

Thomas A. Neff Lecture

Chronic Obstructive Pulmonary Disease A Systemic Disease

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For the first time, the recently published American Thoracic Society/European Respiratory Society chronic obstructive pulmonary disease (COPD) guidelines explicitly recognize that “although chronic obstructive pulmonary disease . . . affects the lungs, it also produces significant systemic consequences” (1). This is somewhat surprising because we have implicitly known for many years that COPD indeed has systemic consequences. For instance, since 1980, we have known that severe COPD can produce significant arterial hypoxemia (thus, presumably, some degree of “systemic” hypoxia) and that domiciliary oxygen therapy can improve survival in these patients without having any noticeable effect on lung function (2, 3). Likewise, for more than 30 years, we have been aware of the fact that some patients with COPD will develop weight loss and eventually cachexia (“pink puffers”), whereas others (“blue blotters”) will not (4). The former is clearly recognized now as a “systemic effect” of COPD (5, 6).

So, what is really new in this field? I believe that what is novel is the realization that COPD is characterized by an abnormal inflammatory response of the lung parenchyma to the inhalation of particles and toxic fumes, mostly tobacco smoking (1), which can also be detected in peripheral blood, thus qualifying it as “systemic inflammation” (5, 6). We have now begun to uncover the origin and consequences of, and seek potential therapy for, this systemic inflammation in COPD, and we are beginning to appreciate that these discoveries may be of great relevance and lead to better management of patients with COPD (5, 6). This presentation first reviews the evidence supporting the presence of systemic inflammation in COPD, then discusses its potential origin and consequences, and finally, discusses potential therapeutic alternatives. Throughout the text, relevant questions, still unanswered, will be identified.

SYSTEMIC INFLAMMATION IN COPD

The Evidence

Many studies have now provided convincing evidence that COPD is associated with increased levels of several proinflammatory cytokines (e.g., tumor necrosis factor α [TNF- α] and its soluble receptors [sTNF-R55 and sTNF-R75], interleukin 6 [IL-6] and IL-8), acute phase reactants (e.g., C-reactive protein [CRP]), oxidative stress, and activation of several inflammatory

cells (e.g., neutrophils, monocytes, and lymphocytes) (5, 6). Gan and associates recently conducted a meta-analysis encompassing all these previous studies (7). Their conclusions are indisputable: COPD is associated with systemic inflammation (7). It is interesting to note, however, that other chronic diseases, such as heart failure, are also characterized by systemic inflammation and that their consequences in these patients are quite similar to those seen (and discussed below) in patients with COPD (8).

Several important questions remain unanswered. First, we do not know if all patients with COPD (or only a subgroup of them) present with systemic inflammation. In other words, we do not know if the presence of systemic inflammation is a distinct phenotypic characteristic of the disease, such as may be the case with the presence (or absence) of pulmonary emphysema. Second, all studies carried out so far are cross-sectional. Thus, we do not know the quantitative and qualitative longitudinal variation of systemic inflammation in a given patient. We know, however, that systemic inflammation (like pulmonary inflammation) appears to burst during the episodes of exacerbation of the disease (9–12). It is therefore likely that the overall level of systemic inflammation changes with time and, it is hoped (*see below*), with therapy.

The Origin

The origin of systemic inflammation in COPD is unresolved and several potential mechanisms could be involved:

1. Tobacco smoking, the main risk factor for COPD (1), self-induces (i.e., in the absence of COPD) systemic inflammation (13). In fact, this systemic inflammation in smokers is believed to contribute significantly to atherosclerosis (14). However, whether the patient with COPD is a current or ex-smoker does not seem to influence significantly the level of systemic inflammation (7). Thus, it is unlikely that tobacco smoking is the sole mechanism explaining systemic inflammation in COPD.
2. An alternative explanation is that the inflammatory process that occurs in the lung parenchyma of these patients (15) “spills over” into the systemic circulation and/or contributes to the priming and activation of different inflammatory cells in their transit through the pulmonary circulation (5). To explore this hypothesis, Vernooy and collaborators (16) compared the levels of a number of inflammatory markers in induced sputum (local inflammation) and plasma (systemic inflammation; Figure 1) in patients with moderate COPD and smokers with normal lung function. These authors could not find a significant relationship between the levels of these inflammatory markers in the lungs and in the peripheral circulation (Table 1) and concluded that systemic inflammation in COPD was not due to an overflow of inflammatory mediators from the local compartment and that the inflammatory

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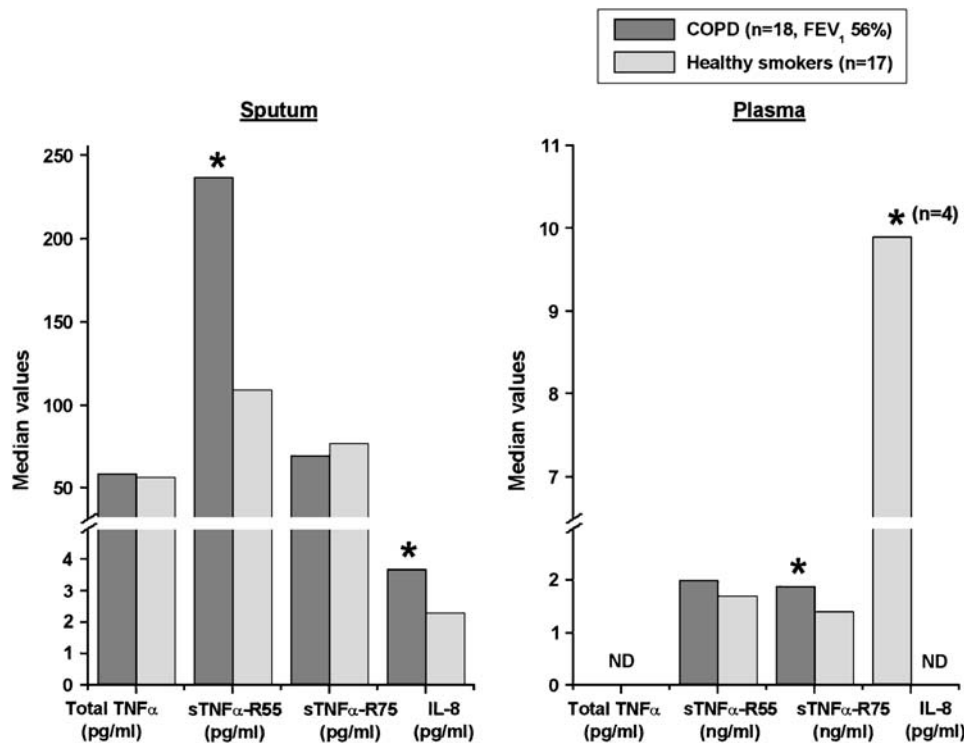


Figure 1. Median values of different inflammatory markers determined in induced sputum (left) and plasma (right) in patients with moderate chronic obstructive pulmonary disease (COPD; n = 18) and smokers with normal lung function (n = 17). IL = interleukin; ND = not determined (below the lower limit of detectability of the measurement); TNF = tumor necrosis factor. * The difference between the two groups was significant. For further explanations, see text. Data are from Reference 16.

responses in the local and systemic compartments are differently regulated (16). Although this study has the merit of being the first to address this important topic, it has several limitations, such as the relatively small number of patients studied, its cross-sectional nature, the fact that control subjects were not perfectly matched in terms of age, sex, and smoking exposure to patients, and the observation that many measurements were below the threshold of detectability (16).

- Another potential mechanism that can theoretically contribute to systemic inflammation in COPD is tissue hypoxia. To explore this, Takabatake and colleagues studied the relationship between arterial hypoxemia and circulating levels of TNF- α and its soluble receptors sTNF-R55 and sTNF-R75 in 27 patients with COPD and 15 age-matched, healthy control subjects (17). TNF- α , sTNF-R55, and sTNF-R75 levels were significantly higher in patients with COPD, and all of them were significantly correlated with the severity of arterial hypoxemia. This was not observed in the healthy control subjects. Overall, these results suggest that arterial hypoxemia in COPD is associated

with activation of the TNF- α system *in vivo* (17). If larger studies confirm this observation, it is conceivable that long-term oxygen therapy may contribute to reduce the burden of systemic inflammation in these patients. This hypothesis has not been tested yet, but, if proven, may well contribute to the prolongation of survival described many years ago in patients receiving domiciliary oxygen therapy (2, 3).

- Skeletal muscle can be another potential site of production of systemic inflammation, particularly during exercise, in patients with COPD (although, as discussed below, skeletal muscle is also a target organ of systemic inflammation in these patients [18]). Rabinovich and coworkers studied 11 patients with COPD (FEV $_1$, 40% of predicted) and six age-matched control subjects, and showed that moderate exercise increases plasma TNF- α levels in the former but not in the latter (19). Other studies also support a role for skeletal muscle as a contributor to systemic inflammation in COPD (20, 21).
- The bone marrow can also be a site of production of systemic inflammation. It is known that chronic smoking in humans causes leukocytosis and induces a number of distinct phenotypic changes in circulating polymorphonuclear leukocytes that are characteristic of chronic stimulation of the bone marrow, such as increased band cell counts with a higher content of myeloperoxidase and enhanced surface expression of L-selectin (13). It is also known that cigarette smoking causes sequestration of polymorphonuclear leukocytes released from the bone marrow in lung microvessels (22). It is therefore possible that the increased number of immature polymorphonuclear leukocytes released by tobacco smoking contributes to the chronic lung inflammation in the so-called susceptible smokers to COPD (13). Yet, the bone marrow is a largely unexplored area in these patients.

TABLE 1. CORRELATION COEFFICIENTS AND p VALUES AMONG THE LEVELS OF DIFFERENT INFLAMMATORY MARKERS DETERMINED IN INDUCED SPUTUM AND PLASMA IN 18 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	R Value	p Value
sTNF α -R55	0.155	0.539
sTNF α -R75	0.068	0.788
IL-8	0.292	0.240

Definition of abbreviations: IL = interleukin; sTNF = soluble tumor necrosis factor.

Data are from Reference 16. For further explanations, see text.

The Consequences

Systemic inflammation can have a variety of consequences in COPD, including weight loss, skeletal muscle atrophy and dysfunction, endothelial dysfunction and cardiovascular disease, osteoporosis, and depression, among others (reviewed in References 5 and 6). Weight loss and skeletal muscle atrophy and dysfunction are, by far, the best characterized (18). We know that unintended weight loss is a poor prognostic factor in COPD, which is responsive to therapy and is independent of the degree of airflow obstruction present (23, 24). We also know that the main cause of weight loss in COPD is skeletal muscle atrophy (5, 6), the latter being in part due to apoptosis (25) and enhanced proteolysis (26). Systemic inflammation and tissue hypoxia likely contribute to these mechanisms because they are well-known inducers of these cellular processes (27, 28).

On the other hand, systemic inflammation is a well-established factor in the pathogenesis of cardiovascular disease (14). The relationship between systemic inflammation and cardiovascular disease in COPD is less well characterized, but it is conceivable that systemic inflammation may contribute to cardiovascular disease in patients with COPD. A rapidly growing body of evidence supports this contention (reviewed in Reference 29). The relationship of systemic inflammation with other so-called systemic effects of COPD, such as osteoporosis and central nervous system abnormalities, is less well established but certainly possible (reviewed in Reference 5).

Finally, an intriguing possibility is that systemic inflammation may “feed back” to the lungs and contribute to enhance the chronic destructive process that characterizes the disease. It is therefore interesting to note that inhibition of the vascular endothelial growth factor (VEGF) receptors causes lung cell apoptosis and emphysema (30), that oxidative stress and apoptosis interact and cause emphysema due to VEGF receptor blockade (31), and that endothelial cell death and decreased expression of VEGF and the VEGF receptor KDR/FLK-1 occur in patients with smoking-induced emphysema (32). Thus, it is entirely possible, although not proven, that systemic oxidative stress (33), and the increased levels of proinflammatory cytokines (most notably, TNF- α [34]) could also contribute to the pathogenesis of lung damage in COPD. If the potential participation of an autoimmune response in the pathogenesis of COPD is finally proven (35–38), this would also support this concept.

Potential Therapies

Quitting smoking and bronchodilator therapy form the cornerstone of treatment in COPD (1). In severe cases, this is complemented with inhaled steroids, oxygen therapy, and rehabilitation (1). Interestingly, many (if not all) of these “standard” therapeutic options have the potential to modify systemic inflammation. As discussed above, chronic smoking causes systemic inflammation in humans. Quitting smoking is therefore likely to reduce this inflammation. The potential effect of bronchodilators on systemic inflammation in COPD is less straightforward, but, by decreasing dynamic hyperinflation, bronchodilators also have the potential to reduce systemic inflammation (39). Inhaled steroids can also contribute to this goal, as shown recently by Sin and coworkers who demonstrated in a randomized controlled study that withdrawal of inhaled corticosteroids increased the baseline levels of one marker of systemic inflammation (CRP) by 71%, and that 2 weeks with inhaled fluticasone (500 μ g twice a day) reduced CRP levels by 50% (40) (Figure 2). Because CRP is believed to contribute to the pathogenesis of atherosclerosis (41), and CRP is known to be increased in the plasma of patients with COPD (5), these biological effects of inhaled ste-

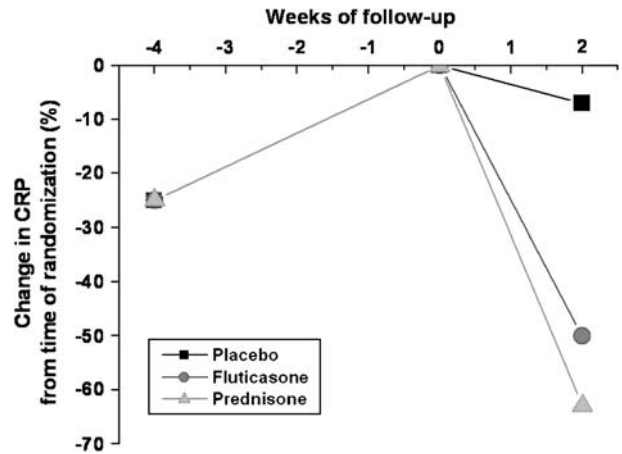


Figure 2. Serial changes of C-reactive protein (CRP) in the three groups studied. For further explanations, see text. Data are from Reference 40.

roids have the potential to reduce the risk of cardiovascular disease in these patients (29). In fact, a very recent retrospective study seems to support this contention (42). The potential antiinflammatory effects of oxygen therapy and rehabilitation have never been explored formally in patients with COPD but, because of the arguments discussed above, should be explored in future studies. Likewise, the use of antioxidant agents, such as N-acetyl-cysteine, is also promising and deserves further study (43, 44). The role of more specific, antiinflammatory therapies to treat systemic inflammation in COPD is a matter of future research. Yet, anticytokine therapy, nuclear factor- κ B blockers, and inducible nitric oxide synthase inhibitors, among others, offer some potential, as recently reviewed (45, 46).

CONCLUSIONS

In summary, COPD can no longer be considered a disease only of the lungs (1). It is associated with a wide variety of systemic consequences, most notably systemic inflammation. A better understanding of its origin, consequences, and potential therapy will most likely prove to be of great relevance and lead to better care of the patients suffering from this devastating disease.

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Exacerbation Of Chronic Obstructive Pulmonary Disease Pan-Airway and Systemic Inflammatory Indices

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