Neurohumoral Activation as a Link to Systemic Manifestations of Chronic Lung Disease*

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COPD is a major cause of death and disability worldwide. Treatment of COPD improves lung function but is unlikely to slow the steady downhill course of the disease or reduce mortality.1 In COPD, numerous abnormalities can be found outside the lung. These include systemic inflammation, cachexia, and skeletal muscle dysfunction. Thus, COPD has been called a systemic disease. Convincing data demonstrate that COPD causes neurohumoral activation. By precedents derived from chronic heart failure and other diseases characterized by neurohumoral activation, we propose that the negative consequences of neurohumoral activation, namely inflammation, cachexia, effects on ventilation, and skeletal muscle dysfunction, give rise to a self-perpetuating cycle that contributes to the pathogenesis of COPD, and which may involve respiratory muscle dysfunction as well as systemic inflammation. This concept may further help explain the increased cardiovascular morbidity and mortality in COPD patients. Currently, little is known about the effect of treatments directed at neurohumoral activation and COPD. As this aspect of COPD becomes better understood, new insights may direct novel therapeutic approaches.

Evidence of Neurohumoral Activation in COPD

Peripheral Sympathetic Activation

Using microneurography of the peroneal nerve, direct evidence of marked peripheral sympathetic activation in patients with COPD and hypoxemia has recently been obtained.6 As compared with age- and sex-matched healthy control subjects, muscle sympathetic nerve activity was twice as high in the patients.
as compared to the control subjects. These results could not be explained by concomitant medication.6

**Cardiac Sympathetic Activation**

Volterrani and colleagues7 were the first to study heart rate variability in the time domain and frequency domain in COPD patients. Their 31 normoxic COPD patients showed depressed heart rate variability with an elevated high-frequency component during normal and controlled breathing, as compared to matched control subjects. Hypoxic neuronal damage was absent and could thus not explain the findings.7 Scalvini and colleagues5 studied COPD patients without evidence of hypoxic neuronal damage in whom all medications were discontinued 24 h before the study. They found depressed heart rate variability with decreased low-frequency and decreased high-frequency components in the patients as compared to the control subjects. Oxygen partially reversed these alterations.9 Similar findings were reported by Bartels and colleagues,9 although a control group was not included in their study.

In patients with α1-antitrypsin deficiency, heart rate variability was reduced as compared to control subjects.10 Heart rate variability correlated with FEV1 and even prognosis (ie, possibility of death or listing for lung transplant). Patients with α1-antitrypsin deficiency but without evidence of lung disease showed normal heart rate variability.10 Depressed heart rate variation was also evident in the heart rate response to different stimuli, such as the Valsalva maneuver in COPD patients.11,12 In one study,13 patients with extrapulmonary ventilatory impairment were investigated. As in the COPD studies, reduced heart rate variability was noted.

In aggregate, the data on heart rate variability clearly demonstrate impaired autonomic control. Elevated heart rate has been noticed for many years in COPD patients and cannot solely be explained by medication.6,5–10,14,15 This finding is most consistent with cardiac sympathetic activation in COPD, given the characteristic positive chronotropic effects of sympathetic activation on heart rate.

**Systemic Neurohumoral Activation**

Plasma norepinephrine was nearly twice as high in 11 normoxic patients with advanced end-stage emphysema as compared to 11 healthy matched control subjects.15 In the setting of an emergency department, patients with acute COPD exacerbations had higher norepinephrine concentrations as compared to asthma patients with acute exacerbations.16 Treatment and blood gas changes did not significantly affect norepinephrine concentrations.16 Reduced 123I-metaiodobenzylguanidine storage in the left ventricular myocardium was noted in 28 COPD patients without hypoxia.17 These findings, together with the increased plasma norepinephrine concentrations found in these patients,17 suggest increased systemic neurohumoral activation with increased myocardial norepinephrine turnover.17 In another study,18 12 COPD patients with hypoxemia were evaluated. Urinary norepinephrine excretion correlated positively with nocturnal time spent with arterial oxygen saturation < 85%; however, urinary norepinephrine did not significantly change following long-term oxygen therapy, except in a subgroup with severe nocturnal hypoxemia.

Plasma renin activity and plasma aldosterone concentration are elevated in patients with hypoxic COPD.19–21 Activation of the renin-angiotensin system is particularly pronounced in patients with secondary erythrocytosis22 and is associated with sodium retention and peripheral edema. In a short-term study20 of patients with hypoxic COPD and pulmonary hypertension, angiotensin receptor blockade lowered systemic and pulmonary vascular resistance, and increased cardiac output. Autonomic dysfunction evaluated by heart rate variability may be linked to sodium and water retention in COPD.23 Hypercapnia has not been shown to play an important role in modulation of the renin-angiotensin system.24

There is therefore consistent evidence of augmented sympathetic nerve traffic, elevated catecholamines, as well as an activated renin-angiotensin system in COPD patients. Given the strong mutual interaction of angiotensin and the sympathetic nervous system,25 this is not unexpected and has been extensively described in patients with heart failure. Indeed, the term neurohumoral activation was coined to portray this association.26

**Methodologic and Historical Notes**

The importance of neurohumoral activation in COPD is not well recognized and is relatively neglected from an investigative perspective. Initially, the altered heart rate response in COPD patients to various maneuvers was explained by autonomic polyneuropathy.11 Stein et al10 were among the first to interpret altered heart rate variability in their patients with obstructive lung disease as evidence of sympathetic activation. That the concept of neurohumoral activation in COPD has not been recognized earlier can be understood by the difficulties inherent in measuring neurohumoral activation in humans. Heart rate variability is simple to evaluate in subjects with sinus rhythm. However, although heart rate variability correlates loosely with parasympathetic activity, it is at best a crude marker of sympa-
thetic activity. Plasma norepinephrine concentration correlates poorly with norepinephrine release since norepinephrine concentration is significantly affected by turnover and clearance. The most valid methods for evaluating sympathetic activity are microneurography and norepinephrine spillover. These methods have been crucial to recent advances in understanding the autonomic nervous system. However, they are also invasive, demanding, and time intensive, and cannot be easily applied to large patient cohorts.

**Possible Mechanisms of Neurohumoral Activation in COPD**

Dyspnea, respiratory motor drive, and autonomic control are anatomically and functionally tightly coupled in the brainstem. Specifically the perception of respiratory discomfort is represented in the sensorimotor integration area of the limbic system that governs autonomic control, and central respiratory motor drive is linked with central sympathetic outflow in the brainstem. These central interactions speak to the construct that dyspnea and increased respiratory drive in COPD may be pathophysiologically linked to heightened sympathetic activation, although the complexity of these interactions within the CNS make it difficult to clearly distinguish cause and effect.

Furthermore, COPD is associated with several homeostatic disturbances that may directly trigger sympathetic activation. Of those mechanisms likely to contribute to neurohumoral activation in COPD, hypoxemia and ergoreflexes are among the most important. Use of β-agonist medications, obesity, and tobacco smoking might also contribute in part in individual patients.

**Hypoxemia and Hypercapnia**

Chronic hypoxia has long been known to trigger a hyperadrenergic state (for review see Hansen and Sander). Acute exposure to hypoxia also increases microneurographic measures of sympathetic activity. Studies in healthy subjects showed that following hypoxia, sympathetic activation is significant and long lasting and compensates to oppose the hypoxic vasodilator mechanism. In COPD, there is evidence of sympathetic activation even in normoxic patients, and daytime blood gases do not correlate with sympathetic activation. It is however possible that nocturnal hypoxemia might contribute to daytime sympathetic activation, as is thought to be the case in patients with obstructive sleep apnea. Although acute hypercapnia also elicits sympathetic activation, there are no data pointing to a role of chronic hypercapnia in any heightened sympathetic drive in COPD.

**The Muscle Metaboreflex**

Oxygen free radicals and products of ischemic metabolism are released during high level contractile activity of skeletal muscle, thereby activating sympathetic excitatory afferents. Accordingly, repeated fatiguing contractions of respiratory muscles in the healthy human show a striking metaboreflex-mediated sympathetic excitation. This aspect of neural circulatory control as relevant to COPD patients has not yet been investigated, but diaphragm remodeling and even injury of the diaphragm may be present in COPD patients. Thus, there is precedent for expecting some degree of metaboreflex-mediated sympathetic activation in COPD.

**Lung Inflation Reflex**

Lung inflation reflexes mediated by pulmonary vagal afferents may also alter sympathetic activity and have been shown to govern the within-breath modulation of muscle sympathetic nerve activity as evaluated by microneurography during normal breathing. In patients with chronic heart failure, sympathetic activation is related to a decrease in tidal volume as well as an attenuated sympathetic inhibitory effect of the lung inflation reflex. Furthermore, slow breathing increases arterial baroreflex sensitivity in these patients. Although there is no direct evidence, it thus seems possible that an altered lung inflation reflex mediates sympathetic activation in COPD.

**The Baroreflex**

Baroreflex sensitivity is reduced in patients with COPD. Arterial and cardiopulmonary baroreflexes strongly influence sympathetic activity in healthy subjects and may contribute to the pathogenesis of heart failure and arterial hypertension, in part because of a permissive role in maladaptive sympathetic activation in these disease conditions.
COPD has been viewed in part as a muscle disease, and inflammatory mediators have been found to be involved in the wasting. As discussed above, neurohumoral activation causes and aggravates striated skeletal muscle dysfunction. There is evidence that this may also be the case in COPD. The diaphragm, as a striated muscle, is crucial for breathing. Any negative effect on the contractile properties of the diaphragm, which is already at a mechanical disadvantage in COPD, will be detrimental for ventilation and potentially for gas exchange as well. The effects of sympathetic activation on the diaphragm or accessory respiratory muscles have not been specifically addressed in previous studies. However, it is reasonable to speculate that the negative effects of sympathetic activation on skeletal muscle function will also apply to the diaphragm and accessory respiratory muscles.

**Cachexia, Systemic Inflammation, and Leptin**

Patients with advanced COPD often suffer from cachexia. Reduced body weight, and especially muscle mass, predicts mortality in COPD. Cachexia is not explained solely by poor food intake, increased energy consumption as a result of lung disease, or medication with β-agonists. It is more likely related to effects of chronic systemic inflammation and circulating leptin. Our knowledge of the impact of the autonomic nervous system on systemic inflammation and immune function stems mainly from two sources: first, animal models show a strong effect of the autonomic nervous system in the regulation of systemic inflammatory responses to endotoxins or other stimuli; second, precedents from congestive heart failure and other diseases characterized by sympathetic activation show a close relationship between sympathetic activation and systemic inflammation. Vagal nerve stimulation, which in this context may be considered an anti-inflammatory treatment markedly improves long-term survival in rats with heart failure. Furthermore, high muscle sympathetic nerve activity contributes to lipid peroxidation and thus to a reduced tendency to gain weight.

Animal studies show a link between inflammatory cytokines, leptin, and cachexia. In patients with COPD, reduced lung function is associated with a variety of systemic inflammatory markers. It is not entirely clear whether the intense inflammatory process in the airways spills over into the systemic circulation or the systemic inflammation augments injuries to the airways. Circulating levels of leptin reflect the amount of adipose tissue and leptin acts to decrease food intake, lipid metabolism, and increases thermoregulation. Leptin levels correlate...
closely with C-reactive protein levels in normal subjects, and in emphysematous COPD patients Schols et al. have found a significant correlation between tumor necrosis factor receptor and plasma leptin. Interestingly, hypoxia induces the promoter of the leptin gene, and the sympathetic and parasympathetic nervous systems are not only involved in mediating the effects of leptin but may also impact on circulating leptin in patients with COPD. Thus, there is a complex interaction between inflammation, leptin, and the autonomic nervous system in mediating cachexia and skeletal muscle wasting in patients with COPD.

**Pulmonary Blood Flow and Bronchoconstriction**

Increased activity of pulmonary sympathetic efferents causes constriction of arterial and, particularly, of pulmonary venous vessels. Therefore, neurohumoral activation in COPD might contribute to pulmonary hypertension.

The lung expresses the highest density of β-adrenoceptors of all organs. Long-term exposure to norepinephrine results in down-regulation and reduced messenger RNA expression of pulmonary β-adrenergic receptors in guinea pigs. In another animal model, elevated plasma norepinephrine release accompanying sympathetic activation due to aortic banding induced down-regulation of β-adrenergic receptors in the lung, reduction of adenylate cyclase activity and thus cyclic adenosine monophosphate-mediated bronchorelaxation. Thus, it can be speculated that sympathetic activation might favor bronchoconstriction.

**Increased Cardiovascular Risk**

In epidemiologic studies, COPD is an independent risk factor for cardiovascular disease. Even modest reduction in forced expiratory volume elevates the risk of ischemic heart disease, stroke, atrial fibrillation, and sudden cardiac deaths twofold to threefold, independent of other risk factors, including smoking. Indeed, lung function is a better predictor of mortality than established cardiac risk factors such as serum cholesterol. Given the established negative connotations of neurohumoral activation for cardiovascular morbidity and mortality as alluded to above, it is reasonable to hypothesize that neurohumoral activation in COPD exposes COPD patients to increased cardiovascular risk. Systemic inflammation as evidenced by a high C-reactive protein might further contribute to cardiovascular risk in COPD.

**Conclusion**

We have presented evidence supporting neurohumoral activation in patients with COPD. By precedents derived from chronic heart failure and other diseases characterized by neurohumoral activation, we propose that the well-established negative consequences of neurohumoral activation, namely inflammation, cachexia, effects on ventilation, and skeletal muscle dysfunction, give rise to a self-perpetuating cycle that contributes to the pathogenesis of COPD, which involves respiratory muscle dysfunction as well as systemic inflammation. This concept may further help explain the increased cardiovascular morbidity and mortality in COPD patients (Fig 1).

Especially relevant, however, is that an important component of COPD treatment involves modulation of autonomic tone, either by β-adrenergic receptor activation or by vagal inhibition. While the symptomatic benefits of these interventions apply in the context of lung function, current therapeutic formulations do not reduce mortality and moreover cause significant systemic side effects, particularly on the heart. Alternative approaches to treatment of COPD (for example the use of β-blockade) currently seem inappropriate, but perhaps no more so than β-blockade for heart failure might have seemed 20 years ago. Indeed, chronic cardioselective β-blockade is remarkably well tolerated. Currently, little is known about the effect of such treatments on neurohumoral activation and COPD. But as this aspect of COPD becomes better understood, and as pharmaceuticals become more target specific, new insights may direct novel therapeutic approaches. However, albeit data supporting this proposal are available, we have to acknowledge that they are limited. Randomized controlled trials investigating measurable end points such as sympathetic activation, quality of life, lung function, hospital admissions, and mortality are thus needed.

![Figure 1. Schematic of the proposed self-perpetuating cycle relating to neurohumoral activation in patients with COPD.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22033/)
References


2. Reid MB. COPD as a muscle disease. Am J Respir Crit Care Med 2001; 164:1101–1102


48 Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999; 115:S36–S47
52 Gosker HR, Lence NH, Franssen FM, et al. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. Chest 2003; 123:1416–1424