EDITORIAL

Measuring Pulmonary Vascular Permeability

The explosion of new knowledge about endothelial cell biology has made it clear that the endothelium is not simply an inert barrier that prevents vascular solute and water loss. However, we must not discount this important function. Clearly, whenever and wherever the endothelial barrier does break down, edema develops and organ function declines. Except perhaps in the brain, never is the development of organ edema so dramatic nor so potentially disastrous as it is in the lung. Even though the interstitial compartment of the lung can nearly double its extravascular water content before gas exchange deteriorates, further accumulation of extravascular fluid often signals the onset of alveolar edema with rapidly fatal consequences if not promptly treated. Thus, it is no surprise that for nearly a century great effort has been expended toward improving our understanding about the biologic mechanisms underlying the control of endothelial barrier function. And at the heart of such studies has always been the problem of how to measure change in barrier integrity or, to use the most commonly applied (though not entirely precise) term, how to measure change in vascular permeability.

Next year is the centennial of Starling's classic hypothesis about the control of transcapillary fluid movement (*1*). Simply stated, Starling showed that oncotic forces generated by plasma proteins balance the hydrostatic pressure that otherwise would drive fluid out of capillaries. In the ensuing decades, his hypothesis has been refined, expanded and quantified mathematically in many forms (*2–6*). These mathematical treatments make clear that permeability (i.e., a general breakdown in capillary membrane integrity) cannot be quantified by any one parameter. This point becomes important when one considers how permeability, and pulmonary permeability in particular, is evaluated clinically. While changes in barrier integrity can often be inferred clinically (e.g., from hemodynamic measurements, chest radiographic patterns or protein concentrations in pulmonary edema fluid), quantitative approaches to measuring vascular permeability are all based on measuring the accumulation of radioactively labeled substances (usually proteins) into the lung (*4–7*). Interestingly, in all cases, the mathematical treatments of the time-activity data from such measurements share a common theoretical basis, despite apparently disparate ultimate expressions for the results (*7–9*). For instance, with appropriate assumptions, it can be shown that the two most common expressions of pulmonary vascular permeability (namely the so-called "transcapillary escape rate" and the "normalized slope index") are mathematically equivalent (*8,9*). Since both expressions describe a parameter which is sensitive to convective and diffusive protein flux, both are, in a sense, compound expressions, influenced by different forces (bulk fluid flow across the membrane, membrane surface area, "pore" size, etc). In any case, studies that use one versus the other expression of vascular permeability differ more in terms of technical factors (tracer, label, choice of detector, timing of data collection, etc.) than in basic theory.

At this point, it is appropriate to ask why one would want to measure pulmonary vascular permeability in humans at all. One good reason, of course, is to understand how and when macromolecules traverse the capillary endothelium in both health and disease. The delivery of chemotactic factors or cytokines into the extravascular space obviously can have an enormous impact on lung function. An equally important reason, however, and in current clinical terms the more important one perhaps, is to use a measure of pulmonary vascular permeability as a marker of acute lung injury.

Recently, a joint conference was held by the American Thoracic Society and the European Society of Intensive Care Medicine (ATS-ESICM) to address current controversies about acute lung injury (*10*). In their report, they defined acute lung injury as "a syndrome of inflammation and increasing permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension." Continuing, they defined the acute respiratory distress syndrome (ARDS) simply as a more severe form of acute lung injury.

I recently challenged this definition as too vague and nonspecific (*11*). Instead, I suggested that the definitions of acute lung injury and ARDS should link characteristic *structural* (i.e. pathological) changes to well-defined changes in *pathophysiology*. Thus, acute lung injury should be viewed in general terms as *any* characteristic pathologic abnormality in the lungs' normal underlying structure which results in a deterioration of normal lung function. ARDS, however, should be considered a specific form of lung injury, albeit one with diverse causes, characterized pathologically by the entity known as diffuse alveolar damage and pathophysiologically by a breakdown in both the barrier and gas exchange functions of the lung, resulting in proteinaceous alveolar edema and hypoxemia.

Notice the central role of "permeability" in either set of definitions. In this regard, it is curious that the ATS-ESICM conference report failed to include any measure of permeability

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in its suggested set of criteria for diagnosing ARDS. The reason seems evident enough: As yet, the treatment of ARDS does not depend on knowing whether or to what extent permeability is abnormal. On the other hand, it can be argued that such a measure would be extremely useful in the conduct of clinical trials or in the interpretation of trial data (*11*). A number of noninvasive techniques are now available for such evaluations at the beside of ARDS patients (*12–14*). The theory, mathematics and limitations of these methods are well understood (*4,7–9*). When used in clinical studies, these methods consistently differentiate high-pressure pulmonary edema from that associated with acute lung injury (*12,13,15*). A limited set of data indicates that they can track the natural history of lung injury (*14,16,17*). Only one study, however, has tried to show that these measures are predictive of the underlying pathologic alveolar damage that is their cause (*18*).

This latter point is critical and leads me to recall again why we make this measurement at all. In general, and certainly clinically, we are not interested in defining the degree of abnormality in permeability for its own sake but because it is predictive of the severity of the underlying lung injury. In turn, such an assessment might or might not be predictive of eventual outcome. Even if this were not the case, it would be useful as a measure of injury severity. Furthermore, it is important to remember that it is the permeability to proteins such as albumin and transferrin that are measured, since, as Starling originally hypothesized, these are the plasma proteins that generate oncotic pressure. Because albumin is quantitatively the major plasma protein, it is logical that most clinical investigators have labeled albumin for studies of vascular permeability. The only rationale for using the most common alternative to albumin (transferrin) is that, in some settings, it is easier to label than albumin, although it has approximately the same molecular weight.

The purpose of these comments is to provide a context for reviewing the study by Abernathy et al. in this issue of *JNM* (*19*). This group, which I believe has performed much of the best theoretical and investigative work in the field, has compared the normalized slope index (one of the measures of vascular permeability referred to above) generated from time-activity data obtained after the administration of radiolabeled dextrans of different size to those obtained with labeled albumin (approximately 70 kDa). The dextrans (6 and 40 kDa) were labeled with both gamma-(^{99m}Tc) and positron-(^{18}F) emitting radioisotopes. The experiments were carried out in an in situ rabbit lung preparation in which the lungs were not injured.

Predictably, the lung accumulation rate (i.e., the normalized slope index) for the 40-kDa dextrans was faster than that for albumin, and in turn, the accumulation rate for the 6-kDa dextrans was faster still. The authors conclude that scan times could be significantly reduced if permeability were evaluated with these smaller molecules and the characteristics of lung permeability could be better defined if tracers of different size and/or electrical charge could be injected simultaneously.

Since, as I have noted, the authors have been instrumental in developing the models and methods often used to evaluate lung vascular permeability, there is little to criticize about the actual conduct of the study. Rather, it is their interpretation of significance with which I have the most difficulty. There is no evidence that "long scan times" are the major, indeed any, impediment to obtaining such measurements clinically. While data collection occurred for 75 min in the current study, no analysis was performed to determine the minimum time necessary to yield comparable results. In other studies, scan times of only 45 min or less have been used (*7*). Furthermore, long scan times are most necessary when permeability is normal since the normal rate of protein extravasation is low. As permeability becomes more abnormal, the time required to obtain useable data becomes shorter. Indeed, noncardiogenic forms of pulmonary edema are often associated with 5-10-fold increases in the escape rate for labeled protein (*11–13*). Comparable changes in the escape rate for the 6-kDa dextrans might conceivably be so short as to even preclude useful kinetic data.

On the other hand, the authors' second conclusion (that the use of labeled dextrans to evaluate lung permeability would help define the permeability characteristics of the lung), gets at the heart of what this measurement is meant to accomplish. While this conclusion is obviously vague, it is still useful to speculate on the possibilities. For instance, the measurements might help define when and to what extent comparably sized and charged molecules, along with their important biologic actions, accumulate in the pulmonary extravascular space. Such information might help us understand how these phenomena affect the development and resolution of lung injury. In terms of water balance, however, it is unlikely that such measurements will provide any new insights, since it is only the larger macromolecules, such as albumin, that are capable of generating an oncotic pressure.

Finally, it is completely unclear what utility a measure of permeability to small dextrans would have as an index of injury severity. The necessary studies would have to show a correlation with other simultaneous changes in lung function, with the pathology that is at the root of the lung injury and eventually with outcome. Should these measurements pass these tests, however, they would truly be a useful new tool in evaluating lung physiology and pathophysiology.

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