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THE RELATIONSHIP BETWEEN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND CARDIOVASCULAR DISEASE (CVD)

Davlatov Shohjaxonbek Qurbonbek o'g'li
Fergana Public Health Medical Institute

Annotation: *Ischemic heart disease (IHD) is a pathological condition that occurs as a result of an imbalance between the oxygen demand of the heart muscle and blood circulation in the coronary blood vessels. Chronic obstructive pulmonary disease (COPD) is a primary non-specific inflammation, and patients develop irreversible bronchial obstruction leading to damage to the distal part of the airways and lung parenchyma, development of emphysema, and exacerbation. IHD is widespread among the elderly population all over the world, including in Uzbekistan, and is considered one of the main causes of death. Observations have shown that 5-8% of men aged 20-44, and 18-24.5% of men aged 45-69 have IHD.*

Key words: *chronic obstructive pulmonary disease, cardiovascular disease, coronary heart disease, peripherial artery disease, n-terminal pro-brain natriuretic peptide, electrocardiogram, dobutamine stress test*

The relationship between Chronic Obstructive Pulmonary Disease (COPD) and Cardiovascular Disease (CVD) is significant, with tobacco abuse being a major shared risk factor. Consequently, these two conditions often coexist and can mutually influence outcomes [1]. Distinguishing the specific contributions of each condition to a patient's symptoms can be challenging due to overlapping symptoms. Various studies have observed the frequent coexistence of COPD and CVD [2-4]. For instance, in a large database from the United Kingdom, encompassing over 1.2 million patients aged 35 and older, nearly 30,000 COPD patients were identified. They were nearly five times more likely to have cardiovascular disease compared to those without COPD [2]. Another study involving 351 patients with advanced COPD revealed clinically significant coronary disease in 60 percent of cases, with 53 percent of cases being occult [3]. In a meta-analysis, patients with COPD had a higher likelihood of receiving a cardiovascular disease diagnosis (OR 2.46; 95% CI 2.02-3.00) compared to patients without COPD [5]. The spectrum of cardiovascular diseases included ischemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the systemic arteries.The presence of comorbid diseases has a substantial impact on clinical outcomes. Numerous observational studies have shown that the coexistence of COPD and cardiovascular disease significantly affects patient outcomes. Cardiovascular morbidity and mortality are notably increased in patients with COPD [6-9]:

- Among 5696 COPD patients, the risk of myocardial infarction (incidence rate ratio [IRR] 2.58 [95% CI 2.26-2.95]) and stroke (IRR 1.97 [95% CI 1.66-2.33]) was elevated in the days to weeks following a COPD exacerbation [6]. - In a drug trial

comprising 911 patients with moderate-to-severe COPD, where the forced expiratory volume in one second (FEV1) was less than 60 percent predicted, at least 27 percent of deaths were attributed to cardiovascular causes [7].

- It has been estimated that for every 10 percent decrease in FEV1, cardiovascular mortality increases by 28 percent, and nonfatal coronary events increase by nearly 20 percent [8]. Conversely, the presence of COPD also has significant effects on morbidity and mortality in patients with CVD [10-13]: In a study involving 3249 patients with acute ST-elevation myocardial infarction, COPD emerged as a strong independent predictor of the composite endpoint of death or cardiogenic shock [10].

- Among 14,346 patients who underwent percutaneous coronary intervention (PCI) at a single center, COPD was identified as a significant independent risk factor for overall mortality, cardiac mortality, and myocardial infarction [11].

In a separate study comparing 860 patients with COPD to 10,048 patients without COPD, those with COPD exhibited a lower mean ejection fraction and a higher prevalence of significant coronary lesions. The COPD group also had a higher mortality rate and a greater rate of repeat revascularization within the following year [12].- A prospective study involving 98 patients with stable COPD, 55 of whom experienced subsequent exacerbations, revealed a connection between increased arterial stiffness and more frequent exacerbations, along with an increase in arterial stiffness during exacerbations. This observation also corresponded with several inflammatory biomarkers in COPD [14]. Additionally, COPD is a recognized risk factor for supraventricular and ventricular arrhythmias.

Dyspnea and chest tightness often manifest as shared symptoms in both Chronic Obstructive Pulmonary Disease (COPD) and Coronary Heart Disease (CHD). In patients with an established diagnosis of COPD, uncontrolled dyspnea and/or chest tightness may originate from either refractory COPD or concurrent CHD. Given the frequent co-occurrence of these conditions and the potential diagnostic ambiguity surrounding these symptoms, healthcare providers responsible for COPD patients should maintain a low threshold for additional diagnostic assessments to detect CHD.

Several nonpharmacologic interventions may help alleviate symptoms and enhance the quality of life in individuals concurrently dealing with COPD and CVD. While these interventions have been evaluated separately in patients with COPD or CVD, their comprehensive examination in the presence of both conditions is limited.

Smoking cessation is pivotal for improving outcomes in patients with coexisting COPD and CVD. Nicotine replacement therapy is recommended for ambulatory COPD patients, even in the presence of CVD. Notably, the use of nicotine replacement therapy is associated with a reduced risk of coronary events, such as cardiac arrest, myocardial infarction, and hospitalization for CVD events, when compared to a placebo. While the initiation of nicotine replacement therapy during a hospitalization for myocardial

infarction is not extensively studied, it is generally considered reasonable to cautiously begin it during the hospitalization or at discharge.

Cardiopulmonary rehabilitation has demonstrated clear benefits in patients with COPD or CVD in separate studies and systematic reviews. However, there is limited data regarding the benefits of exercise training in individuals with both COPD and coronary artery disease (CAD) [19]. Observational studies have produced conflicting results concerning the impact of comorbid CAD on the response to pulmonary rehabilitation.

For patients with stable CAD, the primary treatments for COPD, including inhaled anticholinergic agents, inhaled selective beta-2 agonists, and inhaled glucocorticoids, should be administered in a manner consistent with the approach taken for individuals without CVD. Despite some concerns regarding an increased risk of CVD, these agents and their doses are typically recommended.

Regarding inhaled anticholinergic medications, using a short-acting inhaled anticholinergic (muscarinic) agent as an alternative to inhaled short-acting beta adrenergic agonists (SABAs) or in combination with a SABA for managing acute COPD symptoms is advisable. Long-acting anticholinergic agents, such as aclidinium, glycopyrronium, tiotropium, and umeclidinium, are recommended for patients with COPD who experience frequent symptoms or exacerbations, irrespective of the presence of underlying CVD [1].

When it comes to inhaled beta-2 agonists, they are relatively selective for beta-2 adrenergic receptors. While concerns have been raised about potential mild beta-1 activity associated with these agents, which might lead to adverse effects in patients with COPD and CVD, such as arrhythmias and peripheral vasodilation, the choice of using short-acting inhaled beta agonists for acute COPD symptoms is unaffected by the presence of CAD.

Inhaled long-acting beta agonists (LABAs) are widely employed in COPD treatment. While there is some debate regarding the cardiovascular effects of LABAs, several studies suggest that their use is generally safe in patients with CVD [36,37]. In the Toward a Revolution in COPD Health (TORCH) trial, which compared various treatment groups in patients with COPD over three years, the frequency of cardiac events was not elevated in the groups receiving salmeterol alone or salmeterol plus fluticasone [38]. However, a nested case-control study found an increased risk of cardiovascular events among patients with COPD and new use of a LABA, while prevalent use was associated with a decreased risk. This implies that the risk may diminish with prolonged exposure. Caution is advisable when prescribing LABAs in individuals with severe and/or symptomatic CAD, and a thorough patient assessment and risk stratification are essential to reduce the risk of cardiovascular events in these patients.

Myocardial ischemia poses a challenge as exacerbations of both COPD and CHD often manifest with dyspnea. Patients and clinicians might struggle to pinpoint which ailment requires immediate attention. Classic COPD flare symptoms (such as dyspnea, cough, wheezing, and changes in sputum) are indicative of a pulmonary issue, while new electrocardiographic signs of ischemia may point to cardiac involvement. Alternatively, both organ systems may be implicated, making it difficult to distinguish between them.

For ambulatory COPD patients experiencing symptoms that could potentially stem from myocardial ischemia, we typically initiate a baseline electrocardiogram and perform dobutamine stress imaging. Exercise stress testing may not be suitable due to exercise limitations, and bronchoconstriction can often contraindicate vasodilator radionuclide myocardial perfusion imaging.In cases where patients present to the hospital with dyspnea and chest tightness, an elevated serum cardiac troponin level often indicates the presence of coronary artery disease. Among 242 patients admitted for a COPD exacerbation, 24 displayed an elevated troponin, and 20 reported chest pain and/or serial electrocardiogram (ECG) changes [15]. However, neither chest pain nor serial ECG changes consistently correlated with elevated troponin, suggesting that an elevated troponin during a COPD exacerbation may not necessarily signify myocardial injury. In a separate study, highly sensitive cardiac troponin (hs-cTnT) was measured in 50 patients admitted for an acute COPD exacerbation and 124 stable patients in a pulmonary rehabilitation hospital [16]. The ratio of hs-cTnT in those experiencing a COPD exacerbation was significantly higher than in those with stable COPD, with a ratio of 5.67 (95% CI 4.0-7.86). However, the specific factors leading to an increase in hs-cTnT remained unclear, as neither hypoxic vasoconstriction nor underlying cardiovascular disease (CVD) were conclusively linked to the rise in hs-cTnT.

Undiagnosed heart failure can complicate the diagnosis and management of COPD patients. The prevalence of unrecognized heart failure among ambulatory patients was assessed in a cross-sectional study involving 244 older adults with COPD based on the initial Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [17]. Previously undiagnosed heart failure was identified in 21 percent of cases, with ischemic heart disease being the most common underlying cause. Similarly, for patients admitted to the hospital, symptoms of a COPD exacerbation can overlap with acute exacerbations of heart failure. A study evaluating the ability of N-terminal pro-brain natriuretic peptide (NT pro-BNP) and troponin T to distinguish an acute COPD exacerbation from left heart dysfunction found that 31 percent of the 148 patients were diagnosed with both a COPD exacerbation and heart failure [18]. Several nonpharmacologic interventions may help alleviate symptoms and enhance the quality of life in individuals concurrently dealing with COPD and CVD. While these interventions have been evaluated separately in patients with COPD or CVD, their comprehensive examination in the presence of both conditions is limited. Smoking cessation is pivotal for improving outcomes in patients with coexisting COPD and CVD.

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and risk stratification are essential to reduce the risk of cardiovascular events in these patients. Heart failure – Some studies, though not all, have suggested that beta-2 agonists may have an adverse impact on patients with left ventricular dysfunction. In one review of 1529 patients with left ventricular systolic dysfunction (determined by echocardiography or radionuclide ventriculography), a dose-response relationship was observed between the use of inhaled beta-agonists and the relative risk of hospitalization for heart failure [41]. However, a retrospective study involving 1294 subjects in a heart failure disease management program did not find an increase in mortality associated with the use of beta-2 agonists (HR 1.043, 95% CI 0.771 to 1.412), after accounting for factors such as age, gender, smoking, medications, and comorbidity severity [42]. Arrhythmias – While beta-2 adrenergic agonists have the potential to increase heart rate and may induce cardiac arrhythmias via nonselective beta adrenergic effects, multiple studies have indicated a very low to no increased risk of serious arrhythmias associated with these medications.

Combination LAMA-LABA — The combination of a long-acting muscarinic agent (LAMA) with a LABA is recommended for COPD patients whose respiratory symptoms are inadequately controlled by a single long-acting bronchodilator. The data concerning the cardiovascular safety of these individual agents are mixed but, for the most part, reassuring [1,39,43], as previously discussed. Data from clinical trials and systematic reviews of combination bronchodilator inhalers are limited, but no significant increase in cardiovascular adverse events has been observed: A systematic review comparing a combination of a LABA and tiotropium with either a LABA or tiotropium alone found no notable increase in serious adverse events with the combination inhaler, though specific data on cardiovascular outcomes were not provided [44].In a systematic review encompassing trials comparing LAMA-LABA and LABA-glucocorticoid inhalers for stable COPD (11 studies, 9839 participants), a nonsignificant decrease in serious adverse events was noted in the LAMA-LABA group [45]. In an observational study, cardiovascular events were less frequent in 3842 patients treated with a LAMA-LABA combination, in comparison to a LABA-glucocorticoid inhaler (hazard ratio 0.794, 95% CI 0.623-0.997); the risk of cerebrovascular events did not differ significantly between the groups [46]. Combination inhaled bronchodilator plus glucocorticoid — The available evidence indicates that therapy with combination LABA-glucocorticoid inhalers (e.g., fluticasone and salmeterol) is safe in patients with or at heightened risk of CVD [38,39,47-49]. Several studies support this conclusion, although only the first one was specifically conducted in patients with CVD [49]: In the three-year Study to Understand Mortality and MorbidITy (SUMMIT), which compared the effect of the fluticasone furoate-vilanterol (100 mcg-25 mcg) combination with the individual components and placebo in 16,590 patients with moderate COPD (FEV1 between 50 and 70 percent of predicted) and risk factors for or known CVD, the combination inhaler did not significantly impact all-cause mortality (hazard ratio [HR] 0.88, 95% CI 0.74-1.04)

or composite cardiovascular events (HR 0.93, 95% CI 0.75–1.14). In a meta-analysis involving 10 studies and 10,680 participants, comparing combination inhaled LABA PLUS glucocorticoid with inhaled LABA alone in COPD, no significant difference in mortality was observed (OR 0.92, 95% CI 0.76-1.11) [47]. However, the exclusion criterion for participation in these studies was underlying cardiovascular disease, and the rate of cardiovascular events was not specifically examined. In a randomized trial involving 723 patients with COPD, who were assigned to receive placebo, salmeterol alone, fluticasone alone, or both drugs, the incidence of clinically significant ECG abnormalities was similar among the treatment groups [48]. There were no safety concerns associated with combination therapy in comparison to individual drugs. The combination of fluticasone and salmeterol was also evaluated in the aforementioned TORCH trial [38]. In this group, the incidence of cardiovascular events was not higher when compared to the placebo group [39]. The management of symptomatic CAD in patients with COPD generally follows the same guidelines as for patients without COPD, except for avoiding nonselective beta-blockers in COPD patients due to concerns about the potential induction of clinically significant bronchoconstriction by nonselective agents. Instead, cardioselective beta-blockers (e.g., atenolol or metoprolol) are typically used [50]. Alternative agents for the treatment of ischemia, arrhythmias, or hypertension, which do not carry the risk of bronchoconstriction, can also be considered. Effects of beta-blockers on mortality and COPD exacerbations — There is no evidence to suggest that (cardioselective) beta-blocker therapy adversely affects the respiratory benefits or increases the cardiovascular risk of inhaled long-acting beta-agonists in terms of overall survival and frequency of COPD exacerbations [51,52]. In fact, there is some evidence of cardiovascular and mortality benefits [53-58]. Among 10,884 COPD patients discharged from Danish hospitals after an acute myocardial infarction, beta-blocker use was associated with a lower risk of acute exacerbation of COPD over at least a year of follow-up (multivariable-adjusted HR 0.78, 95% CI 0.74–0.83), independent of COPD severity or exacerbation history [59]. In an observational cohort study of 2230 COPD patients, the use of beta-blockers was associated with lower hazard ratios for both mortality (HR 0.68, 95% CI 0.56-0.83) and exacerbations of COPD (HR 0.71, 95% CI 0.60-0.83) [53].Among patients admitted to the hospital with an acute exacerbation of COPD, the use of beta-blockers is linked to reduced mortality. In an observational study, in which 142 out of 825 patients (17 percent) received beta-blocker therapy, it was associated with a reduced mortality (OR 0.39, 95% CI 0.14-0.99) [54]. In a retrospective cohort study involving 35,082 patients with ischemic heart disease hospitalized with a COPD exacerbation, treatment with a beta-blocker in the first two hospital days did not increase mortality, length of stay, or the likelihood of late mechanical ventilation [56].

SUMMARY

Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) frequently coexist due to shared risk factors such as tobacco abuse, and the presence of one can detrimentally impact the outcomes of the other.

- In patients with severe concurrent COPD and CAD, a range of nonpharmacologic interventions, including smoking cessation, pulmonary rehabilitation, influenza and pneumococcal vaccination, and supplemental oxygen therapy, are recommended to alleviate symptoms, enhance quality of life, and prevent exacerbations, mirroring the approach for patients with COPD in isolation.

- In general, the pharmacological management of patients with both COPD and cardiovascular disease (CVD) aligns with the guidelines applied to patients without these comorbidities.

- For individuals dealing with COPD and CAD, we advise the prescription of a short-acting bronchodilator for as-needed relief from acute COPD symptoms (Grade 1B). Depending on patient preference, a short-acting beta-agonist, a short-acting anticholinergic, or a combination can be employed. In cases where patients are already on a long-acting anticholinergic agent, a short-acting beta agonist is utilized instead of a short-acting anticholinergic for prompt relief from COPD symptoms.

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