Atrial fibrillation in the acute, hypercapnic exacerbations of COPD

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Abstract. - OBJECTIVE: Chronic obstructive pulmonary disease (COPD) has been associated with a high frequency of arrhythmias. Atrial fibrillation (AF) is one of the most common arrhythmias and causes substantial morbidity and mortality. Emerging risk factors for the development of AF include a variety of breathing disorders like COPD. Few studies have analyzed the role of reduced lung function and respiratory acidosis in predicting AF. Aim of the current study was to investigate the role of hypercapnia, pulmonary systolic hypertension and lung function impairment in COPD patients, as risk factors for atrial fibrillation development.

PATIENTS AND METHODS: We evaluated a population of individuals consecutively hospitalized for COPD exacerbation and hypercapnic respiratory failure between January 2012 and January 2013; among them we selected a subgroup of patients presenting a paroxysmal episode of atrial fibrillation. All patients underwent pulmonary function tests, haemogas analysis, electrocardiogram and transthoracic echocardiography.

RESULTS: Among the 193 subjects evaluated, 35 individuals with AF and COPD were enrolled in the study. Risk of new AF was higher in those subjects with lower FEV1 and higher PaCO2 values, also there was a significantly increased prevalence of AF in patients with higher value of Pulmonary Artery Systolic Pressure (PASP), obtained by transthoracic echocardiography. Linear correlation between variables revealed a direct relationships between hypercapnia and PASP and left and right atrial areas.

CONCLUSIONS: Impaired pulmonary function, hypercapnia and high values of PASP are independent predictors of incident AF.

Key Words: Chronic obstructive pulmonary disease, Hypercapnia, Atrial fibrillation, FEV1, Systolic pulmonary artery pressure.

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and causes significant morbidity and mortality. The incidence of AF is higher in elderly patients and its prevalence increases with a shift to aging population. The number of patients with AF is likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of individuals with advanced age, many of whom have ridden out cardiovascular events that would have been fatal in a recent past.

Incidence of AF in men is reported to be increased at 1.5 times the rate in women. AF may be triggered and maintained by either reentrant or non reentrant electrical activity, but the exact electrophysiological mechanisms of its initiation and maintenance are controversial. Disorders (conditions) as: persistent tachycardia, valvular diseases, myocardial ischaemia, systemic hypertension and diastolic dysfunction, lead to excessive pressure or volume overload on the left atrium (LA) which responds with various time-dependent adaptive processes. A micro re-entrant arrhythmia with multiple wavelets and daughter wavelets randomly colliding each other, appears to be crucial for AF development.

The majority of AF originates from the LA and recent evidence shows that sleeves of atrial tissue extending into the pulmonary veins are frequently involved in the initiation of atrial arrhythmias.

Risk factors for the development of AF are aging, male gender, cardiac diseases, smoking habits, diabetes mellitus, hyperthyroidism, hypertension, obesity and hypoxia.

Clinical evidence in critically ill patients indicates a frequent association between cardiac rhythm disorders and metabolic abnormalities.

Atrial arrhythmias could be sometimes asymptomatic or have only minor symptoms. The challenges for the physician are avoiding more severe arrhythmias, identifying and treating precipitating cause, preventing any complication and managing symptoms.

In chronic hypoxic lung disease the function of left heart is usually normal as demonstrated by left ventricular ejection fraction, pulmonary wedge pressure, and cardiac output.
However when coronary disease coexists, hypoxia in association with carbon dioxide retention and respiratory acidosis may precipitate left ventricular failure.

In chronic airflow limitation left ventricular function may also be affected by the wide swings in intrathoracic pressure and by hypertrophy of the right ventricle. Arrhythmias are common in patients with hypoxemia and abnormalities of carbon dioxide tension. Emerging risk factors for the development of AF include a variety of breathing disorders: among them chronic obstructive disease (COPD) has been associated with a high frequency to cardiac arrhythmias.

Reduced lung function and sleep-disordered breathing have been independently associated with increased risk of AF.

Hypoxemia and hypercapnia may be associated with over-compensatory fluctuations in autonomic tone, intrathoracic pressures and cardiac haemodynamics, with possible atrial stretch and remodeling, each of which could lead to AF, particularly when hypercapnia causes a significant decrease in pH values.

Heterogeneous repolarization and arrhythmias are common in COPD patients. On ECG, the presence of AF has been significantly associated with the prolongation of P-wave dispersion but not with pulmonary function, arterial blood gases exchange, and left and right atrial function.

Aim of this study was to investigate the role of hypercapnia, pulmonary systolic hypertension and impairment of pulmonary function in COPD patients, as independent risk factors for the development of atrial fibrillation.

**Patients and Methods**

We analyzed 193 patients consecutively hospitalized, from January 2012 to February 2013 in our respiratory ward (Respiratory Diseases Unit, Policlinico Umberto I, Rome, Italy) for COPD exacerbation and hypercapnic respiratory failure.

COPD exacerbations were defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Hypoxemia was defined by a PaO₂ < 60 mmHg and hypercapnia was defined by a PaCO₂ > 45 mmHg on arterial blood gas analysis (ABG). Baseline demographic characteristics and clinical parameters, routine blood chemistry and ABG were assessed at admission.

All patients underwent blood tests, measurement of systolic and diastolic blood pressure, evaluation of body mass index (BMI), ABG, ECGs, transthoracic echocardiography and pulmonary function tests. ECG were recorded at baseline and during hospitalization and afterward (then) analyzed by the modular ECG analysis system (MEANS).

To verify the diagnosis of AF, all ECGs indicating a diagnosis of AF or atrial flutter or any other rhythm disorder were recorded independently.

In patients with COPD, the ECG may demonstrate a “pulmonary disease pattern” with evidence of right heart strain, right axis deviation, Ppulmonale (P wave amplitude of ≥ 2.5 mm (0.25 mV) in leads II, III, and a VF), or an S1Q3 (S1Q3T3) pattern.

ECG tracings are also of value in establishing the diagnosis of dysrhythmias associated with COPD, in particular multifocal atrial tachycardia (MAT).

This arrhythmia is commonly mistaken for atrial fibrillation, and incorrect interventions may be undertaken. The judgment of a cardiologist was asked and taken as decisive in case of persistent disagreement. All diagnoses of AF were subsequently verified.

All patients underwent transthoracic echocardiography with a commercially available cardiovascular ultrasound system (Vivid E9, GE, Horten, Norway). For the LA, an anteroposterior dimension was measured using 2D-guided M-mode echocardiography. Single-plane area was evaluated from the four-chamber view of the left atrium at end-ventricular systole, ensuring that there was no foreshortening of the atrium. The area was then planimetered with the inferior LA border defined as the plane of the mitral annulus, excluding the confluence of the pulmonary veins and the LA appendage. Single-plane area was also evaluated from the four-chamber view of the right atrium (RA) at end-ventricular systole. Right ventricular systolic pressure (RVSP) and Pulmonary Artery Systolic Pressure (PASP) were determined by continuous wave Doppler echocardiography. Right atrial pressure was estimated according to caval dimensions. Estimation of pulmonary vascular resistance (PVR) was determined as previously described.

Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were measured at baseline using a spirometer (Cosmed, Quark PFT, Pavona, Rome, Italy) with a measurement accuracy within 5% of volume.
Corticosteroids and bronchodilators were not administered prior to PFTs measurements.

According to GOLD criteria, the subjects with airflow limitation and FEV\textsubscript{1} % predicted ≥ 80 were identified as having mild airflow limitation, 50 ≤ FEV\textsubscript{1} % predicted < 80 were described as moderate, and FEV\textsubscript{1} % predicted < 50 were described as having severe airway obstruction. The highest values of FEV\textsubscript{1} and FVC were used in the analysis.

Physical examination was performed and comorbidities were identified on the basis of concomitant therapy and investigations carried out at hospital admission. Among patients who presented an episode of paroxysmal atrial fibrillation, we excluded patients with diseases associated with atrial fibrillation (such as cardiomyopathies, hypertension, atrial sept defect, valvular heart disease, thyroid dysfunction), patients who had an history of AF before admission, patients with severe hydro-electrolyte disorders, patients with neoplasms and/or previous cardiovascular diseases.

**Statistical Analysis**

Continuous variables are presented as mean ± standard deviation (SD), and differences were evaluated by the paired Student t or Wilcoxon test, depending on the shape of the distribution curve. Categorical variables are expressed by count and percentage and compared by χ\textsuperscript{2} or Fisher’s exact test when appropriate.

The Spearman coefficient was used for measuring linear correlation between variables.

The probability values are 2-sided; a probability value < 0.05 was considered to indicate statistical significance.

Statistical analyses were performed by using software SigmaStat (San José, CA, USA). Power analysis was performed using STATA v.11 (College Station, TX, USA).

**Results**

Among the 193 patients consecutively hospitalized for COPD exacerbation and hypercapnic respiratory failure, 42 patients presented an episode of paroxysmal atrial fibrillation (21.7%). Four of them were excluded from the study because of a history of risk factors for the development of atrial fibrillation (3 with history of ischemic heart disease, 1 because of mitral valve prolapse), 2 patients died for cardiac complications, and 1 patient had a diagnosis of cancer. For these reasons, 35 patients with AF and COPD were eligible for the present study. From the remaining 151 patients with COPD, 13 were excluded because of several complications (renal failure, infectious complications, diagnosis of cancer). Thus 138 patients with a COPD exacerbation were included in our study.

Participants baseline characteristics are summarized in Table I.

Subjects with AF were older than subjects without AF, and AF was also more frequent in males than females.

BMI, blood pressure, blood glucose and the presence of diabetes mellitus, and tobacco consumption did not significantly differ between subjects with and without AF.

As shown in Table II, the prevalence of AF was significantly higher in subjects with lower FEV\textsubscript{1} (57.1% ± 7.5 vs 76% ± 8.3; p < 0.05) (Figure 1).

### Table I. Patients demographics and clinical characteristics (data expressed as mean ± Standard Deviation).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=173)</th>
<th>COPD (n=138)</th>
<th>COPD and AF (n=35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male (n, %)</td>
<td>98 (56.6)</td>
<td>75 (54.3)</td>
<td>23 (65.7)</td>
<td>0.785*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>79.1±5.1</td>
<td>79.2±5.4</td>
<td>78.2±4.9</td>
<td>0.611*</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>26.2±2.6</td>
<td>26.1±3.3</td>
<td>26.5±2.1</td>
<td>0.856*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127±16.9</td>
<td>125.8±17.7</td>
<td>135.2±16.2</td>
<td>0.156*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.4±8.2</td>
<td>70.6±9.8</td>
<td>80.2±6.7</td>
<td>0.097*</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>119.3±8.7</td>
<td>119.8±7.2</td>
<td>117.3±9.3</td>
<td>0.773*</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>39 (22.5%)</td>
<td>33 (23.9%)</td>
<td>6 (17.1%)</td>
<td>0.773*</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>125 (72.2%)</td>
<td>106 (76.8%)</td>
<td>19 (54.2%)</td>
<td>0.654*</td>
</tr>
</tbody>
</table>

*Student t-test for unpaired data; *Chi-Squared test; BMI=Body Mass Index; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; COPD: Chronic Obstructive Pulmonary Disease; AF: Atrial Fibrillation.
In addition, AF was more frequent in patients with higher levels of PaCO$_2$ (70.6 mmHg ± 5.3 vs 50.1 mmHg ± 3.5; p < 0.05) (Figure 2).

The echocardiographic results were analyzed by an echocardiologist blinded to the clinical data. There was a significantly increased prevalence of AF in patients with higher value of PASP (45.3 mmHg ± 3.5 vs 35.2 mmHg ± 2.3; p <0.05) (Figure 3) and a positive correlation between PaCO$_2$ and PASP (p <0.001; r 0.50) (Figure 4).

Patients with larger values of LA diameters (45.2 ± 2.1 mm vs 34.2 ± 2.1 mm; p < 0.05) (Figure 5) and areas (33.3 ± 5.0 cm$^2$ vs 21.7 ± 4.0 cm$^2$; p < 0.05) had an increased rate of AF. A direct correlation was observed between the increase in LA area and acute hypercapnia (p < 0.001, r 0.68, and p < 0.001, r < 0.71, respectively) (Figures 6 and 7). RA areas (Figure 8) were larger in AF-COPD patients compared to COPD patients with no AF (30.3 ± 6.5 cm$^2$ vs 24.5 ± 5.2

### Table II. Patients main clinical and instrumental parameters (data expressed as mean ± Standard Deviation).

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD (n=130)</th>
<th>COPD and AF (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$, %</td>
<td>76 ±8.3</td>
<td>57.1 ± 7.5</td>
<td>0.05*</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.02</td>
<td>7.32 ± 0.03</td>
<td>0.2*</td>
</tr>
<tr>
<td>PaO$_2$, mmHg</td>
<td>60.2±4.6</td>
<td>58.5±2.96</td>
<td>0.52*</td>
</tr>
<tr>
<td>PaCO$_2$, mmHg</td>
<td>50.2 ± 3.5</td>
<td>70.6 ± 5.3</td>
<td>0.05*</td>
</tr>
<tr>
<td>HCO$_3^-$, mmol/L</td>
<td>30.2 ± 3.2</td>
<td>35.9±5.3</td>
<td>0.256*</td>
</tr>
<tr>
<td>SO$_2$, %</td>
<td>91.5±2.2</td>
<td>90.2±2.7</td>
<td>0.33*</td>
</tr>
<tr>
<td>EF, %</td>
<td>51.2±2.7</td>
<td>41.3±6.3</td>
<td>0.652*</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>35.2 ±2.3</td>
<td>45.3 ± 3.5</td>
<td>0.05*</td>
</tr>
<tr>
<td>TDLVD, mm</td>
<td>45.7±6</td>
<td>54.3±4</td>
<td>0.024*</td>
</tr>
<tr>
<td>PP, mm</td>
<td>9.2 ± 1</td>
<td>8.9 ± 2</td>
<td>0.67*</td>
</tr>
<tr>
<td>SIV, mm</td>
<td>10.4 ± 2</td>
<td>9.6 ± 3</td>
<td>0.774*</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>34.2±2.1</td>
<td>45.2 ± 2.1</td>
<td>0.05*</td>
</tr>
<tr>
<td>Left atrial area (cm$^2$)</td>
<td>21.7±4</td>
<td>33.3 ± 5</td>
<td>0.05*</td>
</tr>
<tr>
<td>Right atrial area (cm$^2$)</td>
<td>24.5±5.2</td>
<td>30.3 ± 6.5</td>
<td>0.05*</td>
</tr>
<tr>
<td>PVR, wood units</td>
<td>1.3 ± 0.4</td>
<td>2.9 ± 1.6</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

*Student $t$-test for unpaired data; FEV$_1$ = Forced Expiratory Volume in one second; PaO$_2$ = Partial pressure of oxygen; PaCO$_2$ = carbon dioxide partial pressure; HCO$_3^-$ = bicarbonate ion; SO$_2$ = oxygen saturation; EF = ejection fraction; PASP = Pulmonary artery systolic pressure; TDLVD = Telediastolic left ventricular diameter; PP = Left ventricular posterior wall thickness; SIV = Interventricular septum thickness; PVR = Pulmonary vascular resistance.
cm²; \( p < 0.05 \)). Positive correlation also appeared between the increase in RA area and acute hypercapnia \( (p < 0.001, r 0.75) \) (Figure 9).

**Discussion**

Guidelines for the management of AF are based on randomized clinical trials which generally have only a limited number of patients with COPD\(^{22}\).

Emerging risk factors for the development of AF include a variety of respiratory disorders. For example, reduced lung function\(^{10}\) and sleep-disordered breathing\(^{23}\) have been independently associated with increased risk of AF. Obstructive sleep apnea was the strongest predictor of recurrent AF following catheter ablation\(^{24}\).

In a prospective longitudinal study, Terzano et al\(^{25}\) evaluated comorbidity, hospitalization and mortality in COPD. This study showed that arrhythmias, especially AF, were among the most
frequent comorbidities and that REFl index was a predictor not only of mortality but also of frequency and length of hospitalization.

In an analysis of admission to the Veterans Administration Medical System hospital\textsuperscript{26}, the prevalence of AF was 14.3% in COPD patients and 10.4% in controls.

Stevenson et al\textsuperscript{11} found that atrial electrophysiology is altered by acute hypercapnia but not hypoxemia. Structural remodeling results in an electrical dissociation between muscle bundles and local conduction heterogeneities, facilitating the initiation and perpetuation of AF.

This electro-anatomical substrate allows multiple small re-entrant circuits that may trigger the arrhythmia.

With this as background, in our study we looked for a correlation between the increase in RA and LA size and acute hypercapnia. Methods of calculation that rely on measurements of M-mode anteroposterior diameter and two-dimensional area, usually reflect the extent of atrium

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Direct relationship between PaCO\textsubscript{2} and pulmonary artery systolic pressure (PASP) in study subjects.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Values of Left atrium diameter in patients with alone chronic obstructive pulmonary disease (COPD) and patients with COPD and concurrent atrial fibrillation (AF).}
\end{figure}
remodeling and thus characterize an individual patient’s risk for an adverse cardiac outcome even if three-dimensional volume-based methods of chamber quantification have recently evolved.

Subjects with severely-impaired pulmonary function and with a COPD acute exacerbation may frequently have hypoxia. Chronic hypoxia, in turn stimulates sympathetic drive, resulting in an increased risk of AF.

By contrast, acute hypercapnia, and its subsequent reversal, produced some intriguing changes in atrial electrophysiology.

The major cause of hypercapnia in patients with COPD is the impaired matching of ventilation and perfusion which, whether, sufficiently severe, is functionally equivalent to the increase of dead space amount.

Acute hypercapnia may produce depression of myocardial contractility and shifts the oxyhemoglobin dissociation curve to the right, leading to increased release of O₂ to tissues. Moreover, hypercapnia and hypoxemia produce pulmonary arteriolar constriction leading to pulmonary arterial and right ventricular hypertension. The right ventricular hypertension may induce arrhythmias by leading to right atrial dilatation and increasing transmural pressure on endocardial vessels altering the distribution of blood flow. Finally, the
neuro-humoral release of catecholamines may increase ventricular irritability\(^2\).

COPD may cause both hypoxemia and hypercapnia. This association alters adrenergic activity and is expected to have wide-ranging and complex effects on atrial electrophysiology, intracellular \(\text{Ca}^{2+}\)-handling, and propensity to AF\(^{27,28}\). In our study AF has appeared more frequent in patients with lowest PaO\(_2\) levels and acute hypercapnia was found to be a factor significantly associated with the likelihood to develop AF.

Subjects with reduced pulmonary function may have increased pulmonary artery pressure. In patients with COPD, pulmonary hypertension is sometimes caused by a loss of pulmonary vasculature and hypoxic vascular contraction. In some lung diseases, impairment of pulmonary vasculature frequently causes pulmonary hypertension\(^{29}\).

Kang et al\(^{30}\) showed increased pulmonary artery pressure and reduced respiratory function in AF patients. This modification of hemodynamics may induce arrhythmias, such as AF.

In our report we demonstrated that a rise of PASP and PVR, evaluated by transthoracic echocardiography, is associated with an increased risk to develop AF.

We are aware that invasive hemodynamic measurements remain the gold standard method for measurement of pulmonary hypertension. On the other hand although cardiac catheterization was not performed in our patients a significant correlation between echocardiographic parameters and
catheterization parameters has been previously described.\textsuperscript{31,32}

In a prospective study, Buch et al\textsuperscript{10} investigated the relationship between forced expiratory volume in one second (FEV\textsubscript{1}) and risk of first episode of AF. The conclusion of the authors was that reduced forced expiratory volume in one second % predicted is an independent predictor of new onset atrial fibrillation.

The Takahata study\textsuperscript{33} evaluated the association of AF and impaired pulmonary function. The prevalence of AF was 1.5% and was higher in subjects with air-flow limitation, compared to those without, demonstrating that impaired pulmonary function is an independent risk factor for AF in the general Japanese population.

In our study, pulmonary function was also considered. For all patients the airflow limitation was moderate but AF was more prevalent in subjects with lower values of FEV\textsubscript{1}.\textsuperscript{34}

Conclusions

We have demonstrated that, in patients with COPD exacerbations, changes in blood gases, abnormalities in pulmonary functions and hemodynamic alterations resulting from pulmonary hypertension, may lead to the development of atrial fibrillation. These changes lead to critical clinical implications in the diagnosis, prognosis and therapy of these subset of patients, making possible the development of local and systemic, unwanted therapeutic side-effects, increasing the length of hospital stay and the disability, worsening the patient’s quality of life, hindering rehabilitation, enhancing the chances of decline and are associated with large economic and social burdens\textsuperscript{35}, particularly in elderly people with COPD.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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