consistent with previous reports.²¹⁻²³ A major change found was in diastolic function with 36% of the patients having diastolic dysfunction, as previously reported.²⁴ However, none of the echocardiographic parameters was associated with development of AF.

Autonomic disturbances have been described in COPD patients, which may also contribute to the development of AF. In these studies assessing autonomic function by HRV, lower values of HRV indexes reflecting mixed sympathetic and parasympathetic deterioration were reported^{25,26} which may be favorably altered by oxygen supplementation.²⁷ In a study with short-term HRV, blunted response to sympathetic and vagal stimulus was reported.²⁸

In our study, COPD patients had lower time (SDNNIDX, SDANN, SDNN) and frequency (LF and LF/HF ratio) domain HRV parameters com-

Table 4. Comparison Between COPD Patients with and without Atrial Fibrillation

	Atrial Fibrillation (+)	Atrial Fibrillation (–)	P Value
Demography and Pulmonary Function Test Parameters			
Age (years)	64 ± 5	57 ± 10	0.03
Sex (male/female)	14/0	24/2	NS
Duration of COPD (years)	11 ± 7	13 ± 7	NS
Smoking (pack-years)	50 ± 36	51 ± 26	NS
FVC (L)	2.23 ± 0.36	2.01 ± 0.80	NS
FEV1 (L)	1.18 ± 0.35	1.20 ± 0.63	NS
FEV1/FVC (%)	53 ± 13	56 ± 13	NS
Arterial Blood Gases and Echocardiographic Analysis			
PH	7.40 ± 0.03	7.40 ± 0.04	NS
pO2 (mmHg)	66 ± 16	67 ± 15	NS
pCO2 (mmHg)	45 ± 9	46 ± 10	NS
LVMl (g/m2)	132 ± 23	119 ± 29	NS
IVRT (ms)	93 ± 10	95 ± 14	NS
E/A ratio	0.71 ± 0.16	0.88 ± 0.23	0.01
RAD (cm)	4.2 ± 0.5	4.0 ± 0.5	NS
Time and Frequency Domain Analysis			
SDANN (ms)	63 ± 23	93 ± 32	NS
SDNN (ms)	72 ± 23	104 ± 31	NS
SDNNIDX (ms)	31 ± 9	41 ± 15	NS
rMSSD (ms)	27 ± 9	26 ± 10	NS
LF (ms)	10.3 ± 5.3	16.3 ± 8.6	NS
HF (ms)	8.4 ± 4.0	9.0 ± 4.1	NS
LF/HF	1.25 ± 0.47	1.86 ± 0.57	0.015

Abbreviations as in text.

pared to controls. Patients with AF also had significantly reduced SDANN, SDNN, LF, and LF/HF ratio, which implies that the sympathetic component of HRV was compromised. However on logistic regression analysis, these parameters were not retained as independent variables for the development of AF.

Increased PWd, which reflects the inhomogeneous propagation of atrial depolarization, has

been reported to predict the development of AF in different patient groups such as hypertension or after coronary artery bypass grafting.⁹⁻¹² However there is no study on the utility of PWd for predicting the development of AF in COPD patients. In our study, COPD patients had significantly prolonged P-wave intervals ($P_{\max}$, $P_{\min}$, PWd) compared to controls. In addition, COPD patients with AF had significantly longer PWd compared to

Table 5. P Wave Intervals in Study Groups

	COPD			Control N: 33	Statistics
	AF (+) N: 14	AF (–) N: 26	Total N: 40		
$P_{\max}$ (ms)	117 ± 13	110 ± 11 ^c	111 ± 12	93 ± 13 ^a	^{a,c} P < 0.001
$P_{\min}$ (ms)	60 ± 11	66 ± 12 ^c	65 ± 12	54 ± 10 ^a	^{a,c} P < 0.001
P wave dispersion (ms)	57 ± 11 ^b	44 ± 7 ^c	47 ± 10	39 ± 7 ^a	^{a,b} P = 0.001 ^c P = 0.02

^a Controls different from COPD patients; ^b AF(+) COPD patients different from AF(–) COPD patients; ^c AF(–) COPD patients different from controls.
Abbreviations as in text.

COPD patients without AF despite no difference in $P_{\max}$ and $P_{\min}$. P-wave dispersion was found to be associated with the development of AF in COPD patients in logistic regression analysis. However, none of the pulmonary function tests, arterial blood gases, serum electrolytes levels, echocardiography, and HRV parameters which may be implicated for changes in intraatrial conduction velocity and/or refractoriness was correlated with PWD. However increased PWD in COPD patients without AF as compared to controls imply that COPD itself is causally related to increase in PWD.

In conclusion, the development of AF in COPD patients was related to age, changes in autonomic function and PWD, which was retained as the most significant factor. Changes in PWD was related to COPD.

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