Magnetic resonance behavior of normal and diseased lungs: spherical shell model simulations

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Durney, Carl H., Antonio G. Cutillo, and David C. Ailion. Magnetic resonance behavior of normal and diseased lungs: spherical shell model simulations. J Appl Physiol 88: 1155–1166, 2000.—The alveolar air-tissue interface affects the lung NMR signal, because it results in a susceptibility-induced magnetic field inhomogeneity. The air-tissue interface effect can be detected and quantified by measuring the difference signal (Δ) from a pair of NMR images obtained using temporally symmetric and asymmetric spin-echo sequences. The present study describes a multicompartment alveolar model (consisting of a collection of noninteracting spherical water shells) that simulates the behavior of Δ as a function of the level of lung inflation and can be used to predict the NMR response to various types of lung injury. The model was used to predict Δ as a function of the inflation level (with the assumption of sequential alveolar recruitment, partly parallel to distension) and to simulate pulmonary edema by deriving equations that describe Δ for a collection of spherical shells representing combinations of collapsed, flooded, and inflated alveoli. Our theoretical data were compared with those provided by other models and with experimental data obtained from the literature. Our results suggest that NMR Δ measurements can be used to study the mechanisms underlying the lung pressure-volume behavior, to characterize lung injury, and to assess the contributions of alveolar recruitment and distension to the lung volume changes in response to the application of positive airway pressure (e.g., positive end-expiratory pressure). alveolar air-tissue interface; lung magnetic resonance imaging; lung pressure-volume behavior; alveolar recruitment; pulmonary edema

The unique, foamlke structure of the lung produces an NMR free induction decay (FID) in inflated lungs that is shorter than that observed in fully collapsed lungs or in solid tissue (1, 32). This shorter FID has been attributed to the effects of magnetic susceptibility differences between tissue and air (32). Because tissue is slightly diamagnetic, the extensive alveolar air-tissue interfaces perturb the magnetic flux density, causing internal (tissue-induced) magnetic field inhomogeneity (also termed inhomogeneous NMR line broadening), which is responsible for the NMR signal loss (shortening of the FID). Detergent foams, slurries, and shaving cream have also been found to produce shortened FIDs (1, 32).

In previous work (5, 7, 8, 13, 17) the effects of internal magnetic field inhomogeneity on the NMR signal (also called susceptibility effects) have been quantified by measuring a difference signal denoted by Δ. The basic principles underlying the measurement of Δ are discussed in detail in a previous publication (13). Briefly, Δ is the difference between spin-echo signals produced by temporally symmetric and asymmetric spin-echo sequences. A spin-echo sequence (Fig. 1) is symmetric if the time τ from the center of the 90° pulse to the center of the 180° pulse is equal to the time τ′ from the center of the 180° pulse to the center of the echo. The spin-echo sequence is asymmetric if τ ≠ τ′. The magnitude of the temporal asymmetry is expressed by the asymmetry time Δτ = τ′ − τ. Δ is generally determined, by subtraction, from two NMR images (obtained using, respectively, symmetric and asymmetric spin-echo sequences with asymmetry times of 3–6 ms). It is expressed as the difference between the symmetric and asymmetric signal intensities divided by the symmetric signal intensity (see METHODS). In inflated lungs the internal magnetic field inhomogeneity caused by the presence of the alveolar air-tissue interface reduces the asymmetric signal but not the symmetric signal (see METHODS). Therefore, Δ is a measure of the alveolar air-tissue interface effects and reflects the state of lung inflation. For example, Δ is expected to be zero for fully collapsed (nonaerated) lungs and to increase markedly as the lungs are inflated (13).

The connection between lung structure and Δ has been explained in terms of “thick” and “thin” material (16, 17). “Thickness” and “thinness” depend only on relative dimensions, not on absolute dimensions. Thick material (e.g., spheres and cubes) has approximately the same dimensions in three orthogonal directions. Thin material (e.g., thin slabs and rods) has at least one dimension that is significantly less than the other two. Thin material produces a significantly nonzero Δ, whereas thick material produces a virtually zero Δ. The characteristics of Δ for a given structure can be explained in terms of the relative amounts of thick and thin material present in the structure. For example, in fully collapsed lungs, only thick material is present, thus explaining the predicted zero Δ. As the lungs are inflated and the air spaces pop open, thick material is converted to thin material (the alveolar septa in aerated alveoli), and Δ increases rapidly. The results of
measurements of $\Delta$ as a function of the inflation level in excised rat lungs (13, 14) agree with the above theoretical concepts. These measurements have shown that, as predicted, $\Delta$ is very low in degassed lungs, because degassing virtually eliminates the alveolar air-tissue interface. The common observation of a low, but not zero as predicted, $\Delta$ in degassed lungs likely reflects the presence of small, macroscopically undetectable amounts of gas (13, 14). Comparative data (45) indicate that degassing by the oxygen-absorption method is more effective than in vacuo degassing. However, minute amounts of gas can even be found in lungs degassed by the oxygen-absorption method (14). When measured at an asymmetry time of 6 ms in initially degassed normal lungs, $\Delta$ ($\Delta_{6\text{ms}}$) increases markedly with alveolar opening and then varies very little during the rest of the inflation-deflation cycle (13). The behavior of $\Delta$ measured at other asymmetry times ($\Delta_{3\text{ms}}$ and $\Delta_{5\text{ms}}$) is qualitatively similar (13).

These results have interesting physiological implications, because they suggest that $\Delta$ measurements at appropriate asymmetry times are very sensitive to alveolar recruitment and are relatively insensitive to changes in the volume of open air spaces (13). This conclusion is also supported by the results of a comparison of $\Delta$ and morphometric measurements in normal excised rat lungs at two levels of inflation (14) and by theoretical calculations (model simulations of the behavior of $\Delta_{3\text{ms}}$ and $\Delta_{5\text{ms}}$ as a function of lung air content) (13, 16). Therefore, $\Delta$ measurements may provide a means for assessing the roles of alveolar recruitment and distension in the pressure-volume (P-V) behavior of lung. In addition, flooding of alveoli (e.g., in pulmonary edema) would be expected to reduce $\Delta$ significantly, because it obliterates the air-tissue interface, converting thin material to thick material. Simulations of alveolar flooding with use of spherical-shell models (see below) have shown that flooding does indeed dramatically decrease $\Delta$ (16). These predictions have been confirmed experimentally by the results of $\Delta$ measurements in edematous (oleic acid-injured) or saline-filled lungs (14). The strong dependence of $\Delta$ on the state of lung inflation and on pathological conditions affecting the alveolar air-tissue interface suggests the possibility of characterizing lung injury and the response of injured lungs to changes in inflation pressure by $\Delta$ measurements in conjunction with other NMR measurements (e.g., determination of lung water content). This potential for injury characterization is important, because the alveolar air-tissue interface is affected by many experimental and clinical conditions. As mentioned above, a loss of air-tissue interface occurs in experimental or clinical pulmonary edema [e.g., in patients with acute respiratory distress syndrome (ARDS)] because of alveolar flooding and collapse. A clinical example of the response of injured lungs to changes in inflation pressure is the increase in lung volume due to the application of positive end-expiratory pressure (PEEP) in ARDS patients (35). This volume response may result from reopening (recruitment) of collapsed and flooded alveoli and/or from further distension of already open air spaces.

In previous studies (5, 7, 8, 13, 16, 17) we used several lung models to simulate the NMR behavior of lung as a function of the level of inflation. These simulations are based on the assumption that all lung units operate synchronously (i.e., all alveoli are recruited simultaneously and then uniformly distended) and, therefore, behave virtually as a single-compartment system. In the present study our simulations are extended by considering the case of a multicompart-
asynchronously. This approach allows not only a more comprehensive evaluation of the process of lung inflation but also the extension of our simulations to diseased lungs. Multicompartment models can be used to simulate the NMR properties of edematous lungs (in particular, the response of collapsed or flooded alveoli to changes in inflation pressure, such as in the application of PEEP). Our simulations indicate that the two basic mechanisms potentially responsible for the increase in lung volume induced by PEEP (alveolar recruitment and distension) may be distinguished by \( \Delta \) measurements. This distinction is important not only in research, but also in clinical medicine, as discussed below.

In this study a simple multicompartment model is described to predict the response of \( \Delta \) to alveolar recruitment and distension in normal and edematous lungs. Then calculated results are presented and discussed.

**METHODS**

Selection of the lung model. The behavior of \( \Delta \) as a function of the lung inflation level can be simulated by models consisting of a simple air-filled spherical shell or arrays of air spaces in a water medium (5, 7, 8, 13, 16, 17). The air spaces can be spherical (spherical foam), cubical (cubical foam), or polyhedral (Wigner-Seitz) (3). Spherical-foam, cubical-foam, and Wigner-Seitz models are more accurate than the spherical-shell model, because they take into account the magnetic interaction between alveoli. A more detailed discussion of these models can be found elsewhere (16). The Wigner-Seitz model has been used in previous investigations (13, 14) to compare experimental \( \Delta \) measurements in lung with theoretical predictions. However, for the present study we selected a simple spherical-shell model, because the Wigner-Seitz model does not allow regional variations in air space size (which are required to simulate asynchronous and nonuniform volume changes in normal and diseased lungs). In this study the Wigner-Seitz model is used only for comparative purposes, as explained in greater detail below.

The present model simulates the parenchymal (respiratory) portion of the lung and basically corresponds to air and alveolar septal tissue. In the model the term “tissue” (corresponding to the spherical shell of water) refers to the normal lung tissue, which is assumed to consist of 100% water (whereas the real lung tissue contains a nonwater component and ~80% water). The term “water” refers to the extra water that accumulates in the interstitial tissue and in the air spaces in pulmonary edema. Interstitial edema and alveolar flooding are simulated by thickening the spherical water shell and by completely filling the spherical shell with water, respectively.

Spherical-shell model derivations. The spherical-shell model consists of a collection of noninteracting spherical shells, each one representing an alveolus. The great advantage of the spherical-shell model is its mathematical simplicity, which leads to understanding that would be difficult to obtain with more complicated models. Furthermore, previous calculations have shown that spherical-shell results are very similar to those obtained from more sophisticated models. The principal disadvantage of the spherical-shell model is that it does not include the effects of alveoli on each other in perturbing the magnetic flux density. The \( \Delta \) for a collection of noninteracting spherical shells has been described elsewhere (16); for the convenience of the reader, that derivation is briefly outlined here.

The derivation for \( \Delta \) begins with an expression for the \( y \) component of the magnetization of the spin echo at any time after the 180° pulse is applied (29)

\[
M_y = \frac{1}{V_{IT}} \int M_0 e^{-VT_2} \cos (\Delta \phi_1 + \Delta \phi_2) dV
\]

where \( M_0 \) is the thermal equilibrium magnetization, \( T_2 \) is the spin-spin relaxation time, \( V_{IT} \) is the total volume (tissue and water) that produces magnetization, \( \Delta \phi_1 = -\Delta \omega t - \gamma G_{0,x} \xi_1 \) (phase change between the 90° and 180° pulses), \( \Delta \phi_2 = \Delta \omega t + \gamma G_{0,x} (\tau - \tau_2) \) (phase change between the 180° pulse and the echo), \( \Delta \omega = \gamma B_0 + \gamma \Delta B \), \( \omega \), \( \gamma \) is the gyromagnetic ratio, \( B_0 \) is the applied direct-current magnetic field, \( \Delta B \) is the internal magnetic field inhomogeneity induced by the tissue, \( G_{0,x} \) is the magnitude of the x gradient, \( x \) is the distance along the x-axis, and \( \tau \) is the time between the 90° and the 180° pulse (\( \tau_1 \) or \( \tau_2 \) in Fig. 1). Other terms (e.g., \( \tau_1 \) and \( \tau_2 \)) are defined in Fig. 1. Substituting the expressions for \( \Delta \phi_1 \) and \( \Delta \phi_2 \) given above into Eq. 1 and using the convenient definition that \( \tau' \) is the time from the 180° pulse to the peak of the echo so that \( \tau + \tau' = \tau_1 + \tau_2 \) gives

\[
M_y = \frac{1}{V_{IT}} \int M_0 e^{-VT_2} \cos (\Delta \omega (t - 2\tau) + \gamma G_{0,x} (t - (\tau + \tau'))) dV
\]

Because the cosine functions in Eq. 2 at different points in space will be out of phase with each other when \( \Delta \omega \) and \( G_{0,x} \) vary with space, integrating these functions over \( V_{IT} \) reduces \( M_y \), compared with its value if all the cosine functions were in phase. Refocusing of the dephasing caused by \( \Delta \omega \) occurs at \( t = 2\tau \), and refocusing of the dephasing caused by \( G_{0,x} \) occurs at \( t = \tau + \tau' \). The spin-echo signal will be largest if refocusing of both dephasings occurs at the same instant of time, i.e., if \( 2\tau = \tau + \tau' \) and, therefore, \( \tau = \tau' \). Because \( \tau_s = \tau_0 \), the spin-echo amplitude is not reduced by tissue-induced inhomogeneous line broadening for the symmetric signal (Fig. 1). On the other hand, the asymmetric sequence does produce a reduced spin-echo amplitude, because \( \tau_s + \tau_0 \). Thus the difference between the symmetric \( (M_{ys}) \) and asymmetric \( (M_{ya}) \) spin-echo signals can be used as a measure of tissue-induced inhomogeneous line broadening.

This \( \Delta \) is defined as

\[
\Delta = \frac{M_{ys} - M_{ya}}{M_{ys}} \quad (3)
\]

where

\[
M_{ys} = M_y | t = \tau_0 + \tau_2 \times 2 \rho_2 = \frac{1}{V_{IT}} \int M_0 e^{-VT_2} dV \quad (4)
\]

and

\[
M_{ya} = M_y | t = \tau_0 + \tau_2 \rho_2 = \frac{1}{V_{IT}} \int M_0 e^{-VT_2} \cos (\Delta \omega \Delta \tau) dV \quad (5)
\]

and \( \Delta \tau = \Delta \tau_0 - \Delta \tau_2 \). For spherical shells consisting of homogeneous tissue or water, the perturbation of the spatially uniform \( B_0 \) will be on the order of a few parts per million. Consequently, \( M_y \) will be spatially uniform within a few parts per million and, to a good approximation, can be considered
spatially uniform. For homogeneous material, $T_2$ is also spatially uniform. Therefore, assuming that $M_0$ and $T_2$ do not vary with space, we obtain

$$\Delta = 1 - \frac{1}{V_{IT}} \int \cos(\Delta_{0i}\Delta_{T}) \, dV$$  \hspace{1cm} (6)$$

Because $V_{IT}$ in Eq. 6 is the entire volume in which magnetization is produced, $\Delta$ for a collection of noninteracting spherical shells of different sizes is obtained by integrating over all the shells in Eq. 6 to obtain

$$\Delta = 1 - \frac{1}{V_{IT}} \sum_i \int \cos(\Delta_{0i}\Delta_{T}) \, dV$$  \hspace{1cm} (7)$$

where $V_{ti}$ is the tissue and/or water volume of the ith shell (i.e., $V_{ti}$ is the volume that produces magnetization in the ith shell) and $V_{IT}$ is the total magnetization-producing volume of all the shells given by

$$V_{IT} = \sum_i V_{ti}$$  \hspace{1cm} (8)$$

It is convenient to write $\Delta$ for the entire collection of shells, as given in Eq. 7, in terms of $\Delta_i$ ($\Delta$ of the ith shell), defined as

$$\Delta_i = 1 - \frac{1}{V_{ti}} \int \cos(\Delta_{0i}\Delta_{T}) \, dV$$  \hspace{1cm} (9)$$

Solving for $\int \cos(\Delta_{0i}\Delta_{T})$ from Eq. 9, substituting into Eq. 7, and using Eq. 8 gives

$$\Delta = \sum_i \frac{V_{ti}}{V_{IT}} \Delta_i$$  \hspace{1cm} (10)$$

A principal advantage of the spherical-shell model is that $\Delta_B$, contained in $\Delta_{0i}$ in Eq. 9 is easily calculated for a spherical shell (7). Because $\Delta_B$ is a function of $r$ and $\theta$ in standard spherical coordinates, the integral in Eq. 9 must be evaluated by some numerical method. In the calculations described below, we integrated with respect to $r$ using a series expansion for the cosine function and then integrated numerically over $\theta$.

Evaluating Eq. 9 requires choosing a value for the asymmetry time $\Delta_{Ta}$ which is a parameter under the control of the experimenter. For our purposes, the optimum value of $\Delta_{Ta}$ would be one for which $\Delta$ has a strong, but monotonic, dependence on lung inflation. Calculated values of $\Delta$ for spherical-foam, Wigner-Seitz, and spherical-shell models as a function of lung inflation with $\Delta_{Ta}$ as a parameter show that $\Delta$ does increase monotonically with the level of lung inflation, but only for a specific range of values of $\Delta_{Ta}$ (7, 16). Because the variation of $\Delta$ with lung inflation is greater for larger values of $\Delta_{Ta}$ than for smaller values (7, 13), larger values of $\Delta_{Ta}$ would generally be better, but above a certain critical value of $\Delta_{Ta}$ the variation of $\Delta$ with lung inflation is no longer monotonic. For the spherical-foam and Wigner-Seitz models, and in actual lung, we have found the best value of $\Delta_{Ta}$ to be 6 ms; for greater values, the dependence of $\Delta$ on lung inflation is no longer monotonic. For the spherical-shell model, however, $\Delta$ at $\Delta_{Ta} = 6$ ms ($\Delta_{Ta} = 6$ ms) does not vary monotonically with lung inflation, presumably because the spherical-shell model does not take into account the magnetic interaction between adjacent alveoli, which is included in the spherical-foam and Wigner-Seitz models. The best $\Delta_{Ta}$ value for the spherical-shell model is 3 ms, for which the behavior of $\Delta$ ($\Delta_{Ta}$) with lung inflation is very similar to, although not numerically the same as, that predicted for $\Delta_{Ta} = 5$–6 ms with use of more refined models. Thus the simulations based on $\Delta_{Ta}$ for the spherical-shell model are also qualitatively applicable to the prediction of the experimental behavior of $\Delta_{Ta}$. Furthermore, because the spherical-shell model can simulate lung conditions (e.g., asynchronous behavior of parallel lung units) that cannot be analyzed by other models, it can provide valuable understanding not obtainable otherwise. For the above reasons (see Ref. 16 for a more detailed explanation), all the spherical-shell model calculations described in the present study were performed with the assumption that $\Delta_{Ta} = 3$ ms. Results of calculations based on $\Delta_{Ta}$ and the Wigner-Seitz model were used only for comparisons with the spherical-shell model data and with experimental observations.

Because the level of lung inflation can be described in terms of air fraction $[F_A, \text{air content as a fraction of total (air + tissue) volume}]$, it is convenient for subsequent calculations to evaluate $\Delta$ for given $F_A$ values of individual spherical shells and the $F_A$ of a combination of shells. The $F_A$ of the ith spherical shell ($F_{Ai}$) is defined as

$$F_{Ai} = \frac{V_{ai}}{V_{ai} + V_{ti}}$$  \hspace{1cm} (11)$$

where $V_{ai}$ is the air volume of the ith spherical shell and $V_{ti}$ is the tissue volume of the ith spherical shell.

Similarly, $F_A$, the air fraction for a collection of spherical shells, is given by

$$F_A = \frac{\sum_i V_{ai}}{\sum_i V_{ai} + V_{IT}}$$  \hspace{1cm} (12)$$

Solving for $V_{ai}$ from Eq. 11 and substituting into Eq. 12 gives

$$F_A = \frac{1}{1 + \left(\frac{F_{Ai}}{1 - F_{Ai}}\right)\frac{V_{ti}}{V_{IT}}}.$$  \hspace{1cm} (13)$$

Equations 12 and 13 are used subsequently to calculate $\Delta$ for various simulated lung conditions.

Recruitment vs. distension: models of lung inflation. Essentially, lung inflation occurs by two basic processes: 1) recruitment of totally collapsed alveoli and 2) further distension of already open alveoli. Additional mechanisms, changes in alveolar shape and “accordion-like” unfolding of air spaces with no variation in the alveolar surface area (20), are not considered in our simulations, because they are not expected to affect $\Delta$ sizably (unless they are associated with air space recruitment, in which case the predicted effect on $\Delta$ is that of process 1). The respective contributions of recruitment and distension to changes in lung volume vary according to the experimental conditions. For example, recruitment characterizes the inflation of nonaerated (initially degassed) excised lungs or the in vivo response to PEEP of groups of collapsed or flooded alveoli in edematous lungs. In contrast, alveolar distension is generally the mechanism responsible for lung volume changes in normal inflated lungs in vivo or in aerated alveoli in edematous lungs. On the basis of the above concepts, the process of inflation of a completely collapsed lung can be simulated using a model that can behave in two modes: synchronous and asynchronous. In the synchronous mode, all alveoli are recruited simultaneously (by application of an appropriate level of inflation pressure), instantly attaining a given volume, expressed by what we call the opening $F_A$
(which is constant for all alveoli). Then the alveoli gradually distend as the inflation pressure is further increased. The volume changes of the parallel alveolar units are strictly uniform also during this stage of the inflation process. In the asynchronous mode, all the alveoli are initially collapsed, as in the synchronous mode. When an appropriate inflation pressure is applied, some alveoli suddenly open (are recruited), attaining a certain opening $F_A$. Then, as the inflation pressure is further raised, more alveoli open while the previously opened alveoli distend further. This process, in which recruitment and distension occur in a parallel manner, continues until all alveoli are recruited and fully distended. Because the predicted $\Delta$ for a collapsed alveolus is zero, $\Delta$ for a collection of alveoli, some of which are collapsed, will be smaller than $\Delta$ for a collection of alveoli that are open. We expect, therefore, that $\Delta$ calculated by the model in the asynchronous mode would be less than that predicted in the synchronous mode at all lung inflation levels at which alveolar recruitment is incomplete.

RESULTS

$\Delta$ and lung inflation. Figure 2 shows $\Delta_{3ms}$ as a function of $F_A$ ($\Delta$-$F_A$ curves) calculated using the spherical-shell model in the synchronous (solid line) and asynchronous (dashed line) modes. The dashed lines are based on different values of the opening $F_A$ (50–80%, as indicated by arrows). In addition, the asynchronous-mode simulations presented in Fig. 2 assume that, initially, all the alveoli are completely collapsed ($F_A = 0$). Then 5% of the alveoli suddenly open with an opening $F_A$ of 50, 60, 70, or 80%. Subsequently, another 5% open, and the previously opened 5% further distend so that their $F_A$ is now 55, 65, 75, or 85%. Then another 5% open with an $F_A$ of 50–80%, and the $F_A$ of the previously opened alveoli increase 5% each, so that $F_A$ is 60, 70, 80, or 90% for the first 5% and 55, 65, 75, or 85% for the second 5%. When the recruited alveoli distend to $F_A$ of 90%, they are assumed to remain at that $F_A$, distending no further. This pattern continues until all the alveoli are open to $F_A$ of 90%. As expected, in the asynchronous-mode simulation, $\Delta_{3ms}$ rises much more slowly than predicted by the model in the synchronous mode, and the shapes of the two curves are quite different. In contrast, the lines describing the behavior of the model in the asynchronous mode for different opening $F_A$ have very similar shapes, although they differ numerically. To help explain these shapes, Fig. 3 provides an expanded view of the bottom left of Fig. 2, showing only the 70 and 80% curves. Points A and C correspond to 5% of recruited alveoli with opening $F_A$ of 70 and 80%, respectively. At points B and D, 10% of the alveoli are recruited. Point C is only slightly higher than point A, and point D is only slightly higher than point B, indicating that variations in the opening $F_A$ have little effect on $\Delta$. Point C, however, is substantially further to the right than point A, because the opening $F_A$ affects the total $F_A$ significantly. Thus because the opening $F_A$ affects $\Delta$ only slightly but affects $F_A$ substantially, the 80% curve rises less steeply than the 70% curve.

The continuous line and each of the dashed lines shown in Fig. 2 circumscribe an area that encompasses a wide spectrum of possible lung inflation behaviors, ranging from perfect synchrony in the function of the alveolar units (spherical-shell model in the synchronous mode) to a very high degree of asynchrony (alveolar recruitment is distributed over the entire course of the inflation limb of the P-V curve and occurs parallel to distension).

Theoretical predictions and experimental data. The lack of sufficient experimental $\Delta_{3ms}$ data in the litera-
ture prevented a direct comparison of our model predictions with $\Delta_{3ms}$ measurements at various levels of lung inflation. Because the spherical-shell model does not include the magnetic interaction between alveoli, we expect calculated values of $\Delta$ for the spherical-shell model to correlate qualitatively with experimental values, but not numerically. We do expect $\Delta_{6ms}$ for the Wigner-Seitz model in the synchronous mode to correlate numerically with measured values in the lung if the lung is behaving in the synchronous mode. However, as mentioned previously, the Wigner-Seitz model cannot simulate asynchronous behavior, whereas the spherical-shell model can. We have found that the most meaningful way to compare $\Delta_{3ms}$ for the spherical-shell model qualitatively with available experimental results is to simulate experimental data that have approximately the same qualitative relationship to the synchronous-mode, spherical-shell $\Delta_{3ms}$ as published experimental values of $\Delta_{6ms}$ have to the synchronous-mode $\Delta_{6ms}$ calculated from the Wigner-Seitz model. Figure 4 shows the Wigner-Seitz-calculated $\Delta_{6ms}$ as a function of inflation level (also expressed by $F_A$), with the assumption of perfectly synchronous alveolar recruitment/distension. Clearly, the behavior of Wigner-Seitz synchronous-mode $\Delta_{6ms}$ is very similar qualitatively to that of the spherical-shell synchronous-mode $\Delta_{3ms}$ shown in Fig. 2, although the $\Delta_{6ms}$ curve is more markedly nonlinear than the $\Delta_{3ms}$ curve.

Figure 4 also shows four sets of experimental measurements of $\Delta_{6ms}$ obtained in a previous investigation (13) from normal excised unperfused rat lungs, each studied at multiple levels of inflation. The corresponding $F_A$ values were estimated from lung volume measurements by a magnetic resonance (MR) imaging technique (Fig. 4). Figure 5 shows four sets of corresponding simulated experimental data that have approximately the same qualitative relationship to the spherical-shell synchronous-mode $\Delta_{3ms}$-$F_A$ curve as the experimental data in Fig. 4 have to the Wigner-Seitz synchronous-mode $\Delta_{6ms}$-$F_A$ curve. No simulated experimental values were included at $F_A = 0$, because the $\Delta$ corresponding to this experimental point can be affected by the presence of minute (macroscopically undetectable) amounts of gas (see the introduction). To determine the type of lung inflation behavior that might be represented by the simulated experimental data, we used a computer program that tries various combinations of the following four parameters: 1) the $F_A$ at which the recruited alveoli open, 2) the percentage of collapsed alveoli that are recruited at each step, 3) the $F_A$ at which the recruited alveoli distend at each step, and 4) the alveolar $F_A$ at the onset of the inflation process, if the alveoli are not completely collapsed. The program searches for a combination of these four parameters that produces the best fit of the calculated $\Delta_{3ms}$-$F_A$ curve to the simulated experimental data. The resulting curves that fit the four sets of simulated experimental data are shown in Fig. 6; corresponding combinations of the above four parameters are described in the legend of Fig. 6. For three excised lungs (Fig. 6, A–C), the results of our model calculations are consistent with an asynchronous lung inflation behavior, characterized by a wide distribution of alveolar recruitment over the span of lung inflation. In contrast,
in one lung (Fig. 6D), the results of our simulations are consistent with virtually all alveolar recruitment occurring at an earlier stage of inflation. In two of the sets of data shown in Fig. 6 (asterisks and open circles in B and C), the $\Delta_{3ms}F_A$ curve fitted to the simulated experimental data indicates an initial nonzero (although physiologically insignificant) value for $F_A$. This nonzero value likely reflects the presence of minute amounts of gas in conventionally degassed lungs, as discussed above and in the introduction.

Response to PEEP in lung injury. Here, lung injury is modeled as causing alveolar collapse and/or flooding, and the spherical-shell model is used to simulate the response of injured lungs to changes in inflation pressure, such as in the application of PEEP. Alveolar recruitment and alveolar overdistension are two mechanisms potentially responsible for the lung volume changes occurring with PEEP. Because $\Delta$ is affected differently by recruitment and distension, as shown by the results of our previous studies (see above and the introduction), $\Delta$ measurements might distinguish between these two mechanisms.

Figure 7 shows the $\Delta$ for a simulation of the response of a lung with collapsed alveoli to the application of PEEP. Consider a possible lung condition (point A in Fig. 7) in which 40% of the alveoli are collapsed and 60% are inflated to a $F_A$ of 70%. Point A shows $\Delta$ and $F_A$ for all alveoli are open and distended to $F_A = 90\%$. In C, dashed line is calculated with assumption that all alveoli are almost totally collapsed with individual $F_A = 8\%$. Then 12% of alveoli are recruited with opening $F_A = 27\%$. Subsequently, another 12% of alveoli are recruited, and previously recruited 12% of alveoli are further distended to $F_A = 34\%$. Pattern continues until all alveoli are open and distended to $F_A = 90\%$. In D, dashed line is calculated with assumption that all alveoli are simultaneously recruited with an individual opening $F_A = 35\%$. Then 3% of alveoli are further distended to $F_A = 80\%$. Subsequently, another 3% of alveoli are further distended to $F_A = 80\%$ and distended to $F_A = 85\%$. Pattern continues until all alveoli are distended to $F_A = 90\%$.
are identical and because the total number of inflated alveoli is 0.6N, the summation in Eq. 13 reduces to

\[ \sum F_{Ai} \frac{V_{ti}}{1 - F_{Ai}} = 0.6N \frac{0.7}{(1 - 0.7) \sum V_{ti}} \]

and

\[ F_p = \frac{1}{1 + \sum \frac{(0.6)(0.7)}{(1 - 0.7)}} = 0.5833 = 58.33\% \]

The \( \Delta \) for point A is calculated from Eq. 10 to be \( \Delta = 0.6\Delta_i \). From Fig. 7, when \( F_A \) is 70% for the normal lung, we find that \( \Delta_i \) is 86.91%.

We see that although the normal alveoli (n) are inflated to \( F_{An} \) (air fraction for the normal aerated alveoli) of 70%, the presence of the 40% collapsed alveoli lowers \( F_A \) to 58.33% and lowers \( \Delta \) from 86.91% of normal lung at \( F_A \) of 70% to 52.15%. Point B indicates the response to PEEP if none of the collapsed alveoli are recruited and the 60% normal alveoli distend in response to PEEP to \( F_{AI} \) of 79.55% (see Fig. 13), so that \( F_A \) of the entire lung is 70%. Because distension has a much smaller effect on \( \Delta \) than recruitment (see the introduction), point B is only slightly higher than point A. Point C corresponds to partial recruitment, with 15% recruited alveoli opening with an \( F_A \) of 70% and the 60% normal alveoli distending to \( F_{AI} \) of 76.77%, so that the \( F_A \) for the entire lung is 70%. In contrast to the previous case, point C is much higher than point A. Thus recruitment increases \( \Delta \) much more than distension of open alveoli. Points D and E show that increased recruitment results in correspondingly greater changes in \( \Delta \). Recruitment has such a significant effect on \( \Delta \), because it increases the relative amount of thin material and decreases the relative amount of thick material, while the total volume of tissue remains the same.

Figure 8 shows similar calculated data for the response to PEEP of an edematous lung with flooded alveoli. In this simulation, when the alveolus is recruited, the water flooding the air space before recruitment is assumed to be redistributed over the surface of the inflated alveolus and/or moved into the interstitial space (see DISCUSSION). Thus the total amount of NMR signal-producing volume remains the same before and after recruitment, similar to the conditions for recruitment of collapsed alveoli. Figures 7 and 8 show that the presence of the 40% flooded alveoli lowers \( \Delta \) more than the 40% collapsed alveoli. This lower \( \Delta \) occurs because the water flooding the alveoli is additional thick water. Furthermore, recruitment of flooded alveoli causes greater changes in \( \Delta \) than recruitment of collapsed alveoli. This greater change occurs because recruiting flooded alveoli converts the thick water flooding the air space to thin water in (or lining) the alveolar walls, thus converting more thick water to thin water than occurs in recruitment of collapsed alveoli. Moreover,
the presence of the 40% flooded alveoli also lowers \( F_A \) more than the presence of the 40% collapsed alveoli (cf. Figs. 7 and 8), because the extra volume of water flooding the air spaces reduces the total \( F_A \).

Although there are no published experimental data regarding the effect of PEEP on \( \Lambda \) in pulmonary edema, our theoretical predictions can be compared with the results of \( \Delta \) measurements in edematous excised rat lungs at multiple inflation pressures (14). In these lungs, \( \Delta_{6ms} \) rose markedly as airway pressure was increased; on the average, \( \Delta_{6ms} \) was 60 ± 6% at 5 cmH\(_2\)O and 80 ± 5% at 30 cmH\(_2\)O (at the same pressures, it was 84 ± 3 and 82 ± 4% in normal lungs). \( F_A \) could not be systematically determined from lung volume measurements (because no absolute lung volume data were obtained in this study). However, in some edematous lungs fixed at 25–30 cmH\(_2\)O, \( F_A \) could be estimated roughly as \( F_A = 1 - V_r \) (where \( V_r \) is the morphometric lung tissue fraction) and was found to be 0.75–0.82. If these morphometric estimates adequately represent alveolar recruitment over the inflation limb of the lung P-V curve and occurs, at least in part, parallel to distension. These results are in agreement with observations of the P-V behavior of excised lungs (37) and with experimental evidence obtained from morphometric and physiological studies (27, 41).

However, the data from the lung indicated by \( \times \) in Figs. 4, 5, and 6D suggest that, in some lungs, alveolar recruitment may be virtually complete at an earlier stage of the inflation curve. Measurements of \( \Delta \) were conducted under truly static conditions (i.e., each lung inflation level was maintained for several minutes before \( \Delta \) measurements were performed) (13); this procedure can be expected to maximize recruitment at lower inflation pressure levels (37).

The simple, but more flexible, spherical-shell model was used in the present study because of the limitations of the Wigner-Seitz model with respect to the specific purposes of the study (i.e., its inability to simulate regional nonuniformity, see METHODS). Because this model does not account for the magnetic interactions between spherical shells (see METHODS), its predictions cannot be compared numerically with experimental results, but they can be compared qualitatively. Qualitative comparisons between spherical-shell asynchronous-mode calculations and simulated experimental data (see RESULTS) have provided a basis for evaluating the physiological significance of the differences between the calculated synchronous-mode Wigner-Seitz \( \Delta_{6ms} \) data and the experimental measurements shown in Fig. 4 (assuming various patterns of alveolar recruitment and distension). The use of the spherical-shell model with an asymmetry time of 3 ms is justified by our previous theoretical studies and experimental measurements of \( \Delta \) at various asymmetry times and lung volumes (7, 13), which suggest that predictions made using \( \Delta_{3ms} \) can be qualitatively compared with experimental results for a \( \Delta_{3ms} \) range of at least 3–6 ms. Therefore, the spherical-shell model presented in this study provides virtually all the essential theoretical foundation for future experimental studies of the behavior of \( \Delta \) as a function of the inflation level (in particular, the response of \( \Delta \) to recruitment and distension). It can be expected that future systematic comparisons between theoretical and experimental \( \Delta \) data will indicate whether the development of more sophisticated models is warranted.

In the present study the spherical-shell model has been used to calculate theoretical \( \Delta-F_A \) curves on the basis of four parameters, i.e., the \( F_A \) at which the recruited alveoli open, the percentage of collapsed alveoli that are recruited at each step, the \( F_A \) at which the recruited alveoli distend at each step, and the alveolar \( F_A \) at the beginning of the inflation process, if the alveoli are not completely collapsed (see RESULTS). Although there is no unique combination of the above parameters that will fit the experimental data points, the spherical-shell model can clearly assess the roles of alveolar recruitment and distension in the lung P-V behavior. For example, our data suggest that the model can distinguish whether alveolar recruitment is widely distributed over the range of the inflation process (Fig. 6, A–C) or occurs mostly at an earlier stage of this.
process (Fig. 6D). It can be expected that the analysis of
the characteristic changes in the $\Delta$-$F_A$ curve produced
by varying the individual parameters will provide
valuable information on the inflation behavior of nor-
mal and injured lungs. The present preliminary quali-
tative comparison of theoretical and simulated experi-
mental data remains to be extended by systematic
prospective studies specifically designed to character-
ize various possible patterns of lung inflation and the
experimental conditions under which they may occur.

The models used in the present study simulate the
NMR behavior of the parenchymal (respiratory) por-
tion of the lung. Therefore, it is possible that these
models overestimate $\Delta$, which is likely lower in the
nonparenchymal than in the parenchymal lung tissue.
Simple preliminary calculations indicate that correc-
tion for the effect of the nonparenchymal tissue would
cause a downward shift of the curve describing the
relationship between $\Delta$ and $F_A$. However, the agree-
ment usually observed between predicted and experi-
mental $\Delta_{\text{tissue}}$ values at high levels of inflation (13, 14)
suggests that the overestimation is not substantial in
excised unperfused lungs. Furthermore, it can be ex-
pected that our imaging technique will allow the selec-
tion of predominantly parenchymal lung regions in in
vivo measurements of $\Delta$.

Although the level of lung inflation depends on
transpulmonary pressure and experimental $\Delta$ data can
be easily plotted as a function of inflation pressure (13,
14), in our models $\Delta$ is described as a variable depen-
dent on lung volume. This approach is justified by
experimental data (13, 14) that clearly indicate that the
applied pressure does not affect $\Delta$ unless it results in
alveolar recruitment (independently detected as a
change in lung volume). Therefore, the role of inflation
pressure in our simulations is purely instrumental,
because the applied pressure is implied to vary to
produce the volume changes assumed for the calcula-
tions. This approach simplifies our simulations and
serves the main purpose of demonstrating the different
effects of alveolar recruitment and distension on $\Delta$
(and, therefore, the ability of $\Delta$ measurements to distin-
guish these two mechanisms of lung inflation). On the
other hand, the application of the spherical-shell model
can be further refined by assuming changes in inflation
pressure and calculating the corresponding lung vol-
ume changes on the basis of the well-known nonlinear
lung P-V relationship. In this case, the changes in $F_A$
undergone by the parallel alveolar units during infla-
tion will vary according to the P-V curve (instead of
being constant, as in the simulations presented above).
Because of the nonlinearity of the lung P-V curve and of
the relationship between $F_A$ and conventional spiromet-
ic lung volume (see below), the $F_A$ changes at higher
levels of lung inflation will be smaller than those
assumed for the present simulations, thus further
reducing the effect of alveolar distension on $\Delta$. How-
ever, as shown by our calculations, the difference
between the results obtained by these two approaches
is minimal, because the effect of alveolar distension on
$\Delta$ is very small compared with the effect of recruitment.

From a general point of view, the inclusion of pressure
among the factors potentially affecting the behavior of
our models is convenient, because it allows the evalua-
tion of the effects of pathophysiologically and clinically
relevant manipulations, such as the application of PEEP
to promote alveolar recruitment in ARDS patients.

In the present simulations, lung air content is ex-
pressed as a fraction of total lung volume, which
includes tissue volume. As noted above, the lung tissue
volume is assumed to consist of 100% water, thus
representing the NMR signal-producing component of
the spherical-shell model (when the model simulates a
normal lung). Experimentally, for example, in excised
lung studies, the $F_A$ is a convenient index of lung air
content, because it can be obtained, with sufficient
approximation, from conventional measurements of
lung weight (43) and volume (water-displacement tech-
nique) (39). The experimental $F_A$ values used for the
comparison with our theoretical predictions (Fig. 4)
were obtained by an MR imaging technique that has
been shown to agree very closely with the standard
water-displacement method (13). However, when the
model is used to simulate clinical conditions (e.g.,
the effect of PEEP on $\Delta$ in ARDS patients), it may be of
interest to relate the $F_A$ to the much more common ratio
of spirometric lung volume (Vl) to total lung capacity
(TLC). This relationship is defined by the expression
$Vl/TLC = (1 - a)F_A/a(1 - F_A)$, where $Vl$ corresponds
approximately to the air volume, $V_a$ (i.e., $\Sigma V_{al}$ in Eq.
12), ignoring the dead space volume, and $a$ is the value
of $F_A$ at TLC. On the basis of estimates obtained from
published data for lung tissue volume (2, 4, 42, 44) and
conventional spirometric lung volume values calcu-
lated using current prediction equations (6, 11, 12,
22–24, 36), the value of $F_A$ at TLC in normal subjects is
$\approx 90\%$ and is only minimally affected by substantial
variations in lung tissue volume and by using spiromet-
ic lung volume data from various sources or for
different genders. Our estimates assume lung tissue
volumes of 450–900 ml (values in women being $\approx 75\%$
of those in men) (4, 42), an age of 30 yr, and average
anthropometric characteristics according to several
published series (1.75 and 1.60 m height and 75 and 62
kg body wt for men and women, respectively). Accord-
ing to the above calculations, it can be estimated that
$F_A$ values of 50–80% (i.e., in our models the values of $F_A$
that collapsed alveoli are assumed to attain instantan-
eously when recruited) correspond to $Vl/TLC$ of $\approx 10$
–60%. In living humans, these $Vl/TLC$ values corre-
spond to inflation levels encompassing residual volume
and functional residual capacity. In patients with pul-
monary edema, the value of $F_A$ at TLC is expected to be
lower than in normal subjects, mainly depending on the
severity of lung water accumulation. As discussed
above (see Selection of the lung model), in our simula-
tions the extra water accumulated in the interstitial
space and in the alveoli increases the nongas compo-
nent of the total volume of the lung.

Our simulations were performed by assuming differ-
ent values for the opening $F_A$, because the volume
attained by recruited alveoli can be expected to vary
depending on mechanical conditions. For example, studies in experimental animals and in humans (21, 31) indicate that the level of inflation varies throughout the lung. Radioactive gas measurements in normal humans (31) have shown that regional functional residual capacity and residual volume decrease substantially from the top to the bottom of the lung. However, the present results (Figs. 2 and 3) suggest that variations in the opening F_{V}\alpha do not markedly affect the relationship between Δ and the level of lung inflation.

Because the spherical-shell model does not take into account the magnetic interactions between spherical shells, the calculated values of Δ are obtained by simple summation of the individual values for each spherical shell and, therefore, are not dependent on the spatial characteristics of alveolar collapse and flooding. Consequently, no assumptions were made, in the present simulations, regarding the spatial distribution of the collapsed or flooded units. However, regional differences in the behavior of the spherical-shell model can be simulated by separately displaying the values of Δ calculated for different groups of spherical shells (an approach that would closely simulate the results of regional measurements by MR imaging). Although the simulation of the regional behavior of Δ was not considered in the present study, it may be of interest, because in many experimental models (e.g., oleic acid-induced pulmonary edema), as well as in ARDS, lung injury is characterized by marked spatial nonuniformity (15, 18, 25, 26, 33, 40). As implied above, the distribution of alveolar flooding might significantly affect the behavior of Δ in more refined lung models that take into account the magnetic interactions between alveoli.

In our simulations of the response of edematous lungs to PEEP, we have assumed that alveolar recruitment occurs because, as a result of this treatment, the edema fluid filling the air space is redistributed over the surface of the inflated alveolus and/or moved from the air space into the interstitial space (see RESULTS). Therefore, the total water content (including the edema fluid) of the lung model does not vary (although the average NMR signal-producing volume of water per unit model volume decreases as the level of air inflation increases). The assumption regarding the mechanisms of recruitment of flooded alveoli by PEEP is consistent not only with our histological observations (see RESULTS), but also with the results of other theoretical and experimental studies. Staub (43) and Malo et al. (28) calculated that, when flooded alveoli are inflated with air, the edema fluid will redistribute over the alveolar surface to form a thin layer of only a few micrometers. This redistribution is expected to affect Δ, because it creates an air-water interface and transforms thick material (the water filling a flooded alveolus) to thin material (the thin water layer lining a reinflated alveolus). In addition, several studies conducted on liquid-filled excised lungs have documented the transfer of water from the flooded air spaces to the interstitial space (9, 10, 19). Other published data suggest that the application of PEEP in experimental models of pulmonary edema results in inflation of flooded air spaces by moving alveolar water into the interstitial lung space (28, 34).

From a practical point of view, the results of the present study are of interest, because they provide the basic principles for a new nondestructive, and potentially noninvasive, approach to the study of the mechanisms underlying the P-V behavior of the lung. This approach is of particular relevance to the characterization of lung injury. When extended to the analysis of diseased lungs, the spherical-shell model can be used to simulate certain important elements of the lung response to injury, namely, alveolar collapse and edema, and to predict the characteristic effects of these abnormalities on the lung NMR properties. Our simulations of recruitment of collapsed and flooded alveoli in edematous lungs predict that Δ measurements may be used to distinguish recruitment from distension in the lung volume response to changes in airway pressure (e.g., to the application of PEEP). This differentiation is important clinically, because, for example, alveolar recruitment results in improved arterial oxygenation and, therefore, is the desired response to PEEP in patients with ARDS. In contrast, alveolar overdistension has little effect on arterial oxygen and may cause lung damage in these patients (30, 35).

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