Correspondence

Dissociation of Lung Function and Airway Inflammation in Chronic Obstructive Pulmonary Disease: Is It a Real or Statistical Phenomenon?

To the Editor:

We read with interest the article by Lapperre and colleagues (1) wherein it is concluded that "airflow limitation, airway inflammation, and features commonly associated with asthma are separate and largely independent factors in the pathophysiology of COPD." This statement seems to be much too definitive, considering the limitations of the study.

First, the conclusions are based entirely on the factor analysis. The literature data (2, 3), as well as our experience with this analysis (4), indicate that results are highly dependent on the selected set of variables, the relationships between them (linear or nonlinear), and the criteria used about factor structure, and suggest that one should be very careful in their interpretation.

Second, the study is cross-sectional, not longitudinal, which, combined with the heterogeneity of multifaceted chronic obstructive pulmonary disease (COPD), and a variable natural history of the individual disease (5), might be another reason for the authors to arrive at the conclusion about the dissociation of lung function and airway inflammation.

Relationships between airway inflammation and lung function in COPD do exist, but they are not simple and easily detectable, because even the exacerbations are associated with a lower and more variable inflammatory response than those in patients with asthma (6).

These considerations do not diminish the importance of the findings of Lapperre and colleagues (1) regarding the multidimensional profile of COPD and necessity for comprehensive evaluation of the disease.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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From the Authors:

We thank Drs. Kostianev and Marinov for their letter discussing some of the potential limitations of our study, thereby questioning our conclusion that "airflow limitation, airway inflammation, and features commonly associated with asthma are separate and largely independent factors in the pathophysiology of COPD" (1).

We fully agree that the results of factor analysis are dependent on the selected set of variables (2), and we purposely addressed this in the article. For this reason, we also performed additional factor analyses, including different sets of variables, such as pack-years smoked, or neutrophil and eosinophil numbers instead of percentages. As mentioned in the article, these additional analyses resulted in similar factor structures, all suggestive of the independence of inflammatory and functional variables. Nevertheless, repeating the analysis with inclusion of more direct markers of airway inflammation known to be involved in chronic obstructive pulmonary disease (COPD), such as $CD8^+$ lymphocytes, B lymphocytes, or macrophages in the airway wall or parenchyma, may be very valuable. However, histology was not available when we performed the present analysis. We would like to emphasize that standard criteria about factor structure were applied. However, the factor structure does not exclude associations between parameters in different factors. As shown in the article, there were linear relationships between some of the functional and inflammatory markers in our study.

We performed the factor analysis on cross-sectional data of a large group of well-characterized patients. Because exacerbations do indeed influence the inflammatory response, the measurements were postponed if patients experienced a respiratory tract infection within the previous 2 weeks, or an exacerbation requiring oral steroids within the previous 2 months. The patients are presently being followed up longitudinally for 2.5 years, and we intend to monitor the variables included in the factor analysis during this period. We agree with Drs. Kostianev and Marinov that longitudinal studies are needed to investigate whether changes in lung function are associated with changes in inflammation in COPD. We hope to be able to report on this in the future.

Factor analysis is an exploratory analysis, serving to generate hypotheses rather than testing them. Our results do suggest that, although there are univariate linear correlations between functional and inflammatory parameters in stable COPD (as have been reported by many others [3]), these entities represent different dimensions in the pathophysiology of COPD. This may have consequences for the development of therapy, which seems to require more than an antiinflammatory strategy alone.

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"Therapeutic" Carbon Monoxide May Be Toxic

To the Editor:

The report by Dolinay and colleagues (1) once again highlights the remarkable diversity of cellular effects mediated by carbon monoxide (CO). These workers and others have been working for some time toward establishing antiinflammatory effects of CO by mechanisms independent of CO-mediated hypoxia. Many of the "protective effects" of CO are intriguing, although sometimes not clearly distinguished from the cellular effects of lowering tissue oxygen tension, and are sometimes not reproducible in other laboratories (2). In the case of experimental ventilator-induced lung injury (VILI), these authors demonstrated differences in tumor necrosis factor-α elaboration and bronchoalveolar lavage cellularity but no convincing quantitative improvement in the extent of lung injury (for example, by observer-blinded lung injury scores). We were far more alarmed, however, when the authors suggested being "tempted" to move toward clinical trials using CO as a therapeutic agent to antagonize inflammatory processes, such as VILI.

Hypoxic effects of CO were described by Claude Bernard and John Haldane, and it is now clear that there are several additional pathways of cell stimulation mediated by CO. Activation of stress-dependent protein kinases, as shown by the authors and others, may have beneficial effects (1, 3). There are also effects related to perturbation of nitric oxide–dependent pathways that are injurious. Animals exposed for 1 hour to just 50 ppm CO exhibit protein tyrosine nitration in lung and large vessels, a macromolecular capillary leak, and leukocyte sequestration phenomena (4). Human beings exposed for hours to low CO concentrations also exhibit vascular leakage of macromolecules (5). Furthermore, patients with significant coronary or cerebrovascular disease tolerate even low carboxyhemoglobin (COHb) levels poorly.

Giving CO "therapeutically" as suggested by Dolinay and colleagues (1) could also result in blood COHb levels as high as 20% (6). Such CO exposures would be expected to cause brain injury similar to that caused by CO poisoning (7). Furthermore, some of the diseases that may require ventilatory support have been associated with brain injury themselves. One example is acute respiratory distress syndrome. Many patients with ARDS manifest brain injury 1 year after hospital discharge (8); an additional insult from iatrogenically administered CO could conceivably worsen brain-related outcomes.

Our main point is that there is a very real potential for unforeseen injury related to seemingly modest concentrations of CO. Additional information about CO pathophysiology is needed, and it is premature to suggest clinical trials purposefully administering this agent to injured patients.

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"Therapeutic" Carbon Monoxide May Be a Reality Soon

From the Authors:

We thank Drs. Thom, Weaver, and Hampson for their comments in response to our recent report highlighting the antiinflammatory effects of inhaled CO in an animal model of ventilator-induced lung injury (1). The toxicity of CO is well known and we agree entirely with the authors' references to this issue, especially given their significant contributions to the field of CO poisoning. Our laboratory is not focused on studying CO poisoning, but rather in the past 5 years has concentrated on studies to better understand the potential biological effects of CO. This initial interest in the biological function of CO arose from the intriguing paradigm that the heme oxygenase system can generate CO endogenously ($\sim$ 10 ml/day of exhaled CO).

The writers of the letter comment that "many of the 'protective effects' of CO are intriguing, though sometimes not clearly distinguished from the cellular effects of lowering tissue oxygen tension, and are sometimes not reproducible in other laboratories" (2); this is an unfair statement and somewhat misleading to the scientific community. A fair argument should always present both sides of the coin, and the authors were remiss in not referencing or acknowledging the more than 20 published papers from at least 10 independent laboratories (3–8) in the past 5 years that support the paradigm that CO is cytoprotective in both *in vitro* and *in vivo* models of cellular and tissue injury when used in similar or slightly higher concentrations than those in our study (1). We are not stating that the overwhelming

evidence of studies supporting these cytoprotective effects of CO (3–8) will ultimately prove that CO can be therapeutically administered to humans as a viable treatment modality. Only time will tell. We agree that the potential application of CO to human diseases will depend on a more comprehensive understanding of the toxicity, pharmacokinetics, and biology of CO, used at low concentrations.

We are aware of three ongoing human clinical trials for various pathophysiologic disease states where inhaled CO is administered at concentrations similar to those used by us (1). Although it is unknown what results these studies will yield, we can continue to strive for additional and new knowledge to "tempt" us to speculate that some day inhaled CO could serve as a therapeutic modality in human diseases. Obviously, to translate this temptation into reality will require further rigorous investigations, but as scientists we should not stop dreaming of new therapeutic modalities to fight against human diseases.

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