review

The Clinical Assessment of Lung Water*

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The importance of the balance of lung fluid and pulmonary edema in experimental and clinical medicine explains the effort made in the last 30 years to measure lung water content and to develop clinically applicable methods. Pulmonary edema is an essential component of the spectrum of lung reactions to injury. As defined by the Starling equation,[1] damage to the endothelium increases the permeability of the capillary membrane to water and solutes (protein) and represents the pathophysiologic basis of increased-permeability edema (or noncardiogenic edema). An increase in pulmonary capillary pressure (due, for instance, to left ventricular failure) determines the accumulation of lung water by increasing the hydrostatic pressure gradient between capillary and interstitium and explains the pathogenesis of high-pressure (cardiogenic or hemodynamic) pulmonary edema. The alveolar epithelium may play an important role in the development and resolution of alveolar edema.[1] Both the high-pressure type and the increased-permeability type of pulmonary edema have been extensively studied in experimental animals. In experimental pulmonary edema, measurements of lung water by various methods have provided essential information on the magnitude, distribution, and temporal course of the accumulation of water. Pulmonary edema is also a common clinical event in various areas of medicine (as exemplified by the high-pressure lung edema of cardiac patients and the increased-permeability lung edema of patients with the adult respiratory distress syndrome); however, the clinical value of measurements of lung water remains controversial, mainly because all of the available methods have limitations which reduce their sensitivity and accuracy or restrict their spectrum of applications.

The purpose of this review is to analyze the methods for measuring lung water, with specific reference to their clinical application. Since pulmonary edema is an essential element of the adult respiratory distress syndrome and of severe left ventricular failure, particular consideration is given to the use of measurements of lung water in critically ill patients. The present review does not offer a systematic analysis of all available methods for the assessment of lung water. In view of the specific scope of the review, such analysis would be confusing and, in addition, redundant because most of the methods proposed have found very limited application or are no longer in use. The methods for measuring lung water are more comprehensively reviewed elsewhere.[1-3] Three approaches, the thermal-dye dilution technique, the soluble inert gas technique, and the radiographic method deserve discussion because they have been studied more extensively; therefore, it is reasonable to attempt an assessment of their clinical value. Recent high-technology methods applicable to the measurement of lung water content and new approaches to the study of the dynamics of pulmonary fluid exchange are also considered, mainly in view of their potential for future clinical use.

Thermal-Dye Dilution Technique

In the thermal-dye dilution method,[4] a version of the double-indicator dilution technique,[4,5] two indicators are simultaneously injected into the superior vena cava (or more centrally) and sampled from the femoral artery. While one of the two indicators diffuses intravascularly and extravascularly (diffusible indicator), the other remains intravascular (nondiffusible or intravascular indicator). The method estimates the volume of distribution of the two indicators and, by difference, the volume of extravascular water. The original method,[2] using tritiated water and ^{131}I serum albumin (or other indicators) as diffusible and nondiffusible indicators, has never found widespread application because of numerous limitations. In the thermal-dye method,[4] heat and indocyanine green are the diffusible and intravascular indicators. A less popular version of

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the thermodilution technique uses hypertonic saline solution, detectable by measuring changes in the electrical conductivity of the blood as the intravascular indicator.[1,2,5] Because of the diffusing characteristics of heat, the thermodilution method estimates a thermal volume (extravascular thermal volume) which includes not only lung water, but also nonaqueous and extrapulmonary components (contributed by the heart and large vessels); however, the use of the extravascular thermal volume to estimate lung water content is justified because extravascular lung water is by far the predominant component. The thermal-dye method has been tested in experimental animals with normal or edematous lungs by comparing extravascular thermal volume with gravimetric estimates of lung water content. An excellent correlation has been found between the data obtained by the two methods, with correlation coefficients generally above 0.9.[4,6-13]

In swine with experimental hemodynamic lung edema, Bongard and co-workers[14] observed a correlation between thermal-dye measurements of extravascular lung water and postmortem lung morphologic findings. Alveolar flooding did not begin until thermal lung volume had doubled from normal; this finding suggests that the thermodilution technique can detect interstitial pulmonary edema.

The thermal-dye technique has also been used in numerous clinical studies, particularly in critically ill patients, to compare extravascular lung water content with radiologic, hemodynamic, and physiologic data, to follow the course of acute lung injury, and to evaluate the effects of treatment.[15-20] With respect to its clinical application, the thermodilution technique offers several advantages. A small computer allows rapid repeatable determinations and can provide on-line data.[9,15] The instrumentation is portable, so that measurements can be obtained at bedside; however, the thermal-dye technique also has significant limitations. Since this technique is invasive, the application is practically confined to patients in the critical care unit. In normal lungs, thermal-dye measurements overestimate gravimetric water content by inclusion of extrapulmonary tissue and by other mechanisms, as discussed in detail elsewhere.[4-6,9,10] In addition and, more importantly, the delivery of the thermal indicator to the lung tissues is dependent on the distribution of pulmonary blood flow; therefore, the accuracy of the thermal-dye data may be limited in the presence of markedly uneven lung perfusion.[5] Experimental changes in the distribution of perfusion (induced by pulmonary embolization with glass beads) were found to affect the measurement of lung thermal volume in normal and, more markedly, in edematous lungs.[6,8] The dependence of the thermal-dye measurements on perfusion can explain various experimental findings. Lung water content may be markedly underestimated by this technique in pulmonary edema.[4,12,21] The error of measurement is dependent on the type of lung injury (spatially nonuniform, as opposed to diffuse lung injury) and may reflect a redistribution of pulmonary blood flow away from the edematous areas (affecting the distribution of the thermal indicator to these areas).[12,21] A similar mechanism can explain the underestimation of lung water content associated with hemodynamic changes (for instance, a decrease in pulmonary arterial pressure);[13] however, the relationships between thermodilution measurements and hemodynamic changes may also be affected by other factors.[4,7,22] Published data on these relationships are conflicting;[4,7,9,13,22] the discrepancy may in part reflect the interaction of several hemodynamic variables. The possibility that hemodynamic changes may affect the thermodilution measurements in the absence of real variations in the extravascular lung water content is particularly important in critically ill patients, who are often hemodynamically unstable. Recent data[21,23] show that positive end-expiratory pressure (PEEP) can increase the thermodilution values for lung water, although no significant effect has been demonstrated in other studies;[11,24] the increase may reflect a redistribution of lung perfusion (rather than a real increase in lung water content). The data of Carlile and colleagues,[21] suggesting that the response of extravascular thermal volume to PEEP is related to the type of pulmonary injury (focal vs diffuse) support this interpretation. The potential effect of PEEP on the measurement of lung water by the thermodilution technique is clinically important because of the extensive use of this type of therapy in critical care medicine. Dependence on perfusion remains an important problem in the clinical application of the thermodilution technique. Effros[5] has recently discussed the clinical implications of these findings. He has pointed out that in critically ill patients, regional pulmonary blood flow can be altered by thromboembolism, spatially nonuniform lung edema, or PEEP. Therefore, the distinction between a real variation in extravascular lung water content and an artifact due to a change in regional perfusion may be a critical dilemma in the clinical interpretation of thermal-dye measurements.

Soluble Inert Gas Technique

In the soluble inert gas technique,[25] an inhaled soluble inert gas (usually acetylene) equilibrates almost instantaneously with the pulmonary tissues. The remaining alveolar inert gas is more slowly removed by the pulmonary capillary blood, at a rate which is dependent on blood flow. This principle represents the basis for the measurement of the volume of lung tissue and pulmonary capillary blood flow. The rate of disappearance of the inert gas from the alveoli is estimated by a breath-holding technique[25] or, more conveniently, by a rebreathing technique.[26] As pointed out by Overland and co-workers,[27] tissue volume values reflect lung water content; water normally represents a large fraction (about 80 percent) of solid lung tissue and almost all of the increase in tissue volume associated with pulmonary edema. Lung tissue volume has been measured in experimental animals with normal and edematous lungs[26,28-33] and in humans (normal subjects and patients with pulmonary edema);[25-27,34,35] reference values obtained from a group of 90 normal nonsmokers (men and women) have been provided by Crapo and co-workers.[34] In comparative studies performed using different versions of the soluble inert gas technique,[28-30] the correlation between lung tissue volume and gravimetric extravascular lung water or total pulmonary weight varied from poor to good; however, correlation coefficients of up to 0.92 were observed using the rebreathing technique.

The soluble inert gas technique has some potential for clinical application because it is not invasive; measurements are rapid and repeatable. In addition to lung tissue volume, the technique determines pulmonary capillary blood flow; however, the soluble inert gas technique has several limitations. Huchon and associates[32,33] observed that in normal animals, the measurement of lung tissue volume overestimated extravascular lung water content (a finding consistent with other comparative data) but agreed closely with total lung weight; their results indicate that the soluble inert gas technique measures not only extravascular lung water but also a fraction of intravascular water (capillary blood and part of the blood contained in extra-alveolar vessels). The overestimation may also be due, in part, to other technical factors.[32,33] Since the delivery of the soluble inert gas to the alveoli is dependent on the distribution of ventilation, the presence of uneven ventilation is expected to cause significant errors in the measurement of lung tissue volume;[36] according to the theoretic lung model of Petrini and associates,[36] the measurement is also sensitive to the distribution of alveolar volume and lung tissue volume. The presence of these abnormalities of distribution may explain the underestimation of extravascular lung water content or lung weight by the soluble inert gas technique in advanced pulmonary edema.[30,33] The measurement of lung tissue volume by the rebreathing technique (the currently used version of the soluble inert gas technique) is dependent on the rebreathing pattern, thus requiring strict standardization of the procedure.[27,29,32,35] In addition, the criteria used to calculate the lung tissue volume from the rebreathing data are not uniform. Differences in the computational technique have been shown to affect the value of lung tissue volume;[30] however, more recent studies suggest that the effect of these differences may not be substantial.[31,32]

Although not very reliable in severe pulmonary edema or other lung conditions associated with marked maldistribution of ventilation and perfusion, the soluble inert gas technique may find clinical application as a screening test (for instance, in patients at risk for developing lung edema) because of its noninvasiveness and repeatability.[37]

Chest Roentgenography

The examination of the standard chest roentgenogram undoubtedly remains the most popular method for the assessment of pulmonary edema. The obvious advantages of this technique justify the efforts made to develop criteria for estimating the severity of lung edema and justify the numerous studies designed to test the reliability and the clinical value of these criteria. Proposed scoring systems vary in complexity, but all are based on a number of radiologic signs widely considered to be indicative of pulmonary congestion and edema (vascular redistribution, Kerley's lines, peribronchial cuffing, perihilar haze, etc). In most scoring systems, these criteria have been used semiquantitatively to define a small number of grades (0 to 3-5), corresponding to various stages in the development of lung edema (from normal to severe alveolar edema).[16-20,38] Pistolesi and Giuntini[39] have developed a more complex scoring system, which quantitatively estimates the degree of accumulation of lung water on the basis of a relatively large number of radiologic criteria. A good correlation (observed correlation coefficients ranging from 0.62 to 0.89) has been found between the radiographic score and extravascular lung water content measured by the double-indicator dilution technique in cardiac or noncardiac (for the most part, critically ill) patients[16,17,19,20,39,40] and in dogs (control and experimental lung edema);[38] however, these comparisons show discrepancies in individual cases (for instance, not negligible numbers of patients with a normal radiographic score and an increased extravascular lung water content or vice versa[16,18,19]). There is also considerable overlap, in terms of extravascular lung water content, between intermediate radiographic grades.[16,19] Some investigators used the results of their comparisons to estimate the accuracy of the radiographic method,[16,18,19,39] implying the assumption that the double-indicator dilution technique provided the true extravascular lung water content. This assumption is questionable, in view of the various factors limiting the accuracy of the indicator dilution technique.

Using the plain chest roentgenogram, Milne and colleagues[41] have recently been able to differentiate pulmonary edema due to heart disease, chronic renal failure or iatrogenic overhydration, and acute lung injury (increased-permeability edema) with an accuracy of 80 to 90 percent.

The radiographic method has obvious advantages. The chest roentgenogram is easily available and repeatable and can be obtained in ambulatory patients, as well as in critically ill patients. In addition, the roentgenogram provides information on the spatial distribution of pulmonary edema. On the other hand, the radiographic technique has some limitations. The subjectivity of interpretation of the roentgenogram is not negligible, although the discrepancy between observers can be reduced by the use of multiple radiographic criteria.[41] A significant problem in the clinical use of the radiographic technique is the variable quality of roentgenograms obtained under routine conditions. Additional limitations are imposed by other factors capable of affecting the interpretation of the chest roentgenogram, *ie*, position of the patient,[41] lung volume (*eg*, variations associated with mechanical ventilation and PEEP[42]), and the presence of other radiographic abnormalities (*eg*, obstructive lung disease).

Recent Approaches to Measuring Lung Water

Several additional techniques have recently been applied to the assessment of lung water. Although these techniques are still in a preliminary phase of development, they deserve a brief mention because at least some of them might have clinical value in the future.

A quantitative approach to the assessment of lung water content is the measurement of lung density. Lung density, which is normally low because of the characteristic structure of this organ, increases markedly with the accumulation of water in pulmonary edema. Lung density has been estimated in experimental animals and in humans by x-ray densitometry,[38] gamma-ray densitometry,[43] Compton scatter densitometry,[44,45] computed tomography,[46,47] and positron tomography.[48,49] As expected, lung density has been found to increase markedly with pulmonary edema in various animal models[38,43,45,46] and in cardiac or noncardiac patients.[44,47] Spatial and frequency distributions of lung density have also been described using computed tomography in animals with experimental pulmonary edema and in humans (normal subjects and patients with various lung conditions, including acute lung injury).[46,47] A good agreement has generally been found between lung density (gamma-ray densitometry, Compton scatter densitometry, or computed tomography) and gravimetric measurements of lung water;[43,45,46] however, the correlation between x-ray density and gravimetric data is less satisfactory.[38]

Basic principles, specific advantages, and limitations of the techniques for the measurement of lung density are discussed in detail elsewhere.[43,45-48] Limitations common to all of the densitometric techniques are the dependence of density values on the degree of lung inflation and the inability to distinguish extravascular from intravascular lung density (unless more complex procedures are added to the basic measurement).[45,48,49] In addition, all of the previously mentioned densitometric techniques involve some degree of exposure to radiation. In terms of clinical application, x-ray densitometry would certainly be the most convenient technique; unfortunately, the results of validation studies are not encouraging.[38] Computed tomography is now widely available and, like x-ray densitometry, provides topographic information; however, lack of mobility prevents measurements at bedside. The Compton scatter technique is convenient in this respect, because the densitometer can be portable.[45]

Nuclear magnetic resonance techniques have been applied, especially in the imaging mode, to the study of lung water in excised lungs, intact living animals (normal or with various types of experimental pulmonary edema), and human subjects.[50] The regional and frequency distribution of lung water has been determined in experimental animals and in humans.[50] A good agreement has been reported between gravimetric data and measurements using nuclear magnetic resonance,[50] although the slope of this relationship may vary with the type of experimental lung injury;[51] the systematic underestimation of absolute lung water content observed in one study[52] may reflect the influence of removable technical factors. Magnetic resonance imaging offers several advantages because measurements are noninvasive and easily repeatable, provide information on the regional distribution of lung water, and do not involve the use of ionizing radiation. Limitations of the technique are its present inability to discriminate between intravascular and extravascular lung water and its complexity, lack of mobility, and sensitivity to several technical factors.[50] Although in principle, magnetic resonance imaging estimates total lung water content, an undefined fraction of intravascular lung water is presumably undetectable because blood flow affects the nuclear magnetic resonance signal if flow velocity is sufficiently high.[50]

In addition to lung density, positron tomography can provide measurements of regional extravascular lung water and has been tested in experimental animals; values for total and extravascular lung water correlate well with gravimetric measurements.[49] Because of its complexity, this technique at present shows limited potential for clinical application.

A microwave technique[53] has been used to detect and monitor changes in lung water (rather than absolute water content). The technique has potential for clinical application because measurements are noninvasive, and the instrumentation is portable; however, the available experimental data are still preliminary. Motion artifacts represent an important limitation.

Dynamics of Lung Fluid and Solute Exchange

Another potential development in the clinical assessment of lung edema could be the application of experimental methods designed to study the dynamics of pulmonary fluid and solute exchange. In lung injury the flow of water and solutes across the capillary membrane may increase markedly before lung water content becomes detectably abnormal; this discrepancy reflects a compensatory increase in lymph flow. Therefore, compared with the static methods discussed previously (which simply measure static water content), the dynamic methods are expected to be more sensitive to early abnormalities in lung fluid and solute balance. Some dynamic methods (for instance, the measurement of lymph flow in an animal preparation)[1], are valuable research tools; others, such as the external radioflux detection technique[54-56] (which is acceptably invasive and uses portable equipment), are potentially suitable for clinical application.

The external radioflux detection method measures the transvascular flux of tracer protein by counting external radioactivity. Various versions of this method have been tested in experimental animals[56] and in humans (including patients with acute respiratory failure and congestive heart failure).[54-56] Recent data suggest that the method is specifically applicable to the assessment of pulmonary vascular permeability (it detects no abnormalities in hydrostatic edema) and can demonstrate an increased transvascular protein leak when the lung injury is too mild to cause a significant increase in gravimetric water content.[56] Therefore, the measurement of transvascular protein leak can be expected to complement, rather than replace, the determination of lung water content. If applied clinically, the external radioflux detection method could provide valuable information, especially in early lung injury characterized by increased vascular permeability.

The permeability of the alveolar epithelium can be tested by instillation of radioactive indicators into the airways or, more practically for possible clinical applications, by inhalation of the indicators as an aerosol.[1] Recent data suggest that the radioaerosol technique may be helpful in differentiating between cardiogenic and noncardiogenic pulmonary edema.[57]

Conclusions

In analyzing the comparative clinical potential of the various techniques discussed previously, it is appropriate to consider the characteristics of an optimal method for measuring lung water. As stated in a recent workshop,[37] the ideal method should have the following requisites: (1a) *accuracy* and *reproducibility;* (1b) the method should measure extravascular lung water, to differentiate lung edema from pulmonary vascular congestion; (2) *sensitivity* (the method should detect early interstitial lung edema, because the diagnosis of advanced alveolar edema is not a difficult problem); (3) *noninvasiveness* (this requisite is not absolute; see subsequent discussion); (4) *convenience* (reliability, simplicity of operation, portability, and ability to provide rapid on-line measurements are highly desirable characteristics for a clinical method); and (5) *low cost.* In addition, the method should involve no hazard to the patient (for instance, exposure to ionizing radiation). Ability to provide information on the regional distribution of lung water is also a desirable feature. Some of the previous requisites are not absolute, depending on the clinical setting; for instance, the invasiveness of the thermal-dye technique may not preclude its use in critical care. On the other hand, lack of mobility precludes the bedside application of computed tomography or magnetic resonance imaging in the critical care unit but is not an impediment to the use of these techniques, for instance, in ambulatory patients at risk of developing pulmonary edema; however, even if these qualifications are taken into account, it is clear that none of the available techniques for the assessment of lung water meets all of the previously mentioned criteria. This in part explains the presently limited application of these techniques (with the exception of chest roentgenology) in clinical medicine. In addition, there is considerable controversy as to whether a general clinical application of measurements of lung water is really justified. In a group of patients with acute respiratory failure and pulmonary edema, Brigham and associates[58] found that the extravascular lung water content (measured by an indicator dilution technique) was not correlated with arterial oxygen tension and did not predict the outcome; they attributed their observations to a compensatory response to hypoxia. A poor correlation between arterial oxygen tension, or the alveolar-arterial oxygen tension gradient, and extravascular lung water has also been reported by others in experimental animals[10] and in humans.[20] These findings raise some questions about the prognostic value of measurements of lung water, although the findings may simply reflect the limitations of the indicator dilution technique. The poor correlation between arterial oxygen and lung water content suggest that measurements of lung water may provide additional independent information in patients with pulmonary edema; however, these measurements are justified only if a convenient and noninvasive technique can be used. Presently, quantitative roentgenography can best serve this purpose. There is no convincing evidence that the systematic use of other available methods for the study of lung water is indispensable for the clinical assessment and the management of pulmonary edema, although some reports provide examples of practical applications of these methods.[15,16,18,19]

To conclude the present discussion with some predictions, the evaluation of the chest roentgenogram can be expected to remain, at least in the near future, the most generally accepted approach to the clinical assessment of lung water. It is hoped that the use of quantitative criteria in the interpretation of the chest roentgenogram will become more widespread and appropriately standardized. The chest roentgenogram is a traditional complement to the clinical examination, which still maintains a role in detecting and following pulmonary edema. Lung sounds can be recorded and studied objectively by time and frequency domain analysis.[59] Other available methods for measuring lung water (especially the thermal-dye dilution technique) will possibly have some role in clinical medicine as special procedures; their selection will continue to depend on the specific user's goals and on the clinical setting.

This outlook may be changed by the advent of new innovative techniques. In this respect, the potential of recent advanced technologies should not be underestimated. Computed tomography and magnetic resonance imaging are becoming increasingly available; since preliminary experimental data indicate that these techniques can provide quantitative estimates of lung water content and distribution, they should be further developed, standardized, and tested for clinical application. The use of methods developed to estimate the permeability of the alveolar-capillary barrier could contribute additional sensitivity and specificity to the clinical assessment of pulmonary edema.

The number of references is kept to a minimum for reasons of space. A more complete list of references can be obtained, on request, from the author. Additional references can be found in the article cited in reference 37.

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