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PROGNOSIS FACTORS IN PATIENTS WITH COPD AND ATRIAL FIBRILLATION – MINI REVIEW

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Abstract

Chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) are common pathologies in the elderly patient. The simultaneous occurrence of the two conditions influences the quality of life and increases the rate of exacerbations. About two-thirds of patients with atrial fibrillation have dyspnea. Severe dyspnea in the patient with COPD and AF can be difficult to manage, suggesting an exacerbation of the disease, the onset of atrial fibrillation or even a symptom of associated comorbidities, the most common of which being heart failure.

The risk of developing AF in COPD increases with the severity of airflow obstruction. Factors such as smoking, aging, dyslipidemia, the presence of diabetes, hypertension or heart failure influence the prognosis of patients with COPD and AF. Furthermore, oxidative stress, hypoxia, systemic inflammation or immunological changes decrease the survival rate and may favor the recurrence of AF. In the evolution of concomitant COPD- FA cases, proinflammatory cytokines such as tumor necrosis factor α (TNF-α), monocyte chemotactic protein (MCP-1), interleukin-6 (IL-6), interleukin-8 (IL- 8) intervene.

This paper aims at analyzing data related to the factors that would influence the prognosis of patients with COPD and AF.

Keywords: *Chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), proinflammatory cytokines, systemic inflammation.*



Internal Medicine

General Reviews

Rezumat

Bronhopneumopatia obstructivă cronică (BPOC) și fibrilația atrială (FA) sunt patologii frecvent întâlnite la pacientul vârstnic. Prezența concomitentă a celor două afecțiuni influențează calitatea vieții și crește rata exacerbărilor. Aproximativ două treimi dintre pacienții cu fibrilație atrială prezintă dispnee. Dispneea accentuată la pacientul cu BPOC și FA poate fi dificil de manageriat, sugerând o exacerbare a bolii, debutul fibrilației atriale sau chiar un simptom al comorbidităților asociate, cea mai întâlnită fiind insuficiența cardiacă.

Riscul de a dezvolta FA în BPOC crește odată cu severitatea obstrucției fluxului de aer. Factori precum fumatul, îmbătrânirea, dislipidemia, prezența diabetului zaharat, hipertensiunii arteriale sau a insuficienței cardiace, influențează prognosticul pacientului cu BPOC și FA. Mai mult, stresul oxidativ, hipoxia, inflamația sistemică sau modificări imunologice scad rata de supraviețuire și pot favoriza recurența FA. În evoluția cazurilor de concomitență BPOC- FA intervin citokine proinflamatorii, cum sunt factorul de necroză tumorală α (TNF-α), proteina chemotactică pentru monocite (MCP-1), interleukina-6 (IL-6), interleukina-8 (IL-8).

Această lucrare are ca scop analiza datelor referitoare la factorii care ar influența prognosticul pacienților cu BPOC și FA.

Cuvinte cheie: *bronhopneumopatia obstructivă cronică (BPOC), fibrilație atrială (FA), citokine proinflamatorii, inflamație sistemică.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by persistent symptoms and progressive airflow limitation. It is currently the third leading cause of mortality in the world, but the prevalence of the disease is increasing due to exposure to respiratory toxins and the aging of the population[1]. About half of COPD cases remain undiagnosed because the reporting of symptoms occurs when the forced expiratory volume in 1 second (FEV1) represents approximately 50-60% of the predicted value[2]. Delayed reporting of symptoms frequently occurs in smokers or in cases of overlapping of associated chronic conditions. Smoking is the main risk factor, but COPD also occurs in non-smokers with occupational exposure to organic and inorganic dusts, chemical agents, or those with a history of repeated respiratory infections.

Thus, although in the past the prevalence of COPD was high in men and smokers, epidemiological data show an increasing

prevalence in non-smokers and women[3]. Systemic inflammation plays a major role in disease progression, being at the same time a negative prognostic factor in relation to associated comorbidities.

Cardiovascular complications such as arterial hypertension, ischemic heart disease, rhythm and conduction disorders contribute to the worsening of COPD, decrease the quality of life and require special attention in terms of their management. Atrial fibrillation (AF) is the most common arrhythmia in the elderly patient. Studies report that approximately 23% of AF cases present COPD. Furthermore, COPD patients have twice the risk of developing new-onset atrial fibrillation compared to those without COPD. Likewise, the prevalence of AF in COPD increases with COPD severity.

Thus, if the prevalence of AF in stable forms of COPD is of 4.7-15%, in advanced stages of COPD, the prevalence of AF reaches even 20-30%[4, 5]. Although smoking and the aging of the population are common risk factors, currently there are few epidemiological data to attest the pathophysiological changes found in patients with COPD and AF[6, 7]. An important factor that increases the risk of AF in COPD is the enlargement of the left atrium[8]. There are few studies that have investigated this aspect in patients with COPD and AF, but some data mention hyperuricemia and alcohol consumption as triggers of newly diagnosed AF[9,10].

Dyspnea aggravation in the COPD patient represents a challenge for the clinician due to the overlap of COPD symptomatology with that of disease exacerbation or even with the onset of AF. Approximately two-thirds of patients with AF complain of dyspnea[11]. The management of these patients frequently requires the presence of a multidisciplinary team consisting of cardiologist, electrophysiologist and pulmonologist to evaluate and give treatment indications. Given that smoking is the main risk factor for both conditions, quitting smoking may contribute to an improved prognosis[12, 13]. The occurrence of thromboembolic complications and the presence of systemic inflammation lead to an increase in biomarkers associated with the inflammatory syndrome. Patients with AF and COPD associate a higher CHA_2-DS_2-VASc score compared to those without COPD, a more severe development of the disease and an increased risk of cardiovascular death[14].

Impact of inflammatory biomarkers

C-reactive protein (CRP) shows higher values in patients with COPD and AF compared to those in sinus rhythm. Studies show differences in CRP values in patients with paroxysmal AF compared to those with persistent AF. More precisely, CRP is considered a marker of the severity of the disease, high values being found in cases of persistent AF[15].

The risk of AF recurrence after electrical cardioversion or catheter ablation increases with the increase of CRP. Also, the CRP level is directly proportional to the degree of bronchial resistance and also represents a risk factor for the association of cardiovascular comorbidities[16, 17]. Studies report that CRP increases in conditions such as arterial hypertension, obesity, heart failure, which are often found in patients with COPD and AF. On the other hand, further studies are needed to show whether the increase in CRP can precipitate an episode of AF, or occurs as a result of associated conditions[18]. Marcus et al. mention that both CRP and IL-6 show increased values during the AF burst compared to those with a history of fibrillation[19].



Interleukins represent another group of biomarkers participating in the inflammatory syndrome. IL-1 is a cytokine produced by activated macrophages and has been studied in both COPD and AF. IL-1β activation occurs in cases of pressure overload-induced AF[20]. IL-1β has also been studied in COPD. The results of a phase II clinical trial[21] that included patients with moderate-severe forms of COPD, showed that anti-inflammatory therapy based on the IL-1 family has inferior efficacy in COPD compared to bronchial asthma. The underlying reasons for this result could be the delayed diagnosis of COPD, as well as the variety of factors that increase the risk of developing COPD[22].

Another pro-inflammatory cytokine is IL-2, but there are few studies attesting to its role in inflammation in COPD and AF. Hak et al. mention a directly proportional relationship between the level of IL-2 and the risk of AF after coronary bypass[23]. IL-6 is secreted by Th1 lymphocytes and together with IL-2 acts in the hepatocyte production of acute phase proteins. A high level of IL-6 increases mortality through cardiovascular complications and stroke[24]. For COPD, studies report IL-6 as a diagnostic marker of systemic inflammation. Regarding the relationship between IL-6 and COPD prognosis, data in the literature vary, with some studies reporting a negative correlation between FEV1 and IL-6, while others report no relationship between airway obstruction and IL-6[25,26]. Some authors have studied the relationship between the atherosclerotic process and the level of IL-6 in elderly patients. Furthermore, anti-IL-6 therapies could provide benefits for the prognosis of cardiovascular disease in the elderly.

Another factor contributing to the improvement of cardiovascular prognosis in patients over 60 is IL-1β blockade, which has been observed in patients with low serum levels of IL-6[27]. The Cantos study included 4,833 patients with atherosclerosis and looked at the relationship between decreased IL-6 and cardiovascular risk. The results of the study showed a reduction in the rate of cardiovascular mortality as IL-6 levels decreased[28].

Rafaqat et al. mention the relation between IL-6 and left atrium size. Thus, an increased plasma level of IL-6 correlates with increased left atrial dimensions and is a risk factor for AF[29,30]. In the case of coexisting COPD-AF, the increase of IL-6, a marker of systemic inflammation, may also be due to the presence of extrapulmonary complications, such as osteoporosis, diabetes or cachexia. The measurement of IL-6 at the beginning of AF identification in the patient with COPD could be an important factor both in preventing the recurrence of AF episodes and in establishing the incidence of AF in COPD cases[8].

IL-8 is another protein with proinflammatory role, produced by macrophages and is involved in the activation of neutrophils and T lymphocytes. Liuba et al.[31] have analyzed the IL-6, IL-8 and CRP levels from blood samples from femoral vein, right atrium, coronary sinus and pulmonary veins.

The study group consisted of patients with paroxysmal AF, permanent AF, proposed for radiofrequency ablation and a control group consisting of Wolff-Parkinson-White (WPW) patients without AF. Samples were harvested before ablation. The results showed increased values of IL-8 in the femoral vein, right atrium and coronary sinus in patients with AF. At the level of the pulmonary veins, IL-8 did not present significant values. Regarding IL-6 and CRP, there were no differences in the studied groups. In the case of COPD, studies in literature do not provide sufficient data to report the prognostic value of IL-8 in relation to COPD severity. The ECLIPSE study [32] as well as some meta-analyses [33,34] showed that there is no connection between increased IL-8 and the risk of COPD exacerbation. On the other hand, Celli et al. mention that an increased level of IL-8 negatively influences the prognosis and leads to increased mortality[35]. Other studies [36, 37] have shown that patients with stable COPD have higher levels of IL-6, IL-8 and tumor necrosis factor alpha (TNF-α) compared to subjects without COPD.

Systemic inflammation in COPD has long-term effects on muscle mass[38]. The first study to investigate this hypothesis was conducted by Eagan et al. The inflammation markers studied were CRP, IL-1β, IL-6 and TNF-α. Study results show an increase in TNF-α in cachectic subjects. Given that TNF-α is also called cachexin, we can state that systemic inflammation contributes to the accelerated decrease of skeletal muscle in individuals in whom the cachectic process is already initiated[39]. Smoking subjects with COPD show higher values of IL-6 and TNF-α compared to non-smoking subjects with COPD but with a history of exposure to respiratory emissions[40].

Studies in the literature state that the decrease in inflammation reduces cardiovascular risk by reducing endothelial cell apoptosis and vascular resistance. Derella et al investigated the inflammatory syndrome in smoking subjects with COPD who followed a 12-week smoking cessation program. Biological samples for TNF-α determination were collected at baseline and at the end of the smoking cessation program. The results show a significant reduction in TNF-α after 12 weeks of smoking cessation[41].

Other factors that influence the prognosis in COPD-AF coexistence

Hypoxia, hypercapnia, respiratory acidosis and oxidative stress are key points that increase the risk of AF in the COPD patient. Studies mention that hypercapnia leads to the triggering of cardiac arrhythmias by slowing of the conduction velocity, but the cardiovascular risk remains high even after CO_2 has normal values[42, 43]. Exacerbation of COPD requires careful monitoring and correction of hypoxemia and hypercapnia can avoid triggering an episode of paroxysmal fibrillation.

Also, another important factor in addition to those previously mentioned (hypoxia, hypercapnia, oxidative stress, systemic inflammation) is cardiac remodeling, which may increase the risk of AF recurrence[44]. Pauklin et al conducted a study to further research the role of inflammatory biomarkers, fibrosis and oxidative stress in AF recurrence. The study group included 75 patients with



paroxysmal/permanent AF hospitalized for electrical cardioversion or pulmonary vein isolation. The results confirmed the role of inflammation and fibrosis, except for the oxidative stress in AF recurrence[45]. In the case of COPD, studies have shown a strong correlation between oxidative stress and the severity of airflow obstruction in elderly patients[46,47]. Another important factor studied in patients with COPD and AF is the risk of cerebrovascular accident (CVA - stroke), which increases with the diagnosis of AF. Liu et al investigated the likelihood of stroke in the patient with COPD and AF and the possible mechanisms leading to these co-occurrences. 62,163 COPD patients were included in the study, of which 5,235 were diagnosed with AF and 4,177 with stroke. Multiple factors have been identified that lead to the occurrence of stroke. The most important is newly diagnosed AF, to which advanced age, the history of multiple exacerbations and implicitly high doses of inhaled corticosteroids, the presence of metabolic syndrome or associated infections are added[48].

Conclusions

Chronic hypoxemia, persistence of systemic inflammation, and profibrotic processes increase the risk of AF in the COPD patient. Chronic inflammatory conditions such as COPD influence the quality of life and the association of comorbidities increases mortality. Cigarette smoke is a common risk factor for both conditions, but quitting smoking improves the prognosis. Patients with COPD and AF have an increased risk of association of other chronic conditions, such as diabetes, heart failure, ischemic cardiopathy, or stroke, compared to those without COPD. The presence of these comorbidities increases the thromboembolic risk and doubles mortality by cardiovascular events.

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