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CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND HEART FAILURE: CLOSER THAN CLOSE

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SUMMARY – Chronic obstructive pulmonary disease (COPD) and heart failure (HF) both are global epidemics with substantial burden on morbidity and mortality. They present major challenges to healthcare providers and often coexsist. Multiple interactions exist between these conditions. COPD is often responsible for delayed diagnosis of HF and *vice versa*, since both conditions have similar symptoms such as dyspnea and poor exercise tolerance based on the skeletal myopathic response rather than the primary organ failure. Patients with COPD also have an increased risk of developing HF and higher hospitalization and death rates compared with HF patients without COPD. Echocardiography and pulmonary function tests along with natriuretic peptides should be performed and carefully interpreted. Diagnostic assessment of both conditions present in the same patient is often difficult, but therapeutic approach is also often non-adherent to current guidelines. For example, patients with coexisting COPD and HF receive beta-blockers at disappointingly low rates below 20%. Closer collaboration between cardiologists and pulmonologists is required for better identification and management of concurrent COPD and HF.

Key words: *Pulmonary disease, chronic obstructive – diagnosis; Pulmonary disease, chronic obstructive – therapy; Heart failure – diagnosis; Echocardiography; Respiratory function tests*

Introduction

Chronic obstructive pulmonary disease (COPD) is projected to be the fifth leading cause of morbidity and third leading cause of mortality worldwide by 2020[1]. Although major advances in the understanding of COPD have been made in recent decades, the heterogeneity of clinical phenotypes, as well as the variability of clinical course continue to be only partially explained. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was launched in 1997 in order to improve the understanding of the underlying mechanisms of the disease and global awareness of COPD, as well as to reach expert recommendation on the prevention, diagnosis and treatment of COPD. In the first GOLD Workshop Summary Report in 2001, COPD is defined as a disease state characterized by airflow limitation that is not fully reversible and is usually progressive. It has also been stated that the disease is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

The initial COPD ranking system was based on post-bronchodilator spirometry and it has been proven as a useful indicator for treatment, as well as a reliable value to be compared in clinical studies. In other words, in the beginning of our understanding of COPD, the rigidity (and simplicity) of the staging system proved useful. However, it has become evident that the relationship between forced expiratory volume in the first second (FEV_1) and symptoms is far from perfect and that exacerbations are independently associated with a more rapid function decline and increased mortality risk. Moreover, it seems that high symptom scores may originate not only from airflow limitation, but also from comorbidities. For example, in the ECLIPSE study, a subgroup of patients with

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the highest prevalence of comorbidities also had signs of persistent systemic inflammation[2].

Consequently, the GOLD Science Committee adopted the novel approach to annual reviews of the ever growing published data with two major revisions of the GOLD document in 2007 and 2011. The GOLD 2011 assessment proposal includes two additional major criteria: the impact of the disease as perceived by the patient and the risk of future exacerbations. Patients are divided into four major categories: less symptoms and low risk (group A), more symptoms and low risk (group B), less symptoms and high risk (group C) and more symptoms and high risk (group D)[3].

In clinical practice, the list of variables to be included in comprehensive approach to the individual patient is even longer, including lifestyle characteristics such as persistent smoking or the level of physical activity, biological markers of the disease activity and, very important, additional clinical outcomes such as comorbidities or lung hyperinflation.

COPD and Heart Failure

Chronic obstructive pulmonary disease is the fourth commonest cause of death worldwide, and the future does not seem bright, as by the year 2020 COPD will be ranked third. COPD and chronic heart failure (CHF) are both global epidemics and have common determinants (smoking and chronic inflammation), which have been shown to play major roles in the pathogenesis of both diseases. Patients with COPD die mainly from non-respiratory diseases: 25% from cardiovascular diseases, 20%-33% from cancer (mainly lung cancer), and 4%-35% from respiratory diseases, mainly respiratory failure during exacerbations[4].

Among the comorbid conditions associated with CHF, COPD is one that most often delays correct diagnosis of CHF and is responsible for nonadherence to current treatment guidelines, such as beta blockade. On the other hand, until recently it was often enough that only self-reported COPD was considered sufficient to establish the diagnosis. Still, few reports have addressed this often ignored combination, and fewer still from the pneumonologist's point of view.

Prevalence of Coexisting COPD and CHF

In most studies, the estimated prevalence of COPD in patients with CHF ranges from 11% to 52%[5-12]. In recent studies, the prevalence is notably higher. The risk ratio of developing heart failure (HF) is 4.5 (95% confidence interval (95% CI) 4.25-4.95) in COPD patients after adjustment for cardiovascular risk factors and compared with age-matched controls[13]. In the ECLIPSE study, the overall prevalence of HF was 7%, but it increased with the severity of airflow limitation[14].

At least part of the explanation, besides the common risk factors and a rich body of evidence for chronic systemic inflammation and endothelial dysfunction, lies in global aging of the population; almost half of the people aged ≥65 have at least three medical conditions[15].

All these epidemiological data must be considered with some degree of caution because of the reported significant disparities in using confirmatory diagnostic tests amongst practicing clinicians. Up to one-third of patients labeled with COPD do not fulfill GOLD criteria for the diagnosis. A recent US study showed that among 219 patients discharged from a tertiary centre with both diagnoses of COPD and HF, 82% received echocardiography, as opposed to only 36% of patients who received pulmonary function testing, which is much less expensive and time consuming than comprehensive echocardiography[16]. In their prospective REPENSAR study, Macchia *et al*. found that only 6.5% of cardiologists and 12% of pulmonologists had certified or ruled out COPD in patients with CHF, or *vice versa*[17]. COPD independently predicted failure of the ejection fraction of left ventricle (EFLV) assessment by echocardiography during hospital stay in the Italian TEMISTOCLE study[18].

Chronic obstructive pulmonary disease strongly predicts hospitalization rate and duration, and non-cardiovascular mortality in HF patients with 5-year mortality as high as 69% compared to 58% in patients without COPD. Also, respiratory infections are associated with cardiac decompensation in 10%-16% of admissions[19]. On the other hand, the prevalence of unrecognized HF in COPD patients presenting to emergency department with acute dyspnea is 20.9%, and unrecognized HF is a frequent cause of weaning difficulties in COPD patients requiring mechanical ventilation due to severe acute exacerbation of the disease[20].

Typical Clinical Feature: Dyspnea

Dyspnea is the most disabling symptom of COPD, which originates from decrease in the capacity of re-

spiratory muscles to meet an increased mechanical load. Several different mechanisms contribute to this imbalance.

Patients with COPD must generate more negative intrathoracic pressures in order to achieve adequate alveolar ventilation. The pressure output during resting breathing can be more than three times higher comparing with healthy subjects[21]. This means higher oxygen cost of respiration accompanied with less efficiency. Also, inspiratory flow resistance is increased[22], loss of elastic recoil causes higher relaxation volume, minute ventilation is increased up to 50% even during resting breathing, and expiratory flow is limited with delayed lung emptying[23,24].

Hyperinflation decreases the length of the diaphragm and of the rib cage muscles with a significant decrease in the length of the zone of diaphragmatic apposition, so the diaphragmatic contraction is less effective[25,26]. Furthermore, diaphragmatic curvature is also decreased. In the situation when end-expiratory lung volume lies above 70% of the predicted total lung capacity, inspiratory muscles have to work not only against the elastic recoil of the lungs, but also against elastic recoil of the thoracic cage[27].

About half of the patients with moderate-to-severe COPD have parallel reductions in maximal inspiratory and expiratory muscle strength, possibly due to the generalized muscle weakness[27,28]. The mechanisms contributing to this generalized muscle wasting are malnutrition, altered inflammatory cytokine profile with high plasma levels of tumor necrosis factor alpha (TNF-α) with activation of the ubiquitin-proteasome proteolytic pathway[29-31], electrolite and blood gas abnormalities, HF[29], weight loss[28], and steroid myopathy[32].

Inspiratory muscle weakness in patients with CHF is a result of a complex interplay between decreased total number of diaphragmatic actin-myosin cross-bridges[33], reduction in type IIb fibers[34], decreased regional blood flow, activation of the ubiquitin-proteasome proteolytic pathway by TNF-α, decrease in various oxidative enzymes, size and number of mitochondria[35], atrophy of the limb muscle fibers, postcapillary pulmonary hypertension with compensatory vascular remodeling, bronchial congestion, decreased lung compliance and consequently increased work of the diaphragm up to threefold[36-37] and, to some extent, hyperpnea that could predispose to hyperinflation[38,39].

Of note, patients with COPD have similar symptom profiles as those with HF, but dyspnea at rest is usually more pronounced.

Diagnostic Pitfalls

Echocardiography

Transthoracic echocardiography is often influenced by the poor acoustic windows in patients with emphysema; in a recent study, inadequate visualization caused by air trapping caused unsatisfactory results in 10.4% of all examined patients with COPD[40,41]. This proportion is even greater in patients with severe and very severe airflow obstruction in emphysema phenotype[42].

In transesophageal echocardiography, the transducer located behind the heart enables continuous visualization of all four heart chambers without hindrance from lung even during mechanical ventilation. Of note, during transesophageal echocardiography, as well as in interventional cardiology and pulmonology, noninvasive ventilation can reduce the need for deep sedation or general anesthesia and prevent respiratory depression induced by deep sedation[43].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging is the accepted reference standard for estimation of left ventricular (LV) volumes and ejection fraction. It is especially recommended in the evaluation of LV function in patients with inadequate visualization on echocardiographic images and could additionally estimate myocardial fibrosis and predict the risk of arrhythmias in COPD patients[44].

Natriuretic peptides

Natriuretic peptides are targeted at protecting the cardiovascular system from the effects of volume overload. Both atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) induce vasodilatation, natriuresis and diuresis. BNP is secreted in bursts and has minimal storage, unlike ANP which can be released with minor triggers. In the setting of pressure overload or volume expansion, the synthesis of pre-proBNP in ventricular myocardium is initiated and afterwards the cleavage to proBNP and then to BNP and inactive NTproBNP follows[45].

Both BNP and NTproBNP are useful for excluding HF in subjects presenting with acute or worsening dyspnea. They also provide prognostic information as every 100 pg/mL increase in BNP level is associated with 35% increased death risk[46]. Also, BNPs are useful in monitoring the effects of therapeutic interventions and may be used as a tool for screening for subclinical forms of HF. The BNP Consensus Panel Guidelines state that BNP levels lower than 100 pg/mL have high negative and levels higher than 500 pg/mL high positive predictive value for HF. Increased levels of both BNP and NTproBNP are associated with female gender, advanced age, acute coronary syndrome without HF, sepsis, acute respiratory distress syndrome (ARDS) and right HF[45].

Therapeutic Challenges

ACE inhibitors or ARBs

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of treatment in CHF. Moreover, ACE inhibition has been demonstrated to prevent smooth muscle atrophy and improve respiratory muscle strength in patients with HF[47], and these effects could be especially interesting in patients with concomitant COPD. Also, cross-sectional data from 2431 hypertensive subjects found that lower limb muscle mass was larger in the ACE inhibitor group in a manner proportional to the length of use[48]. However, in a recent small randomized controlled study, Shrikrishna *et al*. found that fosinopril treatment for 3 months did not alter muscle atrophy signaling or exercise performance in COPD patients with quadriceps weakness[49].

Andreas *et al*. evaluated the effects of the angiotensin II receptor blocker irbesartan given over 4 months in 60 patients with COPD and FEV_1 of less than 50% of the predicted value and without obvious cardiovascular disease that would necessitate administration of an ACE inhibitor or angiotensin receptor blocker. In this study, irbesartan did not exert significant effect on the primary end-point maximum inspiratory pressure, but there was a trend towards total lung capacity reduction – a finding that probably deserves prospective investigation[50].

In conclusion, despite extensive data on the effects of ACE and angiotensin II type-1 receptor inhibition (ARB) on systemic inflammation and tissue metabolism, the body of evidence on the potential effects on pulmonary inflammation, architecture and vasculature or skeletal muscle functional capacity in COPD, especially in the face of reduced oxygen delivery, is still insufficient. Nevertheless, due to the improved outcome of HF, ACE inhibitors or ARBs should not be denied in concomitant COPD. In the OPTIMIZE-HF cohort, patients with COPD were less likely to be started on ACE-Is/ARBs and aldosterone antagonists during hospital stay and were also more likely to have their ACE-Is/ARBs discontinued[51]. It should be emphasized that the regular use of ACE inhibitors does not induce bronchospasm or increased risk of cough in COPD patients.

Beta blockers

Beta blockers are still generally underused in CHF patients, especially those with concomitant COPD. According to the evidence from 12,440 patients in the ESC Heart Failure Long-Term Registry, beta blockers were prescribed to 72% of hospitalized patients with HF and 89% of patients in the outpatient setting, but only 17% of patients received targeted daily doses[52]. In a recent large sample from primary care in Scotland (N=377,439), the prevalence of established COPD in patients with HF was 25%, but only a small minority (18%) of COPD patients received beta blockers[53].

Beta-1 blockers (B1B) have 20-fold higher affinity for beta-1 receptors (B1R) than beta-2 receptors (B2R) and, although they tend to lose sensitivity at the high end of dose ranging, patients with COPD are generally free of adverse respiratory effects with unchanged FEV_1. Selective B1B do not attenuate B2R agonist-induced bronchodilatatory effects and may actually be beneficial in COPD by enhancing sensitivity to exogenous beta-adrenergic stimulation. Also, recent large observational studies provide some evidence that concomitant long-term use of inhaled antimuscarinic agents or beta agonists along with cardioselective beta blockers actually reduces mortality rates and the risk of exacerbations in patients with COPD[54,55]. According to a systematic review by Etminan *et al*. of nine retrospective cohort studies, beta blockers reduce mortality in COPD, most probably due to their cardioprotective effects[56]. However, several types of biases may have affected the cited results and one should note that studies with negative results are much less likely to be published.

Despite the data collected from meta-analyses, which strongly suggest that selective B1B should not be withheld in patients with mild to severe COPD and HF because their benefits by far outweigh the risks[57,58], beta blockers are less prescribed before admission (21.1% *vs*. 23.8%, p=0.055) in COPD patients, and remain underutilized at discharge (p<0.001)[59].

Carvedilol is the only non-cardioselective beta blocker approved for treating HF. Since there are no robust data supporting the safety in patients with moderate or severe airways disease, it should be avoided when possible in patients with COPD, especially during acute exacerbations.

In conclusion, cardioselectivity is paramount, and therefore metoprolol, bisoprolol and in particular nebivolol should be the first choice treatment.

Inhaled beta-2 agonists

For decades, inhaled beta-2 agonists were strongly associated with adverse cardiac effects in COPD patients with pre-existing cardiovascular disease and an increased risk of CHF decompensation (adjusted OR 3.42; 95% CI 1.99 to 5.86), also with all-cause mortality in patients with CHF[60]. Au *et al*. found direct association between the number of canisters of beta agonist used and the risk of and death from all causes, suggesting caution using beta agonists in patients with left ventricular systolic dysfunction[61]. One might argue that the use of beta agonists, short-acting beta agonists (SABA) in particular, in acute setting merely reflects the degree of dyspnea. In the ACQUIP case-control study, beta agonists in patients with HF were associated with the risk of hospitalization, but adjustment for cardiovascular morbidity, age, beta blocker use, COPD severity and smoking burden made the difference nonsignificant[62]. In short, the poor patient outcomes attributed to beta agonists may actually reflect symptom burden in COPD.

Since long-acting beta agonists (LABA) or/and long-acting antimuscarinic agents (LAMA) are the cornerstone of COPD treatment in all stages for decreasing exacerbation rates, improving lung function and quality of life, prescribing only SABA and/or short-acting muscarinic antagonists (SAMA) for symptom relief and avoiding treating COPD when coexisting with HF would be as erroneous as denying beta blockers to patients with HF.

There is additional concern of triggering supraventricular and ventricular arrhythmias by LABA, LAMA and their combinations. Multifocal atrial tachycardia (MAT), atrial fibrillation and ventricular arrhythmias often complicate the course of COPD, in particular during acute exacerbations. MAT is often associated with the use of theophylline, pulmonary embolism, hypoxemia, and also other disorders such as hypokalemia or hypomagnesemia, and chronic renal failure[63]. The largest trial of 1429 patients with COPD found that the administration of formoterol or salmeterol, the two most often administered LABAs, did not result in a statistically significant increase in atrial arrhythmias[64].

One of the most important risk factors of arrhythmias is acute respiratory failure or, in particular, worsening of chronic respiratory failure during acute exacerbations. One of the most important decisions in the acute clinical setting is well-timed noninvasive ventilation.

Conclusion

Both HF and COPD are global epidemics, especially in the elderly. Both diseases are chronic, progressive, and share many common pathways of low grade systemic inflammation. The prevalence of coexisting HF and COPD is yet unknown and most certainly underestimated. Understanding both diseases with the use of proper diagnostic tools is mandatory in order to achieve earlier treatment and better long-term prognosis. Concurrent COPD may play part of the missing puzzle in the complex pathophysiology of HF, and *vice versa*. Considering the high prevalence of ventricular dysfunction in COPD, routine assessment with either BNP or echocardiography should be considered in COPD patients. On the other hand, pulmonary function tests should be performed in all HF patients. Therefore, closer collaboration between pulmonologists and cardiologists should be warranted in the future. Also, there is an urgent need for large prospective randomized trials on long-term effects of different classes of currently recommended drugs including patients with more advanced disease(s), including those with frequent exacerbations, patients with severe impairment of lung function, heavy symptoms, or those with the asthma and COPD overlap syndrome.

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Sažetak

KRONIČNA OPSTRUKTIVNA PLUĆNA BOLEST I ZATAJENJE SRCA: TAKO BLIZU, A TAKO DALEKO

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Kronična opstruktivna plućna bolest (KOPB) i zatajenje srca među vodećim su uzrocima pobolijevanja i smrtnosti u svijetu. Unatoč brojnim poveznicama, kod bolesnika s kroničnom opstruktivnom plućnom bolešću zatajenje srca ostaje često neprepoznato, no vrijedi i obratno. Kod bolesnika s prethodno utvrđenom KOPB dijagnoza zatajenja srca se često postavlja prekasno, no vrijedi i obratno, ponajviše zbog vrlo sličnih simptoma i znakova bolesti poput zaduhe i intolerancije napora uslijed disfunkcije skeletne muskulature. Bolesnici s KOPB-om imaju viši rizik zatajenja srca, ali i češće hospitalizacije i smrtnost od bolesnika sa zatajenjem srca bez pridružene KOPB. Ehokardiografija, testovi plućne funkcije i određivanje natriuretskih peptida trebaju biti neizostavni dio dijagnostičkog postupka i reevaluacije bolesnika uz bližu suradnju subspecijalista kardiologa i pulmologa sa svrhom ne samo pouzdane dijagnoze, već i optimalnog pristupa liječenju bolesnika s često prisutnim komorbiditetima.

Ključne riječi: *Plućna bolest, kronična opstruktivna – dijagnostika; Plućna bolest, kronična opstruktivna – terapija; Srčano zatajivanje – dijagnostika; Ehokardiografija; Respiracija, ispitivanje funkcije*