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Is Systemic Inflammation Responsible for Pulmonary Hypertension in COPD?

Don D. Sin and S. F. Paul Man

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patients in whom COPD has not yet developed. Perhaps they represent comorbid disease. Clinically, the presence of respiratory symptoms among people with normal lung function may provide an opportunity for interventions that will potentially improve both the quality and duration of life in our patients.

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Is Systemic Inflammation Responsible for Pulmonary Hypertension in COPD?

Mild pulmonary hypertension is a common complication in patients with COPD, even in those without significant arterial hypoxemia, and is independently associated with poor prognosis.^{1,2} Pathologically, the pulmonary vessels in such individuals demonstrate arterial remodeling, which fails to reverse with supplemental oxygen therapy. Curiously, the remodeling process in COPD patients involves all layers of the vasculature and not just the medial (muscular) layer, as would be expected in patients with hypoxia-induced conditions,³ which suggests the involvement of other factors. Other putative causes of pulmonary hypertension in COPD patients include loss of the capillary bed secondary to emphysema, vessel compression from dynamic hyperinflation, endothelial dysfunction related to cigarette smoking, and abnormal proliferation and delayed apoptosis of smooth muscle cells secondary to genetic alterations or infectious agents.³

Although it has been known for years that inflammation plays a prominent role in the airway disease of COPD, the potential role of inflammation in the pathogenesis of vessel disease was not well-studied until the past few years. Seminal work by Peinado and colleagues⁴ showed that the walls of small pulmonary arteries in COPD patients are commonly infiltrated with leukocytes, especially CD8-positive lymphocytes. With disease progression, the extent of the leukocyte involvement in the vessel walls becomes more prominent, and is associated with increased wall stiffness and the failure of vessels to relax properly with adenosine diphosphate stimulation, indicating endothelial dysfunction.⁴

Whether systemic inflammation contributes to this process is not known. However, in other conditions that give rise to pulmonary hypertension, systemic inflammation appears to be an important cofactor in the development of pulmonary vessel disease,⁵ and therapies that mitigate systemic inflammation may attenuate pulmonary pressures. Even in patients with primary pulmonary hypertension, systemic inflammation may play a role, as such patients have elevated levels of tumor necrosis factor (TNF)- α and interleukin (IL)-6 in the systemic circulation compared to individuals without pulmonary hypertension.⁶ These clinical observations are supported by *in*

in vitro models that demonstrate the synergistic effects of inflammation and hypoxia in down-regulating nitric oxide production and inducing endothelial dysfunction in the pulmonary vasculature.⁷

The study by Joppa and colleagues⁸ in this issue of *CHEST* (see page 326) suggests that systemic inflammation may also play a major role in pulmonary hypertension in COPD patients. The authors carefully selected 43 consecutive patients with moderate-to-severe COPD (mean FEV₁, 46% predicted), and performed a variety of clinical, physiologic, and biochemical measurements to determine the relationship between systemic inflammation and pulmonary arterial hypertension. They found that patients with significant pulmonary hypertension had higher levels of circulating C-reactive protein (CRP) and TNF- α . Furthermore, there was a significant linear relationship between serum CRP levels and systolic pulmonary artery pressure in these patients, further emphasizing the likely importance of systemic inflammation in COPD-related pulmonary hypertension. Interestingly, Pao₂ and serum log-CRP levels were the only two significant predictors of systolic pulmonary arterial pressure, and collectively they accounted for 37% of its variation, which is consistent with data from *in vitro* models,⁷ demonstrating the importance of hypoxia and inflammation in inducing endothelial dysfunction in pulmonary vessels.

There were many strengths to the present study, as follows: the detailed collection of lung function and blood gas measurements; the blinding of the echocardiographer to the results of the biochemical measurements; and the sophisticated modeling process to mitigate confounding. There were also some limitations. Due to the cross-sectional nature of the data collection, the direction of causation could not be determined. While we believe that systemic inflammation was at least partially responsible for pulmonary hypertension, reverse causation could not be entirely ruled out. Additionally, we cannot discount the possibility that the vasculature changes may have reflected the "spillage" of inflammation from adjacent airway tissues and was not dependent on systemic inflammation *per se*. It was also possible that a third (unmeasured and unaccounted) factor could have explained the relationship. For example, since systemic inflammation relates to COPD severity, other factors associated with disease progression, such as dynamic hyperinflation, pulmonary emphysema, and oxidant/antioxidant imbalances, could have contributed to the pulmonary hypertension. Although CRP is a robust marker of systemic inflammation, there is little consensus as to whether or not it is a pivotal molecule in effecting vascular disease.⁹ It is plausible that CRP is merely a biomarker of

some other sentinel molecules that may be primarily responsible for pulmonary hypertension in COPD patients. Potential candidate molecules include IL-1 β , TNF- α , IL-6, endothelins, 5-hydroxytryptamine, transforming growth factor- β , and many others.^{1,3} Finally, while two-dimensional Doppler echocardiography is a reasonable and noninvasive method of ascertaining pulmonary arterial pressures, the results are more variable and less reliable in patients with hyperinflated lungs.¹⁰

Notwithstanding these limitations, the findings from the present study have raised the following very important new (and testable) hypothesis in COPD: that systemic inflammation may be involved in the pathogenesis of pulmonary hypertension. The challenge for the COPD research community is to determine the validity of this hypothesis through well-designed clinical and animal studies. COPD is one of the fastest growing diseases globally and is projected to be the third leading cause of mortality worldwide within 10 years.¹¹ The presence of pulmonary hypertension dramatically worsens the already dismal prognosis of COPD patients.² There is therefore a pressing need to develop new therapeutic compounds to combat the epidemic of COPD morbidity and mortality, and to this end the study by Joppa and colleagues has raised systemic inflammation as a potential target for novel discoveries.

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Autotitrating CPAP

How Shall We Judge Safety and Efficacy of a “Black Box”?

“On two occasions I have been asked [by members of Parliament], ‘Pray, Mr. Babbage, if you put into the machine wrong figures, will the right answers come out?’ I am not able rightly to apprehend the kind of confusion of ideas that could provoke such a question.”

Charles Babbage

Medical technology has become increasingly complex and difficult for nonengineers to understand, while at the same time the exigencies of the marketplace have made medical equipment manufacturers reluctant to divulge detailed descriptions of the technology used in their devices. In some cases, this is of minimal or no importance; for instance, the mechanical details of how a bronchoscope tip is deflected are not critical when the clinician can directly observe the results. However, medical devices that collect, filter, and analyze data, providing only the processed version to the clinician, or those that interpose their own judgment in diagnosing a condition or treating a patient must be subject to much more investigation before we can fully trust their functionality. In truth, we can rely on most automated technology only under certain con-

ditions, and these limitations should be fully vetted before the devices are made available to clinicians.

We only need to recall the disastrous case of a computer-controlled radiotherapy device some years ago to realize the potential hazards involved in automated technology that is incompletely tested.^{1,2} In that case, a sequence of control commands not anticipated by the designer prevented the deployment of a target that should have been interposed between a high-energy radiation beam and the patient in order to generate a therapeutic-level secondary emission. With the target missing, patients were subjected to radiation levels far above therapeutic, unfortunately with dire consequences. Closer to home for pulmonary and sleep physicians, it has been well-documented that the brand and model of pulse oximeter influences whether a given respiratory event qualifies as a hypopnea under Medicare guidelines.³ Variations in response time and other computational details inherent in each device alter the lowest value of saturation that will be displayed subsequent to a respiratory event; this can be of critical importance when the event definition requires a $\geq 4\%$ desaturation.

Autotitrating continuous positive airway pressure (CPAP) devices are classic examples of the “black box,” defined in this usage as “any small... box containing a secret, mysterious, or complex mechanical or electronic device.”⁴ In essence, a black box is only known in terms of its output for any particular input; how that output is determined remains hidden. Under US Food and Drug Administration regulations, marketing approval for an autotitrating CPAP device seems to require only that clinical studies demonstrate equivalent ability, in a defined patient group, to suppress sleep-disordered breathing events in comparison with a previously approved apparatus. In most cases, detailed descriptions of the current algorithms that determine the response of the machine to changes in upper airway mechanics and airflow are not explicitly disseminated, and when requested are said to be proprietary. Those descriptions that have been published^{5–8} are associated with early iterations of each apparatus (now > 10 years old) and cannot with certainty be applied to the commercially available versions.

In the absence of detailed information on the algorithms used by these devices to control therapy, they are fair game for studies that evaluate their operation under simulated or real-world conditions. Thus, the two reports on performance testing of autotitrating CPAP machines that appear in this issue of *CHEST* (see pages 343 and 350) are a welcome addition to the literature. Rigau and colleagues⁹ modified their previously described lung simulator, which reproduced real flow and snoring

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