Beta-blockers for the treatment of elderly patients with coexisting heart failure and chronic obstructive pulmonary disease

I beta-bloccanti nel trattamento degli anziani con insufficienza cardiaca e broncopneumopatia cronica ostruttiva

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La broncopneumopatia cronica ostruttiva (BPCO) e l’insufficienza cardiaca (IC) sono tra le principali cause di morte in tutto il mondo. La mortalità e l’incidenza di queste patologie aumenta con l’età. Queste due patologie spesso coesistono e condividono meccanismi fisiopatologici comuni. Nonostante il beneficio indiscusso sulla mortalità e morbidità cardiovascolare in pazienti anziani affetti da IC e BPCO, l’uso di beta-bloccanti è spesso evitato. I trial clinici e i studi di meta-analisi indicano che i beta-bloccanti cardioselettivi non dovrebbero essere evitati nei pazienti con BPCO. Il beneficio che deriva del trattamento con beta-bloccanti sembra superare i loro possibili effetti collaterali. In questo manoscritto descriviamo i meccanismi fisiopatologici comuni coinvolti nello sviluppo della BPCO e IC, e riportiamo le evidenze sull’utilizzo, la sicurezza e il beneficio della terapia con beta-bloccanti nei pazienti anziani.

Parole chiave: Broncopneumopatia cronica ostruttiva, Insufficienza cardiaca, Anziani, Beta-bloccanti, mortalità, Recupero funzionale

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are leading causes of mortality worldwide. The incidences of both COPD and HF increase with age. These chronic diseased frequently coexist among elderly patients and share common pathophysiological mechanisms. HF is characterized by sympathetic nervous system hyperactivity, due to enhanced catecholamine secretion from sympathetic nerve endings and from the adrenal medulla. Accordingly, plasma catecholamine levels may be utilized as circulating biomarkers together with other well known biomarkers in HF, as well as in COPD patients. It is widely recognized that chronic stimulation of the beta-adrenergic receptors by catecholamine exerts toxic effects on the heart and other organs and this deregulation plays a key role in HF pathogenesis and progression. Further, enhanced extrinsic sympathetic nerve activity occurring in HF could induce a simultaneous activation of sympathetic fibers of cardiac visceral fat which might contribute to the adrenergic nerve derangement observed in the failing heart. Despite administration of beta adrenergic receptor agonists induces immediate hemodynamic advantages, long-term treatment with these drugs do not increase survival of HF patients. On the other side, beta-blocker treatment is known to counteract HF progression and to significantly reduce HF-related morbidity and mortality, with positive effects also on right ventricular function. These therapeutic effects are mainly attribute to the ability of beta-blockers to protect the heart from the noxious effects of elevated SNS activity. Moreover, beta-blocker therapy, as well as physical activity, ameliorates adrenergic inotropic response in the failing heart by preventing beta-adrenergic receptor...
desensitization and down-regulation and reduces myocardial oxygen consumption, cardiac interstitial fibrosis, myocyte apoptosis and cardiac adverse remodeling. However, despite these well-recognized therapeutic effects, there is still a general concern among physician in using beta-blocker therapy in COPD patients. One of the most important goal in COPD is the prevention of exacerbations. In animal studies report that treatment with beta-blockers has a protective effect on airway responsiveness, reduces the levels of cytokines like IL-13, IL-10, IL-5, TGF, inflammatory cells in the lung tissue and beta-blocker therapy leads to an up-regulation of beta2-adrenergic receptors in the lung, improving the effectiveness of beta-agonists. In this vein, it is important to mention that preservation of beta2-adrenergic receptor signaling and function is protective also in the heart. The evidence from trials and meta-analyses indicate that cardio-selective beta-blockers should not be avoided in patients with COPD, since the benefit derived from their use seems to outweigh the possible side effects, however this class of drugs remains underused especially in old patients with comorbidities. In the present article we will discuss common pathophysiological mechanisms involved in the development of COPD and HF and we will review evidence derived from trial on beta-blocker use, safety and benefits among elderly patients.

DEFINITIONS AND EPIDEMIOLOGY

HF is defined as an abnormality of cardiac structure and function leading to instability between tissues oxygen demand and the ability of heart to deliver oxygen to tissues. The main clinical manifestations of this complex syndrome are: dyspnea, fatigue and fluid retention which result in limited exercise tolerance, pulmonary congestion and peripheral edema. Epidemiological studies have shown a high prevalence and incidence of HF among the elderly population. About 50% of HF cases are reported in patients older than 70 years and, with each decade of life, its prevalence doubles and its incidence rises up to 10% in elderly subjects over 70 years and is associated with high incidence of HF-related tromboembolisms. COPD is defined as a condition characterized by airflow limitation that is not completely reversible, resulting a post-bronchodilator ratio FEV1/FVC < 70%. Worldwide prevalence of COPD ranges from 7.8% to 26.1% and becomes higher in the geriatric population. COPD is the fourth leading cause of death in Europe and USA. Frequent symptoms in COPD patients are represented by cough, dyspnea and sputum production. The prevalence of HF in COPD patients is reported to be 21-31%. On the other side, the prevalence of COPD in HF patients varies from 7% to 13% in HF outpatients population and from 9% to 51% in hospitalized HF patients.

CARDIOPULMONARY CONTINUUM

The major risk factor for COPD is tobacco-smoking which causes pulmonary inflammation by inducing pulmonary mucus hypersecretion, influx of neutrophils in the lung tissue, oxidative stress and pro-inflammatory cytokines secretion (i.e. IL-1b, IL-6, IL-18). However, these pro-inflammatory changes do not affect exclusively the lung but the entire body through the induction of a systemic low-grade inflammatory status. Mild leukocytosis and elevated fibrinogen and CRP levels characterize this systemic inflammation. This low grade systemic inflammation represents a common characteristic between COPD, coronary artery disease, coronary artery remodeling after revascularization, and HF. Moreover, COPD is associated with development of pulmonary artery hypertension, which in turn may lead to right ventricle dysfunction and HF. Furthermore, obesity and diabetes mellitus which are established determinants of coronary artery disease reduce the ventilatory mechanics and lung function. Finally, SNS hyperactivity, which is a pivotal characteristic of chronic HF, is present also in COPD patients. Based on these common inflammatory pathways and the evidence of frequent coexistence of COPD and HF, the concept of cardiopulmonary continuum has been described. Tumor Necrosis Factor (TNF) appears to have an important role in this common pathway. Indeed, increased levels of TNF, CRP and IL-6, observed in COPD patients, are associated with poor survival, increased hospitalization rates and worsening of general conditions also in HF patients. However, additional studies are needed to better clarify the common pathophysiological mechanism involving COPD and HF in order to improve the treatment strategies in patients affected by both these chronic diseases.
BETA-BLOCKERS USE IN COPD

The use of beta-blockers is often avoided in elderly patients with concomitant HF and COPD despite the well-known benefit on cardiovascular mortality and morbidity recognized also in this population. The main reason is based on the possible side effects of beta-blockers on airways, since these drugs are known to facilitate bronchospasm, by blocking beta2 adrenergic receptors in the lung. Gottlieb et al. 75 reported that in elderly patients with myocardial infarction, treatment with beta-blockers reduced mortality during a follow-up of 24 months. The overall reduction in mortality was 40% in the overall population and 32% among elderly over 80 years. A similar trend was observed in patients with a history of COPD. Thus, taking into consideration the elevated mortality rate observed in these groups of patients, the use of beta-blockers is strongly supported in elderly HF patients with concomitant COPD. However, it is important to underline that in this study different classes of beta-blockers were not compared, COPD patients were not stratified according to the severity of disease, and the mortality rate ratio was not adjusted for any confounders. The use and the efficacy of beta-blockers therapy in elderly patients with COPD or asthma was evaluated by Chen et al. 76. The study sample size was of 54962 patients divided in three sub-groups: patients with COPD or asthma without beta-agonist treatment (12,1%), patients with COPD or asthma under beta-agonist therapy (5,2%) and patients with severe COPD or asthma, treated with beta-agonists and steroids and presenting respiratory exacerbation within one year before acute myocardial infarction (2,7%). The remaining 80% of patients did not present any history of COPD or asthma. Beta-blockers were prescribed in 31,1% of patients with COPD or asthma that were not under beta-agonists therapy, in 21,1% of patients treated with beta-agonists and only in 9,3% of patients with severe COPD or asthma. Patients with COPD or asthma were significantly less likely to be treated with beta-blockers therapy after myocardial infarction. Importantly, this study reported that treatment with beta-blocker was associated with a significant reduction in mortality rate over one year of follow-up also in the subgroup of patients with COPD or asthma who were not under beta-agonist therapy (RR = 0.86, 95% CI 0.73 to 1,00 p = 0,048). Based on these results, the authors concluded that in elderly patients without severe COPD or asthma the use of beta-blockers may be beneficial. In another population of elderly patients with HF the association between beta-blocker use and mortality was examined 77. Patients who received beta-blockers showed a 28% reduction in all-cause mortality and a 35% reduction in HF-related mortality compared to patients not treated with beta-blockers. Importantly, the subgroup of elderly patients with COPD showed even a lower all-cause mortality rate (HR = 0,78; 95% CI: 0,63 to 0,95). Moreover, a trend towards greater therapeutic benefit was reported in patients receiving the highest doses of beta-blockers. However, in this study the authors did not report whether patients presented systolic or diastolic HF and the population was not stratified according to COPD severity. In a 10-year retrospective observational study, a higher mortality risk during hospitalization and 30 days after hospital discharge was observed during hospitalization and was observed in COPD patients with myocardial infarction 78. Recently, Mentz RJ et al. 79 explored the interaction between beta-blocker selectivity and outcome in patients with COPD and systolic left ventricle dysfunction. In the overall population, there were 725 patients with a history of COPD (27%). In line with the results of the other studies, COPD patients were less likely to receive beta-blockers than patients without COPD. Among patients receiving beta-blockers, 40% received a cardioselective beta-blockers and 60% a non-cardioselective one. Within cardioselective beta-blockers, metoprolol and atenolol were more used, while carvedilol was the non-cardioselective beta-blocker more frequently prescribed. Both cardioselective and non-cardioselective agents were associated with lower mortality rate among patients with COPD and, in the overall population, there were no differences between cardioselective and non-cardioselective beta-blockers on mortality rates. However, this study presented a relative short-term follow-up (60 to 90 days). Thus, this study reported that the outcome was not affected by the selectivity of the beta-blocker used in patients with concomitant COPD and HF. Probably, beta-blockers may attenuate the adverse effects of beta-agonists on the heart, such as the facilitation of ischemia and arrhythmia induction. Moreover, there are some non-canonical effects of beta-blockers: some beta-blockers (i.e. carvedilol) have been shown to own same antioxidant effects and to counteract insulin-
resistance. Probably, these beneficial effects of beta-blockers may overweight the potential adverse pulmonary effects. Lee et al. published a cohort study reporting interesting results on the effects of beta-blocker therapy on cardiopulmonary outcomes and mortality in elderly patients with heart disease. The study included 1062 patients over 65 years with COPD or asthma and concomitant coronary artery disease with follow-up of 4 years. Fifteen percent of these patients were under beta-blocker therapy and, within 389 patients presenting a pulmonary exacerbation, 199 were treated with beta-blockers. Interestingly, over a total of 255 deaths 126 were under beta-blocker treatment. Thus, in this study beta-blocker use was not associated with any benefit on mortality. Anyway, it is important to underline that the adherence to beta-blocker therapy has not been considered and the possibility that beta-blocker users were at higher cardiovascular risk could not be excluded. In a Cochrane review of controlled randomized trials long-term administration of cardioselective beta-blockers was not associated with pulmonary symptoms or changes in FEV1, even in a subgroup of patients with severe COPD. However in this review the mean age of patients was 53.8 ± 11.1 years and the trials were of short duration. Recently, another meta-analysis, including 15 observational cohort-studies with a mean follow-up ranging from 1 to 7.2 years, revealed that beta-blocker therapy was associated with a significant reduction in all-cause mortality (RR 0.72; 95% CI = 0.63 to 0.83) and exacerbation of COPD (RR 0.63; 95% CI = 0.57 to 0.71). In subgroup analysis of COPD patients with HF the risk of overall mortality was significantly decreased (RR 0.74; 95% CI = 0.58 to 0.93). However, in this meta-analysis a marked heterogeneity in study size, follow-up and patient mean ages was found. Moreover, COPD diagnosis was exclusively based on clinical criteria, most of the studies did not provide stratification for COPD severity and type or dose of beta-blocker used was not reported. Despite these limitations the meta-analysis supported the safety of beta-blocker in patients with concomitant COPD. However both the American and European guidelines do not indicate a contraindication of beta-blockers use in HF patients with coexistent COPD. However, the management of elderly patients needs expertise and frequent controls in initiating, up titrating and maintaining the beta-blockers therapy.

**CONCLUSIONS**

The low grade systemic inflammation may be a possible interaction between HF and COPD coexistence. This common pathophysiological mechanism is complex and not completely clarified. From the evidence derived from trials beta-blockers therapy is safe in elderly patients with HF and comorbidities, such as COPD. The overall benefit of beta-blocker treatment in elderly patients with HF and COPD overweight the possible side effects derived from this therapy.

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are leading causes of mortality worldwide. COPD and HF incidence and related mortality increase with age. These chronic diseases frequently coexist especially among elderly patients and share common pathophysiological mechanisms. Despite the well-recognized benefit of beta-blockers on cardiovascular mortality and morbidity, this class of drugs is often underused in elderly patients with concomitant HF and COPD. Evidences derived from trials and meta-analyses suggest that cardio-selective beta-blockers should not be avoided in patients with COPD, since the benefit of beta-blockers treatment seems to outweigh the possible side effects. In this review we will discuss common pathophysiological mechanisms involved in the development of COPD and HF and we will review the evidence derived from trials on beta-blocker use, safety and benefits among elderly patients.

**Key words:** Chronic obstructive pulmonary disease, Heart failure, Elderly, Beta-blocker, Mortality, Functional recovery
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