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Research Article

Chronic Obstructive Pulmonary Disease as Risk Factor for Ischemic Cerebrovascular Accident

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Keywords

- Stroke; COPD; Ischemic CVA; Inflammation; Atherosclerosis

Abstract

Rationale: Atrial Fibrillation (AF) is a potent risk factor for ischemic cerebrovascular Accident (ICVA). Inflammation is potential pathogenic factor for atherosclerosis and ICVA. Chronic Obstructive pulmonary disease (COPD) is associated with increased inflammatory markers. Subjects frequently suffer from COPD and AF, may have higher risk for ICVA.

Methods: Single center cross sectional study was performed. All subjects with diagnosis of COPD, AF and ICVA for duration of 5 years were categorized in three groups; COPD, AF, and COPD plus AF. Prevalence of ICVA was compared. Presence of confounding factors affecting ICVA risk was recorded for all subjects; age >65, type 2 Diabetes, Hypertension, peripheral vascular disease, dyslipidemia, and Congestive cardiac failure.

Results: Total charts reviewed were 1821; only COPD 887, only AF 684, and both together 250. ICVA was documented in total 484 (26.6%) subjects. Individuals who had COPD and AF were 1.86 (95% CI 1.34 to 2.58, p<0.001) times as likely to have an ICVA compared to subjects who only have COPD or AF. Prevalence of ICVA was also significantly higher in subjects who have only AF versus those who have only COPD (P<0.001). In logistic Regression model while adjusting for all significantly different confounding factors, AF and COPD was found to be strong predictor of ICVA (p<0.001), much stronger than AF only (p=0.04). Odd ratio was 1.28 (95% CI 1.003 to 1.65) for AF only.

Conclusion: Presence of COPD may increase the risk of ischemic stroke in subjects with Atrial Fibrillation.

ABBREVIATIONS

AF: Atrial Fibrillation; COPD: Chronic Obstructive Pulmonary Disease; ICVA: Ischemic Cerebrovascular Accident; DM: Diabetes Mellitus; HTN: Hypertension; PAD: Peripheral Arterial Disease ; CCF: Congestive Cardiac Failure

INTRODUCTION

Annually, 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing immense burdens on family and community. The World Health Organization (WHO) estimates that a stroke occurs every 5 seconds [1]. Atrial fibrillation (AF) is the most common sustained arrhythmia [2] and confers an independent risk of stroke and death [3]. The role of inflammation in atherosclerosis and stroke has been well-established [4] COPD with Reduced lung function is associated with increased levels of systemic inflammatory markers which may have important pathophysiological and therapeutic implications [5]. COPD is also associated with higher rates of myocardial infarction [6], and an increased risk of the development of cerebral micro-bleeds in deep or infra-tentorial locations [7]. About 14% of COPD subjects suffers from AF [8]. We proposed that COPD may increase the risk of ICVA in subjects with AF. Framingham study provided the risk estimate for risk factors for stroke, age-adjusted incidence of stroke was more than doubled in the presence of coronary heart disease, more than tripled in the presence of hypertension, more than fourfold in subjects with cardiac failure and a near fivefold in subjects with atrial fibrillation [9].Since we wanted to estimate the risk of ICVA in subjects with COPD. Therefore we chose AF to compare this risk estimate associated with COPD. Purpose of the study was to detect if COPD is a risk factor and how significant is the risk associated with COPD comparing to another already established independent risk factor (Atrial fibrillation).

METHODS

Hospital electronic medical records were screened to collect all subjects who have a diagnosis of either COPD (ICD-9 code 496) or AF (ICD-9 code 427.31) for duration of 5 years January 01, 2008 to December 31st 2012. Another list was generated with cross screening with diagnosis of ICVA (ICD-9 Codes code 433, 434, 436), and 2 groups were created one with ICVA and other without ICVA. All subjects were classified into 3 subgroups, only COPD, only AF and COPD and AF together. Charts were manually reviewed by more than 8 researcher and data was collected: age, presence of risk factors for ICVA; diabetes mellitus

(DM), hypertension (HTN), peripheral arterial disease (PAD), dyslipidemia, and congestive cardiac failure (CCF). Prevalence rates were compared among the three groups; only COPD, only AF and COPD and AF together. Study was approved by IRB Hines veterans' Affairs (VA) medical center.

Statistical methodology

Statistical analysis was performed by using IBM SPSS software package (IBM Corporation, Armonk, NY, USA). Categorical variables were analyzed using Chi-square tests. Mantel-Haenszel common odds ratio for ICVA was computed for each of the 3 study groups as odds ratio of one group versus the other two groups (i.e. AF group versus the combined cohort of COPD and COPD plus AF groups). Logistic regression analysis was performed to evaluate potential predictors of ICVA. The dependent variable was ICVA and the following covariates/potential predictors were entered in the equation: age (3 categories: 65 year <, between 65 and 75 years and 75 year >), presence of AF only, COPD only and both AF and COPD, hypertension, diabetes, CCF, dyslipidemia and PAD. Statistically significance was considered at a p value of <0.05 (two sided alpha error<0.05).

RESULTS

Total charts reviewed were 1821; only COPD 887, only AF 684, and both together 250. ICVA was documented in total 484 (26.6%) subjects. ICVA was found to be in 205 subjects (30%) in only AF group, and 180 (20.3%) in only COPD group, while 99 subjects (39.6%) had ICVA in AF plus COPD group (Table 1).

Comparison of AF plus COPD group to only AF group

Our sample was comprised of predominantly male Subjects (98%) and gender difference across groups was not significant. Subjects has similar proportion of elderly (>75 years) (62.4 VS 58.2% p 0.24), hypertensive's (75.6 VS 74.1%, p =0.6), diabetics (33.2 VS 33.9 % p =0.8) while AF plus COPD group has higher proportion of subjects with dyslipidemia (61.2 VS 53.2 % p 0.03) and CCF (42.4 Vs 34.5 % p 0.02).

Comparison of AF plus COPD group to only COPD group

Our sample was comprised of predominantly male Subjects (98%) and gender difference across groups was not significant. AF plus COPD subjects have higher proportion of elderly (>75 years) (62.4 vs 33.8% p <0.01), hypertensives (75.6 vs 61.7%, p< 0.001), diabetics (33.2 vs 25.7 % p =0.02), subjects with dyslipidemia (61.2 vs 47 % p 0.001) and CCF (42.4 vs 14.3 % p <0.001). Only PAD was similar between the 2 groups (13.2 vs 10.1%, p 0.2).

Comparison of only AF group to only COPD group

Subjects were older (>75 years) in only AF group than only COPD group (58.2 VS 33.8%, P<0.001). Hypertension, CCF, dyslipidemia and PAD was more prevalent in only AF group than only COPD group; HTN (74.1% VS 61.7%, p <0.001), CCF (34.5 VS 14.3%, p <0.001), dyslipidemia (53.2 VS 47%, p <0.001), PAD (33.9 VS 25.7 %, p <0.001).

Logistic regression analysis

In logistic Regression model while adjusting for all significantly different confounding factors, AF plus COPD was found to be strong predictor of ICVA (p<0.001), much stronger than AF only (p=0.04). Odd ratio for ICVA was 1.86 (95% CI 1.34 to 2.58, p<0.001) for AF and COPD group versus 1.28 (95% CI 1.003 to 1.65) for AF only.

DISCUSSION

This study shows that subjects with AF and COPD are more likely to have ICVA. Another land mark study (Rotterdam Study) followed 3,115 participants without history of stroke for 18 years for occurrence of stroke. Study demonstrated a higher risk of both ischemic and hemorrhagic stroke in subjects with COPD and revealed the importance of smoking as a shared risk factor [10].

Donaldson et al., analyzed data from 25,857 subjects with COPD entered in The Health Improvement Network database

Table 1: prevalence of outcome measures and confounding variables in sample.

	All	COPD only		AF only		AF+COPD		P value*
N=	1821	887		684		250		
		ICVA+	ICVA-	ICVA+	ICVA-	ICVA+	ICVA-	
N, %		180 (20.2%)	707 (79.8%)	205 (29.9%)	479 (70.1%)	99 (39.6%)	151 (60.4%)	
Age<65 years		7.6%	92.4%	18.1%	81.9%	34.7%	65.3%	<0.01
Age 65-75		30%	70%	23.7%	76.3%	31.5%	71.7%	<0.01
age >75		62.4%	37.6%	58.2%	41.8%	33.8%	66.2%	<0.01
gander(male)		98.4%	1.6%	96.2%	3.8%	97.7%	2.7%	=0.08
comorbid								
hypertension		75.6%	24.4%	74.1%	25.9%	61.7%	38.3%	<0.01
DM		33.2%	66.8%	33.9%	66.1%	25.7%	74.3%	<0.01
dyslipidemia		61.2%	38.8%	53.2%	46.8%	51.3%	48.7%	<0.01
CCF		42.4%	57.6%	34.5%	65.5%	14.3%	85.7	<0.01
PAD		13.2%	86.8%	11%	89%	10.1%	89.1%	=0.38

Foot note: *reported p values are from chi square statistics for difference of variables among 3 groups (AF plus COPD, AF alone, COPD alone).

over a 2-year periods and found that exacerbations of COPD increase the risk of myocardial infarction and stroke [11]. Similarly Feary et al., reviewed the computerized primary care records of 1,204,100 members of a general population aged ≥ 35 years and found that individuals with COPD are substantially more likely to have pre-existing cardiovascular disease, DM or a previous stroke and are at high risk of acute arteriovascular events [12]. Subjects in these studies have coexistent AF and other risk factors for ICVA therefore they could not determine specific role of COPD as risk factor for ICVA with or without AF. Since we collected data for other risk factors for ICVA we were able to detect increase risk associated with COPD for stroke in subjects with AF.

We hypothesize that mechanism of this increase risk is complex and multifactorial including inflammation and anticholinergic medication treatment for COPD. Sin et al analyzed data from Third National Health and Nutrition Examination Survey (n=6629) and found that systemic inflammatory markers were present in participants with chronic airflow obstruction and they were associated with cardiac injury [13]. Many studies found that raised inflammatory markers are associated with atherosclerosis. Inflammatory processes not only promote initiation and evolution of atheroma, but also contribute decisively to precipitating acute thrombotic complications of atheroma [14]. Proinflammatory cytokines contribute to local inflammation and growth of plaque. Intensified inflammatory activation may lead to local proteolysis, plaque rupture and thrombus formation which lead to ischemia and infarction [15]. Inflammation also plays a crucial role in the destabilization of internal carotid artery plaques leading to ICVA [16]. Moreover in patients with cerebral ischemia, early inflammatory processes lead to secondary brain injury [17]. Likewise Singh et al found that Inhaled anticholinergic medications are associated with a significantly increased risk of cardiovascular death, myocardial infarction, or stroke among subjects with COPD [18]. These findings generate some interesting questions; is this risk associated with COPD is more with COPD with exacerbation? Is this risk from smoking or from COPD itself regardless of smoking status? Is this risk modifiable with either the treatment of COPD or with any anti-inflammatory medications?

Our sample analysis suggests that COPD and AF group has ICVA risk 39.6 % while AF alone group has risk of 30% so there is about 9% increase in associated risk for ICVA. While in direct comparison between only COPD and only AF group, COPD is about a half of a risk for ICVA as compared to AF. A prospective trial with COPD versus AF is required to estimate absolute attributable risk associated with COPD. In our sample logistic regression analysis for other included variables determine odds of ICVA for each variable; type 2 diabetes (1.35), HTN (2.51), dyslipidemia (1.51), PAD (1.39), and CCF (1.15), which reemphasize the fact that these variables are established risk factor for ICVA. We adjusted these factors in our logistic regression model for calculation of odds for ICVA in patients with COPD with and without AF.

We identify the following weaknesses of our study. Retrospective studies with data review have weakness that diagnosis reported by physician could be inaccurate, moreover changing coding system may also reduce ability to specifically detect only ischemic stroke. Moreover lack of inclusion of other risk factors for stroke i.e. smoking could also affect results. If we have pack year smoking data on subjects and include it in analysis it may affect the results and weaken the risk attributed to COPD. Reader should take this fact into account and further studies should be considered to address this issue. Cross sectional design produces relatively weaker evidence for COPD as risk factor for ICVA in subjects with AF. Although big sample size with adjustment of other risk factors substantiate the association of COPD as risk factor for ICVA in subjects with COPD. COPD classification and smoking status for our subjects were not known which could provide more detailed observations. Recently developed method for classifying comorbid conditions i.e. weighted index [19] that takes into account the number and the seriousness of comorbid disease may provide better estimate of level of disease severity although since our sample data does not provide details about disease conditions we were not able to utilize these indices. Nonetheless this study provides first evidence for association of COPD as risk factor for ICVA in subjects with AF. We did not review the radiological studies for diagnosis of ICVA instead we used the clinical diagnosis of ICVA. We also did not record the pulmonary function tests result, we relied on clinical diagnosis of COPD by physicians. Although we would argue that majority of diagnosis of COPD are verified by pulmonary functions tests and majority of ICVA are confirmed by radiological findings at our hospital, therefore we believe chance for error in making these diagnosis is very low.

We believe a patient with COPD have dynamic and augmenting risk factors which actually confound risk profile as they already have ongoing inflammation, previous history of smoking with progression of COPD and developing right sided cardiac strain tends to develop atrial fibrillation with advancing age. Moreover COPD subjects tend to have nocturnal hypoxemia further stimulating atherosclerosis and hypercholesterolemia. With increasing age (risk factor for stroke), subjects with COPD are more likely to develop atrial fibrillation and hypertension increasing risk for stroke further. Quite many of patients with COPD are limited in physical activity which leads to weight gain and Sleep apnea which is also a risk factor for inflammation, nocturnal hypoxemia and stroke. Therefore identification of COPD as risk factor for ICVA is very important.

In conclusion, we found that COPD seems to be a risk factor for ICVA in subjects with AF. Prospective studies should be considered to verify this association and clinicians should consider COPD into account for assessing risk for ICVA in subjects with AF.

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