The Association between Chronic Obstructive Pulmonary Disease (COPD) and Atrial Fibrillation: A Review

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Abstract

COPD is one of the leading causes of Mortality & Morbidity in the US and is associated with a wide variety of cardiovascular diseases especially arrhythmias, angina, myocardial infarction and congestive heart failure and is directly associated with the severity of COPD described in the GOLD initiative. COPD is an independent risk factor for AF/AFL. Smoking, hypoxia and inflammation all contribute to AF in COPD patients mainly via atrial remodeling while hypercapnia contributes to it via increasing refractoriness of the atrial musculature and a delay in the return of the refractoriness to normal after resolution of the hypercapnia. The most common EKG abnormality found in patients with COPD is P pulmonale and the PQ interval is the strongest predictor of developing AF. The P wave Dispersion (PwD) was also an independent risk factor for the development of AF and was found to be more in the acute phase than in the stable phase.

The BODE index, an important prognostic score among patients hospitalized with a COPD exacerbation has a direct correlation with the prevalence of AF/AFL while the DECAF score, which was found to be superior to the CURB 65 score as a mortality predictor for hospitalized patients, includes AF as one of the criteria. Chronic hypoxemia is one of the main reasons for altered pulmonary vein anatomy and hence the presence of COPD was identified as an independent risk factor for the recurrence of atrial tachyarrhythmias after catheter ablation in patients with COPD and the absence of COPD was also found to be an independent predictor for a successful electrocardioversion. These patients were also found to have an increased incidence of non-PV foci for the arrhythmias. Oral glucocorticoids were associated with an increased risk of developing AF especially high dose steroids. It is recommended to correct the underlying respiratory decompensation while treating patients with AF as they render the treatment of AF ineffective. Non-dihydropyridine calcium channel blockers should be used as first line rate control agents for AF in patients with concomitant COPD while the β-blockers, sotalol, propafenone can be used in patients with obstructive lung disease who do not have bronchospasm.

Keywords: Chronic obstructive pulmonary disease; Atrial fibrillation

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global public health problem. COPD is a common preventable and treatable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. In 2020, COPD is projected to rank fifth worldwide in terms of burden of disease and third in terms of mortality [1] though presently it is the 4th leading cause of Mortality and the 2nd leading cause of Morbidity in the United States (US) [2].

Extra-pulmonary manifestations of COPD include cardiovascular disease, skeletal muscle dysfunction, osteoporosis, metabolic syndrome depression and lung cancer [1]. COPD is associated with specific electrocardiographic (EKG) abnormalities while an increased incidence of cardiac arrhythmias has been reported which includes atrial fibrillation (AF), atrial flutter (AFL), multifocal atrial tachycardia (MAT) and non-sustained ventricular tachycardia (NSVT) [3]. It is estimated that there were approximately 33.5 million people with AF in 2010 worldwide (20.9 million men [95% uncertainty interval (UI), 19.5-22.2 million] and 12.6 million women [95% UI, 12.0-13.7 million]) [4] and it was also estimated that the burden of AF in the United States alone would increase to at least 5.6 million by 2050 [5].

COPD and Cardiovascular Disease

Patients with diagnosed and/or undergoing treatment for COPD are at a substantially increased risk of hospitalizations and mortality due to heart diseases. In one retrospective cohort study, the prevalence of cardiovascular diseases (CVD) was higher in the COPD group than the control group. After all the cardiovascular risk factors were adjusted for odds ratios of
prevalence were: arrhythmia 1.76 (confidence interval [CI]: 1.64-1.89), angina 1.61 (CI: 1.47-1.76), acute myocardial infarction 1.61 (CI: 1.43-1.81), congestive heart failure 3.84 (CI: 3.56-4.14). There was also an increased risk of hospitalization secondary to cardiovascular causes in the COPD group [6].

The Forced Vital Capacity (FVC), defined as the maximal volume of air exhaled with maximally forced effort from a maximal inspiration, Expressed in liters and the Forced Expiratory Volume in one second (FEV1), defined as the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters are the major determinants of the severity of COPD [1,7]. The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) classifies the severity of airflow limitation as determined by spirometry into 4 grades (GOLD 1, mild, FEV1 ≥80% predicted; GOLD 2, moderate, FEV1 50-79% predicted; GOLD 3, severe, FEV1 <50% predicted; and GOLD 4, very severe, FEV1 <30% predicted) using the fixed ratio, post-bronchodilator FEV1/FVC <0.7 [1]. An association was also established between the severity of airflow obstruction based on the GOLD criteria and the prevalence of CVD which showed that prevalence of CVD was higher among subjects with GOLD 2 (OR 2.9, 95% CI 2.4 to 3.6) and GOLD 3 or 4 COPD (OR 3.0, 95% CI 2.0 to 4.5), compared with normal subjects [8]. The Atherosclerosis Risk in Communities (ARIC) cohort study established an inverse co-relation between the FEV1 and rate of incident AF which was independent of age, gender, BMI, smoking and blood pressure [9].

A recent retrospective study showed that of COPD were associated with an increased likelihood of AF/AFL (23.3% vs. 11.0%, respectively, p<0.0001), NSVT (13.0% vs. 5.9%, respectively, p<0.0001), and sustained ventricular tachycardia (SVT; 0.9% vs. 1.6%, respectively, p<0.0001) and that it remained a significant predictor of AF/AFL and NSVT (p<0.0001 and p<0.0001, respectively) after adjusting for age, gender, tobacco use, obesity, hypertension, coronary artery disease, heart failure, diabetes, anemia, cancer, chronic kidney disease, and rate/rhythm control medications [10]. This article provides a succinct overview of the association of COPD with AF, the arrhythmogenic mechanisms and potential treatment strategies.

### COPD and Atrial Fibrillation: Potential Causes of Arrhythmia and EKG Changes

There seem to be a wide variety of reasons for arrhythmias to occur in COPD beginning from risk factors, its effect in altering cardiopulmonary physiology to the treatment of COPD. Smoking, airway inflammation, hypoxia, hypercapnia, pulmonary hypertension, β-adrenergic agonist and steroids all contribute to ultimately causing or worsening AF [11-15].

Shan et al. attempted to postulate the reasoning for the increased incidence of AF in smokers using a canine model. They concluded that the pro fibrotic response of nicotine in upregulation of expression of Transforming Growth Factor Beta 1(TGF-β1) and TGF-βRII at the protein level, and a 60-70% decrease in the levels of miRNAs miR-133 and miR-590 was critical in atrial remodeling in the canine atrium [16]. Smoking was found to be an independent risk factor in the recurrence of AF/AFL after cardioversion in women while an increased risk of mortality and not arrhythmia was found in men [11].

It has been shown consistently that there exists an inverse relationship between FEV1, FVC with AF. The Copenhagen City Heart Study demonstrated that the Risk of new AF at re-examination was 1.8-times higher for FEV1 between 60-80% of predicted compared with a FEV1 of ≥80% after adjustment for sex, age, smoking, blood pressure, diabetes and body mass index. They also showed that the risk of AF hospitalization was 1.3 times more with a FEV1 between 60-80% of predicted and 1.8 times with a FEV1 of ≤60% compared with a FEV1 of ≥80%, proving that reduced lung function as an independent predictor of AF [17]. It is well documented that oxidative stress and inflammation are two of the major factors in the pathophysiology of COPD and now postulations have also been made of its impact in atrial remodeling and thus causing and potentially worsening existing AF [12].

Hypoxia, commonly seen in patients with COPD, causes an upregulation of Vascular Endothelial Growth Factor (VEGF) secondary to an increase in Hypoxia-induced transcription factor-1α (HIF-1α). Matrix metalloproteinase 9 (MMP9) expression is increased in the atrium in a patient with AF and potentially causes atrial remodeling. It was shown via Immunofluorescence that there was excess production and colocalization of HIF-1α, VEGF and MMP-9 within the endothelium of the atrial arteries in the AF group as compared to patients without AF [13].

Patients with COPD are prone to have acute exacerbations of the disease and common causes for this are usually viral infections of the upper respiratory tract and infections of the tracheobronchial tree [1]. Terzano et al. showed that suboptimal pulmonary function, hypercapnia and high values of pulmonary artery systolic pressure are independent predictors of incident AF [18]. In their experimental sheep model, Stevenson et al. showed the hypercapnia caused an increase in the atrial musculature refractoriness and the conduction time however, intriguingly, there was a delay in only the conduction time to return to normal after the resolution of hypercapnia prompting the theory that this differential recovery time may be the reason for an increased incidence of AF observed in the phase of eucapnia [19].

P pulmonale (P wave ≥0.25 mV in the inferior leads) is usually omnipresent on EKG’s of patients with chronic lung diseases. Hayashi et al, in a digital analysis of EKG’s in a 25 year period showed P-wave duration and PQ interval were significantly longer in the AF group than in the non-AF group (115.4 ± 17.2 ms vs. 107.0 ± 17.2 ms, P=0.0003 and 166.3 ± 23.9 ms vs. 153.2 ± 25.4 ms, P=0.0001, respectively). They concluded that the PQ interval is the strongest stratifier for AF development in patients with P pulmonale [20]. The P wave dispersion (PwD), which is the difference in the maximum and minimum duration of the P wave, was also found to be an independent risk factor associated in the development of AF.
and the PwD was found to be increased more in the acute phase than in stable phase and is greater in patients with more frequent exacerbations suggesting that the PwD could be a target for prediction, prevention and therapy of acute exacerbation of COPD [22].

The BODE index is a multidimensional 10-point scale which integrates body mass index, degree of airflow obstruction and dyspnea and exercise capacity measured in 6-min walk test and the score is directly proportional with mortality. It was shown that patient’s with higher BODE index scores had a significantly greater prevalence of arrhythmias including AF/AFL and SVT [23]. The Dyspnea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation (DECAF) score was introduced by Steer et al, as a predictor of mortality in hospitalized patients with COPD exacerbations. The DECAF score includes the 5 strongest predictors of mortality i.e. MRC Dyspnea Score, eosinopenia, consolidation, acidemia, and atrial fibrillation and was found to be a stronger than the other predictors like the CURB65 [24].

COPD and its Effect on Ablation strategies of AF

COPD has a significant effect on cardiopulmonary physiology but also has an impact in altering the anatomy of the same system because of which it affects outcomes of catheter ablations for AF, its progression and mortality. COPD is associated with hypoxemia and acidosis, which leads to, increased pulmonary vascular resistance. This causes an increased level of inflammatory markers that promotes fibrosis and thus causes structural remodeling of pulmonary vessels [25]. A subgroup analysis of the European Heart Survey (EHS) on AF by de Vos et al, gave rise to the HATCH score while studying AF progression from paroxysmal to persistent. The HATCH score was an abbreviation for heart failure, age, previous episode of transient ischemic attack or stroke, COPD and hypertension, which were all, found to be independent predictors of AF progression [26]. In their study, Roh et al. showed that significant alteration of pulmonary vein (PV) anatomy was related to arrhythmogenicity. They also showed that non-PV foci were more common in the chronic lung disease group (26.7%) than in the control group (5.0%; P=0.025) and all the non-PV foci were located in the right atrium [27]. The impact of COPD on outcomes of catheter ablation in patients with AF in terms of recurrence was evaluated in a prospective study by Gu et al, which showed that non-paroxysmal AF (P=0.013, OR=1.767, 95% CI: 1.129-2.765) as well as the presence of COPD (P=0.029, OR=1.951, 95% CI: 1.070-3.557) were the independent predictors for higher atrial tachyarrhythmia recurrence [28]. Absence of COPD was found to be an independent predictor for a successful electro-cardioversion in patients with AF while the absence of COPD was also an independent predictor of sinus rhythm at a 1 yr follows up [29].

COPD Treatment Causing AF

Inhaled bronchodilator medications continue to remain the mainstay treatment for COPD patients. It includes beginning therapy with a β-2 agonist, an anticholinergic or a combination of the two. A meta-analysis of randomized placebo-controlled trials of β-2-agonist treatment in patients with obstructive airway disease performed concluded that the initiation of treatment increases heart rate and reduces potassium concentrations compared to placebo and it causes adverse cardiovascular events like CHF, AF, etc. likely through these mechanisms along with β-1 adrenergic stimulation [14]. At the same time the side effect profile of tiotropium was studied in the UPLIFT trial and found no difference in the incidence of AF in patients receiving tiotropium vs placebo [30]. Long term glucocorticoid use is well known to cause hypertension, Diabetes Mellitus, Left atrial enlargement, HF and ischemic heart disease all of which can directly or indirectly cause AF. In a population based, case control study current glucocorticoid use was associated with an increased risk of AF or AFL compared with never use (adjusted OR, 1.92; 95% confidence interval [CI], 1.79-2.06) while among new glucocorticoid users; the adjusted OR was 3.62 (95% CI, 3.11-4.22) [15]. In another case control study by van der Hooft et al, findings strongly showed that patients receiving high-dose corticosteroid therapy, not uncommon in the treatment of COPD, are at increased risk of developing atrial fibrillation [31]. Huerta et al. showed that inhaled steroids were not associated with an increased risk of AF or arrhythmias while theophylline and oral steroids were associated with an increased risk of arrhythmias especially AF [32]. In a Meta-Analysis from 2013 on Roflumilast, an increased incidence of AF as compared to placebo was seen however the writers pointed out that this is likely due to chance as most of the studies in the analysis had excluded patients with major cardiovascular events [33].

Treatment Strategies

Per the AHA/ACC/HRS (American Heart Association/ American College of Cardiology/ Heart Rhythm Society) guidelines, optimizing therapy for the underlying lung disease with correction of the hypoxia and acidosis in patients with COPD developing AF is the cornerstone for management as the antiarrhythmic drugs or cardioversion are likely to be ineffective until the respiratory decompensation has been corrected. Bronchodilator agents like Theophylline and β agonists have the propensity to precipitate AF and hence should be avoided in patients with AF. Non β-1 selective blockers, sotalol, propafenone and adenosine are contraindicated in patients with bronchospasm however the β blockers, sotalol and propafenone can be considered in patients with obstructive lung disease who do not have bronchospasm. They also recommend a non-dihydropyridine calcium channel blocker as the first line therapy for rate control in these patients while Amiodarone and Digoxin can also be used, the latter in patients with preserved left ventricular ejection fraction. In hemodynamically unstable patients, direct cardioversion is recommended while AV nodal ablation or ventricular pacing may be needed to control the
ventricular rate with the cardioversion posing challenges of its own as mentioned above [34]. Despite these challenges, there were significant improvements in quality of life scores in patients with COPD post catheter ablation [24]. Kuralay et al. showed that early prophylactic amiodarone in patients with COPD undergoing coronary artery bypass grafting significantly reduced the incidence of post-operative SVT’s including AF/AFL [35].

Conclusion
COPD is one of the leading causes of Mortality & Morbidity in the US. COPD is an independent risk factor for Atrial fibrillation. It is recommended to correct the underlying respiratory decompensation while treating patients with AF as they render the treatment of AF ineffective. The presence of atrial fibrillation is also a predictor for increased mortality in patients admitted to the hospital with COPD. It is thus important to understand this relationship between these two disorders and appropriately manage both these co-morbidities for improved outcomes.

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