P Wave Signal-Averaged Electrocardiography in Patients with Chronic Obstructive Pulmonary Disease

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Introduction. Chronic obstructive pulmonary disease (COPD) is associated with higher incidence of supraventricular arrhythmias. Atrial late potentials (ALP) detected by P-wave signal-averaged electrocardiography (SAECG) could be useful in detecting the patients at risk for supraventricular arrhythmias. Our objective was to assess the role of P-wave SAECG and ALP detection for arrhythmic risk evaluation of the patients with exacerbated COPD.

Methods. We prospectively included 45 patients with exacerbation of COPD and 58 age-matched patients with no history of pulmonary disease in a control group. We performed pulmonary function tests, arterial blood gases, echocardiography, 24-hour Holter monitoring and P-wave SAECG. We measured filtered P-wave duration (FPD), the root mean square (RMS) voltages in the last 40, 30 and 20 ms of the filtered P-wave (RMS 40, RMS 30 and RMS 20), the root mean square voltage of the filtered P-wave potentials (RMS-p), and the integral of the potentials during the filtered P-wave (Integral-p). ALP was defined as FPD > 132 ms and RMS 20 < 2.3 μ V.

Results. Isolated atrial premature beats (APB) and supraventricular tachycardias (SVT) were more frequent in the COPD group. There were no significant differences between groups regarding the P wave SAECG parameters. In the COPD group none of the supraventricular arrhythmias was correlated with ALP or any P-wave SAECG parameters.

Conclusions. The patients with acute exacerbation of COPD but no apparent cardiac disease have a higher incidence of supraventricular arrhythmias. P-wave SAECG analysis and ALP detection have little value in the arrhythmic risk evaluation of these patients.

Key words: COPD, chronic obstructive pulmonary disease, supraventricular arrhythmias, atrial late potential, signal-averaged electrocardiography.

INTRODUCTION

It has long been recognized that chronic obstructive pulmonary disease (COPD) is associated with an increased risk for both supraventricular and ventricular arrhythmias [1] and their occurrence represents a sign of a poor prognosis [2]. Atrial late potentials (ALP) detected by P wave signal-averaged electrocardiography (SAECG) have been demonstrated to be directly linked to the atrial fibrillation development [3, 4]. ALP are low amplitude, high frequency signals which appear at the end of atrial depolarization, primarily as a consequence of delayed or fragmented conduction. We aim to analyze the role of P wave SAECG and ALP detection for arrhythmic risk evaluation of the patients with acute exacerbation of COPD.

[5], presented to our clinic with acute exacerbation of the disease, and 58 age-matched patients without any history of pulmonary disease in the control group. We excluded patients with history or signs of ischemic heart disease, with history of myocardial revascularization or cardiac surgery, significant valvular disease, known atrial fibrillation or other chronic arrhythmias, heart failure or left ventricular ejection fraction (LVEF) <50%, known thyroid dysfunction, permanent bundle block, on antiarrhythmic treatments or with permanent implantable devices. All patients signed a written informed consent. The study protocol was approved by our institution's Ethics Committee. The study population was prospectively included between June 2014 and June 2015 from a single hospital center.

PROCEDURES

MATERIAL AND METHODS

We included 45 patients diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria

Pulmonary function tests

Pulmonary function testing was performed using a Vitalograph Alpha 6000 spirometer (Vitalograph, Ireland) for all patients with COPD. Forced

vital capacity (FVC) and forced expiratory volume in the first second (FEV1) were measured in milliliters and expressed as percentages of the predicted values established by the European Community Respiratory Health Survey. Samples for the arterial blood gases were obtained from the radial artery in all patients with COPD while breathing room air. pH, pO₂, pCO₂ and HCO₃ results were recorded. Also, the oxygen saturation by pulseoxymetry was analyzed in all patients.

Echocardiography

The echocardiographic examination was performed with an iE33 xMATRIX (Philips, The Netherlands) system with 2.5-3.5 MHz transducers. M-mode and 2D-dimensional measurements were done in all standard windows, according to the recommendations of the European Society of Echocardiography. The left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method and pulmonary artery pressure (PAP) was calculated using the modified Bernoulli equation: $PAP = 4 \times (\text{tricuspid systolic jet})^2 + 10 \text{ mm Hg}$.

Holter Recordings

Twenty-four hour ambulatory ECG recordings were obtained with a CardioMem® CM 3000 (GE Healthcare, Germany) system. The recordings were downloaded to a CardioDayHolter software (GE Healthcare, Germany). These were reviewed by a cardiology specialist to confirm 18 hours of clear recording, and the beat classifications were manually checked and corrected. The recordings were screened for atrial arrhythmias defined as isolated atrial premature beats (APB), with a predefined category of patients with more than 70 APB per day (APB>70), and supraventricular tachycardias (SVT) consisting in atrial tachycardias, atrial flutter or atrial fibrillation.

Signal-averaged electrocardiography

SAECG was performed in all patients using a MAC 5500HD (GE Healthcare, Germany) system. The P wave SAECG parameters measured were the filtered P-wave duration (FPD), the root mean square (RMS) voltages in the last 40, 30 and 20 ms of the filtered P-wave (RMS 40, RMS 30 and RMS 20), the root mean square voltage of the filtered P-wave potentials (RMS-p), and the integral of the potentials during the filtered P-wave

(Integral-p). The values were recorded when a noise level <1 µV was obtained, by averaging ≥ 250 beats. ALP was defined as FPD > 132 ms and RMS20 < 2.3 µV [6].

Statistical analysis

Statistical analysis was performed with NCSS 10 Statistical Software (NCSS, LLC. Kaysville, Utah, USA) and Medcalc 15.2 (MedCalc Software, Ostend, Belgium). The normality was tested with D'Agostino-Pearson and Komolgorov-Smirnov tests. Descriptive statistics values were given as mean ± standard deviation and percentage ratios. The differences between groups were analyzed using chi-squared test or Mann-Whitney test as appropriate. The correlations between non-normally distributed variables were obtained using Spearman's correlation test. The impact of factors on the presence or absence of SVT was analyzed using logistic regression with backward method. The p values < 0.05 were considered statistically significant.

RESULTS

The demographic characteristics and clinical examination differences between the COPD patients and the control group are shown in Table 1. As expected, COPD patients have a significantly higher respiratory rate and lower oxygen saturation compared to the control group. Also, the history of smoking and active smoking is more frequent in COPD patients.

Regarding the echocardiographic parameters we did not find any significant differences between the groups, except for a higher systolic pulmonary artery pressure and a statistically non-significant higher diameter of the right ventricle in the COPD patients as shown in Table 2.

The incidence of both APB and SVT was higher in the COPD group. Compared to the control group, among these patients the APB>70 category was more frequent (Table 3).

The P wave SAECG analysis demonstrated no significant differences in any parameters between COPD and control patients, with the exception of RMS 20 which was higher in COPD patients with marginally statistical significance. Moreover, the presence of ALP was the same in both study groups. The results regarding SAECG analysis are given in Table 4.

Table 1
General characteristics

	COPD (n = 45)	Control (n = 58)	p value
Demographics and co-morbidities			
Age, y	64.6 ± 9.2	63.4 ± 9.2	0.8
Male gender, n	32 (71.1%)	31 (53.4%)	0.07
BMI, kg/m ²	30.8 ± 8.6	28.4 ± 4.8	0.6
History of smoking, n	38 (84.4%)	7 (12.1%)	< 0.001
Active smoking, n	27 (60%)	4 (6.9%)	< 0.001
Arterial hypertension, n	25 (55.5%)	35 (60.3%)	0.7
Diabetes mellitus, n	11 (24.4)	7 (12.1%)	0.1
Clinical examination			
SBP, mmHg	132.7 ± 22.9	131.4 ± 14.1	0.7
DBP, mmHg	78.5 ± 15.9	78.9 ± 10	0.8
Heart rate, bpm	84.2 ± 16.3	76.5 ± 16.9	0.1
Respiratory rate, rpm	25.1 ± 7	18.3 ± 3.5	<0.001
Oxygen saturation, %	88.6 ± 6.7	97.64 ± 2.6	<0.001

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure

Table 2
Echocardiographic measurements

	COPD (n = 45)	Control (n = 58)	p value
LA, mm	36.8±7.1	34.0±5.1	0.1
LVESD, mm	34.5±5.9	33.1±6.4	0.4
LVEDD, mm	47.8±5.2	47.4±5.7	0.8
IVS, mm	12.1±1.9	11.5±2.1	0.2
LVPW, mm	11.4±1.6	10.6±1.8	0.06
LVEF, %	55.7±7.5	57.2±3.6	0.2
RA, mm	34.2±5.3	32.5±5.3	0.1
RV, mm	28.2±5.3	26.8±2.8	0.08
sPAP, mmHg	30.1±12.8	19.8±10.7	0.005

LA – left atrium, LVESD – left ventricular end-systolic diameter, LVEDD – left ventricular end-diastolic diameter, IVS – interventricular septum, LVPW – left ventricular posterior wall, LVEF – left ventricular ejection fraction, RA – right atrium, RV – right ventricle, sPAP – systolic pulmonary artery pressure

Table 3
Incidence of supraventricular arrhythmias

	COPD (n = 45)	Control (n = 58)	p value
APB	901.9 ± 1535.4	416.4 ± 876.3	0.04
APB>70	29 (64.4%)	27 (46.5%)	0.07
SVT	27 (60%)	16 (27.6%)	<0.001

APB – atrial premature beats, APB>70 – more than 70 atrial premature beats/24h, SVT – supraventricular tachycardias

Table 4
P-wave SAECG analysis and ALP incidence

	COPD (n = 45)	Control (n = 58)	p value
FPD, ms	126.2 ± 43.8	125.2 ± 38.4	0.9
RMS 40, μV	6.7 ± 3.7	5.5 ± 2.2	0.1
RMS 30, μV	5.9 ± 3.7	4.6 ± 2.1	0.1
RMS 20, μV	4.8 ± 2.9	3.6 ± 1.9	0.04
RMS-p, μV	7.7 ± 2.9	7.3 ± 2.3	0.4
Integral-p, μV*s	755.8 ± 257.9	723.3 ± 296.9	0.3
ALP, n	8 (17.8%)	11 (18.9%)	0.8

FPD – Filtered P wave duration, RMS 40, RMS 30, RMS 20 – root mean square (RMS) voltage of the terminal 40, 30, 20 ms of the filtered P wave, RMS-p – RMS voltage of the entire filtered P wave, Integral-p – integral of the voltages in the entire P wave

In the COPD group there was a statistically significant correlation between FEV1 and FPD ($r_s = 0.49$, $p = 0.001$), RMS 40 ($r_s = -0.46$, $p = 0.002$), RMS 30 ($r_s = -0.48$, $p = 0.001$), RMS 20 ($r_s = -0.38$, $p = 0.01$), RMS-p ($r_s = -0.38$, $p = 0.01$), but no correlations were found between other respiratory tests and P wave SAECG parameters. Also, the pCO_2 was correlated with RMS 40 ($r_s = 0.54$, $p = 0.003$), RMS 30 ($r_s = 0.52$, $p = 0.004$) and RMS 20 ($r_s = 0.46$, $p = 0.01$), but not with other SAECG parameters.

Regarding the echocardiographic measurements, in the COPD group we observed a significant but rather weak correlation between left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) diameters and FPD ($r_s = 0.35$, $p = 0.02$ for LVEDV and $r_s = 0.34$, $p = 0.03$ for LVESV). No other relationships between P wave SAECG and echocardiographic parameters were found.

However, in the COPD group there were no significant differences between patients with ALP and those without ALP regarding the $APB > 70$ category or the incidence of SVT (see Figure 1). In the logistic regression ($r^2 = 0.61$, $p = 0.001$) the presence of SVT in these patients is correlated only with pO_2 and FEV1, but not with any P-wave SAECG parameters. Also, we did not find a relationship between echocardiographic measurements and $APB > 70$ or SVT.

An analysis on subgroups of COPD classes showed no differences in terms of P wave SAECG parameters, including the incidence of ALP (Table 5). The supraventricular arrhythmias seem to appear more frequently in patients with stage IV COPD compared to those with stages I to III, but without reaching statistical significance: $APB > 70$ (73.7% vs 57.7%, $p = 0.17$) and SVT (63.1% vs 53.8%, $p = 0.1$).

Figure 1. ALP and incidence of supraventricular arrhythmias in COPD patients.

Table 5
P-wave SAECG parameters in relation to COPD classes

	Class II-III (n = 26)	Class IV (n = 19)	p-value
FPD, ms	135.1 ± 53.1	115.1 ± 24.8	0.2
RMS40, μV	6.4 ± 3.5	7.4 ± 3.8	0.4
RMS30, μV	5.4 ± 2.6	6.6 ± 4.3	0.5
RMS20, μV	4.5 ± 2.3	5.4 ± 3.5	0.5
RMSp, μV	7.9 ± 3.2	8.1 ± 2.2	0.2
Integral-p, $\mu V \cdot s$	804.3 ± 249	733.9 ± 212.4	0.5
ALP positive, %	23.1	10.5	0.2

FPD – Filtered P wave duration, RMS 40, RMS 30, RMS 20 – root mean square (RMS) voltage of the terminal 40, 30, 20 ms of the filtered P wave, RMS-p – RMS voltage of the entire filtered P wave, Integral-p – integral of the voltages in the entire P wave

DISCUSSION

The patients with COPD are at higher risk for developing supraventricular arrhythmias and their occurrence is associated with poor prognosis [2, 7-9]. Several studies showed that P wave SAECG analysis and the identification of ALP could be used in exposing those patients at risk for atrial fibrillation [3, 4, 10-13]. We aimed to evaluate the role of ALP and P wave SAECG parameters as tools for risk stratification for developing supraventricular arrhythmias in COPD patients. In our study the patients with COPD had a higher incidence of supraventricular arrhythmias, defined as isolated atrial premature beats or supraventricular tachycardias consisting in atrial tachycardias, atrial flutter or atrial fibrillation, compared to a control group. Also, the predefined category of more than 70 APB per day is more frequent in the COPD patients. Regarding the P wave SAECG analysis we did not find significant differences of the values of any parameter, including the presence of ALP, between the COPD and control group. Moreover, in the analysis of the COPD group there were no correlations between ALP and isolated APB or SVT. The predictive role of P wave SAECG was studied in different clinical situations. Steinberg *et al.* [4] and Caravelli *et al.* [10] demonstrated the potential role of P wave SAECG in the prediction of atrial fibrillation after cardiac surgery or coronary artery by-pass grafting. In a prospective study, Yamada *et al.* [6] showed the association between presence of ALP and atrial fibrillation in patients with heart failure. Recently, ALP detection was found useful in patients with ischemic stroke of unknown origin [12]. To date, we did not find any study regarding P wave SAECG in the setting of COPD. Moreover, in comparison with the above mentioned trials we excluded the patients with significant cardiac diseases like ischemic heart disease or heart failure. This and the fact that our patients have mostly normal echocardiographic parameters could be an

explanation for the lack of significant modification of the P wave SAECG parameters. In our study neither the presence of ALP nor any of the P wave SAECG parameters correlated with the supraventricular arrhythmias in the COPD patients. The incidence of SVT was more related with the severity of respiratory function reflected in FEV1 and pO₂, which was also demonstrated in previous studies [14, 15]. This finding lowers the usefulness of P wave SAECG analysis in the prediction of supraventricular arrhythmias during the exacerbations of COPD, especially when there are no significant morphological or functional alterations of the heart.

A limitation of our study is the relatively small population size, recruited from a single center. Also, as our findings are based on a cross-sectional analysis we cannot rule out the role of ALP or any P wave SAECG parameter as predictor for developing arrhythmias in the medium or long term. For this further prospective research is needed.

CONCLUSIONS

The patients with COPD and no apparent cardiac disease have a higher incidence of supraventricular arrhythmias during acute exacerbations, seemingly in direct relationship with the severity of the altered respiratory function. The P wave SAECG analysis and the presence of ALP add little value in the stratification of patients with COPD at risk of supraventricular arrhythmias.

Acknowledgements. This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390.

We thank Marian Miricioiu and Carmen Adam who were responsible for technical aspects of Holter monitoring and SAECG.

Conflicts of interest: none.

Introducere. Boala cronică pulmonară obstructivă (BPOC) asociază o incidență crescută a tahiaritmiilor supraventriculare. Potențialele atriale tardive (ALP) detectate prin metoda „P-wave signal-averaged electrocardiography” (SAECG) ar putea fi utilă pentru identificarea pacienților aflați la risc pentru tahiaritmii supraventriculare. Obiectivul studiului a fost de a determina rolul metodei P-wave SAECG pentru evaluarea riscului aritmic la pacienții cu exacerbare a BPOC.

Metode. Au fost incluși prospectiv 45 de pacienți cu exacerbare a BPOC și 58 de pacienți fără antecedente de boală pulmonară. Au fost analizate funcția

pulmonară, valorile gazelor sanguine, ecocardiografie, monitorizare Holter pe parcursul a 24 de ore și P-wave SAECG. Au fost măsurate duratele unde P filtrate (FPD), voltajul root mean în ultimele 40, 30 și 20 de ms ale unde P filtrate (RMS 40, RMS 30 și RMS 20), voltajul potențialelor root mean square ale unde P 9RMS-p) și integrala potențialelor din timpul unde P filtrate (Integral-p). ALP au fost definite ca $FPD > 132$ ms și $RMS 20 < 2.3 \mu V$.

Rezultate. Bătăile premature isolate atriale (APB) și tahiaritmiile supra-ventriculare (SVT) au fost mai frecvente în grupul cu BPOC. Nu a fost observată nicio diferență privind parametrii P wave SAECG între cele două grupuri. În grupul cu BPOC niciuna dintre tahiaritmiile supraventriculare nu s-a corelat cu ALP sau cu parametrii P-wave SAECG.

Concluzii. Pacienții cu exacerbare a BPOC dar fără boală cardiacă aparentă au o incidență mai mare a aritmiilor supraventriculare. Analiza P-wave SAECG și identificarea ALP au o valoare redusă pentru evaluarea riscului aritmic al acestor pacienți.

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Received August 31, 2015