The lung permeability index: A feasible measurement of pulmonary capillary permeability


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Summary

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Introduction

Pulmonary edema is a leading cause of morbidity and mortality in the Intensive Care Unit. Many factors are involved in its pathogenesis such as elevated intravascular hydrostatic pressure, low colloid-osmotic pressure, insufficient lymphatic drainage, and increased pulmonary capillary permeability.1–5 Daily, physicians face the challenge of approaching a patient with diffuse pulmonary infiltrates. Once they have ruled out infection, or hemorrhage, they must differentiate between cardiogenic and non-cardiogenic pulmonary edema.

It is customary to make the assumption that there is insufficient myocardial performance, if upon assessment of cardiovascular function, one finds the presence of an S3 gallop, a murmur, distended jugular veins, low cardiac output, elevated central venous pressure or pulmonary capillary wedge pressure; then the pulmonary capillary permeability is felt to be normal and thereby the pulmonary edema is deemed cardiogenic in nature. On the other side of the spectrum, if all the myocardial performance and fluid status parameters are normal, it has been hypothesized but no proven that the culprit of the pulmonary edema is increased pulmonary capillary permeability and consequently the diagnosis of non-cardiogenic pulmonary edema is established.

Indeed, there is no gold standard to determine whether or not the pulmonary capillary permeability is increased and therefore, in order to establish the diagnosis of non-cardiogenic pulmonary edema, one must rule out cardiovascular etiology and then make the assumption that the pulmonary capillary permeability is increased. Essentially, there is no way to directly measure pulmonary capillary permeability; moreover, when it is assumed that pulmonary capillary permeability is increased, it is difficult to quantify the degree of alteration of the pulmonary capillary permeability.

Non-cardiogenic pulmonary edema is the hallmark of the acute respiratory distress syndrome (ARDS). It has been hypothesized that the outburst of cytokines, oxygen free radicals, and proteolytic enzymes, which are characteristic of this syndrome, lead to a derangement of the alveolar-capillary membrane. The intercellular or intracellular pores increase in number and size, conducing into a leak of protein and fluid, from the intravascular to the alveolar space, which in turn will attract more fluid by osmosis into the alveolar space. This protein flux has been previously studied using a lung lymph fistula in experimental animal models.6,7 It has been demonstrated that in conditions of elevated hydrostatic pressure, there is an increased flow of a protein-poor fluid into the alveolar space, whereas in condition of sepsis, such as the one following administration of live pseudomonas in experimental models of septic shock, there is an increased flow of a protein-rich fluid.

Due to the inaccessibility of pulmonary lymph in patients with pulmonary edema, studies were developed using aspirates from tracheobronchial edema fluid or bronchoalveolar lavage fluid to determine the protein content of these fluids and compare them with the plasma protein content, obtaining ratios such as edema fluid to plasma protein ratio, and bronchoalveolar lavage fluid to plasma protein ratio with the objective to find a discriminatory factor to determine if the pulmonary edema was of cardiogenic nature or due to increased permeability. The results of these studies revealed that higher values of these ratios (greater than 0.6) were related to non-cardiogenic pulmonary edema.8–16

With the same objective, several studies have been conducted using noninvasive radioisotope techniques, based on the external assessment of radiolabeled protein leakage into the lung, and allowing a quantitative assessment of the rate of extravascular protein accumulation and thereby permitting an estimation of the pulmonary capillary permeability with variable degrees of accuracy.17–21 More recently, Philips et al proposed that the pulmonary vascular permeability index (PVPI) [extravascular lung water (EVLW, ml)/pulmonary blood volume (PBV, ml)] may reflect the severity of acute lung injury.22

The objective of this study was to determine the usefulness of the lung permeability index as described by Mishkin et al in discerning between cardiogenic and non-cardiogenic pulmonary edema as explanation for the development of diffuse pulmonary infiltrates.

Methods

The study was conducted in patients admitted to the medical intensive care unit at The University of Texas M. D. Anderson Cancer Center, who had recently developed diffuse pulmonary infiltrates of undetermined etiology upon chest radiographic examination, who had needed intubation and mechanical ventilator support, and who had been hemodynamically monitored with a pulmonary artery catheter. Pregnant women, patients younger than 18 years of age, patients with chronic heart disease, renal failure, pneumonia, diffuse alveolar hemorrhage, or neoplastic lung disease were excluded. The Institutional Review Board approved the study protocol, and informed consent was obtained from either the patient or the patient’s surrogate prior to enrollment in the study.

Procedures

Lung permeability index (LPI)

Intravenous injection of 20 mCi Technetium Tc99 m human serum albumin (HSA) was administered at minute 0. Ten minutes later, an Apex 409 MA Elscint portable digital gamma camera with GAP collimator and a computer for outlining and analyzing the region of interest (ROI) activities was centered over the right middle lung field lateral to the right pulmonary artery and the initial lung uptake was obtained, then immediately the initial heart uptake was obtained by placing the camera over the left ventricle. Both uptake areas measured one square centimeter. At minute 180, the measurements were repeated and called the final lung and heart uptake. Because the fluids move rapidly, it is imperative to make the evaluation during the first minutes to avoid inaccurate results difficult to evaluate.23 The lung permeability index was then calculated by obtaining the initial and final lung/heart uptake ratios. Then determining the difference between the final and the initial lung/heart uptake ratios, and multiplying it by 100.
LPI = (Final Lung/Heart Uptake Ratio
– Initial Lung/Heart Uptake Ratio) × 100

Bronchoalveolar lavage (BAL)

Bronchoalveolar lavage was performed after minute 180.

The fiberoptic bronchoscope was inserted and wedged in the right middle lobe medial segment. Bronchoalveolar lavage was performed by injecting five 20 ml aliquots of sterile normal saline solution and retrieving it with the same syringe. Total protein content was measured and the measurement was corrected by the dilution factor (Plasma/Bronchoalveolar lavage urea nitrogen ratio).²⁴

Bronchoalveolar lavage total protein content and urea nitrogen were measured with colorimetric tests, using a Johnson & Johnson Vitros 250 Clinical Chemistry Analyzer. The total protein analysis was based on a modification of the biuret reaction.²⁵⁻²⁷ The modification employed is such that cupric ion (Cu²⁺), which binds to an azo dye complex, is displaced by proteins. The urea nitrogen analysis was based on the urease method (GLDH),²⁸ using dry multilayered slides.²⁹ The low range limit of urea nitrogen analysis was 2 mg/dL (0.71 mmol/L urea) for routine use. Specimens giving urea nitrogen results less than 2 mg/dL were diluted 1:2 with pooled serum having a measured urea nitrogen value of 13 mg/dL After correction for the dilution factor, the pooled serum urea nitrogen was subtracted from the result, yielding a measured value of either 0 mg/dl or 1 mg/dl. While the analyzer in use measured urea nitrogen concentrations to tenths of a unit, the result was rounded to, and reported by the analyzer as a whole unit. As a result of the recovery procedure stated above, a final result of 0 mg/dL indicates an actual urea nitrogen concentration between 0.0 mg/dL and 0.4 mg/dL, and a result of 1 mg/dL indicates an actual urea nitrogen concentration between 0.5 mg/dL and 1.4 mg/dL. We assumed a urea nitrogen value of 0.2 when the urea nitrogen analysis displayed 0.

Statistical analysis

We used linear regression analysis to evaluate the association between the lung permeability index and the pulmonary capillary wedge pressure (PCWP), cardiac index (CI), myocardial performance index (MPI) (MPI = CI/PCWP), and bronchoalveolar lavage total proteins, and bronchoalveolar lavage/plasma total protein ratio.

Results

Ten patients were included in the study and the demographics are shown in Table 1. All patients had recently developed respiratory failure and were intubated and mechanically ventilated at the time of the lung permeability index determination. At this time, all the pertinent hemodynamic parameters were obtained. Table 2 discloses the pulmonary capillary wedge pressure (PCWP), cardiac output (CO), myocardial performance index (MPI), which was calculated dividing CO by PCWP and meant the preload-dependent flow, the lung permeability index (LPI), the bronchoalveolar lavage protein content (BAL.PROT), and the clinical diagnoses of the 10 patients.

After correcting the diluted bronchoalveolar lavage we plotted the lung permeability index and the bronchoalveolar lavage total protein (Fig. 1). It showed that knowing the lung permeability index we could predict the protein content of the bronchoalveolar lavage or the protein leakage into the alveolar space and indirectly the degree of alteration of the pulmonary capillary permeability.

Linear regression analysis was performed and we obtained an $R^2 = 0.72$ ($F = 20.0$, $p < 0.01$) with the following equation:

Bronchoalveolar lavage

$\text{total proteins} = \text{lung permeability index} \times 0.2 + 0.16$

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<th>Table 1 Characteristics of the patients.</th>
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Similar correlation was found when LPI was plotted against the BAL/Plasma protein ratio. However, its relationship was not as significant as the one before \( p < 0.05 \).

The correlation of the lung permeability index with the cardiac index (CI) and the pulmonary capillary wedge pressure (PCWP) did not meet statistical significance, despite of some trend.

However, the correlation between the lung permeability index and the myocardial performance index \( (\text{MPI} = \text{cardiac index}/\text{PCWP}) \) was very strong. The linear correlation with an \( R^2 = 0.91 \), and \( p < 0.05 \) is expressed in the following formula: \( \text{MPI} = 0.0042 \times \text{(LPI)} + 0.13 \) (Fig. 2).

**Discussion**

The pathophysiology and management of pulmonary edema have been widely studied. The most frequent noninvasive tool clinicians use is the portable supine chest x-ray to evaluate lung injury, but there are a few studies questioning its accuracy. Most of radiological studies to assess lung water were done not only with posterior-anterior and lateral views of the chest x-ray, but also with non-portable equipment. That is why these studies cannot be well extrapolated to the medical intensive care unit population where we use portable anterior-posterior view chest x-rays.

Using the fiberoptic bronchoscope it was possible to evaluate and also obtain cellular samples, but this technique is too invasive, and moreover there is no specific cellular finding that could indicate us the degree of lung injury. Several reports described that the protein concentration index between fluid obtained from injured lungs and plasma was higher than that obtained from normal lungs.\(^7\)\(^{12,30,\ 31}\) This leads us to the practice of using external methods for the detection of tracer protein equilibration between blood, interstitium, and alveolus, that could be a useful tool to quantify lung injury.\(^32\)

At the present time, it is possible to make this quantification at the bedside and with more accuracy that in the past. The idea of being less invasive is growing, not only because it lower the risks for patients, but also because it is...
less expensive. In the past, physiologists developed many techniques to have a better understanding of the pathophysiology of the cardio-respiratory system, but sometimes these high-risk procedures are not recommended to be used in critically ill patients.

Although we originally conceptualized the lung permeability index (LPI) as with discriminatory power to differentiate cardiogenic pulmonary edema from non-cardiogenic pulmonary edema, as things steadily went through we realized that the protein leak into the lungs is not an on and off phenomenon rather it is a continuum.

We had very few cases that turned out to have pure cardiogenic pulmonary edema with low cardiac output and low lung permeability index, and very few cases with pure non-cardiogenic pulmonary edema with high cardiac output and high lung permeability index. Consequently, we strongly believe the distinction of cardiogenic pulmonary edema versus non-cardiogenic pulmonary edema is a utopia that we do not see frequently in clinical practice.

The measurement of lung permeability index is noninvasive, and also useful at the bedside. It can be used in critically ill patients, and allows quantification of the alveolar-capillary membrane leakage, a very good indicator of lung injury. In this study we found that it correlates very well with the protein content in the BAL fluid, a surrogate of the measurement of the pulmonary capillary permeability.

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Conflict of interest

This is to acknowledge you that none of the authors have disclosed any conflict of interest of any nature in the development of this original work.

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