The Concept of “Organizing Pneumonia”

Inflammation of distal lung structures (alveoli, alveolar ducts, and respiratory bronchioles)—i.e., pneumonia—may in some instances fail to resolve completely and result in varying degrees of organization and fibrosis. The site of this organizing process, however, for reasons that remain unclear, may be predominantly intraluminal with relative preservation of distal air space architecture, or predominantly interstitial, associated with significant architectural distortion. When organization is predominantly intraluminal, characteristic aggregates of proliferating granulation tissue (mainly concentric whorls of fibroblasts and myofibroblasts) are observed within alveoli and alveolar ducts (Masson bodies) as well as respiratory bronchioles. For decades this latter process has been known to occur as a chronic sequela of unresolved bacterial lobar and tuberculous pneumonia and continues to be referred to as organizing pneumonia. This type of organization has also been observed in such varied disorders as collagen vascular disease, “uremic” lung, “rheumatic” pneumonia, experimental paraquat toxicity, and focaly in predominantly interstitial organizing disorders such as hypersensitivity pneumonitis, chronic eosinophilic pneumonia, and usual interstitial pneumonia (UIP), also called fibrosing alveolitis and idiopathic pulmonary fibrosis.

Several clinical reports of predominantly intraluminal organizing pneumonia (ILOP) of no known etiology but associated with collagen vascular disease in some patients have appeared since 1981. The terms organizing pneumonia-like process, relapsing organizing pneumonitis, cryptogenic organizing pneumonia, and, most recently, idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) have been used to describe what appears to be a new nosologic entity. The pathology of this condition and its differentiation from usual interstitial pneumonia (UIP), although alveolar epithelial damage appears to be an early event in both processes, has also been well described.13-15 With respect to nomenclature, to avoid clinical diagnostic confusion, perhaps the aspects of “pneumonia” and “intraluminal organization” only should be stressed. Although bronchiolitis obliterans is also observed pathologically, the predominant clinical profile of idiopathic ILOP is that which results from distal lung structure consolidation rather than from more proximal small airway obstruction; i.e., idiopathic ILOP is mainly characterized by lateralizing radiographic “pneumonic” consolidations associated with ventilatory restriction, rather than a predominantly obstructive ventilatory defect associated with a “military” or “overdistention” radiographic pattern,
which characterizes bronchiolitis obliterans (bronchiolitis fibrosa obliterans).

When organization is predominantly interstitial however, as in UIP, organizing mural intra-alveolar exudate and collapsed, pleated tangles of apposed denuded epithelial basal lamina (BL) are observed to be “incorporated” within the alveolar interstitium. Notably, significant fibroblastic proliferation appears to occur in these sites of BL collapse and apposition.

The potential importance of the two latter changes in the histologic sequence of lung remodeling (healing with scar), as assessed by electron microscopy, has recently been emphasized by Katzenstein and Myers and Katzenstein. In this context, such tissues as renal tubules, cutaneous nerves, skeletal muscle, skin, cornea, and lung experience almost complete restoration of structure and function after injury if the architectural “scaffolding” of the BL remains relatively intact. Conversely, if BL continuity is disrupted, scarring ensues.

These observations raise such questions as (a) whether the degree of organization with fibrosis in interstitial organizing pneumonia of the UIP type is appropriate (normal healing) or inappropriate (exaggerated healing) for the degree and/or type of alveolar epithelial damage; (b) what role the BL itself might play, when altered, in matrix-cellular signaling in the process of lung remodeling; (c) whether surfactant alteration is mainly responsible for initial or sustained collapse and apposition of BL, as a result of its loss of surface tension lowering and/or purported “anti-stick” properties; and (d) after seemingly similar histologic types of initial alveolar injury, what determines whether organization will proceed intraluminally or interstitially. In the former, does the BL “scaffolding” remain relatively intact, yet contain perforations or gaps, perhaps due to neutrophil mediators, resulting in a “Swiss cheese” appearance of the BL, allowing for matrix-alveolar cell trafficking with varying degrees of organization? This question is important, since ILOP appears to be associated with a more sustained connective tissue cellular response with less fibrosis and is fairly responsive to corticosteroid therapy.

Interstitial organizing pneumonia of the UIP type, on the other hand, is associated with more intense collagen deposition and is relatively nonresponsive to current therapy.

Further investigative efforts along these lines may provide new insights concerning the lung’s response to injury, and, we hope, lead to the development of new therapeutic approaches to these disorders.

Stephen B. Sulavik, M.D.
Farmington, CT

References


Division of Pulmonary Medicine, University of Connecticut School of Medicine.
Reprint requests: Dr. Sulavik, PO Box 919, 4 W Mt. Rd., Cawton Center, CT 06020
Progestins and Ventilatory Stimulation

Several lines of evidence indicate that synthetic progestins are relatively strong long-term ventilatory stimulants and, thus, may be useful in the correction of chronic CO₂ retention. First, medroxyprogesterone acetate (MPA) increased tidal volume and lowered Pco₂ despite the presence of potentially powerful inhibitory influences including peripheral blood and cerebrospinal fluid alkalinosis in normal subjects and severe mechanical impairment in patients with COPD. Second, in selected patients with COPD, long-term MPA therapy was more consistent than chronic metabolic acidosis in correcting CO₂ retention. Therefore, progestins are unique ventilatory stimulants which cause hyperventilation in health and disease states independent of measurable changes in classic chemical stimuli.

The mechanism of ventilatory stimulation by progestins is not mediated by the level of progesteronal activity. Some hormones with marked progesteronal activity such as anhydrohydroxyprogesterone or 19-norethynyltestosterone show no stimulatory effect on ventilation. MPA has 15 times the progesteronal activity of progesterone and yet the ventilatory response in normal males treated with MPA is half that observed during pregnancy. Chlormadinone acetate (CMA) has ten times the luteinizing action as MPA but produces the same amount of ventilatory stimulation. In this issue of Chest (p 1073), Tatsumi et al report that CMA was used at one tenth the dose previously reported and caused a similar degree of ventilatory stimulation. A role for estrogen-inducible progesterone receptors has been proposed as the reason for the variable ventilatory response in human studies and between species.

Selection criteria are necessary to predict a ventilatory response in patients with chronic CO₂ retention.

Patients with obesity-hypoventilation syndrome and chronic mountain polycythemia are good candidates for progesterone therapy. Patients with COPD and severe mechanical limitation (FEV₁<0.5 L) and those who are unable to lower PaCO₂ greater than 5 mm Hg with voluntary hyperventilation are unlikely to respond to long-term ventilatory stimulation. Patients with acute ventilatory failure due to a deterioration of lung function are less likely to benefit because of the predominant contribution of mechanical and ventilation-perfusion impairment rather than an insufficient inspiratory effort. Patients with primary alveolar hypoventilation do not respond consistently. Patients with obstructive sleep apnea do not benefit from progesterone. However, the role of progesterone in patients with sleep apnea and daytime CO₂ retention is less well defined. A beneficial effect of synthetic progestins in the treatment of central sleep apnea is suggested by studies of periodic breathing at high altitude, since MPA caused a reduction in oscillations in oxygen saturation. These clinical observations indicate that progesterone is an effective ventilatory stimulant in patients who have an inadequate inspiratory effort relative to the degree of mechanical and ventilation-perfusion abnormality.

Patients with COPD who correct their CO₂ retention report either no increase or a decrease in dyspnea. Noncorrectors with more severe mechanical impairment may experience an increase in dyspnea. Clinical improvement is occasionally dramatic, but is not well correlated with improvement in blood gas values. Decreased libido and impotence occur in about 20 percent of patients.

The use of long-term progesterone therapy in patients with CO₂ retention is limited, especially in patients with COPD, because the long-term effect of ventilatory stimulation on oxygen delivery and pulmonary hypertension has not been well documented. In contrast, improvement in tissue oxygenation is suggested, in patients with obesity-hypoventilation syndrome and chronic mountain polycythemia, by a decrease in hematocrit following improvement in PaO₂. Widespread use of synthetic progestins is further limited by the small number of patients whose CO₂ retention is due to an insufficient inspiratory effort rather than to a predominantly mechanical or neuromuscular abnormality.

James B. Skatrud, M.D.
Madison

Associate Professor of Medicine, University of Wisconsin.

REFERENCES
2 Tyler JM. The effect of progesterone on the respiration of patients