Beneficial Effects of Reducing Pulmonary Edema in Patients with Acute Hypoxemic Respiratory Failure

In patients with acute hypoxemic respiratory failure (AHRF), the airspace is flooded from leaky pulmonary vessels and alveolar membranes, which causes blocking of oxygen transfer from the airspaces into the blood. This sequence of events results in hypoxemia, reduced oxygen delivery, hypercapnia, and death if corrective therapy is not applied. Although patients with AHRF die most often of multiple organ failure complications, several reports support the notion that strategies to actively reduce pulmonary edema reduce the length of stay of these patients in the intensive care unit (ICU) and are associated with reduced mortality. Compelling evidence shows that pulmonary vascular leakage is reduced by lowering the pulmonary vascular pressure. This has been shown to improve alveolar gas exchange in animal models of acute lung injury. One clinical study reported no relationship between edema and mortality in AHRF. Yet this study did not evaluate the effects of an intervention on edema or mortality; rather, it described the associations, or lack thereof, across a population of patients with AHRF.

We contend that reducing edema formation and/or increasing edema clearance could reduce the duration of mechanical ventilation and ICU therapy, thus preventing the complications associated with an ICU stay. Our recent retrospective study of 40 patients with AHRF stratified the patients by age and APACHE II scores and demonstrated that patients undergoing therapy that reduced their pulmonary capillary wedge pressure (Ppw) by 5 mm Hg or more had a significantly lower mortality than patients whose Ppw was not reduced (29 percent vs 75 percent). The association of reduced Ppw with survival in this retrospective study is compatible with the findings in prior reports of improved survival with negative fluid balance and with reduced lung water, and could signal a cause-and-effect relationship; it may also mean that survivors of AHRF are endowed with better ability to have lower Ppw.

The work of Schuller and co-workers in the present issue of Chest (see page 1068) suggests that positive fluid balance in patients with AHRF is associated with poor outcome. Schuller et al evaluated the influence of changes in fluid balance and Ppw on ICU survivorship in 89 patients with pulmonary edema requiring pulmonary artery catheterization. Although this report represents a retrospective analysis of a companion prospective study, their data show unequivocally improved survival in patients who had decreased Ppw, fluid balance, and body weight.

The rationale for the therapeutic approach of reducing pulmonary capillary leak by reducing the hydrostatic pressures across the pulmonary microcirculation is based on the Starling equation for liquid flux across the pulmonary capillaries, which determines the rate of edema formation. The net amount of extravascular water in the lungs results from a balance between passive processes determining edema formation (pressure- and concentration-driven solute and water fluxes) and edema clearance (determined by active processes, epithelial solute transport and lymphatic pumping). Understanding alveolar fluid flux requires knowing the relative roles and interplay of these mechanisms, which contribute in a different way at different stages of lung injury. For example, in patients with AHRF the resultant diffuse alveolar damage is characterized by sequential phases: an early exudative phase, when edema rapidly accumulates, and a later proliferative phase, when alveolar reparative processes take place. During the acute exudative phase, alveolar flooding occurs due to the endothelial and, more important, the epithelial damage. Apparently, during the early exudative phase of lung injury, when permeability to solutes is increased, the passive mechanisms for edema formation predominate and determine the net amount of extravascular lung water. Edema clearance is impaired at this time due to epithelial damage and decreased active Na⁺ transport. Hence, during the acute exudative stage of lung injury, strategies to reduce preload Ppw are important in effecting edema reduction. Conversely, during the proliferative-reparative phase of lung injury, when epithelial permeability is being restored, alveolar edema clears faster. This is probably due to the repopulation of the alveoli by epithelial type 2 cells, which contain more Na⁺/K⁺ ATPases per cell than epithelial type 1 cells, which in turn increase active Na⁺ transport and alveolar clearance.

The importance of restoring epithelial permeability and effecting edema clearance was recently demonstrated in mechanically ventilated patients with AHRF. The results of this study support the hypothesis that active ion transport across the alveolar epithelial barrier is the primary mechanism for clear-

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7 Hooper RG, Kearl RA. Established ARDS treated with a sustained course of adrenocortical steroids. Chest 1990; 97:139-43
ance of edema fluid from the airspaces. Furthermore, this study suggests that increased edema clearance results in improved survival of mechanically ventilated patients with respiratory failure; in contrast, patients whose lung injury was associated with prolonged microvascular leak did not survive. Accordingly, specific treatments to reduce or prevent acute lung injury are required; unfortunately, they are not yet available. Until they are, measures to reduce the leak and to clear edema may reduce the adverse effects of lung edema. The study by Schuller et al further supports the notion that edema reduction in patients with AHRF is beneficial, perhaps by decreasing the need for and complications of mechanical ventilation.\(^6\)

Of course, reducing preload in critically ill patients may reduce their cardiac output (Qt) and oxygen delivery (Qo2); accordingly, we seek the lowest Ppw compatible with an adequate Qt and Qo2. By definition, this approach never introduces shock or inadequate perfusion of specific organs because careful continuous attention detects hypoperfusion early and corrects it by increasing Ppw, especially with red blood cell transfusion to increase Qo2; alternatively, at the first signs of hypoperfusion, we employ low-dose dopamine (1 to 3 \(\mu\)g/kg/min) and add dobutamine (2 to 10 \(\mu\)g/kg/min) to restore adequate Qt and Qo2 at the reduced Ppw.\(^7\) Note that this approach does not have a Ppw target, because in some patients with AHRF, a Ppw of 15 mm Hg is the least value providing adequate perfusion, while in others a Ppw value of 0 mm Hg is associated with adequate perfusion. This approach necessitates that the intensivist use right heart catheterization data to push each patient to his limit of adequate perfusion, a process of ongoing titration quite different from “monitoring the central hemodynamics” in that there are no alarms for the wedge pressure and Qt other than in the physician’s intellect. This approach will be more effective in the early stages when edema is the problem, and less effective when fibrosis becomes the larger problem. Such a process also requires adjustment between patients, for intensivists would not push a 70-year-old patient with severe atherosclerosis as close to the limit of hypoperfusion as they would a 20-year-old previously healthy patient. Yet in both cases, the aim is to minimize pulmonary edema accumulation without inducing complications, thereby reducing the time for edema clearance.

Until a definitive prospective study is available, the benefit of reducing edema formation in the early stages of lung injury by reducing the hydrostatic pressures across the pulmonary circulation should not be underestimated. Also, strategies are being developed to enhance active Na\(^+\) transport and edema clearance, which may be beneficial in the early proliferative-reparative phase of lung injury.

**REFERENCES**

Well-differentiated Neuroendocrine Carcinoma

A Designation Comes of Age

In this issue (see page 1053), Lequaglie and colleagues describe a retrospective analysis of their ten-year experience with resected, well-differentiated neuroendocrine carcinoma (WDNC). Their work confirms and extends the observations of others that WDNC is a clinicopathologic entity distinct from other neuroendocrine tumors of the lung, including carcinoid tumor and small cell lung carcinoma (SCLC).1,2 Utilizing morphologic criteria defined by Gould et al.,3 the authors identify 19 cases of resected WDNC. Significantly, while six of the first 12 cases were diagnosed as atypical carcinoids, the remaining six cases had originally been diagnosed as SCLC, thereby reinforcing the observation that some WDNCs are misdiagnosed as SCLC. Refinements in the morphologic diagnosis of WDNC by Warren and co-workers4 clearly demonstrate that, while the WDNC category encompasses tumors originally diagnosed as atypical carcinoids, it also includes tumors that may be incorrectly diagnosed as SCLC, particularly when diagnostic material is limited to small bronchoscopic biopsy specimens or cytologic preparations. In our experience,5 these cases represent a large majority of long-term survivors with a diagnosis of SCLC. Similar morphologic observations have been made in cytotologic studies of bronchial specimens, and criteria have been established for the cytdiagnosis of WDNC.6

In their analysis of the clinical data, Lequaglie and co-workers suggest that surgery may be the treatment of choice for patients with localized WDNC. Prospective studies based on careful histologic subtyping and clinical staging should define the role of primary surgical therapy and adjuvant therapies in the treatment of patients with WDNC. Additionally, immunohistochemical and flow cytometric analyses of these tumors may provide adjunctive prognostic data useful in the management of WDNC.5,6 Immunohistochemical studies of SCLC with monoclonal antibody SCCL 175, an antibody directed against SCLC, have shown that the expression of the antigen defined by this antibody can distinguish WDNC and SCLC and that its expression is associated with shorter patient survival times.7 The use of flow cytometric DNA analysis is still unclear, although it also may provide supportive prognostic information in classifying neuroendocrine carcinomas of the lung.

The strength of any tumor classification system depends on its ability to be reproducibly applied by pathologists and its utility to clinicians for the treatment of patients. Mounting evidence indicates that recognition of WDNC as a distinct type of pulmonary neuroendocrine neoplasm fulfills these criteria. The prospective recognition of WDNC will allow the development of new therapeutic modalities. Meanwhile, it is also clear that new tools must be found to objectively define the different neuroendocrine carcinomas of lung.

Vincent A. Memoli, M.D.
Hanover, New Hampshire

Dartmouth-Hitchcock Medical Center.

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Management of Parapneumonic Effusions

Approximately 40 percent of patients with acute bacterial pneumonia will have an associated pleural effusion.8 Most of these parapneumonic effusions will resolve with only the administration of antibiotics.1,2 I have used the term complicated parapneumonic effusion for a parapneumonic effusion that requires tube thoracostomy for resolution or which has a culture positive for bacteria.1 In the clinical situation, one would like to identify as early as possible those individuals who will need chest tubes, since a free-flowing complicated parapneumonic effusion can progress to a multiloculated effusion in a matter of hours.3 Once the complicated parapneumonic effusion becomes loculated, its management is much more difficult.1,5

Whether or not an individual with a parapneumonic effusion requires tube thoracostomy depends on several different factors. The bacteria responsible for the underlying pneumonia are important; parapneumonic effusions due to Staph aureus or anaerobic bacteria