TREATMENT OF THE PATIENT WITH COPD AND CARDIOVASCULAR DISORDERS

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Annotatsiya: *Yurak ishemik kasalligi(YuIK)- Yurak mushaklarini kislarodga bo'lgan talabi va koronar qon tomirlaridagi qon aylanish orasidagi muvozanat buzilishi natijasida yuzaga keladigan patologik xolat xisoblanadi.*

O'pkaning surunkali obstruktiv kasalligi(O'SOK)-birlamchi nospetsifik yallig'lanish bilan kechib, bemorlarda nafas yo'llari distal qismi va o'pka parenximasi shikastlanishi, emfizema rivojlanishi va avj olib boruvchi qaytmas bronxial obstruksiya shakllanadi. YuIK butun dunyoda, jumladan, O'zbekistonda ham kata yoshdagi aholi orasida keng tarqalgan va o'limga olib keluvchi asosiy sabablardan biri xisoblanadi. O'tkazilgan kuzatuvlar 20-44 yosh erkaklarning 5-8%, 45-69 yoshdagilarning esa 18-24.5% YuIK borligini ko'rsatgan. Katta yoshdagi ayolarda esa bu ko'rsatkich 13-15% ni tashkil etadi. Bugungi kunning dolzarb muomosi COVID-19 infeksiyasining o'pkaning surunkali obstruktiv kasalliklari bilan qo'shilib kelgan yurak ishemik kasalliklari mavjuda bemorlarning yurak qon tomir sistemasining klinik-funksional holati, uning kechishi hamda o'lim ko'rsatkichi yuqori ekanligi ma'lum, ya'ni O'zbekistonda vafot etgan bemorlarning soni 15% yuqori qismi O'SOK natijasida yuzaga kelgan YuIKning og'irlashuviga to'g'ri keladi.

Kalit so'zlar: *O'pkaning surunkali obstruktiv kasalligi, Yurak-qon tomir kasalliklari, Yurak koronar tomirlar kasalliklari, Periferik arteriya kasalliklari, N-terminalpro-miya natriuretik peptidlari, Dobutamin stess test Elektrokardiogrammasi.*

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. In older women, this figure is 13-15%. Today's urgent problem is the clinical and functional state of the cardiovascular system of patients with ischemic heart diseases combined with chronic obstructive pulmonary diseases of the COVID-19 infection, it is known that the course and mortality rate are high, more 15% of the number of patients who died in Uzbekistan correspond to the aggravation of UIC caused by COPD.*

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

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD), which includes coronary heart disease, peripheral artery disease, and cerebrovascular disease, share tobacco abuse as a major risk factor. Thus, these two disorders commonly coexist. In addition, CVD is a leading cause of death among patients with COPD.

COPD/CVD RELATIONSHIP

COPD and CVD frequently coexist, and the presence of one can affect outcomes in the other [1]. As symptoms can overlap, differentiating the relative contributions of these diseases to a given patient's symptoms can be challenging. Coexistence of COPD and CVD — The frequent coexistence of COPD and CVD has been observed in several studies [2-4]. As an example, a study from a large United Kingdom database of more than 1.2 million patients over age 35 identified almost 30,000 patients with COPD; these patients were nearly five times more likely to have cardiovascular disease than those without COPD [2]. In a separate study of 351 patients with advanced COPD, clinically significant coronary disease was identified by angiography in 60 percent and was occult in 53 percent [3]. In a meta-analysis, patients with COPD were more likely to be diagnosed with cardiovascular disease (OR 2.46; 95% CI 2.02-3.00) than patients without COPD [5]. The cardiovascular diseases included ischemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the systemic arteries. Impact of co-morbid disease on outcomes — A large number of observational studies have found that the coexistence of COPD and cardiovascular disease has an important impact on clinical outcomes.

Cardiovascular morbidity and mortality in patients with COPD [6-9]:

●Among 5696 patients with COPD, an increased 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 noted in the days to weeks after an exacerbation of COPD [6].

●In a drug trial that included 911 patients with moderate-to-severe COPD (forced expiratory volume in one second [FEV1] <60 percent predicted), the cause of death was cardiovascular in at least 27 percent [7].

●It has been estimated that for every 10 percent decrease in FEV1, cardiovascular mortality increases by 28 percent and nonfatal coronary events by almost 20 percent [8].

Effect of COPD on morbidity and mortality in patients with CVD [10-13]:

●In a study of 3249 patients with an acute ST-elevation myocardial infarction, COPD was a strong independent predictor of the composite end-point of death or cardiogenic shock [10].

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

●A separate study of patients undergoing PCI compared subjects with and without COPD (860 and 10,048, respectively). The patients with COPD had a lower mean ejection

fraction and a greater number of significant coronary lesions. The COPD group also carried a higher mortality rate and a greater rate of repeat revascularization within the subsequent year [12].

●A prospective study examining 98 patients with stable COPD, 55 of whom experienced a subsequent exacerbation, demonstrated a relationship between increased arterial stiffness and more frequent exacerbations and also a rise in arterial stiffness during exacerbations that offers a linkage for these observations. The degree of arterial stiffness was also related to several inflammatory biomarkers in COPD [14].COPD is also a risk factor for supraventricular and ventricular arrhythmias.

The symptoms of dyspnea and chest tightness are common to COPD and coronary heart disease (CHD). In patients with known COPD, uncontrolled dyspnea and/or chest tightness could be due to refractory COPD or concomitant CHD. Due to the frequent co-existence of these diseases and the potential diagnostic uncertainty of the symptoms, physicians caring for patients with COPD need to have a low threshold for performing additional diagnostic testing to identify CHD.

Myocardial ischemia — Since exacerbations of both COPD and CHD are often signaled by dyspnea, patients and clinicians may find it challenging to know which disease requires urgent treatment. Classic symptoms of a COPD flare (eg, dyspnea, cough, wheezing, and change in sputum) may point correctly to the lung, while new electrocardiographic signs of ischemia may prove that the heart is the culprit. Alternatively, both organ systems may be involved and difficult to distinguish.

For ambulatory patients with COPD and symptoms that could be attributable to myocardial ischemia, we typically perform a baseline electrocardiogram and dobutamine stress imaging, as exercise limitations may preclude exercise stress testing, and potential bronchoconstriction is often a contraindication to vasodilator radionuclide myocardial perfusion imaging.

For patients presenting to the hospital with dyspnea and chest tightness, an elevated serum cardiac troponin frequently, but not always, indicates the presence of coronary artery disease. Among 242 patients admitted for an exacerbation of COPD, 24 had a raised troponin and 20 had chest pain and/or serial electrocardiogram (ECG) changes [15]. However, neither chest pain nor serial ECG changes were statistically associated with elevated troponin, suggesting that a raised troponin in the context of a COPD exacerbation is not necessarily indicative of myocardial injury. In a separate study, highly sensitive cardiac troponin (hs-cTnT) was measured in 50 patients admitted with an acute exacerbation of COPD and 124 stable patients in a pulmonary rehabilitation hospital [16]. The ratio of hs-cTnT in those with a COPD exacerbation was significantly higher than those with stable COPD, ratio 5.67 (95% CI 4.0-7.86). However, the specific determinants of hs-cTnT elevation were unclear, as neither hypoxic vasoconstriction nor underlying cardiovascular disease (CVD) were statistically associated with the increase in hs-cTnT.

Heart failure — Unrecognized heart failure can be a problem in the diagnosis and management of patients with COPD. The frequency of undiagnosed heart failure among ambulatory patients was examined in a cross-sectional study of 244 older adults with COPD based on the initial Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [17]. Previously unrecognized heart failure was identified in 21 percent, and ischemic heart disease was judged to be the most common cause of heart failure. Similarly, for patients presenting to the hospital, symptoms of an exacerbation of COPD overlap with acute worsening of heart failure. In a study examining the ability of N-terminal pro-brain natriuretic peptide (NT pro-BNP) and troponin T to differentiate an acute exacerbation of COPD from left heart dysfunction, 46 of the 148 patients (31 percent) were judged to have both a COPD exacerbation and heart failure [18].

A number of nonpharmacologic therapies may help reduce symptoms and improve quality of life in patients with concomitant COPD and CVD. These interventions have been evaluated in patients with either COPD or CVD, but have not been examined extensively when both diseases are present.

Smoking cessation — Smoking cessation is essential to improving outcomes in patients with comorbid COPD and CVD.

Nicotine replacement therapy is indicated for ambulatory patients with COPD despite the presence of CVD. The risk of coronary events (eg, cardiac arrest, myocardial infarction, admission to the hospital for CVD events) is lower among users of nicotine replacement than placebo. The issue of whether nicotine replacement can be started during a hospitalization for myocardial infarction has not been well studied, but cautious initiation during the hospitalization or at the time of discharge is thought to be reasonable.

Cardiopulmonary rehabilitation — A number of studies and systematic reviews have demonstrated the benefits of exercise training in patients with either COPD or CVD, but data are more limited regarding the benefit of exercise training in patients with comorbid COPD and CAD [19]. Observational studies have yielded conflicting results regarding the effect of comorbid CAD on the response to pulmonary rehabilitation.

The mainstays of treatment for COPD include the inhaled anticholinergic agents, inhaled selective beta-2 agonists, and inhaled glucocorticoids; roflumilast and theophylline are less commonly used. For patients with stable coronary artery disease (CAD), we treat symptomatic COPD with the same agents and doses that we would for someone without CVD, despite some concerns about increased CVD risk as noted below.

Inhaled anticholinergic medications — An inhaled short-acting anticholinergic (muscarinic) agent (eg, ipratropium) is suggested as an alternative to inhaled short-acting beta adrenergic agonists (SABAs) or in combination with a SABA for acute symptoms of COPD. Long-acting anticholinergic agents (eg, aclidinium, glycopyrronium, tiotropium, umeclidinium) are recommended, regardless of underlying CVD, for patients with COPD who have frequent symptoms or exacerbations [1]. Beta-2 agonists — The inhaled beta-2 agonists (eg, albuterol, terbutaline, formoterol, indacaterol, olodaterol, salmeterol,

vilanterol) are relatively selective for beta-2 adrenergic receptors. However, the possibility has been raised that mild beta-1 activity associated with these agents might cause the following adverse effects in patients with COPD and CVD:

●The possible induction of arrhythmias by stimulation of cardiac beta-adrenoreceptors

●Reflex activation of adrenergic mechanisms by causing peripheral vasodilation

●Downregulation of myocardial beta-2 receptors, potentially worsening heart failure associated with left ventricular systolic dysfunction

●Provocation of hypokalemia by intracellular translocation of potassium or hypoxemia through worsened matching of ventilation and perfusion

Short-acting beta agonists — Short-acting inhaled beta agonists (eg, albuterol, levalbuterol) are the preferred bronchodilators for treatment of acute symptoms of COPD, based on their rapid onset of action. This choice is unaffected by the presence of CAD. It is reassuring that among 12,090 patients age 55 or older with COPD, short-acting inhaled beta agonists did not increase the risk of fatal or nonfatal myocardial infarction [35]. The management of acute exacerbations of COPD is discussed separately.

Long-acting beta agonists — Inhaled long-acting beta agonists (LABAs) are widely used for treatment of COPD; data are generally reassuring regarding their safety in patients with CVD [36,37]. Several studies have specifically evaluated the cardiovascular effects of LABAs.

●Cardiovascular events – The Toward a Revolution in COPD Health (TORCH) trial compared salmeterol alone, fluticasone alone, salmeterol plus fluticasone, and placebo in 6112 patients with COPD over three years [38]. The frequency of cardiac events was not increased in the salmeterol alone group or the salmeterol plus fluticasone group [39]. In contrast, a nested case control study found an increased risk of cardiovascular events (ie, emergency department visit or hospitalization for coronary heart disease, cardiac arrhythmia, heart failure, or ischemic stroke) among 37,719 patients with COPD and new use of a LABA (adjusted OR 1.50, 95% CI 1.35-1.67), while prevalent use was associated with a 9 percent decrease in risk [40]. This suggests the risk may subside with prolonged exposure. While the randomized trial has limitations due to exclusion of patients with underlying cardiovascular disease, the case control design has limitations due to potential confounding and lack of adjudication of cardiovascular events. Caution is therefore advised when prescribing these agents in people with severe and/or symptomatic CAD. Thorough patient characterization and risk stratification prior to the use of LABAs may reduce the risk of cardiovascular events in CAD patients.

●Heart failure – Some but not all studies have suggested that beta-2 agonists may have an adverse effect in patients with left ventricular dysfunction. In a review of 1529 patients with left ventricular systolic dysfunction (by echocardiography or radionuclide ventriculography), the relative risk of hospitalization for heart failure followed a dose-response relationship with the use of inhaled beta-agonists [41]. In contrast, a

retrospective study of 1294 subjects attending a heart failure disease management program did not find an increase in mortality associated with beta-2 agonist use (HR 1.043, 95% CI 0.771 to 1.412) after adjusting for age, gender, smoking, medications, and severity of co-morbidities [42].

●Arrhythmias – While beta-2 adrenergic agonists have the potential to increase heart rate and may increase cardiac arrhythmias via nonselective beta adrenergic effects, a number of studies have shown a very low to no increased risk of serious arrhythmias with these medications..)

Combination LAMA-LABA — The combination of long-acting muscarinic agent (LAMA) plus a LABA is suggested for patients with COPD whose respiratory symptoms are not well-controlled with a single long-acting bronchodilator. Data regarding cardiovascular safety of the individual agents is mixed, but largely reassuring [1,39,43], as described above.

Data from clinical trials and systematic reviews of combination bronchodilator inhalers are more limited, but have not noted an increase in cardiovascular adverse events:

●A systematic review comparing the combination of a LABA plus tiotropium with a LABA or tiotropium alone found no significant increase in serious adverse events with the combination inhaler, although separate data on cardiovascular outcomes was not provided [44].

●In a systematic review of 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 lower in 3842 patients treated with a LAMA-LABA combination, compared with a LABA-glucocorticoid inhaler (hazard ratio 0.794, 95% CI 0.623-0.997); the risk of cerebrovascular events was not different between groups [46].

Combination inhaled bronchodilator plus glucocorticoid — The evidence suggests that therapy with combination LABA-glucocorticoid inhalers (eg, fluticasone and salmeterol) is safe in patients with or at increased risk of CVD [38,39,47-49]. The following studies support this conclusion, although only the first one was specifically performed in patients with CVD [49]:

●In the three-year Study to Understand Mortality and MorbidITy (SUMMIT), the effect of fluticasone furoate-vilanterol (100 mcg-25 mcg) combination was compared 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 [49]. Relative to placebo, the combination inhaler did not affect 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 (10 studies, 10,680 participants) that compared combination inhaled LABA PLUS glucocorticoid with inhaled LABA alone in COPD, there was no significant difference in mortality (OR 0.92, 95% CI 0.76-1.11) [47]. However, underlying

cardiovascular disease was an exclusion criterion for participation, and the rate of cardiovascular events was not examined.

●In a randomized trial of 723 patients with COPD who were assigned to placebo, salmeterol alone, fluticasone alone, or both drugs, the incidence of clinically significant ECG abnormalities was comparable among the treatment groups [48]. There were no safety concerns for combination therapy compared to the individual drugs.

●The combination of fluticasone and salmeterol was also evaluated in the TORCH trial mentioned above [38]. The incidence of cardiovascular events was not increased in this group, compared to placebo [39].

The management of symptomatic CAD in patients with COPD generally follows the same guidelines as for patients without COPD, except that we avoid nonselective beta-blockers in patients with COPD due to concerns about the induction of clinically important bronchoconstriction by nonselective agents. Instead, we typically use a cardioselective beta-blocker (eg, atenolol or metoprolol) [50]. Alternative agents for the treatment of ischemia, arrhythmias, or hypertension that do not carry the risk of bronchoconstriction can also be considered.

Effects of beta-blockers on mortality and COPD exacerbations — In terms of overall survival and frequency of COPD exacerbations, there is no evidence to suggest that (cardioselective) beta-blocker therapy reduces the respiratory benefits or increases the cardiovascular risk of inhaled long-acting beta-agonists [51,52], and there is some evidence of cardiovascular and mortality benefit [53-58].

●Among 10,884 patients with COPD 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, use of beta-blockers is associated with reduced mortality. In an observational study, in which 142 out of 825 patients (17 percent) received beta-blocker therapy, beta blocker therapy was associated with reduced mortality (OR 0.39, 95% CI 0.14-0.99) [54].

●In a retrospective cohort study of 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) share tobacco abuse as a risk factor and commonly coexist. The presence of either disease can adversely affect outcomes of the other.

●In patients with concomitant severe COPD and CAD, a number of nonpharmacologic therapies (eg, smoking cessation, pulmonary rehabilitation, vaccination against influenza and pneumococcus, supplemental oxygen) are indicated to reduce symptoms, improve quality of life, and prevent exacerbations, as in patients with COPD alone.

●In general, the pharmacologic management of comorbid COPD and cardiovascular disease (CVD) follows the same guidelines as for patients without comorbid disease.

●For patients with COPD and CAD, we recommend that a short-acting bronchodilator be prescribed for use as-needed for relief of acute symptoms of COPD (Grade 1B). Either a short-acting beta-agonist, a short-acting anticholinergic, or a combination can be used, depending on patient preference. For patients on a long-acting anticholinergic agent, a short-acting beta agonist is used instead of a short-acting anticholinergic agent, for quick relief of COPD symptoms.

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