European Review for Medical and Pharmacological Sciences 2014; 18: 2908-2917

Atrial fibrillation in the acute, hypercapnic exacerbations of COPD

C. TERZANO, S. ROMANI, V. CONTI, G. PAONE, F. ORIOLO, A. VITARELLI

Respiratory Diseases Unit, School of Specialization in Respiratory Diseases, University of Rome "Sapienza", Policlinico Umberto I, Rome, Italy

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, haemogasanalysis, 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, FEV_1, 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[1]. 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[2]. AF may be triggered and maintained by either reentrant or non reentrant electrical activity[3], 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[4,5].

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.

Corresponding Author: Claudio Terzano, MD; e-mail: cterzano@tin.it

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[6,7].

Arrhythmias are common in patients with hypoxemia and abnormalities of carbon dioxide tension[8,9]. 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[10].

Hypoxiemia 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[11], particularly when hypercapnia causes a significant decrease in pH values[12].

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[13,14].

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[15]. Hypoxemia was defined by a $PaO_2 < 60$ mmHg and hypercapnia was defined by a $PaCO_2 > 45$ 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)[16].

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, P pulmonale (P wave amplitude of ≥ 2.5 mm (0.25 mV) in leads II, III, and a VF), or an S1Q3 (S1Q3T3) pattern[17,18].

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[19]. Right atrial pressure was estimated according to caval dimensions[20]. Estimation of pulmonary vascular resistance (PVR) was determined as previously described[21].

Forced expiratory volume in 1 second (FEV_1) 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 PFTs measurements.

According to GOLD criteria, the subjects with airflow limitation and FEV_1 % predicted ≥ 80 were identified as having mild airflow limitation, 50 ≤ FEV_1 % predicted < 80 were described as moderate, and FEV_1 % predicted < 50 were described as having severe airway obstruction. The highest values of FEV_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^2 or Fisher's exact test when appropriated.

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 Josè, 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_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).

Variables	Total (n=173)	COPD (n=138)	COPD and AF (n=35)	*p*-value
Gender: Male (n, %)	98 (56.6)	75 (54.3)	23 (65.7)	0.785 [b]
Age (years)	79.1±5.1	79.2±5.4	78.2±4.9	0.611 [a]
BMI (kg/m^2)	26.2±2.6	26.1±3.3	26.5±2.1	0.856 [a]
SBP (mmHg)	127.6±16.9	125.8±17.7	135.2±16.2	0.156 [a]
DBP (mmHg)	72.4±8.2	70.6±9.8	80.2±6.7	0.097 [a]
Fasting blood glucose	119.3±8.7	119.8±7.2	117.3±9.3	0.773 [a]
Diabetes mellitus (n, %)	39 (22.5%)	33 (23.9%)	6 (17.1%)	0.773 [a]
Current smokers (%)	125 (72.2%)	106 (76.8%)	19 (54.2%)	0.654 [a]

[a]Student *t*-test for unpaired data; [b]Chi-Squared test;
BMI=Body Mass Index; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; COPD: Chronic Obstructive Pulmonary Disease; AF: Atrial Fibrillation.

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

Variables	COPD (n=130)	COPD and AF (n=30)	*p*-value
FEV_1 %	76 ±8.3	57.1 ± 7.5	0.05 [a]
pH	7.38 ± 0.02	7.32 ± 0.03	0.2 [a]
PaO_2 mmHg	60.2±4.6	58.5±2.96	0,52 [a]
$PaCO_2$ mmHg	50.2 ± 3.5	70.6 ±5.3	0.05 [a]
HCO^{3-} mmol/L	30.2 ± 3.2	35.9±5.3	0.256 [a]
SO_2 %	91.5±2.2	90.2±2.7	0.33 [a]
EF %	51.2±2.7	41.3±6.3	0.652 [a]
PASP mmHg	35.2 ±2.3	45.3 ± 3.5	0.05 [a]
TDLVD mm	45.7±6	54.3±4	0.024 [a]
PP mm	9.2 ± 1	8.9 ± 2	0.67 [a]
SIV mm	10.4 ± 2	9.6 ± 3	0.774 [a]
Left atrial diameter (mm)	34.2 ± 2.1	45.2 ± 2.1	0.05 [a]
Left atrial area (cm^2)	21.7 ± 4	33.3 ± 5	0.05 [a]
Right atrial area (cm^2)	24.5 ± 5.2	30.3 ± 6.5	0.05 [a]
PVR wood units	1.3 ± 0.4	2.9 ±1.6	0.05 [a]

[a]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.

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

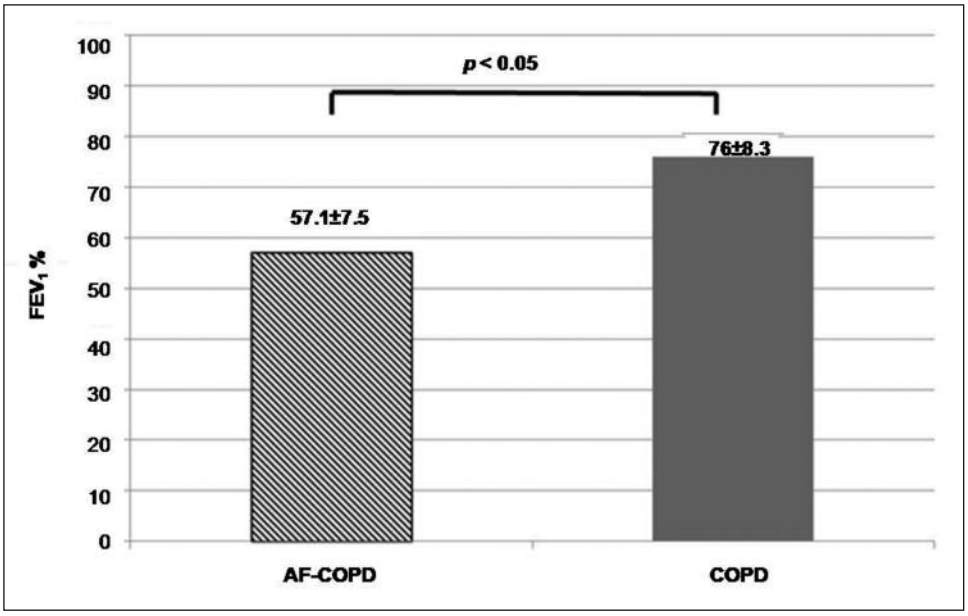

Figure 1. Values of Forced Expiratory Volume in one second % predicted (FEV_1) in patients with alonechronic obstructive pulmonary disease (COPD) and patients with COPD and concurrent atrial fibrillation (AF).
*p 0.05 vs COPD patients with AF and patients with alone COPD.

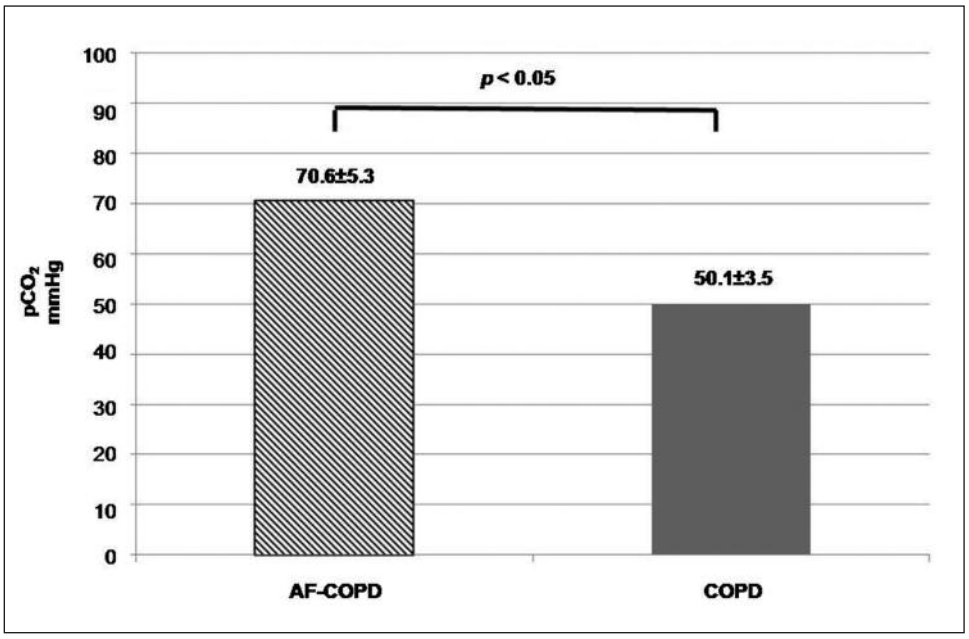

Figure 2. Values of $PaCO_2$ in patients with alone chronic obstructive pulmonary disease (COPD) and patients with COPD and concurrent atrial fibrillation (AF).

cm^2; $p < 0.05$). 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

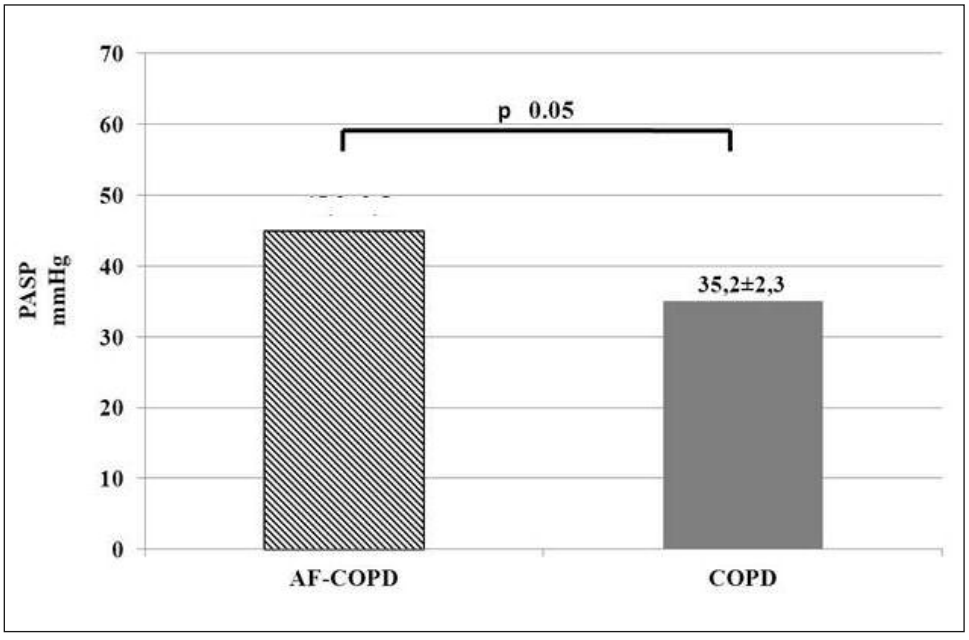

Figure 3. Values of Pulmonary Artery Systolic Pressure (PASP) in patients with alonechronic obstructive pulmonary disease (COPD) and patients with COPD and concurrent atrial fibrillation (AF).

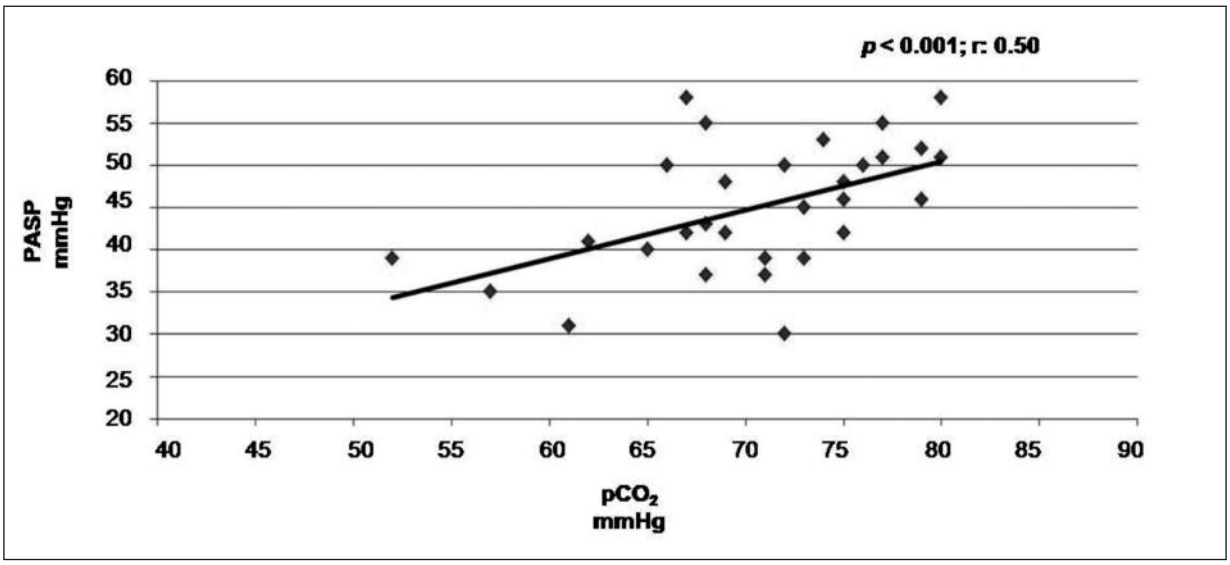

Figure 4. Direct relationship between $PaCO_2$ and pulmonary artery systolic pressure (PASP) in study subjects.

frequent comorbidities and that REFI 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[26], the prevalence of AF was 14.3% in COPD patients and 10.4% in controls.

Stevenson et al[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

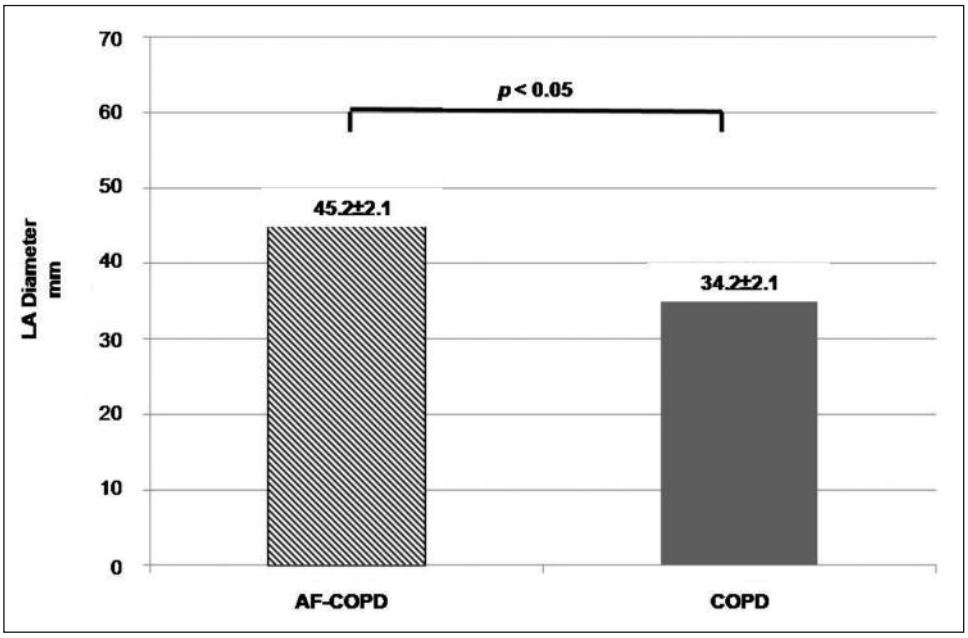

Figure 5. Values of Left atrium diameter in patients with alonechronic obstructive pulmonary disease (COPD) and patients with COPD and concurrent atrial fibrillation (AF).

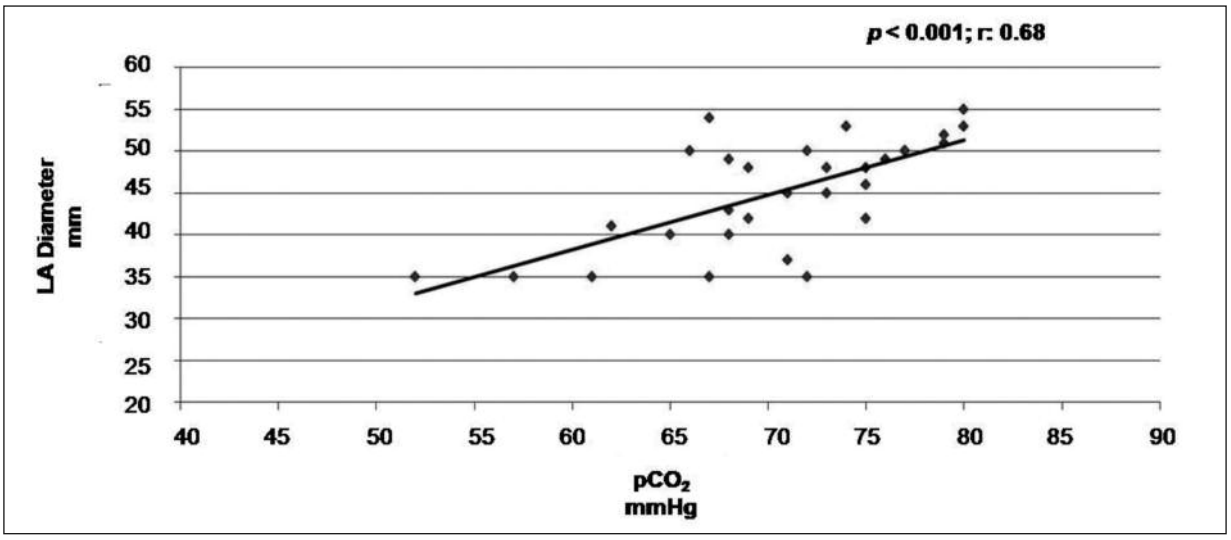

Figure 6. Direct relationship between the increase in Left Atrial (LA) Diameterand acute hypercapnia in study subjects.

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[23].

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 O_2 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

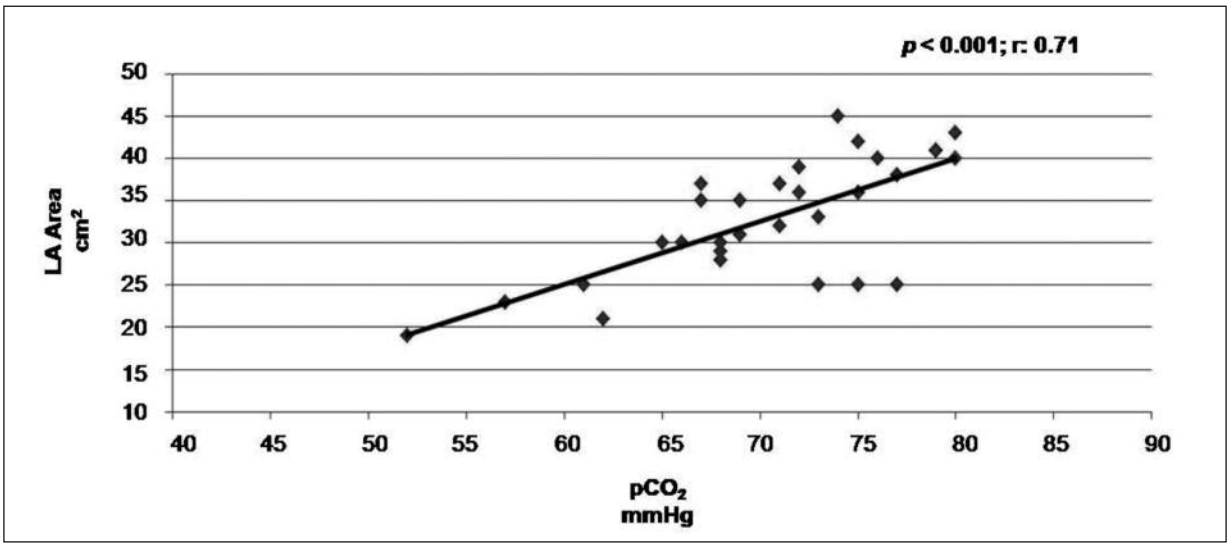

Figure 7. Direct relationship between Left Atrial (LA) Area and acute hypercapnia in study subjects.

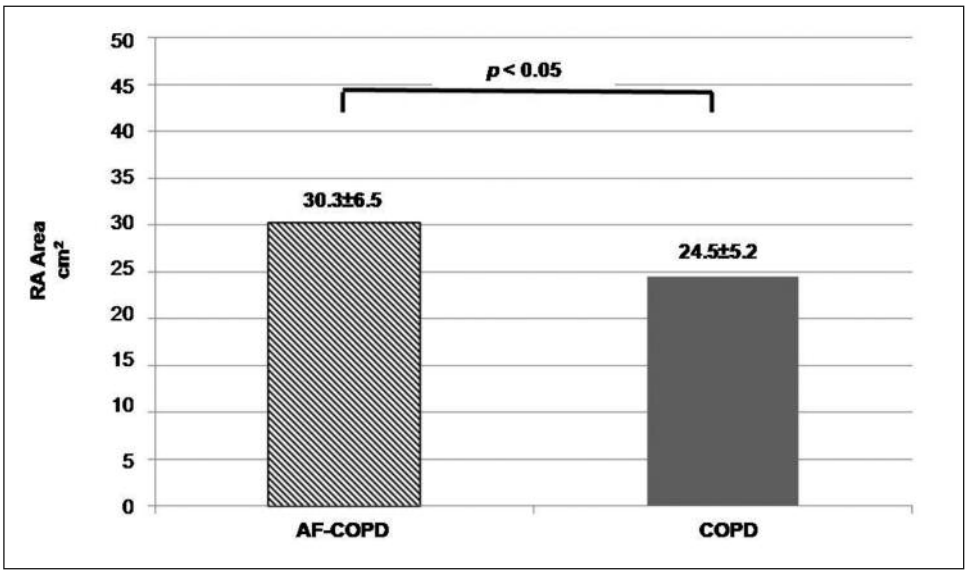

Figure 8. Values of Right Atrial (RA) Area in patients with chronic obstructive pulmonary disease (COPD) and patients with COPD and concurrent atrial fibrillation (AF).

neuro-humoral release of catecholamines may increase ventricular irritability[12].

COPD may cause both hypoxiemia and hypercapnia. This association alters adrenergic activity and is expected to have wide-ranging and complex effects on atrial electrophysiology, intracellular 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 vasculatures 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

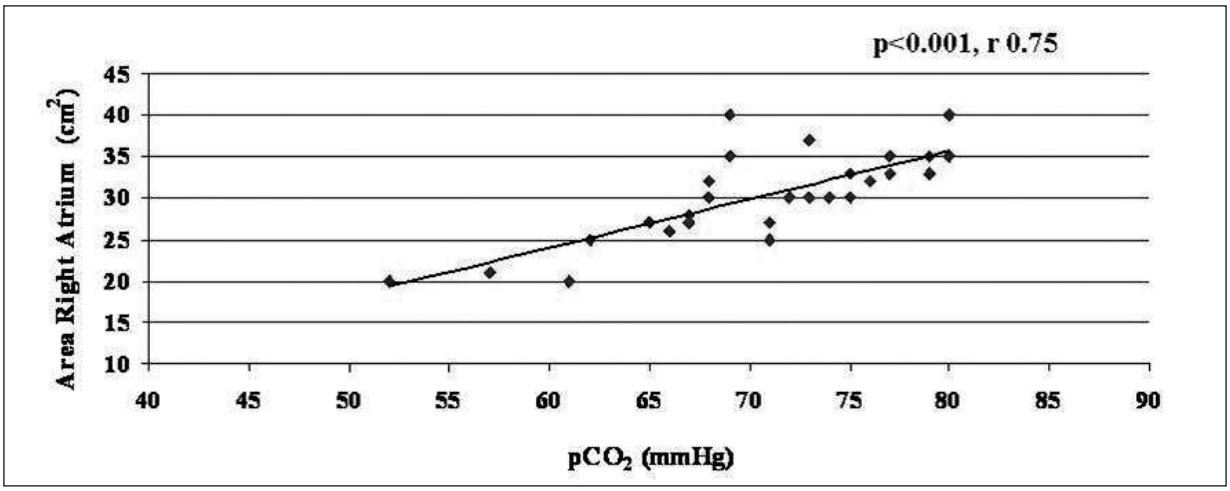

Figure 9. Direct relationship between Right Atrial (RA) Area and acute hypercapnia in study subjects.

catheterization parameters has been previously described[31,32].

In a prospective study, Buch et al[10] investigated the relationship between forced expiratory volume in one second (FEV_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[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_1.

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[34,35], particularly in elderly people with COPD.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004; 110: 1042-1046.
2) Wolf PA, Benajamin EJ, Belanguer AJ, Kannel WB, Levy D, D'Agostino RB. Secular trends in prevalence of atrial fibrillation: the Framingham study. Am Heart J 1996; 131: 790-795.
3) Workman AJ, Kane KA, Rankin AC. Cellular bases for human atrial fibrillation. Heart Rhythm 2008; 5: S1-S6.
4) Gramley F, Lorenzen J, Jedamzik B, Gatter K, Koellensperger E, Munzel T, Pezzella F. Atrial fibrillation is associated with cardiac hypoxia. Cardiovasc Pathol 2010; 19: 102-111.
5) Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Indipendent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA 1994; 271: 840-844.
6) Bemis CE, Serur JR, Borkenhagen D, Sonnenblick EH, Urschel CW. Influence of right ventricular filling pressure on left ventricular pressure and dimension. Circ Res 1974; 34: 498-504.
7) Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT II, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 1979; 301: 453-459.
8) West JB. Causes of carbon dioxide retention in lung disease. N Engl J Med 1971; 284: 1232.
9) Price HL. Effects of carbon dioxide on the cardiovascular system. Anesthesiology 1960; 21: 652.
10) Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003; 21: 1012-1016.
11) Stevenson IH, Roberts-Thomson KC, Kistler PM, Edwards GA, Spence S, Sanders P, Kalman JM. Atrial electrophysiology is altered by acute hypercapnoea but not hypoxiemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. Hearth Rhythm 2010; 7: 1263-1270.
12) Claudio Terzano. Fisiologia, fisiopatologia e terapia dei disturbi dell'equilibrio acido-base in Terzano C. Malattie dell'Apparato Respiratorio. Springer, Italy, 2006; pp. 177-190.
13) Tükek T, Yildiz P, Akkaya V, Karan MA, Atilgan D, Yilmaz V, Korkut F. Factors associated with the development of atrial fibrillation in COPD patients: the role of P-wave dispersion. Ann Noninvasive Electrocardiol 2002; 7: 222-227.
14) Bhatt SP, Nanda S, Kintzer JS. Arrhythmias as trigger for acute exacerbations of chronic obstructive pulmonary disease. Respir Med 2012; 106: 1134-1138.
15) Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease 2009. Global Initiative for Chronic obstructive Lung Disease (GOLD).
16) Van Bemmel JH, Kors JA, van Herpen G. Methodology of the modular ECG analysis system MEANS. Methods Inf Med 1990; 29: 346-353.
17) Maeda S, Katsura H, Chida K, Imai T, Kuboki K, Watanabe C, Kida K, Ohkawa S, Matsushita S, Ueda K. Lack of correlation between P pulmonale and right atrial overload in chronic obstructive airways disease. Br Heart J 1991; 65: 132-136.
18) Shine KI, Kastor JA, Yurchak PM. Multifocal atrial tachycardia. Clinical and electrocardiographic features in 32 patients. N Engl J Med 1968; 279: 344-349.

19) Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30: 2493-2537.

20) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-1463.

21) Rudski LG, Lai WW, Afilalo J, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713.

22) FusterV, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S; Task Force on Practice Guidelines, American College of Cardiology/American Heart Association; Committee for Practice Guidelines, European Society of Cardiology; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J 2006; 27: 1979-2030.

23) Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep disordered breathing. The Sleep Heart Health Study. Am J Respir Crit Care Med 2006; 173: 910-916.

24) Jongnarangsin K, Chugh A, Good E, Mukerji S, Dey S, Crawford T, Sarrazin JF, Kuhne M, Chalfoun N, Wells D, Boonyapisit W, Pelosi F Jr, Bogun F, Morady F, Oral H. Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2008; 19: 668-672.

25) Terzano C, Conti V, Di Stefano F, Petroianni A, Ceccarelli D, Graziani E, Mariotta S, Ricci A, Vitarelli A, Puglisi G, De Vito C, Villari P, Allegra L. Comorbidity, hospitalization and mortality in COPD: results from a longitudinal study. Lung 2010; 188: 321-329.

26) Mapel DW, Dedrick D, Davis K. Trends and cardiovascular cormobidities of COPD patients in the Veterian Administration Medical System. COPD 1991-1999; 2: 35-41.

27) Workman AJ, Rankin AC. Do hypoxemia or hypercapnia predispose to atrial fibrillation in breathing disorders, and, if so, how? Heart Rhythm 2010; 7: 1271-1272.

28) Workman AJ. Cardiac adrenergic control and atrial fibrillation. Naunyn-Schmied Arch Pharmacol 2010; 381: 235-249.

29) Ryu JH, Krowka MJ, Pellikka PA, Swanson KL, McGoon MD. Pulmonary hypertension in patients with interstitial lung diseases. Mayo Clin Proc 2007; 82: 342-350.

30) Kang H, Bae BS, Kim JH, Jang HS, Lee BR, Jung BC. The relationship between chronic atrial fibrillation and reduced pulmonary function in cases of preserved left ventricular systolic function. Korean Circ J 2009; 39: 372-377.

31) Yong G, Khairy P, De Guise P, Dore A, Marcotte F, Mercier LA, Noble S, Ibrahim R. Pulmonary arterial hypertension in patients with transcatheter closure of secundum atrial septal defects: a longitudinal study. Circ Cardiovasc Interv 2009; 2: 455-462.

32) Vitarelli A, Sardella G, Di Roma AD, Capotosto L, De Curtis G, D'Orazio S, Cicconetti P, Battaglia D, Caranci F, De Maio M, Bruno P, Vitarelli M, De Chiara S, D'Ascanio M. Assessment of right ventricular function by three-dimensional echocardiography and myocardial strain imaging in adult atrial septal defect before and after percutaneous closure. Int J Cardiovasc Imag 2012; 28: 1905-1916.

33) Shibata Y, Watanabe T, Osaka D, Abe S, Inoue S, Tokairin Y, Igarashi A, Yamauchi K, Kimura T, Kishi H, Aida Y, Nunomiya K, Nemoto T, Sato M, Konta T, Kawata S, Kato T, Kayama T, Kubota I. Impairment of pulmonary function is an independent risk factor for atrial fibrillation: the Takahata study. Int J Med Sci 2011; 8: 514-522.

34) Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006; 27: 397-412.

35) Simoni-Wastila L, Blanchette CM, Qian J, Yang HW, Zhao L, Zuckerman IH, Pak GH, Silver H, Dalal AA. Burden of chronic obstructive pulmonary disease in medicare beneficiaries residing in long-term care facilities. Am J Geriatr Pharmacother 2009; 7: 262-270.