

# Right Heart Failure as a Risk for Stroke in Patients with Chronic Obstructive Pulmonary Disease: A Case-Control Study

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*Background:* Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory condition characterized by complex lesions of the lungs and other organs as well as a progressive obstruction of the airway. In COPD patients, heart failure (HF) is associated with worse conditions such as inflammation, arterial stiffness, and increased risk mortality. However, the association of HF, COPD, and stroke are unclear; the examination of the role of HF, especially right HF, about increased risk of stroke in COPD patients has not been studied. We aimed to determine if right HF is a risk factor for stroke in patients with COPD. *Materials and methods:* A case-control study of patients with COPD was carried out. The cases were defined as COPD patients with ischemic stroke and control COPD patients without stroke. *Results:* A total of 162 patients with COPD were analyzed: COPD with stroke (n = 35) and COPD alone (n = 127). COPD patients with right HF were at a greater risk of stroke compared with patients without right HF (odds ratio 3.03, 95% confidence interval 1.13-10.12, p = .044) adjusted for confounding factors. *Conclusions:* Right HF is an independent risk factor for stroke, probably because of cerebrovascular stasis secondary to congestion of the superior vena cava. **Key Words:** Chronic obstructive pulmonary disease—heart failure—right heart failure—stroke. © 2017 National Stroke Association. Published by Elsevier Inc. All rights reserved.

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## Introduction

In 2020, chronic obstructive pulmonary disease (COPD) will be the third most common cause of death in the world, with increasing prevalence and mortality.<sup>1-5</sup> COPD is a chronic inflammatory condition characterized by complex lesions of the lungs and other organs as well as a progressive obstruction of the airway. The bronchial obstruction and inflammation are the most important underlying physiopathologic factors. Smoking contributes to many systemic and clinical complications<sup>6,7</sup> that result in the development of cardiovascular risks.<sup>8</sup> COPD is frequently associated with cardiovascular diseases that contribute to worse condition.<sup>5,9</sup> Between 30% and 50% of COPD mortality has been attributed to cardiovascular conditions.<sup>4,10</sup>

Heart Failure (HF) plays an important role in the prognosis of COPD patients. COPD is associated with an increase in the risk of HF (hazard ratio 2.94, 95% confidence interval [CI] 2.46-3.51).<sup>11</sup> COPD patients with HF have twice the risk of mortality (hazard ratio 2.1, 95% CI 1.2-3.6) compared with COPD patients without HF.<sup>12</sup> In addition, COPD patients have greater oxidative stress and extensive cardiovascular damage than patients with uncomplicated COPD.<sup>13,14</sup> Many COPD patients develop pulmonary vascular changes—predominantly pulmonary hypertension that eventually leads to right heart failure (right HF). The essential common denominators are vascular remodeling and deregulation of smooth muscle.<sup>15,16</sup> Ventricular dysfunction in COPD patients are associated to arterial stiffness. Sabit et al found a significant relationship between arterial stiffness and the forced expiratory volume at 1 second (FEV<sub>1</sub>) in COPD patients, the right ventricular dysfunction related to airways obstruction, which suggests that cardiovascular risk increases with greater COPD flow obstruction.<sup>17,18</sup> Moreover, previous studies have shown that impairment in lung function (FEV<sub>1</sub>) is related to an increased risk of stroke. Some authors suggest that impairment in the lung function may reflect impairments in cardiac function.<sup>19,20</sup>

On other hand, one of the major disabling cardiovascular complications related to COPD is stroke, which is the second-leading global cause of death, behind ischemic heart disease.<sup>21</sup>

As far as we know, the association of COPD and stroke has been observed in population studies, and although it is unknown whether association involves causation—for example whether both are caused by an inflammatory process or hypoxemia—strokes have occurred more frequently during exacerbations of COPD. Admittedly the variables can be confusing because some of them, such as smoking, are risk factors for both COPD and stroke. However, the association between HF, COPD, and stroke is unclear, and the examination of the role of HF, especially right HF, in increased risk of stroke in COPD patients has not been studied.

The purpose of our study was to examine if right HF is a risk factor for stroke in COPD patients.

## Material and Methods

A case-control study was performed using a database of COPD patients. The subjects were selected from patients of our Heart Failure and Respiratory Distress Clinic in the Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas” in Mexico City. We included subjects who were diagnosed with COPD and whose diagnoses were confirmed by spirometry after administration of a bronchodilator ratio FEV<sub>1</sub>/forced vital capacity (FVC) less than 70% together with clinical signs such as cough, production of phlegm, and shortness of breath, between January of 1999 and July of 2015. The information was collected when the patients were clinically stable without previous exacerbations in the last 3 months. Comorbidity variables were coded using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10): stroke ischemia (ICD-10 diagnosis code I63), diabetes (ICD-10 diagnosis code E11), arterial hypertension (ICD-10 diagnosis codes I10-I15), cholesterolemia (ICD-10 diagnosis code E78.0), pulmonary embolism (ICD-10 diagnosis code I26), ischemic heart disease (ICD-10 diagnosis code I20-I25), peripheral vascular disease (ICD-10 diagnosis code I73), obstructive sleep apnea (ICD-10 diagnosis code G47.3), asthma (ICD-10 diagnosis code J45), and atrial fibrillation (ICD-10 diagnosis code I48). We also collected demographic variables: age, gender, respiratory function, smoking, and COPD. COPD were classified according to the guidelines of the Global initiative for Obstructive Lung Disease (GOLD) class.<sup>22</sup> Heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction were diagnosed according to the guidelines of the European Society of Cardiology.<sup>23</sup>

This study was approved by the Research and Ethics Committees at Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas” (Project Approval Number E04-15).

### *Case and Control Definition*

The cases were defined as COPD patients with ischemic stroke according to ICD class (ICD-10 diagnosis code I63). The controls were defined as COPD patients without stroke. COPD was classified according to GOLD class. Patients with atrial fibrillation and asthma and subjects who developed stroke before right HF were excluded. A total of 35 cases and 127 controls were selected; we had 3 controls per case.

### *Exposure Assessment*

The exposure factor was the right HF identified by echocardiography data according to the guidelines of the European Society of Cardiology: tricuspid annular plane

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