“Radical” Link Between Chronic Obstructive Pulmonary Disease and Cardiovascular Disease?

Tomasz J. Guzik, Tomasz Grodzicki

See related article, p 459–467

Cardiovascular complications, such as cor pulmonale, have been well characterized in severe chronic obstructive pulmonary disease (COPD). However, although this is a direct hemodynamic consequence of lung disease, cardiovascular involvement in COPD is much more complex. The majority of patients experiencing COPD die because of cardiovascular disease (CVD) rather than respiratory failure, with coronary artery disease and heart failure being the prominent specific causes of death. Cross-sectional analyses of >1.2 million patient records showed that COPD was associated with increased risk of CVD (odds ratio, 4.98; 95% confidence interval, 4.85–5.81) and of stroke (odds ratio, 3.34; 95% confidence interval, 3.21–3.48) and this risk persisted after controlling for confounding by sex and smoking status and stratifying for age. Indeed, reduced pulmonary function, no matter what the cause, is associated with increased cardiovascular mortality or myocardial infarction. Each 10% of reduction in forced expiratory volume in 1 second (FEV1; which is a measure of obstructive lung dysfunction) increases the risk of cardiovascular death by 28% and of a nonfatal cardiovascular event by 20%. This ranks decreased FEV1 only second to smoking as a cardiovascular risk factor, placing it ahead of dyslipidemia or hypertension in patients with COPD.\(^1\)

The mechanisms of the relationship between CVD and COPD remain unclear. Initially increased cardiovascular morbidity and mortality has been attributed to smoking being a common major risk factor for both diseases; however, even in subjects who have never smoked in their life, FEV1 reduction persists as a major cardiovascular event predictor.\(^1\) Obviously other common risk factors such as air pollution or shared genetic susceptibility (matrix metalloproteinase or oxidative stress genes such as epoxide hydrolase and glutathione-s-transferase) may play a role in linking COPD to CVD. The major hypothesis linking the 2 conditions is, however, related to the inflammatory nature of both diseases. Chronic inflammatory process in the bronchi leads to their remodeling and obstructive dysfunction. Activation of neutrophils, lymphocytes, and monocytes, as well as increased levels of C-reactive protein or interleukin-6 levels, is the hallmark of the disease. Importantly, all of these proinflammatory responses are critical in mediating cardiovascular risk.

Endothelial dysfunction, characterized by loss of nitric oxide (NO) bioavailability, is an important mechanism for cardiovascular morbidity and mortality. It precedes and accompanies the development of atherosclerotic plaques and is characteristic for heart failure. Indeed, COPD is associated with severe endothelial dysfunction. Endothelial function, measured by flow-mediated dilatation, is much more depressed in nonsmoking COPD subjects than in smokers without COPD. Importantly, in a study of 60 subjects with COPD, FEV1 and major indicators of inflammation such as leukocyte count or C-reactive protein were identified as major independent predictors of endothelial dysfunction.\(^4,5\)

In the current issue of Hypertension, Ives et al\(^6\) show that vascular endothelial function is impaired and vascular stiffness is increased in patients with COPD. Importantly, they demonstrate that free radical production may be involved in mediating the link between COPD and vascular dysfunction, as oral antioxidant cocktail administration acutely restored vascular function back to that of controls.

Studies showing effectiveness of oral antioxidant vitamin treatments always raise our caution, given the lack of protective cardiovascular effects of antioxidants in large randomized clinical trials. However studies such as the present article by Ives et al\(^6\) use antioxidants to better understand mechanisms of human disease. Such studies raise a possibility that antioxidants might still be effective in selected populations of patients with extremely high oxidative stress and inflammation such as observed in COPD. In such settings, the predominant action of antioxidants may be through limiting chronic inflammation rather than directly affecting NO bioavailability in the vessel wall. However, although studies presented here should stimulate discussion, data available at present do not support the idea that any antioxidant cocktail may be effective in preventing CVD.\(^7\)

Although Ives et al\(^6\) indicate that reactive oxygen species may link COPD to vascular dysfunction, the mechanism of such involvement remains unclear. There are several possible explanations, which need to be investigated further. First, it is possible that chronic systemic inflammation associated with COPD leads to the development of vascular oxidative stress, which then impairs NO bioavailability (Figure). However, this classical view of the involvement of superoxide anion in vasculature dysfunction does not take into account that reactive oxygen species production is particularly high locally, in the
lungs and bronchi of patients with COPD. Superoxide anion, hydrogen peroxide, and other reactive oxygen species lead to lipid peroxidation and activate signaling pathways, such as mitogen-activated protein kinases, nuclear factor-κB, or AP2 transcription factors. This, in turn, leads to an increased expression of lung chemokine and cytokine production and drives local inflammation (Figure). Chronic local inflammation is dysfunctional and evokes systemic responses, which may affect the vessels causing vascular dysfunction. Indeed in the present study, COPD subjects show higher leukocyte counts including increased neutrophils, lymphocytes, and monocytes. Unfortunately, the authors do not report C-reactive protein or interleukin-6 levels that would enable us to better characterize systemic inflammation. It would be very informative to know the effects of antioxidant treatment on these inflammatory markers because this could shed light on the protective effects reported by Ives et al.

In fact, the use of inhaled steroids, which potently inhibit local inflammation in the bronchi, in subjects with COPD has been linked to a significant decrease of the incidence of cardiovascular events. Whether inhaled or systemic antioxidants could have an additional effect remains unclear, given the potency of inhaled steroid preparations.

Interestingly, the authors of the present study do not observe any relationship between the severity of COPD and vascular dysfunction or the antioxidant-induced improvement of vascular function. This may indicate that several other modifying factors, such as obstructive sleep apnea or use of inhaled medications, might modify the relationship between COPD and vascular function.

Although this study sheds some light on COPD-related vascular dysfunction, several limitations should be carefully considered while interpreting these results. First, although the patients were reasonably well characterized, several clinical aspects might affect the interpretation of data. Obstructive sleep apnea, which is known to cause endothelial dysfunction, was excluded only based on clinical questionnaire. Similarly, current smoking status is based on patient history. Finally, the major concern in this study is increased occurrence of hypertension in subjects with COPD. The authors have gone to great lengths to statistically address this issue. This included analysis of subgroups matched for the incidence of hypertension, analyzing only subjects without hypertension or most importantly using ANCOVA with hypertensive status as a covariate. All of these approaches showed that vascular protection by antioxidant vitamins in COPD was independent of the presence of hypertension. However, determination of blood pressure or heart rate responses to antioxidant treatment used would add a lot to potential interpretation of these data.
This study, however, draws our attention to the fact that chronic inflammation, vascular dysfunction, and oxidative stress are strongly linked to hypertension. Indeed, large epidemiological studies have clearly shown increased incidence of hypertension (odds ratio, 1.6; 95% confidence interval, 1.3–1.9) in COPD, and links between lung function and hypertension extend beyond obtrusive disorders.

Another very important aspect that may affect cardiovascular risk and vascular function in COPD is the treatment of COPD itself. Several studies have pointed out that COPD treatment, particularly with β2-mimetics and anticholinergic bronchodilators, might increase cardiovascular risk. However, the effects of these treatments directly on vascular function are predominantly unclear. Moreover, after initial reports, larger and randomized trials, such as TORCH (Towards the Revolution in COPD Health), have shown that long-acting inhaled β2-mimetics neither used alone nor in combination with steroid showed an increase in the risk of cardiovascular events in patients with moderate to severe COPD. This analysis in fact indicated possible long-term benefit in reducing cardiovascular mortality, which can be attributed to better disease control in patients using combination therapy. However, the effect of inhaled COPD treatments on vascular function in COPD remains to be elucidated and should be addressed in specifically designed studies.

Finally, an important question that remains is whether we can extrapolate these findings in patients with COPD to other obstructive pulmonary disorders associated with decreased FEV1 such as asthma. Bronchial asthma is associated with high degree of chronic bronchial inflammation and is also associated with increased cardiovascular mortality. However, its links to endothelial dysfunction are not as well characterized as in COPD.

In summary, oxidative stress seems to provide a link between chronic obstructive pulmonary disease and the risk of cardiovascular morbidity and mortality and hypertension through its effects on vascular dysfunction. This may represent a common mechanism for vascular dysfunction in disorders associated with chronic inflammation, of which COPD is a prime example.

Sources of Funding
This study was supported by FNP/2009/02 Welcome study. T.J. Guzik is supported by the Welcome Trust Senior International Fellowship.

Disclosures
None.

References
"Radical" Link Between Chronic Obstructive Pulmonary Disease and Cardiovascular Disease?

Tomasz J. Guzik and Tomasz Grodzicki

Hypertension. 2014;63:444-446; originally published online December 9, 2013; doi: 10.1161/HYPERTENSIONAHA.113.02623

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/63/3/444

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/