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TREATMENT OF HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Hypertension and COPD

Hypertension is one of the most prevalent non-communicable diseases in the world, affecting 30–40% of the adult population. It is frequently associated with other diseases (e.g. diabetes mellitus, chronic kidney diseases, bronchial asthma, and chronic obstructive pulmonary disease — COPD) which may influence the selection of proper anti-hypertensive drugs. According to WHO data, 250 million people suffer from COPD worldwide, accounting for 5% of total mortality [1, 2]. The incidence of COPD is rapidly increasing all over the world. It is the only cause of death with increasing incidence and it is estimated that it will have become the third most prevalent, after stroke and myocardial infarction, by 2030 [1]. COPD occurs predominantly in cigarette smokers. It is a slowly progressing disease characterised by airflow obstruction within the airways and/or pulmonary parenchyma. Symptoms and complications may include shortness of breath, poor exercise tolerance, chronic productive or non-productive cough, wheezing, respiratory failure, and *cor pulmonale*. Most patients suffering from these symptoms are not aware of their disease or their treatment is insufficient.

The most common co-morbid diseases in COPD are hypertension (28%), diabetes mellitus (14%), and ischaemic heart disease (10%) [2, 3]. According to international data, the prevalence of COPD among patients with hypertension is similar to that of the general population, thus the coincidence of the two diseases may affect 2.5% of the adult population. COPD is regarded as an independent risk for cardiovascular diseases. Among patients with COPD, the prevalence of heart failure is 4×, coronary heart disease is 2×, angina pectoris and myocardial infarction are 2.5×, peripheral artery disease and arrhythmias 2.4×, and stroke is 1.5× higher than in the general population [4]. Furthermore, there is a pathogenetic link between COPD and hypertension, as hypoxia may enhance the production of free radicals and endothelial dysfunction, leading to hypertension and its cardiovascular complications.

Separate guidelines are available for the diagnosis and treatment of these diseases [5, 6]. However, these issues are not discussed jointly in international guidelines.

The *goals of COPD treatment* are to reduce long-term lung function decline, prevent and treat exacerbations, reduce hospitalisations and mortality, relieve disabling dyspnoea, and improve exercise tolerance and health-related quality of life. The treatment of COPD includes inhaled therapies (anticholinergic agents, long-acting β-2 adrenoceptor agonists, and corticosteroids), pulmonary rehabilitation programmes, and the use of supplemental oxygen [5]. These drugs may affect the cardiovascular system (heart rate, blood pressure) and may increase the incidence of cardiovascular events (angina pectoris, myocardial infarction) [7].

The *goals of antihypertensive therapy* [8] are to normalise blood pressure, prevent cardiovascular morbidity, decrease mortality, extend lifespan and improve the quality of life for patients [6]. Treatments include lifestyle modifications (smoking cessation, reduction of salt or energy intake, increasing physical exercise) and drugs (diuretics, beta-blockers, calcium channel blockers, ACE-inhibitors, angiotensin II type 1 receptor antagonists, direct renin inhibitor, α-1 blockers, imidazolin I-1-receptor or α-2 adrenoceptor agonists, and sometimes direct vasodilators or 5-hydroxytryptamine modifiers). Because many of these anti-hypertensive drugs can affect airway function, the treatment of hypertension in patients with airway dysfunction is complex.

Treatment of hypertension in patients with COPD

Therapy involves non-pharmacological treatment as well as drug therapy. *Non-pharmacological treatment* must include smoking cessation to prevent further deterioration of airway function and to decrease cardiovascular morbidity and mortality. Moderate physical exercise in patients with hypertension and COPD with pulmonary rehabilitation programmes provides improvements in respiratory symptoms, quality of life, and exercise endurance (6-minute walk test) [5].

Pharmacological therapy of hypertension involves, in most patients, drug combinations. For the selection of suitable drugs, in addition to COPD, several other factors should also be considered: concomitant risk factors and co-morbidities (e.g. dyslipidaemia, hyperuricaemia, diabetes mellitus, chronic kidney disease), the effects of drugs used for COPD on the cardiovascular system and their interaction with antihypertensive drugs, as well as the effect of antihypertensive drugs on airway function. There is no conclusive evidence from randomised clinical trials (RCTs) that anti-hypertensive drugs reduce mortality or morbidity in hypertensive patients with COPD. This is due to the fact that the trials were too small, did not follow the patients for a long enough period of time, and frequently failed to report all important outcomes. There have been, however, meta-analyses showing that cardio-selective β-blockers reduce cardiovascular morbidity and mortality in these patients. Furthermore, there is insufficient RCT evidence to determine which drug is most effective. Therefore, it is important for the physician to know that this is one of the clinical settings where treatment is not always supported by RCT evidence but is based on case-control studies or experts' opinions.

Diuretics (DIU)

The results of randomised, controlled clinical trials for diuretics in COPD are not available. In principle, diuretics may be beneficial for the elimination of fluid retention developing in heart failure that frequently complicates COPD and also hypertension. Diuretics may inhibit pulmonary vascular remodelling. Acetazolamide has been found to increase ventilation in COPD. However, DIU may decrease the plasma level of potassium, and this effect may be added to the hypokalaemic effects of steroids and β-2 adrenoceptor agonists, drugs that are frequently used in COPD. DIU may also worsen CO_2 retention, metabolic alkalosis-related hypoxia in hypoventilation patients, increase haematocrit and deteriorate mucus secretion in bronchi. Therefore DIU are not recommended for universal use in hypertensive patients with COPD [9–11].

Indapamide might be an exception to this rule, as in a 28 week study of hypertensive patients with COPD on standardised bronchodilator therapy, blood pressure decreased by 48/30 mm Hg (mean value) and respiratory function improved over the same period [12].

β-adrenoceptor antagonists (BBL)

The worsening or precipitation of asthma by non-selective β-blockers is well-recognised, but the cardio-selective β-1-adrenoceptor blockers and those exerting mild β-2-agonist activity (e.g. celiprolol), or those which, in addition to their high β-1 selectivity, increase the endogenous production of nitric oxide (NO) (nebivolol), affect airway function to either a much lesser extent, or not at all.

Therapy with selective β-1 blockers is not contraindicated in cases of chronic airway obstruction, and has also been proved to decrease total as well as cardiovascular mortality. In addition to these beneficial effects, they may also decrease the incidence of acute exacerbations of airways obstruction [13–16]. Therefore, if needed in patients with COPD for hypertension or coronary heart disease, highly selective β-1 blockers can be recommended. The meta-analysis by Salpeter et al. [17] indicated that non-selective BBL decreases while cardio-selective BBL improves the bronchodilatatory effects of β-2 mimetics due to β-2 receptor up-regulation.

Calcium channel blockers (CCB)

CCBs induce smooth muscle relaxation in bronchi and inhibit the decrease in forced expiratory volume (FEV1), either induced by physical activity or metacholine. They may slightly potentiate the β-2 receptor mediated bronchodilation and decrease non-specific bronchial reactivity; therefore, use of CCBs may be beneficial in hypertensive patients with COPD. Clinical experience has shown that these drugs usually do not exert severe side effects on the airways. However, it is important to note that CCBs may worsen the normal ratio of perfusion/ventilation, and consequently increase hypoxia; therefore, oxygen saturation monitoring is recommended [9, 10]. Hard end-point data on the use of CCBs in hypertensive patients with COPD has yet to be published.

Angiotensin-converting enzyme inhibitors (ACEI)

It has been known for years that ACEIs may cause coughs and exacerbate, or even induce, asthma. 10% of the reported adverse effect of ACEIs is bron-

chospasm. However, these anti-hypertensive agents have been proven to decrease cardiovascular morbidity and mortality of hypertensive patients as well as those with coronary heart disease and heart failure. They also decrease COPD-induced hospitalisation of patients. ACEIs may reduce the renin-angiotensin-aldosterone (RAAS) stimulation-related hypokalaemic effects of β-2 receptor agonists [18], agents that are frequently used in COPD. It is important to note that the incidence of ACEI-related cough was not more frequent in patients with chronic bronchitis than in other populations [19]. However, ACEIs may worsen the clinical stage in patients with asthma. The increased availability of bradykinin (which increases cough) and substance P (which causes bronchoconstriction) probably contribute to this unwanted effect [10]. Unfortunately, studies including hypertensive patients with COPD are scarce; the duration of trials have been short, patients were not randomised, and there were no control groups involved. In these trials, ACEI-related side effects were rare, although the tolerability of drugs was good.

Angiotensin receptor blockers (ARB)

An important advantage of this anti-hypertensive class against ACEIs is that they practically do not cause cough, and ARB-related angioneurotic oedema is very rare. Patients with a history of ACEI-induced cough tolerate ARB as well as they do a placebo [20]. However, in one study, losartan increased cough, a side-effect thought to be related to the inhibition of the endogenous release of nitric oxide [7]. Contrary to this finding, in another study, losartan inhibited the metacholine-induced bronchospasm, and consequently decreased the reduction of FEV_1 [21]. Angiotensin AT-1 receptor blockade is useful because the hypoxia stimulates the sympathetic nervous system and consequently the RAAS [9, 10].

α-1 adrenoceptor antagonists

In general, these drugs do not affect airway resistance. Prazosin was found to partially inhibit cold air-induced broncho-constriction. The deteriorated airway function in COPD was not changed by these drugs; therefore they may be used in hypertensive patients with COPD [9].

α- + β-adrenoceptor antagonists

Labetalol does not change airway resistance, but carvedilol, probably because of its very weak α-1 blocking property and of strong non-selective β-blockade, may potentially increase bronchial spasm; therefore, these drugs may not be the best choice for anti-hypertensive treatment of patients with COPD. However, in patients with heart failure, carvedilol did not worsen airway function [9].

5-Hydroxytryptamine modifiers

These drugs are rarely used in the treatment of hypertension. Urapidil, in addition to its 5-hydroxytryptamine modifying (5-HT1A receptor stimulating) action, has a peripheral α-adrenoceptor blocking property. Both effects cause broncho-dilation; therefore, urapidil may also be a treatment option for hypertensive patients with chronic airway obstruction [9].

α-2 adrenoceptor agonists

These drugs decrease central sympathetic tone, decrease the activity of RAAS, and relatively increase the parasympathetic tone. Consequently, the susceptibility of patients for bronchospasm may increase. The α-2 adrenoceptor agonists may potentiate the histamine-induced bronchial spasm; therefore, they cannot be suggested for use on hypertensive patients with COPD [9].

There is no data regarding the use of more specific drugs for inhibiting central sympathetic tone, such as the *imidazoline I1-receptor agonists* (rilmenidine, moxonidine) in hypertensive patients with COPD.

Conclusions

In patients with hypertension complicated by COPD, it is essential to include non-pharmacological measures (e.g. moderate physical exercise, dietary regulations, salt restriction) in anti-hypertensive therapy. It is absolutely crucial to stop smoking.

For pharmacological treatment of hypertension, there is no strict rule because individual patients may respond differently to different drugs and drug combinations. CCBs, RAS blockers, preferably ARBs, or CCB/RAS blocker combinations, as the initial drugs of choice are recommended. If the response is poor, thiazide diuretics, highly cardioselective β-1 adrenoceptor-blocking agents, especially those with ancillary properties (e.g. nebivolol or celiprolol), or α-1 adrenoceptor antagonists can be considered. Consequently, it is important to adopt a flexible approach.

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