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A portable single-sided magnet system for remote NMR measurements of pulmonary function

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Abstract

In this work, we report initial results from a light-weight, low field magnetic resonance device designed to make relative pulmonary density measurements at the bedside. The development of this device necessarily involves special considerations for the magnet, RF and data acquisition schemes as well as a careful analysis of what is needed to provide useful information in the ICU. A homogeneous field region is created remotely from the surface of the magnet such that when the magnet is placed against the chest, an NMR signal is measured from a small volume in the lung. In order to achieve portability, one must trade off field strength and therefore spatial resolution. We report initial measurements from a ping-pong ball size region in the lung as a function of lung volume. As expected, we measured decreased signal at larger lung volumes since lung density decreases with increasing lung volume. Using a CPMG sequence with $TE=3.5$ ms and a 20 echo train, a signal to noise ratio ~ 1100 was obtained from an 8.8mT planar magnet after signal averaging for 43 s. This is the first demonstration of NMR measurements made on a human lung

with a light-weight planar NMR device. We argue that very low spatial resolution measurements of different lobar lung regions will provide useful diagnostic information for clinicians treating Acute Respiratory Distress Syndrome as clinicians want to avoid ventilator pressures that cause either lung over distension (too much pressure) or lung collapse (too little pressure).

Introduction

NMR with portable and single-sided magnets

Since the early days of NMR, it became increasingly clear that for certain applications, a departure from the conventional MRI/NMR hardware design was needed. Various fields from food, polymer and rubber product testing to assessments of artwork demanded NMR with portable capabilities [1, 2]. Well-logging was the initial impetus for alternative approaches where measurement of rock formation, pore structure and moisture distribution needed to be performed noninvasively. Thus was born the inside-out NMR concept, where the NMR detection region was outside the RF coil, which was located inside the bore hole, and where the Earth's magnetic field was used to polarize the spins [3]. The low sensitivity stemming from the very small Earth's field was later remedied by employing permanent magnets also located inside the bore hole to produce a remote B_0 field. Perhaps the most notable development in this area is the NMR-MOUSE (MOBILE Universal Surface Explorer), which combines a permanent magnet and RF-coil in a single-sided compact design [4]. NMR-MOUSE designs, however, are limited to a detection region immediately adjacent to the magnet surface. The non-uniformity of the magnetic field inherent in unilateral configurations is used to encode the coordinate in the direction orthogonal to the magnet's surface thus providing the capability of measuring characteristics such as the dependence of the proton density on depth and the self-diffusion coefficient in liquid samples. At about 2 kg mass, the NMR-MOUSE has a field of ~0.5 T and a gradient of ~10-20 T/m in a region 10-30 mm deep [4].

Other devices rely on a region of magnetic field uniformity, where first-order (and higher order) gradients are negligible; this precludes the kind of depth profiling afforded by the NMR-MOUSE, but detects a larger ensemble of polarized spins and narrows the bandwidth of the signal, thereby increasing the signal-to-noise ratio (SNR) of the measured spectrum [5-7]. An example of such a device is the NMR-MOLE (MOBILE Lateral Explorer) [8, 9]. This 6 kg device is 200 mm in diameter and consists of 8 cylindrical bar magnets uniformly spaced over a circle, at the center of which an additional magnet is placed to create a region of field homogeneity ("sweet spot") above the surface. This region is centered on a saddle point, where one of the vector components of the magnetic field is locally maximal in one direction and minimal in the two orthogonal directions. The magnitude of the two minimal vector components is zero at the saddle point. By adjusting the tilt angle of the bar magnets it is possible to adjust the position of the sweet spot. The field uniformity achieved is 15 parts per thousand (ppt) over a region between 4-16 mm from the surface and with the central field equal to 77 mT.

A very high uniformity (0.25 parts per million, ppm) configuration was realized by Perlo et al. [10]. This device consists of large bar magnets spanning 28×28×12 cm, with smaller bar

magnets placed near the middle to shim the field and improve uniformity. The sweet spot is located 5mm above the surface, has an area of $\sim 5 \text{ mm}^2$ and is 0.5 mm thick. Such high uniformity allowed Perlo et al. to clearly observe chemical shifts in mixtures such as water and crude oil.

A detailed and comprehensive review of many single-sided and other portable magnet configurations can be found in references [1, 2, 11]. Our group has also studied single-sided magnet designs [6, 7]. Here we have developed a prototype system to achieve a penetration depth of $\sim 8 \text{ cm}$ while maintaining a mass of $\sim 10 \text{ kg}$. The rationale for this is the clinical need for a portable, light-weight MR device to probe the pulmonary parenchyma at the bedside in the intensive care unit (ICU).

Medical applications of the Magnetic Resonance Lung Density Monitor (MR-LDM)

A major source of morbidity and mortality in the medical intensive care unit is Acute Respiratory Distress Syndrome (ARDS). It is estimated that there are almost 200,000 cases of ARDS in the United States each year and more than 70,000 deaths [12]. ARDS is a syndrome characterized by altered pulmonary mechanics primarily due to surfactant dysfunction, with consequent deterioration of gas exchange. Physiologically appropriate transport of O_2 and CO_2 in the lung is only possible when alveoli (the site of gas exchange) are open and ventilated, throughout the respiratory cycle. This happens when the local elastic recoil of the lung exceeds critical opening and closing pressures in that region [13, 14]. These thresholds are not violated under normal physiologic conditions except perhaps during maneuvers of maximal exhalation. The result is that the lung is, to a large extent, homogeneously inflated and ventilated (there is a modest vertical gradient in both inflation and ventilation associated with gravity). In ARDS, however, there is marked influx of protein rich edema fluid into the alveolar airspaces [15]. This leads to surfactant dysfunction which compromises the stability of regional inflation [16] and results in regional heterogeneity in collapsed and overdistended lung regions. The former is typically seen in gravitationally dependent lung regions; the latter in gravitationally superior regions. Lung regions where recoil during the respiratory cycle fails to exceed the critical opening pressures remain collapsed, with significant cardiac right-to-left shunt and associated hypoxemia [16]. Lung regions that cycle above and below the opening and closing pressures can repeatedly collapse and reopen, with associated mechanical trauma leading to further lung injury [17, 18]. And those regions remaining open may be subject to overdistension.

A therapeutic intervention to prevent both of these processes (one of which was recognized since the earliest descriptions of ARDS [19]) is to set a positive lower limit to pressures in the ventilator at the end of exhalation (positive end-expiratory pressure, PEEP) with a target such that all alveoli remain open and ventilated. The application of PEEP in patients with ARDS usually increases arterial oxygenation, but the extent to which it decreases mortality is controversial [20-22]. One explanation for the lack of a clear benefit is that inadequate levels of PEEP have been used in clinical trials, owing to inaccuracies in the approximations used to determine lung recoil in many ventilated patients [23]. A greater difficulty, however, is presented by the observation that the lungs of patients with ARDS respond heterogeneously to PEEP. A pressure sufficient to open a severely affected lung unit

(typically gravitationally dependent) may also overdistend a less affected unit and thereby directly contribute to mechanical injury. Indeed, it has been demonstrated that even with current ventilator strategies, patients with ARDS continue to elaborate inflammatory markers and evidence other signs of ongoing lung injury [24]. The “best PEEP” for a given patient therefore is one that strikes the best compromise between maximizing recruitment (opening non-ventilated lung units using higher PEEP) and minimizing over distension (using lower PEEP). It is, moreover, by no means clear that the concept of a “best PEEP” is sufficient for clinical practice, insofar as it assumes a steady state response of the lung to whatever PEEP is chosen. By contrast, there are a variety of “recruitment maneuvers”, involving transient increases in PEEP, followed by return to baseline levels. These are done in the hope of recruiting previously collapsed regions, and then returning to levels which do not further damage the rest of the lung through continued barotrauma.

To obtain the best PEEP, and importantly to assess the efficacy of recruitment maneuvers, requires information about regional as well as global pulmonary mechanics. In principle, this can be obtained by taking a CT scan at various levels of PEEP, or following recruitment maneuvers. However, this is clearly not practical in the context of the ICU where patients are critically ill. For that reason, current practice aims to “optimize” PEEP using one of a variety of mechanical measurements obtained from the ventilator, all of which represent the average mechanics of the whole lung [23-25]. In the case of a lung with heterogeneously altered mechanics (the case in the majority of patients with ARDS) this approach can be misleading. The mechanical response of pathologic regions (typically located in the gravitationally dependent areas) can be masked by the response of the other portions of the lung. What is critically needed is a method that is rapid, portable, and local – i.e. a bedside measure of regional pulmonary mechanics.

We propose a Magnetic Resonance Lung Density Monitor (MR-LDM) to meet this need. Figure 1 shows a schematic of lung density vs. airway pressure, where the optimal ventilator strategy is determined by the maximal slope of the volume/pressure relationship, bounding pressures below by PEEP (green line) and above by Peak Inspiratory Pressure (PIP). A key point is that this approach is “global”; it does not distinguish the heterogeneously distributed pulmonary mechanics. Having the ability to characterize, however crudely, the regional state of inflation and ventilation will inform the clinician in setting ventilator pressures and recruitment maneuvers to maintain a balance between life threatening levels of hypoxemia and further ventilator induced lung injury through barotrauma. Importantly, our approach with this new technology will allow a real-time bedside determination of the efficacy of both PEEP levels and “recruitment maneuvers”.

In order to employ MR at all at the bedside in an ICU setting, the NMR system needs to be portable. This imposes restrictions on the weight and dimensions of the apparatus, leading to compromises in its measuring capabilities. The usual advances in medical imaging focus on higher and higher resolution, which by definition precludes its application at the bedside. We adopt the exact opposite approach: Our explicit goal here is to sacrifice high spatial resolution to achieve what critical care physicians really need – a coarse ($\sim 20 \text{ cm}^3$) but clinically relevant and real-time bedside assessment of the state of inflation and ventilation of lung regions to achieve optimal ventilatory strategies. Here we report initial NMR

measurements in a healthy human lung demonstrating the ability to detect different states of inflation. This is the first time such pulmonary measurements have been made with a light-weight single-sided, low field NMR device.

Experimental

Portable MR Design

Traditional MRI is not practical for critically ill patients, particularly for real time assessments of ventilatory strategies. This is due in large part to the fact that MRI systems require specialized suites, including an RF shielded room, an equipment room, and the designation of MRI-safe zones. Further, transporting and placing a critically ill patient in the bore of a typical MRI clinical scanner has significant attendant risks. Our goal is a portable MR system, that can be used at the bedside, and that can be used in real time to monitor lung function as ventilatory settings are changed.

The fulfillment of this goal requires that, firstly, the magnet be made compact. Secondly, the equipment itself must replace an MRI dedicated room with an instrument no larger than that of a half-height equipment rack. It must not require a dedicated RF shielded room. At the MR technical end, we wish to eliminate switched gradient coils and their associated power supplies. This last criterion leads to a spectroscopic approach where spins from a localized region (target volume) are measured. This in turn reduces the amount of equipment, simplifies system design, and permits low field operation. A low B_0 magnetic field reduces magnetic field safety concerns; however, sensitivity is then an issue. This is mitigated by making the size of the target volume much larger than the size of a typical imaging voxel in a clinical scanner.

Magnet

Design—We have chosen a single-sided or planar magnet design, as this provides maximum accessibility to the patient, i.e. one can probe the patient from a single side. Traditional designs, such as the NMR-MOUSE are not a good choice for our application, because they have small target volumes with a correspondingly small penetration depth. Our approach overcomes this by using an anti-parallel dipole configuration consisting of two equal and oppositely directed dipoles spaced apart from each other [6], and which provides a B_0 parallel with the surface of the magnet. An equally efficient configuration is the parallel-dipole model [5], which provides a B_0 perpendicular to the surface of the magnet. We selected the former configuration as this allows us to situate the RF surface coil between the magnet poles. Our single-sided magnets are designed to be positioned primarily beneath a supine patient (other configurations are clearly possible), allowing interrogation of a moderate volume inside the lung. Due to weight, bulk, and power supply considerations, we chose to use permanent magnets.

Aspect Ratio—It is informative to quantify how the volume, magnetic remanence (B_r), and configuration of the permanent magnet material affects the sweet spot. Note that field strength and location do not uniquely determine a magnet's configuration. A simple model may be created based upon the anti-parallel dipole model [6]. If for example we have two

permanent magnet blocks, then each block may be approximated by a dipole located at the center of mass of each. The volume of each permanent magnet block is given by the product of its surface area (A) and height (h) (or thickness); the strength of each dipole is given by the product, $B_r Ah$. The separation between the two anti-parallel dipoles is the distance $2a$ (see Figure 2). The field magnitude B at the saddle point is then given by

$$B = \frac{24}{5^{5/2} \pi a^3} B_r Ah, \quad (1)$$

and saddle points occur at a distance $a/2$ above (and below) the line connecting the centers of the two dipoles. The distance b of the saddle point above the surface of the magnet is given by $b = (a - h)/2$ (see Figure 2). Note that b is important as it is the effective penetration depth. We express the surface area in terms of a^2 ($A = \gamma a^2$). For any given permanent magnet configuration, the field strength can be increased by maximizing the surface area A subject to design constraints such as RF coil placement. Assuming the surface of each permanent magnet assembly is square, the theoretical maximum for γ is 4 as a further increase would cause the two magnet volumes to overlap. Substitution of a with the expression for b in Eq. [1] gives

$$B = B_M \frac{h}{2b + h}, \quad (2)$$

where $B_M = 24 \gamma B_r / (5^{5/2} \pi)$. The maximum field possible, B_M is obtained in the limit of infinite thickness h and large surface area (γ). For a field strength $B < B_M$, the thickness of the magnet is given by

$$h = \frac{2bB}{B_M - B} \quad (3)$$

These equations predict that large magnetic fields are possible, as B_M is on the order of 0.5 T for commonly available permanent magnet materials. However, large field strengths are only obtainable at the expense of substantial magnet volumes. Also, the existence of a remote saddle point is predicated on $b > 0$, which in turn requires that $a > h$. Thus the aspect ratio, a/h , must be greater than one in order to have a saddle point. This leads to practical magnet configurations that have relatively large surface dimensions compared to their thickness. For a magnet to be portable, its size and weight must be suitable for the application. In this paper we demonstrate a prototype system with a field strength of ~10 mT.

Field strength and SNR considerations—Here we estimate the target volume we will need for a 10 mT field strength in order to obtain a similar SNR as from a 1.5 T clinical scanner. A very conservative estimate of the drop in SNR due to the much lower field strength is a factor of 6400 ($\text{SNR} \sim B_0^{7/4}$ [26]). Thus, voxels of ~1 mm³, typical for MR Imaging, would need to be enlarged to ~6.4 cm³ to achieve the same SNR. On the other hand, since our interest lies primarily in pulmonary studies where the parenchymal density is ~0.2 g/cm³, there is an additional factor of 5 that reduces our SNR. Increasing the sampled

volume by another factor of 5 brings its value to 32 cm^3 . Thus we estimate our target volume will need to be on the order of 30 cm^3 .

Magnetic field and RF field simulations—A numerical simulation framework was created to test various magnet configurations and assess the merits and shortcomings of new designs. The simulation environment was developed as a set of routines in MATLAB (The Mathworks, Natick, MA), to model the magnetic field from current sources and magnetic dipoles. The Biot-Savart law was used for the former category: the current sources are defined as a given configuration of wires that can e.g. be wound into a solenoid. Each wire is subdivided into small current elements and the differential magnetic fields generated by all elements are added to obtain the total field.

For permanent magnets, a (usually convex) volume is designed in CAD software. This volume can be subdivided into small equal elementary sub-volumes. The elementary magnetic fields produced by dipoles at the center of each such volume could then be superposed to produce the total field. However, in order to accelerate this calculation, we adopted an approach that exploits the fact that each dipole can be computationally treated as two monopoles – one positive and one negative magnetic “charge”. For such a construct, the calculation of the field is analogous to the case of an electric field dipole produced by two equal and opposite electric charges. A further simplification is that the “charges” of axially contiguous dipoles cancel each other out except for the unpaired “charges” at the ends. The field contribution is calculated using only the two magnetic monopoles that populate the two pole surfaces of the elementary permanent magnet volume. This greatly reduces the computational burden.

Another aspect of the simulations concerns the estimation of the NMR signal. The remote region that is detected with NMR is the volume surrounding a field saddle point. The bandwidth of both the receiver and the RF coil as well as the B_I spatial profile determine the contribution from each spatial position to the overall signal. The simulation environment therefore includes a module to assess the total NMR signal observed for a specified phantom and RF coil. This calculation is informative as it is important to quantify which parts of the phantom/body are contributing to the measured signal and with what weighting factors. For this calculation, we used the B_y component of the permanent magnet field and the orthogonal B_I component at each spatial location. Note that this is an approximation since the direction of B_o deviates increasingly from the y direction as one moves farther away from the saddle point.

Field Mapping and Saddle Point Determination—We have constructed a mapping rig employing linear motion systems (Techno, Inc.) that is capable of positioning the magnetic field probe (Hall probe) at specified coordinates. A LabView program controls a system of servo motors and acquires the data measured from a Hall probe using a 3-axis LakeShore 460 Gaussmeter. The spatial accuracy of the unit is 0.1 mm. An extended arm is used to hold the Hall probe to minimize field distortions created by the motors.

The saddle point is a field extremum. Whether the extremum is a maximum or minimum along x , y and z can be easily determined from the magnet geometry. In practice, the position

of the saddle point was estimated from the gradient and curvature along mapping trajectories. A total of 7 mapping points could be used to find the coordinates of the saddle point [27]. This procedure is iterated until the position of the saddle point was determined to within 1 mm.

Construction—The magnet was constructed from two rectangular arrays of small NdFeB magnets. The two arrays are oppositely magnetized (perpendicular to the plane of the array). The superposition of the respective fields creates two saddle points, one on either side of the planar assembly.

The permanent magnet assemblies are held together by a 1/2" thick acrylic frame, such that the distance between them is adjustable. This allows one to change the dimension a and hence change the field strength and location of the saddle point. Each magnet assembly contains 240 cubic NdFeB magnets (each cubic magnet with side dimension of 12.5 mm), configured in two layers of permanent magnet cubes contained within acrylic grids, with a 20×6 grid of permanent magnets per layer. We used NdFeB magnets based on their high energy product, which is a specification that quantifies the magnetic flux per unit volume [28]. Although NdFeB has a higher temperature coefficient compared to SmCo, we chose NdFeB because of its higher field strength and coercivity, because the temperature fluctuations that affect the Larmor frequency are much slower than our data acquisition times. Each assembly is 31 cm long, 9.2 cm wide and 2.5 cm tall and the inner edges of the two assemblies are separated by 30 cm.

RF components

Coil—The RF transmit/receive coil is a short solenoid (radius and height are both 5 cm) built of 54 turns of Litz wire (type 1 40/38), which significantly reduces coil resistance at low frequencies. This design optimizes SNR [29] when used as a surface coil. The large number of turns increases the inductance and reduces the tuning capacitance to a practical value. A power dependent detuning of the coil was noted and was reduced by distributing the tuning capacitance into 3 equal sections in the coil. Because we use a high inductance coil, its resistance is significantly greater than the resistance in the connecting coaxial cable. This allows us to conveniently place the tuning and matching circuit at a distance from the coil without suffering any loss of coil Q . The RF coil is placed in the middle of the system, between the poles, in such a way that its upper loop is at the same level in the z direction as the upper surface of the cubes. The coil is tuned to 374 kHz (proton Larmor frequency at 8.8 mT) and has an unloaded Q of 280. At these frequencies, there is no measurable loading of the coil. Thus, calibrations of power settings may be made on phantom samples and then conveniently applied to subjects or samples under study.

Other System Components—A Tecmag Apollo NMR spectrometer, with a 500 W Tomco RF amplifier, was used for all measurements reported here. A desktop computer interfaced to the Tecmag system provided for data storage and a user interface. The Tecmag system utilizes NTNMR software, which provides a graphical pulse sequence development interface. The front end consists of a broadband Miteq bipolar preamp (AU1583) and a passive T/R switch (lumped element quarter wave design with crossed signal diodes).

Currently the system is placed in a 10' 4"W $\times$ 7' 1/2"L $\times$ 8' 2"H Faraday cage (Lindgren, Cedar Park, TX), which suppresses the noise by a factor of more than 40 dB.

Localization

The inhomogeneity of the main magnetic field of the MR-LDM magnet in tandem with the properties of the RF coil provides a uniquely defined spatially localized region for the measurement of a NMR signal (Figure 3). It is possible to control the size of the interrogated volume through the transmit/receive bandwidths of the spectrometer. Importantly, using a large receiver bandwidth, one can acquire the signal from a large volume and subsequently reduce the size of the interrogated volume by post processing to include a smaller range of frequencies. The shape of this volume and the weighting for spins located at different locations is determined by the combination of the distributions of the values of the main magnetic field as well as that of the RF field of the coil (see Figure 4).

Figures 3 A-D depict the simulated distribution of the y-component of magnetic field (the only non-zero component at the saddle point) created by a model of permanent magnet dipoles for our configuration. Each contour line on these plots traces the spatial locations with a particular magnetic field value. The density of the lines represents the rate of change in the orthogonal direction, hence giving an idea of uniformity. As one can see, the center of the plot contains the most uniform region of the field, although the same field values also extend away from the center (along the contour lines). The central region, however, has the highest field homogeneity and therefore contributes commensurately more to the signal; the contribution to the overall signal from spatial locations outside the central region is correspondingly less. In addition, the contribution of a particular point in space to the total NMR signal is weighted by the value of the B_1 field at that point. Finally, the resulting distribution function is weighted by the distribution of spin density throughout the sample (lung vs. non-pulmonary tissue) and by the quality factor of the coil, as it determines the width of the Lorentzian frequency response of the coil-receiver system.

To determine the shape of the expected NMR spectrum, we extended the simulations to include both B_0 and B_1 contributions. We estimated the expected signal from a cylindrical phantom 12 cm in diameter and 16 cm tall. The phantom consists of two homogeneous parts and is designed to roughly simulate a human chest: the bottom portion represents a layer of extrathoracic tissue such as muscle, fat, interstitium, etc. (4 cm) and the upper portion represents lung parenchyma (8 cm). The density values in extrathoracic tissue and lung were set to be 1 and 0.2, respectively. This allowed evaluation of the signal contributions from different regions. This is particularly important since even a small volume of extrathoracic tissue, due to its 5x higher proton density, has the potential to significantly contribute to the signal. This effect is essentially the relatively homogeneous volume region spilling over outside the targeted pulmonary parenchyma volume, thus compromising the relationship between the MR-LDM signal and absolute lung density.

NMR Experiments

Ring-Down Elimination— T_2^* for our magnet geometry is quite short. Therefore, it is important to acquire data immediately after RF excitation. The RF coil has a time constant

given by $\tau = Q/2\omega$, so the coil ring-down worsens at higher Q values and lower frequencies. There are two consequences to this. First, the rising and falling edges of the RF pulse are now characterized by the long time constant of the coil, which distorts the pulse waveform (Figure 8B). Second, if $\tau \gg T_2^*$, the decaying tail of the RF pulse can saturate the receiver preamplifier or superpose on the NMR signal.

To address these problems, we apply additional RF pulses to reduce the ring-down. This method, which we call Ring-Down Elimination (RDE), has been described previously [30, 31]. Two additional hard pulses with amplitudes V_0 and V_2 and corresponding durations of t_0 and t_2 precede and follow the main hard pulse (with parameters V_1 and t_1 respectively). The preceding pulse “accelerates” the rise of the main pulse and straightens its leading edge; the last pulse does the same by compensating the excess tail with its negative voltage. For the RDE implementation, we adjusted the amplitudes of the pulses to achieve a minimal ring-down. The optimal values of V_0 , V_2 (equivalently t_0 , t_2) depend on the characteristic frequency and time constant of the coil. The following settings provided the best RDE for 90° pulses: $V_1/V_0 = 0.2$, $V_2/V_0 = 0.87$, $t_0 = t_2 = 35 \mu\text{s}$, $t_1 = 85 \mu\text{s}$. The same amplitude ratios and durations were used for the RDE of refocusing pulses with the exception of $t_1 = 205 \mu\text{s}$.

Pulse sequences and Data processing—To take advantage of the long T_2 times at low fields, all NMR measurements using the MR-LDM employed Carr-Purcell-Meiboom-Gill (CPMG) echo trains, $90_x - \tau - (180_y - 2\tau)_n$. Ring-down elimination was applied to all pulses in the sequence. In spite of the fast recovery time of the preamp (30 μs) and the use of RDE pulses, the ring-down signal was still visible upon averaging. Further improvement in RDE was achieved through phase cycling and averaging. For example, the phase of both the 90° pulse and the receiver were phase cycled as $[x, -x, y, -y]$ while the 180° pulses were correspondingly cycled as $[y, y, x, x]$. This scheme allows for the ring-down signal from the 180° pulse to be averaged out.

Most of the data processing took place as follows. All data collected with the MR-LDM device was acquired using a CPMG train. To optimize the signal to noise ratio, we post processed the data using a matched filter approach [32]. Briefly, T_2 was measured by fitting the CPMG multi-echo train to an exponential decay and each echo was then multiplied by a matched filter or weighting factor, $\exp[-n \cdot TE(n)/T_2]$, where n is the echo number and $TE(n)$ is the echo time for the n^{th} echo. The weighted, echoes were then averaged. This average was then fit to a Gaussian function to obtain a second matched filter, which was then used to apodize the data by multiplication of the averaged echo by the fitted Gaussian. This was followed by Fourier transformation of the apodized data and phase correction to obtain the reported spectral data.

Phantom measurements—We used a 3D printer (Stratasys, Objet30) to print three “density phantoms”: plastic cylinders (12 cm diameter and 11 cm height) of identical overall volume, with volumetric water fractions of 100% (D100), 50% (D50) and 10% (D10). This was achieved by printing the phantoms either completely hollow (in the case of 100% content) or as a solid plastic cylinder filled with axial channels such that the local water volume fraction was 50% or 10%. The diameters of these channels were 4.1 mm for D50 and 1.8 mm for the D10. We estimated that the true densities of the D50 and D10 phantoms

relative to the D100 phantom were 47.1 and 9.4 percent for D50 and D10, respectively. We used nickel sulfate hexahydrate in 3.4 g/L concentration in water to match the T_1 relaxation time of lung tissue at our field strength.

We measured the NMR signal from these phantoms with both the MR-LDM system and a 3T clinical scanner (Skyra, Siemens Medical Solutions). The measurements from the two systems were then compared.

For the MR-LDM measurements of the density phantoms, we used a CPMG sequence with $TR = 750$ ms, a 50 echo train, and $TE = 3.5$ ms. 256 averages were collected. For T_1 measurements, we used a saturation recovery method that included a 100-echo CPMG readout. Although the MR-LDM system does not employ gradients, the T_2^* on our system is very short, which results in full dephasing of the transverse magnetization between RF pulses. We tested whether applying multiple saturation pulses would improve the magnetization saturation and determined that four 90° pulses were sufficient. These four pulses were separated by 500, 250 and 150 μ s [1]. To determine T_1 , measurements were made at 12 different recovery times ranging from 1 ms to 1.5 s.

The data were processed according to the outline in “Pulse sequences and Data processing” above. The real part of the spectrum was integrated over the peak and fit to $S_m = S_0 \cdot [1 - \exp(-t_m/T_1)] + C$, where t_m and S_m are the m^{th} recovery time and the signal measured for this time, respectively, and C is a constant offset arising from imperfect saturation.

For the T_2 measurements, we used the same saturation recovery data, but selected only the data with saturation times $>5T_1$. Data processing was similar to the previous case except the echo train data were not averaged. The real part of the signal was integrated over the peak and fit to a single exponential decay.

For the relative density measurements, CPMG data were collected with a $TR > 5T_1$ with 256 averages of the 100-echo train. The total acquisition time was about 3 min. At least 10 separate measurements with each of the phantoms were performed to assess reproducibility. The data were processed in the same manner as before using T_2 weighted averaging and Gaussian apodization. The real part of the spectrum was then integrated over the peak.

For the 3T measurements, we used a 3D RF-spoiled gradient echo sequence (FLASH 3D) with $TE/TR = 1.4/4.4$ ms, $\alpha = 20^\circ$. Data matrix size was $768 \times 768 \times 176$, resulting in a resolution of $0.4 \text{ mm} \times 0.4 \text{ mm} \times 0.8 \text{ mm}$ ($\sim 0.13 \text{ mm}^3$ voxel size).

Regions of interest (ROIs) were defined in the images obtained at 3 T from each of the density phantoms. Masks were created based on these ROIs such that unity was assigned to pixels with a signal above a threshold chosen to be well above the noise and zero was assigned to all other pixels within each ROI. The mean of each mask is then directly proportional to the water concentration of the phantom. These normalized densities were then compared to the MR-LDM relative density measurements.

In vivo measurements—All human measurements were done in accordance with an IRB approved protocol. For *in vivo* measurements, the MR-LDM was placed in a specially built

bed to hold the device. The subject lay on top of the MR-LDM such that the uniform field region was within the upper-middle part of the right lung, just under the shoulder-blade. *In vivo* measurements at Total Lung Capacity (TLC), Functional Residual Capacity (FRC) and Residual Volume (RV) were performed on a healthy human volunteer during a 43 s breath-hold. Over this time, an average of 72 CPMG echo trains were acquired. Each train contained 20 echoes separated by 3.5 ms. The same data processing routine described above was used for *in vivo* data. The real part was integrated over the NMR signal peak for each of the breath-holds at RV, FRC, and TLC. To evaluate the reproducibility of the *in vivo* measurement, we performed 10 repeat measurements at each lung volume. The SNRs were calculated at each lung volume as the ratio of the integral of the peak of the real part over the standard deviation of the noise.

Since the relaxation time measurements took longer than the allowed breath-hold time for our protocol, *in vivo* T_1 and T_2 measurements were performed while the subject was free breathing. Thus, these measurements reflect the average relaxation time from a range of lung volumes.

Results

Starting with specifications for the penetration depth appropriate for the lung (~8 cm) and the weight of the magnet (<10 kg), we used simulations to compare various designs. Figure 2 shows the results from the design we ultimately chose. The simulation shows a saddle point located at 86 mm above the magnet's surface with field strength of 8.8 mT and a range of 28 ppt over an 8.2 cm^3 volume centered on the saddle point. Based on this design we built our prototype system (Figure 5). Its total weight is ~12 kg, of which NdFeB magnets' weight is ~8 kg. The magnets are contained in a frame of $[54 \times 37 \times 4] \text{ cm}$ and generate a field strength of 8.8 mT. Using the mapping rig, the actual penetration depth was measured to be 82 mm and with a field range of 28 ppt over a volume of 8.2 cm^3 (see Figure 6). The temporal stability of the field strength at the saddle point revealed a maximum change of up to 40 μT over a period of 18 hours.

As designed, the MR-LDM is expected to only be sensitive to protons located within the remote homogeneous field region. To test this, we simulated the signal from a cylindrical phantom with two spatially distinct regions and where the two regions were assigned density and relaxation times of muscle and lung tissue. Figure 4 shows the simulated weighted distribution of the field within the phantom volume. The butterfly-like shape in the cylinder outlines the volume that contributes to the signal in Figure 4A. The spatial location of each point that contributes to the histogram in Figure 4A is shown in 4B. It is readily observed that the density of points decreases rapidly as one moves away from the saddle point. Therefore, even though points outside the region immediately surrounding the saddle point contribute to the signal within the bandwidth, their net contribution is small due to the point density decrease. The color of the points maps their offset from the central frequency. Note that the muscle (pink portion of the cylinder) contributes negligibly to the signal.

To further verify the MR-LDM's localization, we measured and simulated the NMR signal from a 2 cm thick, 5 cm diameter cylindrical phantom filled with doped water, as a function

of distance from the magnet surface. As can be seen from Figure 7, the measurement is in good agreement with the simulation.

Even in the target region, there is a significant inhomogeneity in the magnetic field resulting in very short T_2^* values ($\sim 113 \mu\text{s}$). To maximize SNR, we used a spin echo CPMG train to take advantage of relatively long T_2 values. Ring-down elimination (RDE) on the RF coil improved the RF pulse profile (Figure 8) and minimized the echo time, thus improving the SNR. After RDE implementation, we were able to reduce TE by 0.4 ms. In phantom measurements, we observed an SNR improvement by a factor of 2.3. Figure 8 shows the RF pulses (B) and NMR signals (C) before and after RDE.

Free-breathing *in vivo* T_1 and T_2 values measured in lung on the MR-LDM were 135 ± 35 and 62 ± 16 ms, respectively (Figure 9). We adjusted the concentration of nickel sulfate hexahydrate solution used in the phantoms to best match the measured T_1 . The measured relaxation times in the phantoms were $T_1 = 127 \pm 24$ ms and $T_2 = 111 \pm 6$ ms.

Figure 10A shows images collected on the clinical 3T scanner with the ROIs used in each of the density phantoms. We found excellent agreement between the normalized density measurements at 3T and those obtained with the MR-LDM. In addition, the normalized density agreed extremely well with the designed relative density of the phantoms, as shown in Figure 10B.

The results of measurements in our subject at the three lung volumes are shown in Figure 11. Ten repeat measurements at each lung volume established a reproducibility of 2.2%, 6.1% and 4.9% at RV, FRC, and TLC, respectively. The SNR of a single 43 s breath-hold protocol, calculated as the ratio of the real signal integral to the standard deviation of the noise, was > 1100 , 1900 and 2200 for TLC, FRC and RV respectively.

Discussion

Therapeutic efforts in ventilator strategy to achieve improved gas exchange, especially in ARDS, target recruitment maneuvers, either in the form of stepwise increases in PEEP, with low tidal volumes to protect overdistended lung regions, or in the form of transient increases in volume to recruit collapsed regions followed by monitoring subsequent levels of oxygenation. The data shown in Figure 5 demonstrate that density can be measured as long as the sample being measured and the calibration phantom have similar T_1 and T_2 . This is potentially problematic insofar as the relaxation time constants or relative contributions of different tissue types are unknown *in-vivo*. However, this is likely to be a minor effect, because at the very low field strength where we operate, the relaxation times (on the order of 100 ms) do not vary greatly with tissue type. For example, according to the NMR Data Handbook for Biomedical Applications [33], T_1 for a very wide variety of soft tissue types ranges from ~ 100 -200 ms and T_2 ranges from ~ 50 -80 ms. These values agree with our own recent measurement of *in-vivo* human tissues (see Results section) made with the MR-LDM. In addition, since the density between collapsed and distended lung is different by a factor of >3 , an absolute calibration is not necessary to assess the response to recruitment maneuvers. It follows that, consistent with our goal of assessing the efficacy of such maneuvers, a

calibration phantom with T_1 and T_2 in the range of what is measured for the lung will suffice.

Despite evidence that absolute density can be measured in an unknown homogeneous phantom if corrections are applied for differences in T_1 and T_2 from a calibration phantom, measurement of absolute lung density in the lung is more difficult. If the MR-LDM signal truly reflects the parenchymal density, the ratio of signals from the RV and TLC measurements should be at least ~ 3 . The actual ratio observed was 1.48. This behavior is consistent with the fact that some of the signal comes from (i) mismatch of the homogeneous field region to the desired target volume and (ii) the fact that non-parenchymal structures may lie within the desired targeted measurement region. An example of localization mismatch would be a contribution to the signal from muscle, fat, heart, and mediastinal structures. Examples of non-parenchymal structures within the targeted volume are major blood vessels. These non-parenchymal structures do not change their density with different levels of inflation and would result in a signal ratio from RV to TLC that is systematically less than that from the parenchyma per se. Both of the above mechanisms mean that with our current configuration, we cannot measure absolute lung density. Despite this, we argue that relative levels of lung recruitment can be assessed with the current system.

Conceptually, if one assumes that some fraction f of the MR-LDM signal arises from pulmonary parenchyma whereas the remainder $(1-f)$ comes from structures whose density does not change with the level of ventilation, then the signal change we measure from changing lung volume only comes from the fraction f . If ρ_p is the parenchymal density, then changes in measured signal with different lung inflation levels or levels of recruitment will reflect changes in $f\rho_p$. We refer to this as a fractional density.

At present, ventilator pressures in the ICU are adjusted by measuring the overall global response in lung volume to changes in airway opening pressure provided by the ventilator. The slope of air volume vs. ventilator pressure is characterized by a “strain index”, which is a global response of the lung. In effect, the MR-LDM will provide a local lung fractional density response to ventilator pressure changes thereby providing a quantity reflecting a localized “strain index”. This in turn will allow the clinician to optimize ventilator settings, in the sense of balancing regional alveolar over-distension in one region against alveolar collapse in another region, thus assessing the efficacy of PEEP settings or recruitment maneuvers. With respect to the anticipated distribution of overdistension and collapse respectively in the gravitationally superior and dependent regions (ventral and dorsal if the patient is supine), the vertical location of the saddle point can be moved by sliding the MR-LDM along a vertical axis while keeping the magnet surface against the chest. This will provide a coarse estimate of the vertical gradient in lung inflation. To be sure, the spillover of the volume sampled will encounter more non-lung tissue such as the heart as the probe is moved more ventral. Nevertheless targeting regions anatomically known from a prior CT scan, which virtually all patients have had, will guide the interpretation of this confounding issue. Such targeting from a prior scan is also important in obese individuals, where it is important to identify the vertical location where the most dorsal region of the lung can be probed without significant interference of other tissues.

Our initial tests presented here indicate the existing SNR is adequate for use in the ICU for ARDS patients. In addition, because these patients are on ventilator support for many days at a time, there are no stringent limits on the time allowed for data acquisition. Thus data can be collected with higher SNR than that achievable in a case of a breath-hold acquisition. Further, one can observe lung density response as a function of changes in ventilator volumes through ventilator-triggered data acquisition at different parts of the ventilatory cycle.

Although the physical deployment at the bedside is yet to be done, one possibility is to have the MR-LDM inlaid into the bed (as shown in Figure 5), where the subject lies supine on top of the bed. Other possibilities, however, include deployment of the device on a gantry that allows arbitrary positioning of the device against an accessible surface of the body. In principle, this is feasible in both lateral decubitus and prone postures.

A successful application of this technology at the bedside will require obviating the need for an RF shielded room. To address this we are developing an active noise cancellation framework (34–36), widely used in acoustic technology but minimally yet implemented in NMR technology (37).

Conclusion

We have built a very low field (8.8 mT) light-weight, planar magnet MR device that is sensitive to changes in pulmonary density, sacrificing spatial resolution ($\sim 20 \text{ cm}^3$) to achieve the goal of monitoring, in real time, changes in recruitment of previously collapsed lung regions in the setting of the ICU. Initial measurements in healthy humans demonstrate that signal intensity changes with lung inflation; phantom measurements demonstrate that this relationship is linear. We have, for the first time, made direct measurements of lung inflation in humans with a light-weight planar NMR device. We argue that this approach, even with the sacrifice of resolution, can assess the efficacy of recruitment maneuvers at the level of regional lung aeration, upstream of the consequences to blood gases. This in turn will provide physicians in critical care the specific information needed to interpret ventilator strategies – specifically the trade-off between recruitment and overdistension -- which in conjunction with blood gases can be used to more rationally determine optimal ventilator strategies for critically ill patients.

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Figure 1.

Schematic of Lung Density vs. ventilator pressure. One desires to set the ventilator such that (i) the value of PEEP is sufficiently high to prevent any region of the lung from collapsing, and (ii) the Peak Inspiratory Pressure (PIP) is sufficiently low that it does not over distend any regions of the lung.

Figure 2.

A diagram of the geometrical configuration of the antiparallel permanent magnet system. The South face of the magnet is depicted in blue, while the North face is in red, with arrows showing the corresponding field directions at each face. Each magnet assembly is a rectangular block 1 inch in height with sides d_1 and d_2 , and surface area $A = d_1 \cdot d_2$. The distance between the centers of the mass of the assemblies is $2a$, while the field uniformity region is at the distance b above the magnet's surface level.

Figure 3.

Map of the magnetic field in a cube with 20 cm side surrounding the saddle point, created by the anti-dipole magnet assembly (simulation). The magnets are shown as grey blocks, while the RF coil is shown as a dark red cylinder between the magnet blocks. A region with a reduced line density (increased field homogeneity) can be seen at the intersection of three planes (A). The red (B), green (C) and blue (D) colors are used to distinguish the contours in the three orthogonal planes. Each contour line on these plots represents an iso-field value for the particular vector component that is plotted. The difference in magnetic field between each contour line is constant and therefore the density of the lines represents the rate of change in the orthogonal direction. The contour line separations in the XZ- (B), YZ- (C), and XY- (D) planes are 3.14 G, 11.74 G and 4.28 G, respectively.

Figure 4.

Simulated spectrum(A) based on a cylindrical phantom(B) consisting of two parts: the bottom portion (pink) represents muscle tissue (density of 1 g/cm³), while the top portion (light-grey) is representative of a lung tissue (density of 0.2 g/cm³). The points inside the cylinder resembling a “butterfly in a jar” shows the spatial locations that contribute to the spectrum on the left, calculation of which includes the weighting factors from B1, Q of the coil, sample density and the bandwidth restriction. The color of a given spatial point in the butterfly-shape is meant to show both the frequency and the height of the bin of the histogram to which the signal originating at that point contributes. As can be seen in B, the majority of the signal comes from points located in the lung region hence the muscle tissue contributes negligibly to the signal (30 points of the “butterfly” are located within the muscle, while 1900 are within the lung).

Figure 5.
Picture of the MR-Lung Density Monitor prototype.

Figure 6.

Measurements of the field around the saddle point. A computerized mapping rig was used to find the location of the saddle point and measure the field values around it. The three curves reflect the change in the field values along the X, Y and Z axes.

Figure 7.
NMR signal response function to a 2 cm thick phantom as a function of distance from the surface of the planar magnet to the center of the phantom.

Figure 8.

Ring down elimination (RDE). (A) The diagram of the ring-down elimination implementation. In order to accelerate the rise and fall of the pulse shape, pre- (amplitude of V_0 , duration of t_0) and post- (amplitude of V_2 , duration of t_2) pulses are applied. (B) RF pulse shapes of the 90° (85 μ s long) and 180° (205 μ s long) pulses before and after the RDE implementation. For RDE pre- and post pulses were chosen as follows: amplitudes of $V_1/V_0 = 0.2$, $V_2/V_0 = 0.87$, and durations of $t_0 = t_2 = 35 \mu$ s. The same pre- and post- pulses were used for all 90° and 180° pulses. (C) Sample echoes from spin echo trains obtained before and after RDE application. Please note that x-axis represents the acquisition points, and not the acquisition times. After RDE implementation, the echo times were reduced by 0.4ms.

Figure 9.

Relaxation times (T1 and T2) in the lung tissue measured in vivo at 8.8 mT. $T1 = 135 \pm 34$ ms and $T2 = 65 \pm 16$ ms. Blue points in both A and B are the collected data, while red lines are the fits.

Figure 10.

(A) Density Phantoms. (A) D₁₀, D₅₀ and D₁₀₀ correspond to phantoms with 10, 50 and 100 percent volumetric concentration of water. Red, blue and green lines outline the regions of interest used for concentration calculations outlined in the text. (B) Relative density measurements at 3T and MR-LDM (blue axis) are in agreement, as well as there is an agreement between the relative density measurements with MR-LDM and calculations based on the geometry of the phantom (green axis).

Figure 11.

NMR signal from a volunteer at RV, FRC and TLC. These are averages of 72 repetitions of a 20-echo CPMG train. The SNR of a single acquisition, calculated as the ratio of the phased signal integral to the standard deviation of the noise, was 1100, 1900 and 2200 for TLC, FRC and RV, respectively.