Determination of lung water content and distribution by nuclear magnetic resonance imaging

Antonio G. Cutillo, MD, Alan H. Morris, MD, David C. Ailion, PhD, Carl H. Durney, PhD, and Thomas A. Case, BS

NMR imaging techniques are applicable to the assessment of lung water content and distribution because the NMR signal is, under certain conditions, proportional to tissue proton density. NMR imaging is noninvasive, easily repeatable, free from ionizing radiation, and particularly suitable for the assessment of spatial lung water distribution. Lung water content and distribution have been estimated in excised animal lungs and in intact dead or living animals, under normal conditions and in various types of experimental pulmonary edema. Excised human lungs and human subjects have also been studied. Published data indicate that measurements of lung water content by NMR imaging techniques are feasible. These techniques estimate lung water spatial distribution with satisfactory accuracy and excellent resolving power. The application of NMR imaging techniques poses several problems and limitations, but available data suggest that most of the problems can be solved. NMR imaging has the potential to become a powerful tool for lung water research. Prospects of clinical application are also encouraging; numerous applications can be foreseen, although lack of mobility of NMR imaging systems may be a significant limitation in critical care medicine.

INTRODUCTION

Nuclear magnetic resonance (NMR) techniques, which are based on the magnetic properties of certain atomic nuclei, have found important applications in experimental and clinical medicine. Proton NMR is of great interest in this respect, particularly because the magnetic properties of hydrogen protons have been utilized to develop promising imaging techniques (although proton NMR can also be applied in a nonimaging mode). The principles of proton NMR have been discussed in numerous recent publications[1–10] and are summarized in the Appendix, at the end of this article.

An important application of NMR imaging techniques is the determination of lung water content and distribution (water content can also be measured using NMR in a nonimaging mode). This application is based on the principle that, under certain conditions, the NMR signal is directly related to proton density and therefore can be a measure of tissue water concentration. Because of the widespread interest in noninvasive methods for the determination of lung water, the potential of NMR in this respect has been explored by several groups. Although the results of the above studies are promising, the available data are largely preliminary, and the development of accurate, standardized methods for determining lung water content and distribution is still in progress.

SIGNIFICANCE OF LUNG WATER MEASUREMENTS

Measurements of lung water content are of obvious important in research. Interstitial and intraalveolar water accumulation is an essential component of the limited spectrum of lung reaction to injury. Experimental models of pulmonary edema produced by increased pulmonary intravascular pressure[11] or by toxic agents increasing pulmonary microvascular permeability (alloxan, o-naphthylthiourea, oleic acid, *E. coli* endotoxin, etc.)[12–14] have been studied in various animal species. In these studies, lung water measurements can be used to quantify the severity of pulmonary injury. Although lung water content can be accurately determined by the classic gravimetric technique,[15,16] studies of experimental pulmonary edema have suffered from lack of nondestructive methods capable of providing accurate and easily repeatable measurements. Convenient methods for the assessment of lung water distribution are also needed, because pulmonary edema tends to be gravity dependent,[14] and lung injury caused by various toxic agents may be characterized by different patterns of distribution of water accumulation.[17] [Certainly hydrostatic pulmonary edema is gravity dependent but there is a good deal of evidence that capillary permeability edema can be distributed non-gravitationally and, once present, does not shift with gravitational change.—Ed.]

AGC: Department of Internal Medicine, University of Utah. AHM: Department of Internal Medicine, University of Utah; and LDS Hospital. DCA, TAC: Department of Physics, University of Utah. CHD: Department of Electrical Engineering, University of Utah, Salt Lake City, Utah.

Reprints: A. G. Cutillo, Division of Respiratory, Critical Care & Occupational Pulmonary Medicine, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, UT 84132.

This work was supported in part by National Heart, Lung, and Blood Institute Grants 3-R01-HL-23746 and 5-R01-HL-31216.

J Thorac Imag 1986;1(3):39–51

Although pulmonary edema is an extremely common occurrence in medicine, the clinical significance of lung water measurements is more controversial, at least from a practical point of view. In a group of patients with acute respiratory failure and pulmonary edema, extravascular lung water measured by an indicator dilution technique was not correlated with arterial oxygenation and did not predict the outcome.[18] This finding, which likely reflects a compensatory mechanism preserving oxygenation (decreased perfusion to poorly ventilated edematous regions of the lung), suggests that water accumulation is not the sole determinant of respiratory impairment in pulmonary edema, and may limit the prognostic value of lung water measurements. Even if this dissociation between lung water content and arterial oxygen is confirmed by more extensive evidence, the application of lung water measurements will provide additional information and is justified provided the measurements can be made simply and atraumatically. Additional clinical studies in larger series of subjects and at multiple stages of water accumulation are clearly needed. [The degree of "dissociation" between quantity of edema and arterial oxygenation appears to be greatest in patients with permeability edema, less in patients with cardiogenic edema, and least in patients with overhydration or renal edema. For example, in permeability edema even with small to moderate quantities of edema arterial oxygen may be very low whereas in overhydration, even with large quantities of edema, arterial oxygen may be little affected. The single most important linking factor that appears to explain these differences is perfusion. In permeability edema actual vascular blockage is present. In cardiac failure, pulmonary blood flow is diminished but still present, whereas in overhydration pulmonary blood flow is increased. If one is able to determine which type of edema is present, one will then have a clearer idea of the relationship between lung water and arterial oxygen. We agree strongly with Cutillo's statement that studies of larger series of patients at multiple stages of lung water accumulation are needed—Ed.] Determinations of regional lung water distribution as a function of time (during water accumulation and recovery) in different types of pulmonary edema (eg, high-pressure versus increased permeability edema) are also required. With the exception of quantitative analysis of plain chest radiographs,[19–21] the clinical potential of methods capable of providing noninvasive, relatively rapid and easily repeatable measurements of lung water content and distribution is virtually unexplored.

Emphasis has recently been placed on the need to develop clinical methods capable of assessing the dynamic aspects of lung liquid and solute exchange.[22] Compared with static lung water content measurements, dynamic methods would detect abnormalities of liquid balance at an earlier stage of disease. However, since the effects of factors protecting lung liquid balance (for instance, lymph flow) are, at present, not clinically measurable or quantitatively predictable, determinations of lung water content would also be required at some stage of the disease, to assess the extent of fluid accumulation. The value of lung water content measurements, relative to that of determinations of liquid and solute exchange, with respect to the prediction of patient outcome, is unexplored.

METHODS FOR MEASURING LUNG WATER

Available techniques for the measurement of lung water content are listed below:

- Gravimetric technique[15,16]
- Histology, morphometry[16,23–25]
- Double indicator-dilution technique[16–17,23,26–29]
- Soluble inert-gas technique[16,30,31]
- Radiographic method[16,19–21,23]
- Radiographic-helium dilution method[32]
- Transthoracic electrical impedance technique[16,23,33–35]
- Microwave technique[36,37]
- Compton-scatter densitometry[38,39]
- Computerized axial tomography[40,41]
- Positron emission tomography[42,43]
- Transthoracic γ-ray attentuation[44]
- Nuclear magnetic resonance techniques (see text)
- External radioflux detection[45–47] (This method measures pulmonary transcapillary protein flux, but has also been used to determine lung water distribution.[45])

A systematic discussion of the non-NMR methods for measuring lung water is beyond the scope of the present article. In general, all of the non-NMR methods present limitations affecting their accuracy or their range of applications. Examples of these limitations are destructiveness (gravimetry, histology); invasiveness (indicator dilution technique, external radioflux detection); exposure to ionizing radiation (radiologic methods, indicator dilution techniques, external radioflux detection, positron emission tomography); dependence on the distribution of perfusion (indicator dilution techniques) and ventilation (soluble gas technique); sensitivity to extraneous factors, such as changes in body position or level of lung inflation (transthoracic electrical impedance and microwave techniques, radiological techniques, Compton scatter densitometry); and accuracy limited to relative changes in water content (transthoracic electrical impedance and microwave techniques).

Compared with other available methods for measuring lung water, the NMR techniques offer several advantages. NMR lung water measurements are nondestructive and noninvasive; in addition, they are relatively rapid and easily repeatable. Detection of lung water by NMR techniques is not dependent on

ventilation and perfusion. This is an important advantage because, for instance, perfusion dependence (failure of injected indicators to reach poorly perfused or unperfused lung regions) significantly limits the accuracy of the indicator-dilution technique, especially in pulmonary edema, leading to a systematic underestimation of lung water content.[16] Since the NMR image contains spatial information, NMR imaging is particularly suitable for quantifying the regional distribution of lung water. Finally, the NMR method does not involve the use of ionizing radiation. The most important limitations of NMR imaging of lung at the present stage of development, are its susceptibility to errors due to cardiorespiratory motion and its inability to discriminate between intravascular and extravascular water.

NMR TECHNIQUES FOR LUNG WATER STUDIES

A detailed description of the imaging and nonimaging NMR systems and methods used to study lung water is beyond the scope of the present article and can be found in specific reports and in numerous general publications.[1-6,8-10,48,49] Basically, NMR imaging systems consist of a resistive or superconductive magnet to apply the static magnetic field, an NMR pulse spectrometer to produce the signal, gradient coils and associated drivers to provide spatial resolution, and a computer subsystem to generate the NMR pulses and display and analyze the data. Nonimaging systems are essentially similar, consisting of the same basic components with the exception of the gradient coils.

Several investigators[50-61] have used imaging techniques based on the spin-echo pulse sequence.[4,6-10] This sequence is characterized by a 90° rf pulse followed by a 180° "refocusing" pulse, which produces an echo signal (Fig 1) by reversing the loss of coherence between precessing protons due to inhomogeneity of the external magnetic field or to applied magnetic field gradients (see Appendix). Important variables in the spin-echo sequence are the echo time (TE) between the 90° pulse and the spin echo, and the repetition time (TR) between the 90° pulses of consecutive 90°-180° sequences, repeated for averaging; TR is largely the time required to allow T_1 relaxation between repeated pulse sequences.

A line-scan imaging technique[62] has been applied to assess lung water content and distribution in excised rat lungs and in intact living rats.[51,54,55] In this technique, which is based on the application of three orthogonal magnetic field gradients and a selectively irradiating 90°-180° pulse sequence to produce a spin echo, a two-dimensional image is obtained from a series of one-dimensional line scans (each line scan representing a narrow pencil-shaped region of the specimen). Planar imaging techniques are more efficient than the line-scan method because they can obtain data from a whole plane (a slice of the specimen) at one time. The spin-warp imaging technique,[1,63] a version of the two-dimensional Fourier transform technique which has been used to estimate lung water content in experimental animals (sheep),[58] excised human lungs,[57] and living human subjects,[58] is based on the application of a selective 90° rf pulse and three orthogonal field gradients; the protons in the selected plane are frequency-encoded (along the X direction) and phase-encoded (using a variable amplitude Z gradient). A set of spin echoes is obtained, from which a two-dimensional image of the plane is generated by Fourier analysis. The combination of frequency and phase encoding provides spatial information within the selected plane. A two-dimensional Fourier transform technique using a different pulse sequence to obtain spin echoes[64] has been applied to the assessment of lung water distribution in human subjects.[54,55,61] Compared with the planar techniques, the line scan method is less affected by errors due to artifacts from the chest wall; this represents a significant advantage for lung studies.

Multislice imaging[64,65] further improves the efficiency of the NMR technique. In this method, spin-echo sequences are sequentially applied to multiple adjacent slices of the specimen during TR (which is much larger than TE); therefore, multiple images are obtained during TR (instead of one, as in the standard spin-echo technique), thus substantially reducing the data acquisition time. Multislice NMR imaging has been used for lung water studies in animals and humans.[53]

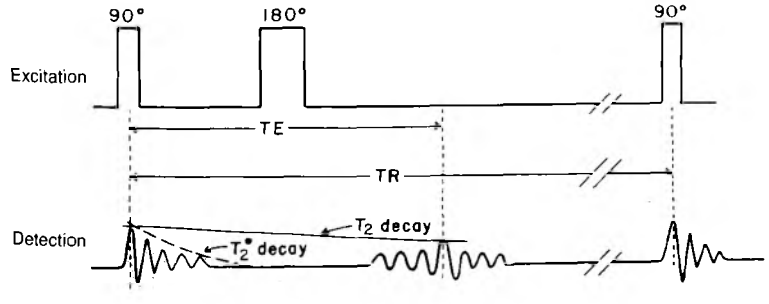

Fig 1. Spin-echo pulse sequence. T_2 = spin–spin relaxation time; T_2^* = transverse relaxation time (including effects from magnetic field inhomogeneity); TE = echo time; TR = repetition time. Reprinted with permission from Scherzinger AL, Hendee WR: Basic principles of magnetic resonance imaging—an update. *West J Med* 1985;143:782–792.

The spin-lattice relaxation time T_1 has been determined in various investigations of lung water[59,60,66–72] using the saturation recovery pulse sequence (90° rf pulse at variable intervals after a saturating 90° pulse)[7–9,73] or the inversion recovery (180°-90°) pulse sequence.[2,3,7–9,73] T_2 has been determined[59,60,72] using the Carr-Purcell sequence (a 90° pulse followed by repeated 180° pulses, to obtain a series of spin echoes).[73]

NMR LUNG WATER MEASUREMENTS: ANIMALS AND HUMANS

In 1976, Lauterbur and associates[66–69] reported the results of studies of the relation between the spin-lattice relaxation time T_1, and gravimetric lung water content. In normal and edematous dog lungs, these investigators found a linear relation between spin-lattice relaxation rate ($1/T_1$) and dry-to-wet lung weight ratio. On the basis of these data, they concluded that NMR imaging could be applied to the quantitative assessment of pulmonary edema.[66] The relation between T_1 and gravimetric and lung water content has recently been confirmed by various investigators[59,60,71,72] in imaging and nonimaging studies of excised and in vivo lungs from various animal species (rabbit, dog, rat). A correlation between T_2 and gravimetric lung water content has also been observed, although less consistently.[59,60,72] More generally, Ling and Tucker[70] showed a relationship between T_1 and gravimetric water content in various mouse and rat tissues, including lung. Results of numerous lung T_1 and T_2 measurements in man and various animal species have recently been tabulated by Bottomley and coworkers.[74]

A close linear relation between NMR signal intensity and gravimetric water content has also been demonstrated by NMR spectroscopy in small samples of rat[50] and sheep[58] lung tissue.

Hayes and associates[50] tested the feasibility and validity of NMR measurements of lung water content and distribution in a phantom and in normal or edematous rat lungs, using a line-scan imaging technique.[62] Using known water concentrations in the phantom as the reference standard, the error of measurement was, on the average, less than 5% (0% to 12% under various conditions, including simulation of a pleural effusion). Good agreement was also found between NMR and gravimetric data in excised rat lungs. Regional lung edema, simulated by intrabronchial saline instillation, was detected in excised and in situ rat lungs.

In another study,[51] the distribution of lung water was assessed by the same line-scan technique[62] in small rat lung tissue specimens. Absolute lung water content was obtained from the NMR signal intensity and compared with spatially matched gravimetric measurements. The study showed a good correlation between the data obtained by the two methods; the results also demonstrated the excellent spatial resolution achievable by the NMR imaging technique (water content differences were detected between lung tissue slices of 0.076 mL).

MacLennan and coworkers[58] directly estimated the water content of excised sheep lungs using a spin-warp pulse sequence and found that their NMR values tended to be lower (by about 20%, on the average) than gravimetric water content; factors possibly contributing to this discrepancy are discussed below.

In anesthetized living sheep, Carrol and coworkers[53] estimated lung water content from measurements of the NMR signal intensity by a spin-echo imaging technique. They tested the effects of some technical factors (repetition time, cardiac gating in combination with respiratory gating) on NMR signal intensity. In addition, they found a gradient of relative signal intensity which was related to gravity (with the animals in the prone or supine positions); a similar gradient was observed in dogs by Hedlund and colleagues.[56] Since extravascular water is apparently not gravity dependent in normal lungs in vivo,[14,75] the gradient may reflect a variation in the intravascular compartment. The gradient is consistent with the gravity-dependent pattern of distribution of pulmonary blood flow.[75] In the study of Carrol and colleagues,[53] NMR signal intensity increased in sheep with high-pressure pulmonary edema induced by inflation of a balloon catheter in the left atrium; the increase in signal intensity was related to gravity, presumably reflecting the distribution of extravascular lung water, which is gravity dependent in pulmonary edema.[14] Similar data were obtained by Nicholson and coworkers[76] in a dog model of pulmonary edema. Schmidt and coworkers[59] performed in vivo NMR imaging studies of normal and edematous rat lungs (oleic acid-induced pulmonary edema) using the spin-echo technique, and observed a good correlation between NMR signal intensity and gravimetric lung water content.

The representation of lung water distribution as a function of spatial position is a conventional approach, analogous to ventilation and perfusion maps obtained by radioisotope techniques. In addition to this approach, a new display of the NMR data has recently been proposed,[54,55] which describes the distribution of lung water as a function of water density ρH_2O. The new method displays the distribution of fractional lung volume V_f (number of pixels at a given density divided by the total number of pixels) with respect to water density ρH_2O (water content per unit volume). Therefore, the display is a normalized frequency distribution of ρH_2O. Theoretically, ρH_2O is expected to vary from 0 g/mL (air) to about 0.8 g/mL (blood and solid lung tissue). Fig 2 shows the V_f versus ρH_2O distribution in a coronal plane through an excised rat lung at two levels of inflation. The average value of ρH_2O at an inflation pressure of 20 cm H_2O compares well with the water density value of 0.13 g/mL, estimated from morphometric measurements.[77] Fig 3 compares the V_f versus ρH_2O distribution in excised lungs from a normal rat and from a rat with oleic acid-induced pulmonary edema (characterized by marked spatial nonuniformity in lung water content).

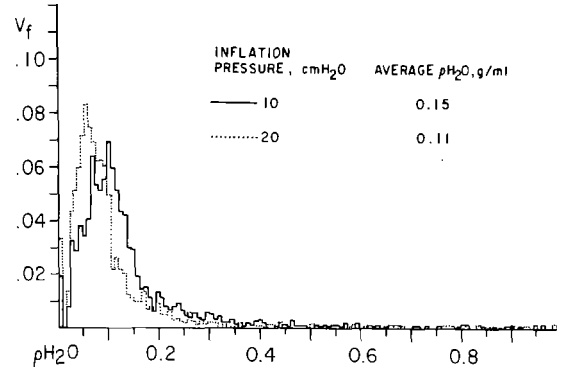

Fig 2. Distribution of fractional lung volume V_f with respect to water density ρH_2O (water content per unit lung volume, g/mL) in a coronal section through an excised lung preparation from a normal rat; V_f is expressed as number of pixels at a given ρH_2O divided by total number of pixels. Data obtained at two levels of lung inflation.

Similar observations have been made in intact live rats (with normal lungs or pulmonary edema). Abnormal V_f versus ρH_2O distributions have also been obtained in other types of experimental pulmonary edema, for instance after intrabronchial instillation of saline.[54,55] It should be pointed out that the conventional spatial display and the density distribution are complementary (rather than competitive) approaches, each defining a different aspect of lung water distribution.

Studies of lung water content and distribution in humans are still preliminary. Johnston and colleagues[57] measured proton density and T_1 by the spin-warp technique[63] in excised normal or abnormal human lungs. They demonstrated a significant increase in proton density in edematous lung areas, relative to normal areas. Interestingly, Johnston and co-workers found no differences in T_1 between normal and edematous lungs. Published data obtained from in vivo lung water measurements in humans are very limited. Carrol and colleagues[53] and Lallemand and colleagues[52] preliminarily measured NMR lung signal intensity in human volunteers, to assess the influence of some technical factors (repetition time, cardiac and respiratory gating) and gravity, also studied in sheep. They confirmed in humans the finding of a gravity-dependent gradient of signal intensity in the supine and prone positions, probably reflecting a redistribution of pulmonary perfusion.[75]

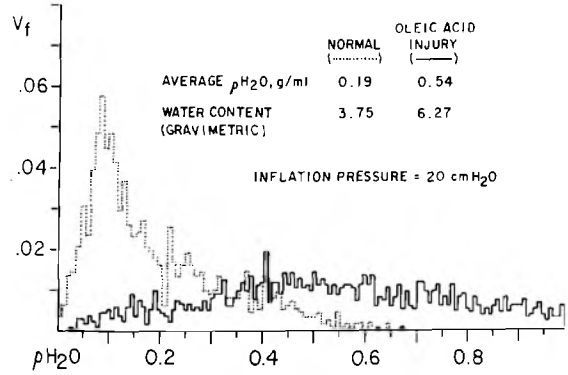

Fig 3. Distribution of fractional lung volume V_f, with respect to water density, ρH_2O (see Fig 2 for further details), in coronal sections through excised lungs from a normal rat, and from a rat with pulmonary edema induced by oleic acid injection (0.23 mL/kg, intravenously). Results of gravimetric measurements (right lung) are expressed as lung water content per unit dry lung weight.

The distribution of fractional lung volume as a function of water density (V_f versus ρH_2O, obtained from data collected by a two-dimensional Fourier transform technique),[64] has recently been described in normal subjects.[54,55,61] However, results of absolute lung water content measurements by the spin-warp technique have been disappointing,[58] the NMR values being only 60% to 80% of those expected on the basis of postmortem gravimetric determinations (and even less, if values are compared with in vivo total lung water content). The measurement error may reflect the influence of several factors, including partial saturation of lung tissue (one-second pulse repetition time), motion artifacts, loss of signal due to blood flow, and underestimation of peripheral lung tissue at the boundary with the chest wall.

NMR BEHAVIOR OF INFLATED LUNG

Recent studies[78–81] have shown that the NMR free induction decay (FID) of inflated lungs is short, compared with that of airless lung or solid organs, for example liver.[80(Fig 1)] Theoretical and experimental data[61,78–81] suggest that the short FID reflects the presence of internal (tissue-induced) magnetic field inhomogeneity (as opposed to external, magnet-induced inhomogeneity). This internal inhomogeneity is likely due to local differences in magnetic permeability, reflecting the diamagnetic properties of air and water, at the alveolar (air/water) interfaces of the inflated lung. The degree of shortening of the FID is likely related to the ratio of the total surface area of the air/water interface to the volume of solid lung tissue; therefore, this NMR property of the lung has interesting morphometric implications, still to be explored. The results of calculations based on a lung model characterized by spherical air bubbles in a water medium show good agreement with those of studies on phantoms consisting of spherical glass shells filled with water.[61]

The above observations have led to the development of a contrast technique based on the application of symmetric and asymmetric spin-echo sequences to produce a pair of images from which a subtraction image is obtained.[61,78–81] The subtraction image likely reflects the signal from water experiencing the air/water interface effect. Figs 4 and 5 show pairs of images, and the corresponding subtraction images,

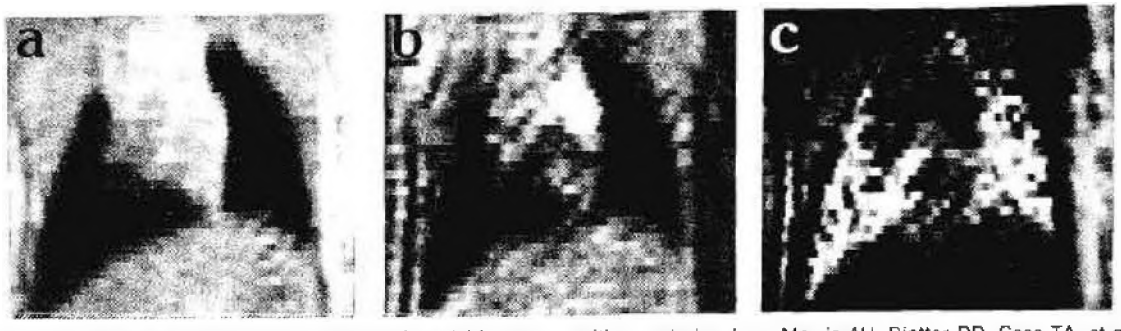

Fig 4. Coronal sections through an intact dead rat. **(a)** Image produced with symmetric gradients. **(b)** Image produced with asymmetric gradients. **(c)** Subtraction image [**a-b/a**]. Reprinted with permission from Morris AH, Blatter DD, Case TA, et al: A new nuclear magnetic resonance property of lung. *J Appl Physiol* 1985;58:759–762.

obtained in intact rats. In these images, the mediastinal structures and the chest wall are removed by subtraction (Figs 4c and 5c). The symmetric image from a rat with experimental pulmonary edema (Fig 5a) shows areas of increased density in the right and left lower lobes and in both perihilar regions. The subtraction image (Fig 5c) suggests that the regions of increased density in the lower lung are partially inflated (water protons are affected by the air/water interface); in contrast, the perihilar densities, which are removed by subtraction, likely represent nonaerated lung (intraalveolar edema or complete lung collapse). The new subtraction technique has several potential applications, including image enhancement of lung tissue (the signal from solid tissues becomes less intense or disappears in the subtraction image), quantitation of regional lung inflation, and assessment of the distribution of lung water according to its position with respect to the lung gas/tissue interface (which may enhance the discrimination between interstitial and intraalveolar edema).

ESTIMATION OF LUNG WATER CONTENT FROM NMR DATA

The published data reviewed above show that lung water content has been estimated by two criteria: indirectly, by measuring the NMR relaxation times T_1 and T_2; and directly, from the intensity of the NMR magnetization (proton density).

Relaxation times

Estimation of lung water from T_1 or T_2 measurements is supported by experimental evidence indicating that in animal tissues T_1 and T_2, or the more frequently used reciprocals $1/T_1$ and $1/T_2$ (relaxation rates), vary with water content[59,60,66–69,72–74,82,83]; this relationship is also predictable from models describing the state of water in biologic systems.[82,83] However, the relaxation times T_1 and T_2 are also affected by numerous factors, which have been classified by Mathur-De Vré[84] as intrinsic biologic factors, extrinsic physical factors and data treatment.

Animal tissues contain two fractions of water: free water and water associated with biologic macromolecules (bound water). Because of its interaction with macromolecules, bound water exhibits restricted motion.[73,74,83–88] Assuming a fast exchange of protons between free and bound water compartments,[82–84,89] the spin-lattice relaxation rate $1/T_1$ for a given tissue is a weighted average of the relaxation rates of the two phases

$$1/T_1 = X_f(1/T_1)_f + X_b(1/T_1)_b$$

where $(1/T_1)_f$ and $(1/T_1)_b$ are the relaxation rates for

Fig 5. Coronal sections through a sedated living rat (spontaneously breathing), 1 hour after injection of 0.23 mL/kg oleic acid intravenously (**a,b,c**, see Fig 4). Reprinted with permission from Morris AH, Blatter DD, Case TA, et al: A new nuclear magnetic resonance property of lung. *J Appl Physiol* 1985;58:759–762.

free and bound water, and X_f and X_b are the respective water fractions. In animal tissues the overall relaxation rate $1/T_1$ is significantly affected by $(1/T_1)_b$, which is much greater than $(1/T_1)_f$. Therefore, the overall relaxation time T_1 is markedly influenced by a change in the ratio of free to bound water. An increase in water content, associated with an elevated ratio of free to bound water, can be expected to cause a large increase in T_1. The "relaxation time amplification effect"[82,84] due to the magnitude of $(1/T_1)_b$ is illustrated by the empirical relationship described by Mansfield and Morris[82]: $\Delta T_1 = 7.94\Delta X$, where the constant 7.94 is in seconds. The expression shows that a small variation in fractional water content is associated with a large variation in T_1. The spin–spin relaxation time T_2 is also affected by macromolecular-water interactions. Because of the aforementioned biologic factors, T_1 and T_2 differ from tissue to tissue, and in the same tissue under various physiologic or pathologic conditions.[6,59,60,66–70,72–74,84] The differences depend not only on total water content and state of water, but also on other factors, such as the presence of nonwater protons (for instance, lipid protons)[6,81,90,91] and that of paramagnetic substances (for instance, molecular oxygen or manganese)[1,6,73,84]; the effects of a paramagnetic compound, the gadolinium-DTPA (diethylenetriaminepentaacetic acid) complex, on T_1 and T_2 have recently been studied.[59,92–94]

The effect of extrinsic factors (eg, frequency and temperature dependence) and sample or data treatment (eg, in vitro vs in vivo measurements, analysis of magnetization decay/growth curves) are extensively discussed by Mathur-De Vré[84] and Bottomley and coworkers.[74] The problem posed by multiexponential magnetization decay curves is considered below.

For the purposes of the present discussion, it is of interest to consider the above concepts with respect to the lung. The pulmonary interstitial space contains a dense matrix consisting of collagen, elastin, and proteoglycans[95–99]; therefore, a fraction of the interstitial water is associated with these and other macromolecules (including plasma proteins), while the remaining water is present in the free state.[73,85,87] Interstitial water accumulation in pulmonary edema leads to disruption of the matrix,[11,97] presumably with an increase in the free water fraction. As discussed above, this can be expected to cause a large increase in T_1; therefore, T_1 measurements should be a sensitive detector of pulmonary edema. Some published data support this prediction, showing a marked increase in T_1 with lung water accumulation[59,60,66,72]; however, other data do not confirm the above observations.[57] A systematic comparison of the relative sensitivity of various NMR parameters to changes in lung water content would be of considerable interest.

Proton density

As indicated above, lung water quantitation by the NMR method is based on the principle that the intensity of the NMR signal is proportional to the concentration of hydrogen nuclei (proton density) in the specimen. According to this principle, water density (water content for unit volume) is obtained by comparing the NMR signal from the specimen with that from pure water. However, NMR signal intensity is also dependent on the proton relaxation times T_1 and T_2, blood flow, and other factors (presence of nonwater protons and paramagnetic substances). The effect of the paramagnetic compound gadolinium-DTPA on the intensity of the NMR signal from normal and edematous lungs in living rats has recently been studied by Schmidt and coworkers[59]; the data obtained by these investigators, and their implications with respect to the determination of lung water, are considered below. In the simplest case, following a radiofrequency pulse, the intensity of the NMR signal decays exponentially with a characteristic time T_2. On the other hand, since the longitudinal component of magnetization returns to its equilibrium value with a characteristic time T_1, the amplitude of the NMR signal will be reduced if TR (time between consecutive rf pulse sequences) is too short to allow full recovery of magnetization.

Blood flow affects the NMR signal by various mechanisms related to motion of proton spins; these mechanisms have recently been reviewed.[48,100–102] The effects of blood flow are complex, varying with flow velocity and different NMR imaging techniques; blood flow is usually associated with a decrease in signal intensity, but an enhancement is also possible, under certain conditions.[48,100] In experimental animals and in humans, Lallemand and coworkers[52] and Hedlund and coworkers[56] have demonstrated changes in the intensity of the NMR signal from lungs related to the cardiac cycle; likely, these changes at least in part reflect the behavior of pulmonary blood flow.

On the whole, using the spin-echo technique as an example, the effects of the above factors on NMR signal intensity (I) can be described by the following equation:

$$I = N_{(H)}f(v)(e^{-TE/T_2})(1-e^{-TR/T_1})$$

where $N_{(H)}$ is proton density, f(v) a function expressing the effect of blood flow, T_1 and T_2 the spin-lattice and spin–spin relaxation times, respectively, TE and TR the spin echo delay and the repetition time, respectively.

The above equation indicates that accurate lung water measurements require appropriate correction of signal intensity on the basis of the T_2 value for the sample and the selected TE. The simple assumption of a T_2 value from published data is probably inadequate, especially for lung water measurements, because T_2 has been shown to vary with lung water content.[59,60,72] In recent measurements of water content and distribution in excised rat lungs and in living rats by a line-scan spin echo technique,[51,54,55] the signal intensity was corrected for the T_2 decay, assumed to be de-

scribed by a single-exponential curve. This assumption is based on the results of measurements of spin-echo amplitude at various echo times.[51] The above correction procedure is approximate, because published evidence indicates that the T_2 relaxation process may be multi-exponential[74,82,84,88,103]; this finding is consistent with the heterogeneity of biologic systems characterized by multiple water compartments.[82–84,86,88,103] However, the assumption of a single-exponential T_2 decay curve appears to be a reasonable approximation in lung water measurement, as indicated by the good agreement observed between NMR lung water values based on this assumption and gravimetric data.[51]

The importance of the relation between T_1 and NMR signal intensity is demonstrated by the data of Carrol and coworkers[53]; in experiments on humans and sheep these investigators found that a variation in repetition time from 0.5 to 3.5 seconds was associated with an average 160% increase in signal intensity. The T_1 dependence of NMR signal intensity can be taken into account, in lung water content measurement, by using repetition times largely exceeding the T_1 value for the sample, to allow complete recovery of the longitudinal component of magnetization.

Repetition times of 3 to 4 seconds should be sufficient for this purpose, being at least four- to fivefold larger than the T_1 values measured in normal lungs from various species.[74] Measurements in normal excised rat lungs have shown that the T_1 dependence of NMR signal intensity is practically negligible at repetition times exceeding 4 seconds (D.C. Ailion and colleagues, unpublished observations). Repetition times of 3 to 4 seconds should also provide a reasonable safety margin for lung water measurements in pulmonary edema, which is associated with an increase in T_1[59,60,66–69,71,72]; T_1 values as high as 0.9 second have been reported in edematous dog and rat lungs.[59,60,66,72] The long T_1 of lungs, especially in pulmonary edema, imposes a substantial increase in data acquisition time. In addition, a long repetition time tends to enhance the effects of motion on the NMR images.[53]

If a reduced data acquisition time is desirable, the repetition time can be decreased and the NMR signal intensity can be corrected using an assumed T_1 value. This method has been used for water content determinations in normal excised rat lungs (in which separate measurements had shown a relatively narrow range of variation of T_1).[51] The accuracy of the correction is limited when larger changes in T_1 are associated with water accumulation in pulmonary edema; this limitation should be considered if short repetition times are used to maximize the ability of the NMR technique to monitor rapid variations in lung water content in pulmonary edema. As discussed above, the data acquisition time can also be reduced by multislice imaging,[64,65] in which multiple adjacent slices of the specimen are imaged during the relatively long repetition time. In in vivo NMR imaging studies of normal and edematous rat lungs, Schmidt and colleagues[59] found that the administration of gadolinium-DTPA complex enhanced the NMR signal intensity from edematous lung tissue in images obtained using a short repetition time (0.5 second); this effect is due to a marked shortening of T_1 produced by the gadolinium-DTPA compound. Therefore, as suggested by Schmidt and colleagues,[59] gadolinium-DTPA could be used to reduce data acquisition time.

The NMR data are presently not corrected for blood flow (this factor is further considered in the next section).

LIMITATIONS AND PROBLEMS IN LUNG WATER DETERMINATION BY NMR

The application of NMR imaging to quantitative studies of lung, in particular to the determination of lung water content and distribution, poses significant problems. In NMR proton imaging the signal from the lung is weak because of the low normal water density of this organ. Assuming normal average values for lung volume and water content,[22,104] lung water density can be expected to vary, in vivo, from 0.18 g/mL at functional residual capacity (resting end-expiratory volume) to 0.10 g/mL at total lung capacity. Because of this limitation (in addition to the problem posed by respiratory motion), some investigators have questioned the role of NMR imaging in the quantitative assessment of lung water, at least from a clinical point of view. In contrast, experimental studies reviewed above indicate that NMR imaging can provide quantitative estimates of lung water content and distribution. The discrepancy is at least in part due to technical factors. Most lung images in humans have been obtained at magnetic fields of 0.35 T or less. In contrast, some lung water measurements in experimental animals have been made at a magnetic field of 1.0 T,[50,51,54,55] and therefore at a better signal-to-noise level because the NMR signal increases with the strength of the magnetic field.[105,106] The relationship between signal-to-noise ratio and field strength has stimulated interest in imaging systems using higher magnetic fields. It has been shown that the contrast-to-noise ratio (difference in NMR signal between two tissues divided by the noise) also tends to increase with magnetic field strength, and human images have been obtained at 1.5 T.[105] Imaging systems for animal research can operate at fields exceeding 2 T. The use of higher magnetic fields can be expected to facilitate the application of the NMR imaging techniques to the determination of lung water, especially in human subjects. As reported above, quantitative NMR data have been obtained from lungs in human subjects using imagers operating at 0.35 to 0.5 T. However, several technical problems may set limits to high field imaging.[49,105,106]

A comparison of an imaging system recently used to measure lung water in excised rat specimens or in liv-

ing rats[62] with an imager currently used for human studies[64] shows differences (in addition to that in magnetic field strength) that are relevant to the problem of lung water determination. The animal system uses a line-scan technique with an echo time of 15 ms, whereas the human system uses the two-dimensional Fourier transform method, with a minimum echo time of 28 ms; assuming a T_2 of 30 ms for inflated lung, the irreversible signal loss associated with the echo time is 40% for the animal system versus 60% for the human system. Compared with the human imager, the animal system has a higher filling factor (the coil encloses the animal more tightly). In a solenoidal coil, the filling factor is a measure of the relationship between the volume of the sample and the volume of the coil; a high filling ratio increases the signal-to-noise ratio, but in human imaging this advantage is counterbalanced by decreased subject's comfort.

Recent data indicate that strict temporal symmetry of the gradient sequence is important for quantitative lung studies.[78-81] NMR measurements of inflated lungs are very sensitive to small degrees of asymmetry, which can be present and remain undetected in diagnostic and laboratory imaging systems. Estimates from FID determinations of fully inflated lungs indicate that the signal loss associated with asymmetries of 1 and 2 ms can be as high as 30% and 50%, respectively.

The effects of respiratory motion on NMR imaging have been studied in phantoms,[107-109] human subjects,[52,107,108,110,111] and experimental animals.[53,112] Respiratory motion degrades the image by producing various types of artifacts (blurring, phantom images). The magnitude of these effects depends on the breathing pattern[111] and on the particular NMR method used (for instance, two-dimensional Fourier transform techniques are more sensitive than the line-scan method to respiratory motion). Image degradation is reduced by respiratory gating (using the signal from a flow meter, thoracograph, abdominal belt, or thermistor),[53,107,110,111] which can be combined with cardiac (ECG) gating.[53,107,111] Respiratory gating significantly increases data acquisition time (100% or more, unless a special breathing pattern with prolonged postexpiratory pause is adopted).[107] Using mechanical ventilation synchronous with the pulse sequences and in combination with cardiac gating in dogs, Hedlund and associates[112] have recently obtained images comparable with those generated during apnea. A recent method, in which the amplitude of the phase-encoding gradient is approximately matched to the phase of the respiratory cycle, has recently been shown to be effective in removing artifacts due to respiratory motion[113] (N. Plec, personal communication).

Respiratory motion can also affect quantitative lung studies by altering the NMR signal. In vivo imaging studies of dog lungs have shown a higher signal-to-noise ratio during apnea than during mechanical ventilation.[60] In the two-dimensional Fourier transform techniques (including the spin-warp technique), motion has a signal-cancelling effect during signal averaging and can mix chest wall signal into lung regions; in addition, motion causes uncertainty in the definition of the lung margin at the boundary with the chest wall. As discussed above, motion artifacts may partly explain the low lung water values observed by MacLennan in healthy human subjects.[58] Uncertain lung margin definition induced by respiratory motion may also affect the line-scan technique[62] recently used to measure lung water distribution in living anesthetized rats,[54,55] but this effect is much less marked than in the spin-warp technique. On the whole, the role of respiratory motion in lung water determination is still inconclusive because of lack of systematic comparisons of measurements obtained with and without gating. Recent data suggest that nongated measurements satisfactorily monitor lung water changes in rats.[55] Carrol and coworkers[53] have obtained similar results in sheep by using high frequency ventilation instead of gating, as proposed by Hedlund and coworkers.[114] Carrol and colleagues[53] have pointed out that cardiac gating may affect lung water measurements by modifying the signal from flowing blood.

Since both intravascular and extravascular protons contribute to the NMR signal, a major problem to be solved in the application of NMR techniques to the measurement of lung water is discrimination between intravascular and extravascular water. The problem is important because an increase in lung density or total water content may reflect, for instance, pulmonary edema, vascular congestion, or atelectasis. However, it should be noted that, in vivo, a fraction of intravascular lung water is not detectable by NMR imaging because of the aforementioned effects of large vessel (high velocity) blood flow on the NMR signal. This signal loss may be reflected by the low NMR lung water values observed by MacLennan and colleagues[58] in human subjects. In addition, average human lung water density values obtained in vivo by NMR imaging[54,55,61] were substantially smaller than those predicted from normal total water content and lung volume data. These limited preliminary data suggest that NMR lung water values include only part of the intravascular water content. A possible solution to the problem of discrimination between intra- and extravascular lung water could be provided by a more precise definition of the relationship between pulmonary blood flow and intensity of the NMR signal from the lung. Preliminary data on the relationship between NMR signal intensity from the lung and cardiac cycle have been reported by Lallemand and coworkers[52] and Hedlund and coworkers.[56] The undetected intravascular lung water fraction is expected to depend on the magnitude and serial distribution of blood flow velocity. Therefore, an estimation of the extravascular fraction of NMR water content is probably achievable, but must await further studies.

The complex technology involved in the determina-

tion of lung water content and distribution by the NMR imaging method can be expected to set limits to the clinical application of this method. The incompatibility between the operation of NMR systems and the presence of ferromagnetic materials represents an additional practical problem, especially in critical care medicine. Although available data indicate that no significant biologic hazards are associated with exposure to electromagnetic fields (static magnetic fields, rapidly varying magnetic field gradients and radiofrequency pulses) at the levels presently used in NMR imaging,[6,48,65] special precautions are required for patients with metallic implants (for instance, surgical clips, joint implants, cardiac pacemakers).[48,65,115–117] In critically ill patients, the problem of lung water measurement by NMR imaging is further complicated by interference with monitoring instruments and supportive equipment. Some data relevant to this problem are already available. Although most ventilators are metallic and electronically controlled, the use of mechanical ventilation is not absolutely incompatible with NMR imaging. NMR signal intensity has been measured in sheep ventilated by a high-frequency ventilator located in an adjacent room.[53] High quality NMR images have been obtained in human subjects mechanically ventilated by a fluidic volume ventilator (no electronic components) immediately adjacent to a 0.5-T imager.[118] A fluidic high-frequency jet ventilator developed using plastic components[114] was not affected by magnetic fields up to 2.2 T. A recent study of compatibility of intravenous therapy (using infusion pump devices) with NMR imaging[119] showed that two types of infusion pump devices failed to meet the manufacturer's specifications for accuracy when exposed to the magnetic field of an NMR imager; however, a third type of infusion device was not affected. Although preliminary, these data suggest that the problems of incompatibility between NMR imaging instrumentation and current medical equipment are solvable.

Because of the complex instrumentation involved in NMR imaging, and the magnetic interaction between the imager and its environment, an NMR imaging unit requires careful site planning and has limited mobility, at least at the present stage of development.[10,120] Although this problem is not an absolute impediment to the clinical application of NMR methods for determining lung water content and distribution, it may represent a limitation in critically ill patients because it precludes bedside measurements.

CONCLUSIONS

Published evidence indicates the feasibility of measurements of lung water content and distribution by NMR imaging techniques. The application of these techniques to lung water studies is complicated by several problems and limitations, some of general interest (inability to differentiate intravascular from extravascular water, complexity and limited mobility of NMR imaging systems), others related to the structure–function characteristics of the lung (weak and rapidly decaying lung NMR signal, image artifacts due to respiratory motion). However, various groups have been able to obtain adequate NMR signal from lungs, and further improvement in the signal-to-noise ratio is technically achievable (for instance, by increasing magnetic field strength); respiratory gating can be performed using current monitoring equipment. Differentiation of extravascular from intravascular water is an important but potentially solvable problem. Preliminary data show that various problems posed by the use of NMR imaging techniques in critical care medicine can be solved, the prominent limitation in this area (but not necessarily in other areas of clinical medicine) being lack of mobility of NMR imaging systems (a disadvantage common to other, more established techniques, such as computerized axial tomography). Therefore, while there is little doubt that NMR imaging has the potential to become a powerful, versatile tool for lung water research, the extent of its future clinical use (especially in critical care medicine) is more difficult to predict, although a wide spectrum of applications can be foreseen and available preliminary data are, on the whole, encouraging. The practical application of NMR lung water measurements will depend mainly on the development of rapid and convenient techniques.

Future progress in the application of NMR imaging to the study of lung water could be made in the following directions: (1) Development and standardization of the most suitable imaging techniques for accurate, rapid measurement of lung water content under various conditions (animals or humans, research or clinical applications); optimization of technical characteristics (such as magnetic field strength and pulse sequence) and methods to minimize motion artifacts. (2) Development of methods for discriminating extravascular from intravascular water. (3) Systematic measurements of lung water content by optimal NMR imaging techniques in animals and humans (under normal conditions and in various types of experimental or clinical pulmonary edema, with particular attention to the time course of lung water accumulation). Comparison of the response of NMR signal intensity and relaxation times (T_1 and T_2) to lung water changes. (4) Assessment of lung water distribution in experimental animals and in humans under normal and pathologic conditions; search for characteristic patterns of water distribution in various types of experimental or clinical pulmonary edema. (5) Studies of the specific NMR behavior of the lung (characterized by a short free induction decay in the state of inflation) and of its implications with respect to experimental and clinical NMR imaging. These studies include the application of new techniques capable of enhancing the lung tissue in NMR images. The development of adequate models explaining the specific

NMR properties of lungs may lead to the description of new aspects of lung water distribution (according to position with respect to the air/tissue interface), with possible interesting implications for the study of pulmonary edema.

APPENDIX
Basic Principles of NMR Imaging

Basically, hydrogen nuclei (protons) have a magnetic dipolar moment and tend to align preferentially in the direction of an externally applied magnetic field H_o; this alignment results in a net nuclear magnetization M. In fact, the hydrogen protons precess around the axis of H_o at an angular frequency (Larmor frequency) $\omega o = {}_{\gamma}H_o$, where γ is a constant for each nuclear species (the gyromagnetic ratio). If the precessing protons are irradiated with a radiofrequency (rf) pulse of the same frequency as their precessional frequency, the nuclear magnetization is tilted away from the axis of the magnetic field H_o, and its component in a plane perpendicular to H_o (transverse component of M) can be measured by rf amplifiers. The amplitude of the NMR signal decays with time, mainly because of dephasing of the precessing protons (due to magnetic field inhomogeneity). The decay (free induction decay FID) is quantified by decay constant T_2, or spin–spin relaxation time (in a perfectly homogeneous external magnetic field). The more rapid FID resulting from external, magnet-induced, field inhomogeneity is quantified typically by a shorter decay time T_2^*. Reorientation of the nuclear magnetization with H_o (following the radiofrequency pulse) is characterized by T_1 (the spin-lattice relaxation time).

If the applied magnetic field H_o is uniform across the specimen, all protons precess essentially at the same frequency and therefore are not spatially resolvable. Spatial resolution can be obtained by applying a magnetic field gradient (ie, a magnetic field whose strength varies linearly with position across the specimen). Because of this gradient, the protons in various positions in the specimen will experience magnetic fields of different strengths and thus precess at different frequencies (since the Larmor frequency, ω_o, is directly proportional to the strength of the applied magnetic field H_o, see equation above). The contributions of differently located hydrogen nuclei to the NMR signal can be separated from one another by Fourier analysis, and two- or three-dimensional images of proton density (concentration of hydrogen nuclei) at each location in the specimen can be generated.

REFERENCES

1. Kaufman L, Crooks LE, Margulis AR (eds): *Nuclear Magnetic Resonance Imaging in Medicine*. New York: Igaku-Shoin, 1981.
2. Gore JC, Emery EW, Orr JS, et al: Medical nuclear magnetic resonance imaging: I. Physical principles. *Invest Radiol* 1981;16:269–274.
3. Fullerton GD: Basic concepts for nuclear magnetic resonance imaging. *Magn Reson Imaging* 1982;1:39–55.
4. Gadian DG: *Nuclear Magnetic Resonance and Its Applications to Living Systems*. New York, Oxford University, 1982.
5. Pykett IL, Newhouse JH, Buonanno FS, et al: Principles of nuclear magnetic resonance imaging. *Radiology* 1982;143:157–168.
6. Partain CL, James AE Jr, Rollo FD, et al: *Nuclear Magnetic Resonance (NMR) Imaging*. Philadelphia, WB Saunders, 1983.
7. Axel L: Relaxation times and NMR signals. *Magn Reson Imaging* 1984;2:121–130.
8. Hendee WR, Morgan CJ: Magnetic resonance imaging. Part 1-Physical principles. *West J Med* 1984;141:491–500.
9. Koutcher JA, Burt CT: Principles of imaging by nuclear magnetic resonance. *J Nucl Med* 1984;25:371–382.
10. Young SW: *Nuclear Magnetic Resonance Imaging*. New York, Raven, 1984.
11. Crandall ED, Staub NC, Goldberg HS, et al: Recent developments in pulmonary edema. *Ann Intern Med* 1983;99:808–822.
12. Brigham KL: Lung edema due to increased vascular permeability, in Staub NC (ed). *Lung Water and Solute Exchange*. New York, Marcel Dekker, 1978.
13. Teplitz C: Pulmonary cellular and interstitial edema, in Fishman AP, Renkin EM (eds): *Pulmonary Edema*. Bethesda, Md, American Physiological Society, 1979.
14. Prichard JS: *Edema of the Lung*. Springfield, Charles C Thomas, 1982.
15. Gump FE: Lung fluid and solute compartments, in Staub NC (ed): *Lung Water and Solute Exchange*. New York, Marcel Dekker, 1978.
16. Casaburi R, Wasserman K, Effros RM: Detection and measurement of pulmonary edema, in Staub NC (ed). *Lung Water and Solute Exchange*. New York, Marcel Dekker, 1978.
17. Carlile PV, Gray BA: Type of lung injury influences the thermal-dye estimation of extravascular lung water. *J Appl Physiol* 1984;57:680–685.
18. Brigham KL, Kariman K, Harris TR, et al: Correlation of oxygenation with vascular permeability-surface area but not with lung water in humans with acute respiratory failure and pulmonary edema. *J Clin Invest* 1983;72:339–349.
19. Milne ENC: Correlation of physiologic findings with chest roentgenology. *Radiol Clin North Am* 1973;11:17–47.
20. Pistolesi M, Giuntini C: Assessment of extravascular lung water. *Radiol Clin North Am* 1978;16:551–574.
21. Milne ENC, Pistolesi M, Miniati M, et al: The radiologic distinction of cardiogenic and noncardiogenic edema. *Am J Roentgenol* 1985;144:879–894.
22. *Workshop on Clinical Use of Lung Water Measurements*. U.S. Dept Health and Human Services, Public Health Service, NIH publication No. 86-2355, 1985.
23. Staub NC: Pulmonary edema. *Physiol Rev* 1974;54:678–811.
24. Weibel ER: Morphometric estimation of pulmonary diffusion capacity. I. Model and method. *Respir Physiol* 1970;11:54–75.
25. Weibel ER: *Stereological Methods*. Orlando, Fla, Academic Press, 1979.
26. Lewis FR, Elings VB, Sturm JA: Bedside measurement of lung water. *J Surg Res* 1979;27:250–261.
27. Noble WH, Kay JC, Maret KH, et al: Reappraisal of extravascular lung thermal volume as a measure of pulmonary edema. *J Appl Physiol* 1980;48:120–129.
28. Sibbald WJ, Warshawski FJ, Short AK, et al: Clinical studies of measuring extravascular lung water by the thermal dye technique in critically ill patients. *Chest* 1983;83:725–731.
29. Sivak ED, Richmond BJ, O'Donavan PB, et al: Value of extravascular lung water measurement vs. portable chest x-ray in the management of pulmonary edema. *Crit Care Med* 1983;11:498–501.
30. Friedman M, Kaufman SH, Wilkins SA Jr: Analysis of rebreathing measurements of pulmonary tissue volume in pulmonary edema. *J Appl Physiol* 1980;48:66–71.
31. Overland ES, Gupta RN, Huchon GJ: Measurement of pulmonary tissue volume and blood flow in persons with normal and edematous lungs. *J Appl Physiol* 1981;51:1375–1383.
32. Armstrong JD, Gluck EH, Crapo RO, et al: Lung tissue volume estimated by simultaneous radiographic and helium dilution methods. *Thorax* 1982;37:676–679.
33. Pomerantz M, Baumgartner R, Lauridson J, et al: Transthoracic electrical impedance for the early detection of pulmonary edema. *Surgery* 1969;66:260–268.
34. Van De Water JM, Miller IT, Milne ENC, et al: Impedance plethysmography. A noninvasive means of monitoring the thoracic surgery patient. *J Thorac Cardiovasc Surg* 1970;60:641–647.
35. Van De Water JM, Mount BE, Barela JR, et al: Monitoring the chest with impedance. *Chest* 1973;64:597–603.
36. Iskander MF, Durney CH, Shoff DJ: Diagnosis of pulmonary edema by a surgically noninvasive microwave technique. *Radiol Sci* 1979;14:265–269.
37. Iskander MF, Durney CH: Microwave methods for measuring changes in lung water. *J Microwave Power* 1983;18:265–275.
38. Gamsu G, Kaufman L, Swann SJ, et al: Absolute lung density in experimental canine pulmonary edema. *Circ Res* 1979;14:261–269.

39. Webber CE, Coates G: A clinical system for the in vivo measurement of lung density. *Med Phys* 1982;9:473–477.
40. Hedlund LW, Effman EL, Bates WM, et al: Pulmonary edema: A CT study of regional changes in lung density following oleic acid injury. *J Comput Assist Tomogr* 1982;6:939–946.
41. Hedlund LW, Vock P, Effman EL, et al: Hydrostatic pulmonary edema: An analysis of lung density changes by computed tomography. *Invest Radiol* 1984;19:254–262.
42. Wollmer P, Rhodes CG, Hughes JMB: Regional extravascular density and fractional blood volume of the lung in interstitial disease. *Thorax* 1984;39:286–293.
43. Schuster DP, Mintun MA, Green MA, et al: Regional lung water and hematocrit determined by positron emission tomography. *J Appl Physiol* 185;59:860–868.
44. Simon DS, Murray JF, Staub NC: Measurement of pulmonary edema in intact dogs by transthoracic γ-ray attenuation. *J Appl Physiol* 1979;47:1228–1233.
45. Prichard JS, Lee GDeJ: Measurement of water distribution and transcapillary solute flux in dog lung by external radioactivity counting. *Clin Sci* 1979;57:145–154.
46. Gorin AB, Kohler J, DeNardo G: Noninvasive measurement of pulmonary transvascular protein flux in normal man. *J Clin Invest* 1980;66:869–877.
47. Sugerman HJ, Tatum JL, Burke TS, et al: Gamma scintigraphic analysis of albumin flux in patients with acute respiratory distress syndrome. *Surgery* 1984;95:674–682.
48. Budinger TF, Lauterbur PC: Nuclear magnetic resonance technology for medical studies. *Science* 1984;226:288–298.
49. Hanley P: Magnets for medical applications of NMR. *Br Med Bull* 1984;40:125–131.
50. Hayes CE, Case TA, Ailion DC, et al: Lung water quantitation by nuclear magnetic resonance imaging. *Science* 1982;216:1313–1315.
51. Cutillo AG, Morris AH, Blatter DD, et al: Determination of lung water content and distribution by nuclear magnetic resonance. *J Appl Physiol* 1984;57:583–588.
52. Lallemand DP, Brasch RC, Gooding CA, et al: NMR imaging of lung parenchyma. *Magn Reson Med* 1984;1:190–191.
53. Carrol FE Jr, Loyd JE, Nolop KE, et al: MR imaging parameters in the study of lung water. A preliminary study. *Invest Radiol* 1985;20:381–387.
54. Cutillo AG, Morris AH, Ailion DC, et al: Lung water distribution by nuclear magnetic resonance (NMR). *Am Rev Respir Dis* 1985;131:A415.
55. Cutillo AG, Morris AH, Ailion DC, et al: Quantitative assessment of lung water distribution by NMR imaging, in: *Book of Abstracts*. 4th Annual Meeting, Society for Magnetic Resonance Medicine, Berkeley, Calif, 1985.
56. Hedlund L, Herfkens R, Deitz J, et al: Cardiac cycle correlated changes in MR signal intensity in thoracic blood vessels and lung, in: *Book of Abstracts*, 4th Annual Meeting, Society for Magnetic Resonance Medicine, Berkeley, Calif, 1984.
57. Johnston PW, MacLennan FM, Simpson JG, et al: Nuclear magnetic resonance imaging of pulmonary infarction and oedema in excised cadaver lungs. *Magn Reson Imag* 1985;3:157–161.
58. MacLennan FM, Foster MA, Smith FW: Measurement of total lung water from magnetic resonance images, in: *Book of Abstracts*. 4th Annual Meeting, Society for Magnetic Resonance Medicine, Berkeley, Calif, 1985.
59. Schmidt HC, McNamara MT, Brasch RC, et al: Assessment of severity of experimental pulmonary edema with magnetic resonance imaging. Effect of relaxation enhancement by Gd-DTPA. *Invest Radiol* 1985;20:687–692.
60. Wexler HR, Nicholson RL, Prato FS, et al: Quantitation of lung water by nuclear magnetic resonance imaging. A preliminary study. *Invest Radiol* 1985;20:583–590.
61. Ailion DC, Case TA, Blatter DD, et al: New imaging techniques for lung and fat, in: *Proceedings, 7th Specialized Colloque AMPERE, Bucharest, 1985*, to be published.
62. Crooks LE: Selective irradiation line scan techniques for NMR imaging. *IEEE Trans Nucl Sci* 1980;NS-27:1239–1244.
63. Edelstein WA, Hutchison JMS, Johnson G, et al: Spin warp NMR imaging and applications to human whole-body imaging. *Phys Med Biol* 1980;25:751–756.
64. Crooks L, Arakawa M, Hoenninger J, et al: Nuclear magnetic resonance whole-body imager operating at 3.5 KGauss. *Radiology* 1982;143:169–174.
65. Scherzinger AL, Hendee WR. Basic principles of magnetic resonance imaging—an update. *West J Med* 1985;143:782–792.
66. Lauterbur PC: Feasibility of NMR zeugmatographic imaging of the heart and lungs. Presented at the Engineering Foundation Conference on Comparative Productivity for Noninvasive Medical Diagnosis, New England College, Henniker, NH, 1976.
67. Lauterbur PC, Frank JA, Jacobson MJ: Water proton spin-lattice relaxation times in normal and edematous dog lungs. *Phys Canada* 1976;32:33.9 (Dig 4th Int Conf Med Phys).
68. Frank JA, Feiler MA, House WV, et al: Measurement of proton nuclear magnetic longitudinal relaxation times and water content in infarcted canine myocardium and induced pulmonary injury. *Clin Res* 1976;24:217A.
69. Frank JA: Quantification of pulmonary edema by nuclear magnetic resonance-spin-lattice relaxation time and water content. MSc thesis, State University of New York, Stony Brook, 1977.
70. Ling GN, Tucker M: Nuclear magnetic resonance relaxation and water contents in normal mouse and rat tissues and in cancer cells. *J Natl Cancer Inst* 1980;64:1199–1207.
71. Slutsky RA, Brown JJ, Andre MP: NMR relaxation times in edematous and dehydrated rabbit lungs. *Radiology* 1983;149(P):47A.
72. Skalina S, Kundel HL, Wolf G, et al: The effect of pulmonary edema on proton nuclear magnetic resonance relaxation times. *Invest Radiol* 1984;19:7–9.
73. Beall PT, Amtey SR, Kasturi SR: *NMR Data Handbook for Biomedical Applications*. New York: Pergamon Press, 1984.
74. Bottomley PA, Foster TH, Argersinger RE, et al: A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1-100 MHz: Dependence on tissue type, NMR frequency, temperature, species, excision, and age. *Med Phys* 1984;11:425–448.
75. West JB (ed): *Regional Differences in the Lung*. New York, Academic, 1977.
76. Nicholson RL, Prato FS, Wexler HR, et al: NMR imaging of lung water in an animal model of pulmonary edema. *J Can Assoc Radiol* 1983;34:340–341.
77. Crapo JD, Barry BE, Foscue HA, et al: Structural and biochemical changes in rat lungs occurring during exposures to lethal and adaptive doses of oxygen. *Am Rev Respir Dis* 1980;122:123–143.
78. Ailion DC, Case TA, Blatter DD, et al: Applications of NMR spin imaging to the study of lungs. *Bull Magn Res* 1984;6:130–139.
79. Ailion DC, Blatter DD, Case TA, et al: Asymmetric imaging, in: *Proceedings, 22nd AMPERE Congress* Zurich, Switzerland, Schippert & Co., 1984.
80. Morris AH, Blatter DD, Case TA, et al: A new nuclear magnetic resonance property of lung. *J Appl Physiol* 1985;58:759–762.
81. Blatter DD, Morris AH, Ailion DC, et al: Asymmetric spin echo sequences. A simple new method for obtaining NMR ^{1}H spectral images. *Invest Radiol* 1985;20:845–853.
82. Mansfield P, Morris PG: *Advances in Magnetic Resonance*, New York, Academic Press, 1982, Suppl 2: *NMR Imaging in Biomedicine*.
83. Taylor DG, Bore CF: A review of the magnetic resonance response of biological tissue and its applicability to the diagnosis of cancer by NMR radiology. *CT* 1981;5:122–134.
84. Mathur-De Vré R: Biomedical implications of the relaxation behaviour of water related to NMR imaging. *Br J Radiol* 1984;57:955–976.
85. Berendsen HJC: Specific interactions of water with biopolymers, in Franks F (ed): *Water—A Comprehensive Treatise*, vol 5. New York, Plenum, 1975.
86. Mathur-De Vré R: The NMR studies of water in biological systems. *Prog Biophys Mol Biol* 1979;35:103–134.
87. Derbyshire W: The dynamics of water in heterogeneous systems with emphasis on subzero temperatures, in Franks F (ed): *Water—A Comprehensive Treatise*, vol 7. New York, Plenum, 1982.
88. Fullerton GD, Potter JL, Dornbluth NC: NMR relaxation of protons in tissues and other macromolecular water solutions. *Magn Reson Imag* 1982;1:209–228.
89. Sloan DL, Samuelson GL, Ailion DC, et al: Protein hydration changes in the formation of the nicotinamide adenine dinucleotide complexes of glyceraldehyde 3-phosphate dehydrogenase of yeast. II. The spin lattice relaxation of solvent water protons. *J Biol Chem* 1973;248:5424–5427.
90. Cameron IL, Ord VA, Fullerton GD: Characterization of proton NMR relaxation times in normal and pathological tissues by correlation with other tissue parameters. *Magn Reson Imag* 1984;2:97–106.
91. Foster MA, Hutchinson JMS, Mallard JR, et al: Nuclear magnetic resonance pulse sequence and discrimination of high- and low-fat tissues. *Magn Reson Imag* 1984;2:187–192.
92. Brasch RC: Work in progress: Methods of contrast enhancement for NMR imaging and potential applications. A subject review. *Radiology* 1983;147:781–788.
93. Brasch RC, Weinmann H-J, Wesbey GE: Contrast-enhanced NMR imaging: Animal studies using gadolinium-DTPA complex. *Am J Roentgenol* 1984;142:625–630.
94. Weinmann H-J, Brasch RC, Press W-R, et al: Characteristics of Gadolinium-DTPA complex: A potential NMR contrast agent. *Am J Roentgenol* 1984;142:619–624.
95. Low FN: Lung interstitium, in Staub NC (ed): *Lung Water and Solute Exchange*. New York, Marcel Dekker, 1978.
96. Prockop DJ: Collagen, elastin, and proteoglycans: Matrix for fluid accu-

mulation in the lung, in Fishman AP, Renkin EM (eds), *Pulmonary edema*, Bethesda, Md, American Physiological Society, 1979.
97. Gil J: Alveolar wall relations. *Ann NY Acad Sci* 1982;384:31–43.
98. Taylor AE, Parker JC: Pulmonary interstitial spaces and lymphatics, in *Handbook of Physiology*. Section 3: *The Respiratory System*, vol 1; Fishman AP, Fisher AB (vol 1 eds). Bethesda, MD, American Physiological Soc, 1985.
99. Turino GM: The lung parenchyma—a dynamic matrix. *Am Rev Respir Dis* 1985;132:1324–1334.
100. Axel L: Blood flow effects in magnetic resonance imaging. *Am J Roentgenol* 1984;143:1157–1166.
101. Bradley WG, Waluch V, Lai KS, et al: The appearance of rapidly flowing blood on magnetic resonance images. *Am J Roentgenol* 1984;143:1167–1174.
102. Crooks LE, Kaufman L: NMR imaging of blood flow. *Br Med Bull* 1984;40:167–169.
103. Diegel JG, Pintar MM: Origin of the nonexponentiality of the water proton spin relaxations in tissues. *Biophys J* 1975;15:855–860.
104. Morris AH, Kanner RE, Crapo RO, et al (eds): *Clinical pulmonary function testing. A manual of uniform laboratory procedures*, ed 2. Salt Lake City, Intermountain Thoracic Society, 1984.
105. Hart HR, Bottomley PA, Edelstein WA, et al: Nuclear magnetic resonance imaging: Contrast-to-noise ratio as a function of strength of magnetic field. *Am J Roentgenol* 1983;141:1195–1201.
106. Crooks LE, Arakawa M, Hoenninger J, et al: Magnetic resonance imaging: Effects of magnetic field strength. *Radiology* 1984;151:127–133.
107. Ehman RL, McNamara MT, Pallack M, et al: Magnetic resonance imaging with respiratory gating: techniques and advantages. *Am J Roentgenol* 1984;143:1175–1182.
108. Nelson AD, Alfidi RJ, Kopiwoda S, et al: Experimental characterization of motion artifact in NMR images. *Magn Reson Med* 1984;1:285–286.
109. Wood ML, Henkelman RM: MR image artifacts from periodic motion. *Med Phys* 1985;12:143–151.
110. Prato FS, Nicholson RL, King M, et al: Abolition of respiratory movement markedly improved NMR images of the thorax and upper abdomen. *Magn Reson Med* 1984;1:227–229.
111. Runge VM, Clanton JA, Partain CL, et al: Respiratory gating in magnetic resonance imaging at 0.5 Tesla. *Radiology* 1984;151:521–523.
112. Hedlund L, Deitz J, Nassar R, et al: Ventilation for magnetic resonance imaging of normal and injured lung. *Am Rev Respir Dis* 1985;131:A417.
113. Bailes DR, Gilderdale DJ, Bydder GM, et al: Respiratory ordered phase encoding (ROPE): A method for reducing respiratory motion artifacts in MR imaging. *J Comput Assist Tomogr* 1985;9:835–838.
114. Hedlund L, Deitz J, Lischko M, et al: A high frequency jet ventilator for NMR imaging. *Invest Radiol* 1984;19:S42.
115. Davis PL, Crooks L, Arakawa M, et al: Potential hazards in NMR imaging: heating effects of changing magnetic fields and RF fields on small metallic implants. *Am J Roentgenol* 1981;137:857–860.
116. New PFJ, Rosen BR, Brady TJ, et al: Potential hazards and artifacts of ferromagnetic and nonferromagnetic surgical and dental materials and devices in nuclear magnetic resonance imaging. *Radiology* 1983;147:139–148.
117. Pavlicek W, Geisinger M, Castle L, et al: The effects of nuclear magnetic resonance on patients with cardiac pacemakers. *Radiology* 1983;147:149–153.
118. Dunn VD: Magnetic resonance imaging and mechanical ventilation, in: *Book of Abstracts*. 3rd Meeting, Society for Magnetic Resonance Medicine, Berkeley, Calif, 1984.
119. Engler MB, Engler MM: The effects of magnetic resonance imaging on intravenous infusion devices. *West J Med* 1985;143:329–332.
120. Ross RJ, Thompson JS, Kim K, et al: Site location and requirements for the installation of a nuclear magnetic resonance scanning unit. *Magn Reson Imag* 1982;1:29–33.