



COPD and bronchodilators: should the heart pay the bill for the lung?

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Treatment with bronchodilators in COPD patients should take into account cardiovascular comorbidities <http://ow.ly/gMIG30aAwTK>

Cite this article as: Agabiti N, Corbo GM. COPD and bronchodilators: should the heart pay the bill for the lung? *Eur Respir J* 2017; 49: 1700370 [<https://doi.org/10.1183/13993003.00370-2017>].

The question

The pharmacological treatment of patients with coexisting cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) is challenging, because some drugs for COPD patients should be used with caution in patients with CVD, and *vice versa*. The crucial question on cardiovascular safety of long-acting bronchodilators, *i.e.* long-acting β_2 -agonists (LABAs) and long-acting anti-muscarinic agents (LAMAs, principally tiotropium), has no definitive answer. Because of different mechanisms of action, the combination of these drugs is expected to be more effective than the individual components in the maintenance treatment of COPD [1]. Evidence available from randomised controlled trials and observational studies on increased risk of cardiovascular adverse events is large but difficult to summarise because of complex methodology, different comparison groups and potential bias in each study [2–5]. Results are controversial and inconclusive. The risks of combining LABAs and tiotropium for the treatment of COPD are still unclear. Whether COPD patients treated with long-acting bronchodilators have increased risk of heart failure, or patients with both COPD and heart failure have higher risk of adverse events, remain open questions.

What the study adds

In this issue of the *European Respiratory Journal*, the study presented by SUISSA *et al.* [6] interestingly contributes to the ongoing debate. The focus is on the concurrent use of long-acting bronchodilators. A large COPD patient cohort was selected from the UK Clinical Practice Research Datalink for 2002–2012 and followed up over 1 year. Compared with monotherapy, adding a second long-acting bronchodilator (either a LABA or tiotropium) did not increase the risk of myocardial infarction, stroke or arrhythmia. However, a statistically significant 16% increase in the risk of heart failure was found with the addition of a second long-acting bronchodilator rather than monotherapy; the increase was higher (23%) when patients with previous diagnosis of heart failure (about 3% of the whole study population) were excluded. Large numbers from real-world settings, sophisticated analytical approaches and sensitivity analyses led to robust results, considering the known limits of observational studies on the comparative effectiveness and safety of drugs. The fact that the use of two long-acting bronchodilators was found to be safe, in terms of major cardiovascular events, is reassuring and supports the guidelines/recommendations regarding the use of fixed-dose combination bronchodilators. However, the effect on heart failure is relevant and deserves some additional consideration.

Received: Feb 21 2017 | Accepted: Feb 22 2017

Conflict of interest: None declared.

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Relationship between COPD and CVD

Heart–lung interactions are complex, particularly in the context of heart failure. CVD is undoubtedly the most significant non-respiratory contributor to both morbidity and mortality in COPD. The prevalence of CVD in patients with COPD was found to range from 7.1% to 31.3% for heart failure, from 4.7% to 60% for ischaemic heart disease, from 0.3% to 29% for arrhythmia and from 6.9% to 9.9% for stroke [7, 8]. The strong overlap between the two conditions is due to shared similar risk factors, such as ageing, smoking, exposure to environmental pollution, metabolic disorders and altered inflammatory response [7, 9]. On the one hand, the increased risk of CVD persists after adjustment for common risk factors, suggesting that COPD plays a role in the development of CVD [7]. On the other hand, COPD patients with a more severe reduction of forced expiratory volume in 1 s have a greater risk of occurrence of heart failure, atrial fibrillation and myocardial infarction [7]. COPD is frequent and often undiagnosed among patients with heart failure (with rates from 13% to 38%) [10] and is associated with higher mortality [11]. Over the last few years, researchers and clinicians have focused on the autonomic nervous system, which is impaired in both COPD and CVD [12]. Heart rate variability is frequently used as a measure of autonomic control. It has been found that COPD patients have a reduced heart rate variability [13] and that autonomic control during exercise is altered [14]. A reduction in heart rate variability reflects a sympathetic activation; this is a prognostic factor in ischaemic heart disease [15], heart failure, hypertension and stroke [16]. Clinical trials on the safety of these drugs on cardiovascular autonomic control have been performed [17, 18], but the absence of adverse effects could not be excluded, because of the selection of samples and the short duration of the studies. The complex relationship between CVD and COPD is summarised in figure 1.

Relationship between COPD and heart failure

Heart failure is a complex syndrome owing to the inability of the heart to pump sufficient blood to meet the needs of the body's tissues. It represents the end stage of cardiac disease, mostly following coronary disease or hypertension. Two distinct clinical syndromes have been identified: heart failure with reduced ejection fraction (HFrEF), *i.e.* EF <40%, which is characterised by abnormalities in left ventricular systolic function, progressive chamber dilation and eccentric remodelling, and heart failure with preserved ejection fraction (HFpEF), *i.e.* EF ≥50%, which presents normal or near normal systolic function and evidence of diastolic dysfunction with concentric remodelling or hypertrophy [19]. Heart failure with mid-range EF (*i.e.* EF range 40%–49%) has recently been labelled [19]. About half of patients with heart failure have a normal ejection fraction [20].

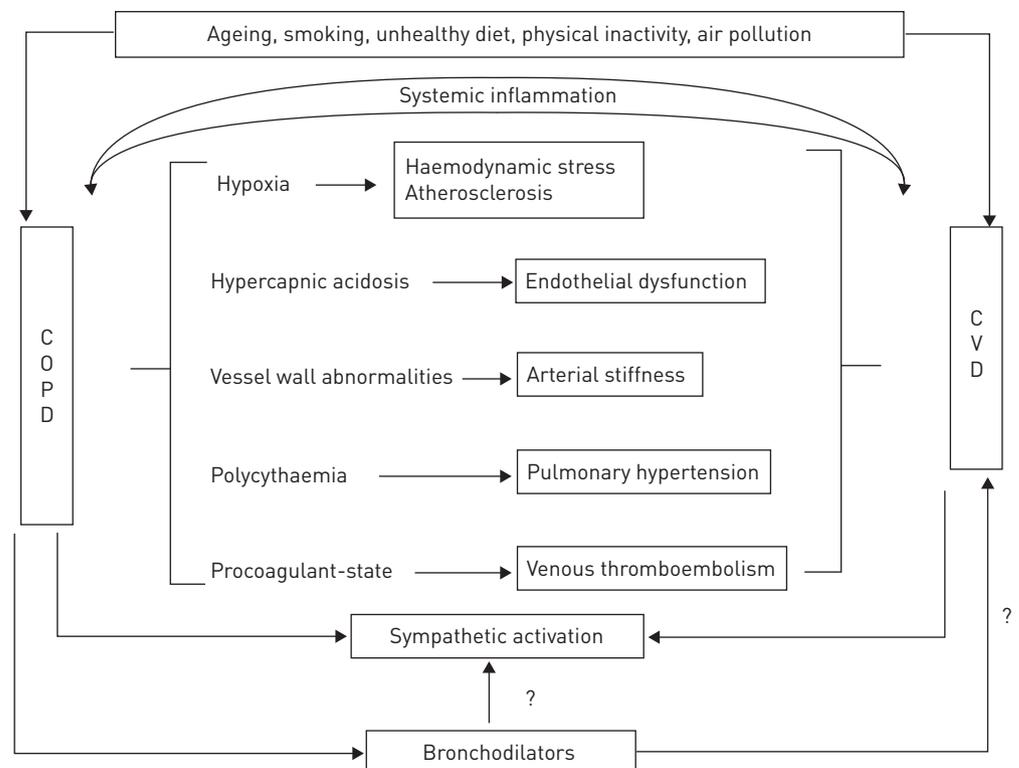


FIGURE 1. The complex interaction between chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD).

Although patients with heart failure present similar clinical signs and symptoms, it is important to distinguish the various forms of heart failure because they differ in pathophysiology, structural changes in the cardiac muscle, neuro-humoral and inflammatory molecular mechanisms, epidemiology, potential susceptibility to environmental triggers and response to treatment [19]. Some biomarkers have been linked to the heart failure subtypes. For example, plasma B-natriuretic peptide concentration in patients with HFpEF was lower than in patients with HFrEF, and highly sensitive troponin T was significantly associated with development of HFrEF; in contrast, growth factor GDF, cystatin C and urinary albumin excretion were significantly associated with the development of HFpEF [21]. Opportunities and challenges of old and new pharmacological treatments of heart failure patients have been updated in the clinical guidelines [22]. However, the role of both beta-blockers and ACE/ARB (angiotensin-converting enzyme/angiotensin receptor blocker) in HFpEF is not well established and there is no evidence-based optimal therapeutic protocol for HFpEF [22].

In this respect, the finding from the study by SUISSA *et al.* [6], that concomitant use of long-acting bronchodilators influences the incidence of new heart failure (hazard ratio 1.21 among those with no heart failure diagnosis before cohort entry), suggests that these drugs play a role in the development of heart failure in COPD patients in a 1-year follow-up period. Accurate identification of COPD subgroups that are potentially more vulnerable to cardiac drug toxicity is crucial. Measuring coexisting cardiac diseases, subtypes and severity of heart failure, conditions/comorbidities associated with poor prognosis such as peripheral artery disease or diabetes, and severity of lung function impairment is challenging, but cannot be fully achieved in large observational studies based on healthcare electronic databases. Because clinical presentation is fundamental to the diagnosis of heart failure, and heart failure and COPD share both risk factors and clinical presentation, making the correct diagnosis may be difficult [23]. Acute respiratory symptoms may have mixed pulmonary and cardiac origin [24]. Echocardiography is the cornerstone for the diagnosis of heart failure, but in patients with pulmonary emphysema, air trapping may alter echocardiographic acoustic windows, leading to poor image quality in many COPD patients [25]. Moreover, N-terminal pro-brain natriuretic peptide may improve the diagnostic accuracy of heart failure in stable COPD [26].

Rigorous measurement of drug use that is potentially dangerous for the heart is another crucial point in pharmacological safety research, with a particular focus on potential interaction between drugs and a consideration of patients' adherence to medical prescription and how this changes over time. The increased risk of heart failure resulting from the addition of a LABA rather than tiotropium (hazard ratio 1.28 *versus* 1.11) compared with the risk of monotherapy is another interesting finding from the work of SUISSA *et al.* [6], and the hypothesis of a trigger action of LABAs in precipitating heart failure cannot be ruled out. Longer follow-up studies could elucidate this aspect. Mechanisms for decompensated heart failure are complex and not fully understood. Multiple risk factors have been proposed and include ischaemia, arrhythmia, respiratory infections, COPD exacerbations and air pollution [19, 27].

Conclusions

SUISSA *et al.* [6] have added important data to the ongoing debate on the cardiac safety of long-acting bronchodilators. Given the rapid development of new molecules to treat COPD, there is a need for timely information from high-quality studies on both the effectiveness and safety of single drugs alone, and their combination. Efforts should be made to interpret and summarise findings originating from different research approaches, *i.e.* randomised controlled trials and observational studies, to guide decision-making from both clinical and drug-regulatory perspectives [28, 29]. COPD patients with concomitant CVD diseases represent a big everyday challenge for clinicians. Cardiologists and pulmonologists should work together in the context of an integrated care approach to optimise the management of the complex multimorbid COPD population [30].

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