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Detecting Pulmonary Capillary Blood Pulsations Using Hyperpolarized Xenon-129 Chemical Shift Saturation Recovery (CSSR) MR Spectroscopy

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Abstract

Purpose—To investigate whether chemical shift saturation recovery (CSSR) MR spectroscopy with hyperpolarized xenon-129 is sensitive to the pulsatile nature of pulmonary blood flow during the cardiac cycle.

Methods—A CSSR pulse sequence typically employs RF pulses to saturate the magnetization of xenon-129 dissolved in lung tissue followed, after a variable delay time, by an RF excitation and subsequent acquisition of a free-induction decay. Thereby it is possible to monitor the uptake of xenon-129 by lung tissue and extract physiological parameters of pulmonary gas exchange. In the current studies, the delay time was instead held at a constant value, which permitted observation of xenon-129 gas uptake as a function of breath hold time. CSSR studies were performed in 13 subjects (10 healthy, 2 chronic obstructive pulmonary disease [COPD], 1 second-hand smoke exposure), holding their breath at total lung capacity.

Results—The areas of the tissue/plasma and the red-blood-cell peaks in healthy subjects varied by an average of $1.7 \pm 0.7\%$ and $15.1 \pm 3.8\%$, respectively, during the cardiac cycle. In 2 subjects with COPD these peak pulsations were not detectable during at least part of the measurement period.

Conclusion—CSSR spectroscopy is sufficiently sensitive to detect oscillations in the xenon-129 gas-uptake rate associated with the cardiac cycle.

Keywords

Hyperpolarized xenon-129; Chemical Shift Saturation Recovery; CSSR Spectroscopy

Introduction

Over the past 20 years, lung imaging using hyperpolarized noble gas MRI has provided many fascinating insights into lung ventilation (1–4), lung structure (5–9), and lung function in the form of oxygen uptake (10–15). Various MR techniques have been developed that permit the quantification of function and classification of disease in the form of phenotypes that exceed the capabilities of more established, clinical modalities such as chest x-rays, CT scans or conventional pulmonary function tests. In particular, hyperpolarized xenon-129 (HXe) MR imaging and spectroscopy has matured greatly in the past few years due to the improved availability of xenon gas polarizers and large advances in xenon-129 polarization technology (16,17). The resulting image quality is now approaching that of the more commonly used hyperpolarized helium-3 MRI.

The next frontier for hyperpolarized gas MRI of the lung is the assessment of the gas exchange processes between the airspaces and the lung tissue, as well as the subsequent gas transport by the pulmonary circulation. Xenon-129 proves to be a very suitable tool for such purposes since it is much more soluble in water (Ostwald solubility at 37°: ~0.089) and biological tissues (Ostwald solubility at 37°: ~0.17) (18) than helium and exhibits a large change in chemical shift of about 200 ppm from the gas-phase (GP) resonance upon dissolution (19). The chemical shift difference between gas-phase and dissolved-phase HXe translates into a frequency difference of approximately 3.5 kHz at 1.5 T, which facilitates independent manipulation and observation of these two spectral regions. Thus, at sufficiently high field strengths, the presence of distinct dissolved-phase (DP) resonances not only permits direct MR imaging (20–25) of the DP magnetization but also quantification of the gas exchange processes between the GP and the DP compartments. At the level of alveolar gas exchange, the lung parenchyma can be conceptually broken into two components: a) the static lung tissue that comprises the septal walls and b) the flowing blood consisting of the blood plasma and the red blood cells (RBCs). In the human lung, the HXe resonances of lung tissue and blood plasma overlap at about 198 ppm while HXe bound to hemoglobin inside the RBCs exhibits a separate resonance at about 218 ppm (3,26). It is important to keep in mind that the xenon gas exchange between all of these compartments is bidirectional. As a consequence, shortly after the inspired HXe has reached the alveolar sacs, a dynamic equilibrium is established between the septa and the alveolar airspaces. Similarly, a dynamic equilibrium is reached between the blood and the airspaces, but the ongoing perfusion processes result in a spatially and temporally more inhomogeneous concentration distribution. Although the xenon concentration distribution cannot be controlled, the steady-state magnetization distribution can be disturbed through the application of narrow-bandwidth RF saturation or inversion pulses that selectively affect only the dissolved-phase regions of the spectrum. Due to its bidirectional nature, the gas exchange process can then be measured as either an associated decrease in the GP magnetization or a regrowth of the DP magnetization. The latter is usually assessed spectroscopically by varying the delay time between the RF saturation and subsequent acquisition of free induction decays using a technique referred to as “uptake” spectroscopy (27,28), Dynamic Xenon Spectroscopy (29), Replenishment Spectroscopy (20) or, most commonly, chemical shift saturation recovery (CSSR) (30–33) spectroscopy. Since only about 2% of the HXe in the lung is dissolved in

the tissue, the DP magnetization will be replenished from the GP magnetization pool even after numerous RF saturation pulse applications. Thus, the HXe uptake by the DP as a function of time can be acquired during a single breath hold.

The xenon uptake curve as measured by CSSR spectroscopy has to be fitted to a model function in order to extract certain global parameters of the underlying lung physiology such as the surface-to-volume ratio, the alveolar wall thickness and the pulmonary transit time. Over the years various uptake models of ever-increasing complexity have been proposed in the literature, but all of them either neglected the contributions of the blood flowing through the pulmonary capillaries entirely (30,34) or assumed the flow rate to be constant in time (20,28,35–37). However, if the pulsatile nature of the blood flow induces oscillations in the xenon gas uptake, the subsequent fitting of these models to the measurement data might be problematic and could potentially give rise to large errors in the extracted parameters. In this work, our goal was to investigate to what extent CSSR spectroscopy is susceptible to the pulsatile nature of pulmonary blood flow during the cardiac cycle and whether such measurements might provide additional insights into the function of normal and diseased lungs.

Methods

Human Subjects

Experiments were performed under a physician's investigational new drug application for MR imaging with HXe using a protocol approved by our Institutional Review Board. Written informed consent was obtained from each subject after the nature of the procedure had been fully explained. The study group was composed of 10 healthy, nonsmoking subjects, 2 with smoking-related COPD (GOLD Stage III), and one age-matched, clinically healthy subject with a history of high exposure to second-hand smoke (Table 1). Spirometry was performed immediately before and after the imaging session using a hand-held device (Koko; PDS Ferraris, Louisville, CO). Per investigational new drug requirements, 12-lead electrocardiography (HP Pagewriter XLI; Hewlett Packard Co., Palo Alto, CA) was performed in subjects 40 years or older immediately before and after MR imaging. Female subjects received a urine pregnancy test prior to imaging and were excluded from participation if pregnant. Before the subject was placed in the RF coil for MR imaging, a test dose of xenon (not hyperpolarized) was administered to evaluate whether the subject would experience any side effects secondary to xenon's anesthetic properties. Throughout the imaging session the subject's heart rate and oxygen saturation level were monitored (3150 MRI Patient Monitor; Invivo Research Inc., Orlando, FL), and the subject was assessed for central nervous system side effects of the inhaled xenon. All studies were supervised by a physician.

Gas Polarization and Administration

Enriched xenon gas (87% xenon-129) was polarized by collisional spin exchange with an optically pumped rubidium vapor using a prototype commercial system (XeBox-E10; Xemed, LLC, Durham, NH) that provided gas polarizations of 30–40%. Immediately before MR data acquisition, 0.5 L of HXe gas was dispensed into a 600-ml Tedlar bag (Jensen Inert

Products, Coral Springs, FL) and connected to one arm of a plastic Y connector. The other arm of the Y connector permits the attachment of a second Tedlar bag filled, for instance, with nitrogen or air. However, this capability was not used in our studies. Starting from residual lung volume (RV), the subjects were asked to inhale the HXe gas from the bag and either subsequently hold their breath or continue inhalation of room air and then hold their breath at total lung capacity (TLC).

HXe Data Acquisition

A CSSR spectroscopy pulse sequence usually consists of four repeating elements (Fig. 1): 1) Selective RF saturation of the DP resonances followed by gradient spoiling of residual transverse magnetization; 2) a delay time τ separating the RF saturation from the RF excitation; 3) an RF excitation covering the GP (low flip angle) and DP (high flip angle) resonances; and 4) sampling of the free induction decay (FID). Due to the size of a human chest coil and the power limitations of the broadband amplifiers in clinical MR systems, it is frequently not possible to employ 90° RF saturation pulses that have a sufficiently large bandwidth to completely saturate all DP resonances at the same time. Therefore, we implemented a 3-pulse RF saturation scheme that consists of 2-ms Gaussian pulses applied first at 198 ppm (TP), then at 218 ppm (RBC) and finally at 208 ppm (in between resonances) followed by a short spoiler gradient. To minimize unintended spin-inversion effects in the overlapping frequency bands, each RF pulse also had a different phase (180°, 0°, 90°). The delay time τ between the final saturation RF pulse and the excitation RF pulse determines the time period during which hyperpolarized xenon atoms from the alveolar airspaces can enter the lung tissue and replenish the depleted DP magnetization. To sample the entire xenon uptake curve, τ is typically varied from a few milliseconds to several hundred milliseconds for the different spectral acquisitions within a single breath hold. For reference purposes, we performed one breath-hold study with this “conventional” arrangement. However, since it was the objective of this work to quantify xenon uptake solely as a function of time, τ was held at a fixed value between 50 and 300 ms for all other studies. A 1.2-ms Gaussian RF excitation pulse was used to generate a free induction decay. (To maximize the signal-to-noise ratio in our measurement, the voltage of the RF excitation pulse is set to the maximum selectable value for our coil (about 225V). As a consequence, the actually applied excitation flip angle varied from subject to subject as a function of the individually calibrated reference voltage.) The signal was sampled for 30.72 ms with 1024 sampling points. The resulting repetition time was equal to $\tau + 40$ ms. A total of 32 spectra were acquired during each breath hold. In the subsequent temporal analysis, the first of the acquired spectra was used to define an arbitrary breath hold time zero to which all subsequent spectra were time referenced.

MR acquisitions were performed using a 1.5T commercial whole-body MR scanner (Avanto; Siemens Medical Solutions, Malvern PA) equipped with the multinuclear imaging option, permitting operation at the xenon-129 resonant frequency of 17.6 MHz. Two RF coils were used for the experiments, including a flexible, circularly-polarized, vest-shaped chest RF coil (Clinical MR Solutions, Brookfield, WI) and a rigid, custom-built, linearly-polarized chest RF coil. Both RF coils were blocked at the proton resonance frequency to permit proton MRI to be performed with the RF coil in place. The subject was positioned

supine on the scanner table with the RF coil around their chest. Breath-hold scout images were obtained using conventional proton MRI for positioning of the xenon-129 acquisitions. Next, the subject inhaled a gas mixture containing approximately 200 ml of HXe and a breath-hold acquisition was performed for calibration of the scanner center frequency and transmitter voltage. The CSSR acquisitions were then performed using the inflation levels and delay times listed for each subject in Table 1.

Data Analysis

All post-processing and data analysis was performed using MatLab (Mathworks, Natick, MA, USA). The sampled data were apodized by a squared cosine function, zero-filled to 2048 points, Fourier transformed and phased to first order. The GP peak area was determined analytically by fitting a Gaussian function to the GP resonance. Especially for short delay times, the two dissolved-phase resonances deviated too much from a Gaussian or Lorentzian line shape for analytical fitting and, thus, were integrated numerically. To account for T1 and RF-pulse induced magnetization decay, both sets of peak integrals were corrected with a monoexponential decay function of the type $A \exp(-t/T1_{app})$ fitted to the TP peak integrals, where A is the amplitude, $T1_{app}$ is the apparent T1 of the signal decay and t is the elapsed breath hold time. For an assessment of the approximate relative pulsation amplitude, the mean of the temporal extrema of the peak integrals were computed and the averaged maximum value was divided by the averaged minimum value.

Simulations

As mentioned above, in conventional CSSR spectroscopy analytical xenon uptake models are fitted to the DP peak integrals obtained to quantify lung function. The more advanced models capture the saturation of stationary lung tissue by passive diffusion of the xenon atoms as well as the active pulmonary xenon gas transport by the blood plasma and the RBCs (20,28,35–37). Once the model of choice has been fitted to the experimental data it is then possible to extract physiological lung parameters such as the blood flow rate and alveolar wall thickness. Taking a set of “normal” parameters from a healthy subject participating in an unrelated study as reference, we used the analytical model proposed by Patz et al (35) to predict what changes in the underlying physiological parameters might induce the observed RBC signal oscillations. Three different scenarios were considered: 1) Normal vessel diameter, flow velocity 50% of normal (diastole model); 2) Normal vessel diameter, flow velocity 200% of normal (systole model 1); and 3) Vessel diameter 120% of normal, flow velocity normal (systole model 2). Note that the absolute model parameters are of little importance for this simulation compared to the relative differences between the scenarios. These simulations were performed using MatLab (Mathworks, Natick, MA, USA).

Results

In Fig. 2, the area of the RBC peak as a function of delay time τ between RF saturation of the DP region and the subsequent RF excitation is shown for the one healthy subject in whom a variable delay time was used. Usually, for a CSSR study the spectra from a breath hold are obtained with a pseudo-random order for the τ values. However, for this reference

measurement, τ was increased monotonically from its lowest (3 ms) to its highest (900 ms) value to better visualize any peak fluctuations in the time domain. Although not perceptible during the steep rise of the RBC peak area for small τ , a significant oscillation of the data points about the curve fitted to the measurement, using the theoretical model described by Patz et al (35), is readily apparent for longer delay times.

Figure 3 illustrates the signal behavior of the three HXe spectral peaks (gas, TP, RBC) in a healthy subject during a breath hold, before and after correcting for signal decay based on the TP peak. The study was performed at TLC (top row) and RV (bottom row) in the same subject using a fixed delay time of $\tau = 100$ ms. The uncorrected signals appear to diminish exponentially over the course of the breath hold, albeit not necessarily at the same rate. In particular the RBC signal is further modulated by an oscillatory component. At TLC, correcting the three peak areas by the decay of the TP peak eliminates all time-dependent signal decreases. At RV, on the other hand, even the corrected TP signal has a concave appearance, indicating behavior more complex than exponential decay. Further, the gas signal is overcorrected and now increases exponentially with time.

Some of the measurements from Figure 3 are rescaled in Figure 4 for a more in-depth analysis. Figures 4a and 4d show the normalized TP and RBC signal evolutions as a function of time during a breath hold at TLC and RV, respectively. At this scale it is apparent that the TP signal also exhibits temporal oscillations, although with a relative change that is roughly 10 times smaller than the RBC signal oscillations. Also, the RBC oscillations are more pronounced at TLC ($12.0 \pm 2.1\%$) than at RV ($8.0 \pm 0.4\%$) but at both lung inflation levels the TP and RBC oscillations appear completely synchronized (Figures 4b and 4e). Figures 4c and 4f depict the dissolved-phase region of the pulmonary HXe spectrum at a local minimum (solid line) and a neighboring local maximum (dotted line) in the RBC oscillation, and serve as verification that the observations are purely due to a change in the peak areas and are not based on any erratic spectral artifacts. The pulsation frequency determined from the temporal spacing of the plot extremes is approximately 1 Hz and, within the accuracy of the temporal sampling rate of the spectra, is in excellent agreement with the pulse rate assessed simultaneously by a pulse oxymeter during the breath holds.

As illustrated by the repeat measurements in Figures 5a-c the pronounced pulsation in the RBC peak is detected very reliably in healthy subjects. The identification of the much weaker TP peak pulsation appears to be less consistent. Nevertheless, due to the excellent synchronization of the pulsations in both peaks, the RBC plot can sometimes be used to assist in the characterization of the TP oscillations. In Figure 5d the timelines for the RBC peak from Figure 5a through 5c are plotted on top of each other and rescaled such that the highest local maximum that was part of the rhythmic pulsation was normalized to 1.0. This combination plot shows that while the temporal dynamics during the three separate breath holds were very similar, the observed relative oscillation amplitude varied by about 50% from study to study. For the 10 healthy subjects in our studies we found average pulsation amplitudes of $1.7 \pm 0.7\%$ and $15.1 \pm 3.8\%$ for TP and RBC oscillations, respectively.

By changing the delay time τ while keeping the remaining sequence timing unaltered, the temporal sampling rate of the peak pulsations can be adjusted. Figure 6 depicts the time-

dependent dissolved-phase peak amplitudes for delays of 50, 100, 200 and 300 ms ($TR = 90$, 140, 240 and 340 ms, respectively) obtained during 4 consecutive breath holds in the same subject. For small values of τ the pulsation characteristics are delineated clearly due to the high temporal resolution (i.e., short TR) but only a few complete oscillations are captured. A longer τ reduces the achieved sampling rate but covers more oscillations. Also, since more fully polarized xenon enters the bloodstream for long delay times than for short delays the overall signal-to-noise ratio (SNR) increases as well. However, for $\tau > 100$ ms we found the sampling rate to be too low for adequate analysis. In principle, the breath holds could be extended for short delay times to increase the number of observed oscillations. Nevertheless, the apparent $T1$ with which the gas-phase magnetization decays during the breath hold is dominated by the number of RF saturation pulses applied at the dissolved-phase frequency. Thus, for short delay times the rapid stream of saturation pulses decreases the gas-phase magnetization so quickly that an extension of the breath hold would only marginally increase the number of detectable oscillations.

The oscillation amplitude was found to be only weakly dependent on τ . Figure 7a exhibits the average relative change in the RBC signal between a local maximum and a neighboring minimum in Figure 6 while the error bars indicate the standard deviation over 3–4 periods. Considering the low sampling rate relative to the pulsation frequency (~ 1 Hz) for $\tau > 100$ ms (Figure 6d) the uncertainty in the location of the local extrema is considerably larger than for shorter delay times and, hence, the relative change as well as the standard deviations for the 200 ms and 300 ms bars have to be assumed to be more of an estimate for the actual values. Despite the uncertainty in the quantification of the pulsation amplitudes, the results can still serve as guide for additional insights when compared to simulated blood flow scenarios (Fig. 7b). Within the framework of this model, the predicted pulsation amplitude would be the ratio between the systole model 1 or model 2 scenarios and the diastole scenario for a given delay time (Fig. 7c). The parameters chosen for the two systole models (flow velocity 200% of normal in systole model 1 and vessel diameter 120% of normal in systole model 2) result in both cases in predicted oscillation amplitudes of approximately 20% for delay times of a few hundred milliseconds, which stands in good agreement with the experimental measurements shown in Fig. 7a. However, a qualitative comparison between Figs. 7a and 7c reveals that the observed weak dependence of the oscillation amplitude on τ does not agree well with the assumption that changes in the RBC peak signal between diastole and systole are predominantly caused by changes in the blood flow rate. Rather, the measurements indicate a variation in blood volume such as in the form of a change in the vessel diameters.

For an initial assessment of whether lung disease may impact the observed signal oscillations, the pulsation quantification was also performed in two GOLD stage 3 COPD subjects (55 yo and 57 yo) and an approximately age-matched second-hand smoker (51 yo) without a history of lung disease. As illustrated in Figure 8a, the pulsations for the TP and the RBC peak are very pronounced and synchronized in the SHS subject. On the other hand, in neither of the two studied COPD subjects, a stable pulsation is apparent (Figures 8b and 8c). Nonetheless, an intermittent pulsation of the RBC peak is still discernible (Figure 8b: $t > \sim 2$ s; Figure 8c: $t < \sim 2$ s), indicating that the lack of observable pulsation is probably not just due to a low signal-to-noise ratio.

Discussion

CSSR measurements permit the observation of HXe gas uptake by the lung parenchyma as well as the pulmonary blood flow, and thereby provide insights into global lung function. By varying the delay time between an RF pulse that selectively saturates the dissolved-phase xenon magnetization and the subsequent acquisition of an MR spectrum, the amount of time available for xenon atoms to leave the alveolar airspaces and to enter the lung tissue can be controlled with sub-millisecond precision. This high temporal precision, coupled with a xenon tissue diffusion constant that is drastically reduced relative to that in air, enables a non-invasive assessment of physiological parameters of microscopic biological structures with dimensions far below the spatial resolution limit of MRI. Several static and dynamic models for xenon uptake by the lung tissue have been developed over the years, but all of them either neglect blood flow or assume it to have constant flow rate. However, in our CSSR studies, in deviation from these models, we found the DP peaks to oscillate during the breath hold. Although pulse oximeter readings were not recorded during the breath holds, and the heart rate of the subjects was not constant (it generally increased from the beginning to the end of the breath hold), there appeared to be at least good empirical agreement between the oscillation of the DP peak areas and a subjects' heart rate. Thus, the most likely explanation for the observed phenomenon is blood-flow related changes tied to the cardiac cycle. In this work we have presented evidence that the pulsatile nature of the pulmonary capillary blood flow cannot only be detected by CSSR spectroscopy, but that its impact is so large that the existing xenon uptake models in their current form could potentially yield highly variable results, in particular when fitting the delay-time dependence of the RBC peak. A random arrangement of the delay times in a CSSR spectroscopy study could mitigate the problem. However, the linear part of the RBC xenon uptake curve is usually not sampled very heavily and each research group uses their own sampling arrangement that may be more or less sensitive to pulsation. Hence, it might be advisable to "stress-test" a given delay-time arrangement with regard to its sensitivity to signal oscillations in the 1 Hz regime and optimize its robustness. Dissolved-phase imaging techniques, on the other hand, are likely to be less affected since they lack RF saturation pulses such that the acquired signal is actually a temporal average of the HXe distribution over multiple repetition times.

The signal from the TP peak is dominated by HXe dissolved in the lung tissue itself; only a small fraction originates from HXe in the blood plasma. Also, the Ostwald solubility for xenon in RBCs is approximately three times higher than that for xenon in blood plasma (38). Hence, it comes as no surprise that relative signal changes due to blood volume variations secondary to pulsatile flow are about 9 times higher (15.1% vs 1.7%) in the RBC than in the TP peak amplitude. Several components are likely to affect the dynamics of the xenon gas uptake by rhythmic changes throughout the cardiac cycle: the initial uptake by the lung tissue, diffusion through various cell membranes and blood plasma culminating in a weak binding to hemoglobin, and finally the actual transport by the plasma and RBCs. Further, for the signal pulsations to be visible in a global spectroscopic measurement, they have to be sufficiently phase coherent throughout the entire lung.

For the studies presented in this work all signals (GP, RBC and TP) were corrected for the exponential decay of the TP signal with time constant T_{1app} . Since we also aimed to

quantify the time-dependent variations of the TP signal such an approach could be inherently problematic and, if it can be assumed that during a breath hold all spectra are acquired under identical conditions, a correction by the GP signal decay is generally advisable. Unfortunately, the assumption does not hold in general, as illustrated in Figure 3. At TLC T_{1app} is virtually identical for the GP and TP signals. However, at RV the GP signal amplitude decays much more rapidly from spectrum to spectrum than at TLC and the ratio between the dissolved-phase and the gas-phase peaks decreases steadily throughout the breath hold. We propose that this phenomenon can be explained by the circumstance that at RV about 2–3 times as much xenon is dissolved in the lung tissue than at TLC due to the higher alveolar xenon concentration at RV. As a consequence, the GP magnetization depolarizes very quickly in lung regions with high surface-to-volume ratios (i.e., the alveoli) but much more slowly in regions with lower surface-to-volume ratios (i.e., the conducting airways). Since we measure only a single global signal this preferential gas-phase depolarization in the alveoli changes the composition of the anatomical signal origins during the breath hold and the effect is particularly strong at RV. Thus, to be consistent in our evaluation of the oscillation amplitudes at RV and TLC we always used the TP T_{1app} for signal correction. For this kind of CSSR studies it might even be good practice to compute T_{1app} for both, the GP and the TP signal, to alert the investigator that, if significant differences become apparent, the interpretation of the study results may need to be adjusted accordingly.

In one of the healthy subjects, the CSSR measurements were repeated three times at RV and at TLC, which revealed considerable differences in the oscillation amplitudes of up to 50% for different breath holds and a dependence on the lung inflation level. It is currently unclear what caused these large fluctuations in the observed oscillation amplitude. One possible explanation might be that the minima and maxima are too sharp to be accurately localized by the employed sampling rate of 100 ms. The measurements further indicate that at least the RBC oscillations are on average approximately 50% higher at TLC than at RV (the TP oscillations could not be reliably quantified in this subject at either lung inflation). Since the alveolar air pressure in the lung at TLC is higher than at RV, it is expected that more capillaries are clamped off or that the capillary diameter is smaller during diastole (39). As a consequence, the relative changes in the RBC peak amplitude throughout the cardiac cycle are also much more pronounced at TLC than at RV. We therefore decided to perform all subsequent studies at TLC.

The choice of delay time for the CSSR measurement is not straightforward and needs future optimization that may be pathology dependent. Clearly, the shorter the delay time, the higher the maximum sampling rate of the measurements and the more accurate the characterization of the pulsatile xenon gas uptake. Nevertheless, the trade-off is that the dissolved-phase signal following a shorter delay between RF saturation and data acquisition is generally lower. Additionally, the composition of the RBC signal is delay-time dependent since at shorter delay times the RBC signal is diffusion-dominated while at longer the delay times the balance shifts to transport dominance (see Fig. 2). In our initial studies we found a 100 ms delay time to provide a reasonable compromise, but more in-depth investigations will be necessary.

Unfortunately, the CSSR measurements are not sufficiently sensitive to pin down the exact origins of the measured signal pulsations. The most likely factors for the increased DP signals during systole are an increase in vessel diameter, the opening of additional capillaries through recruitment or a combination of the two. Either case would be described by the proposed model scenario “Thick Vessels” within the error of the measurement. Nevertheless, the simulations indicate a low likelihood that the observed signal pulsations are caused by variations in blood flow velocity alone. Rather, the predominant factor appears to be an oscillation in the capillary blood volume throughout the cardiac cycle such that during systole the faster blood flow and the increased capillary volume or surface area may both contribute to the higher observed dissolved-phase signal.

In healthy subjects, the observed pulsations reflect differences in gas uptake by the blood plasma and RBCs throughout the cardiac cycle. However, since the spectroscopic measurements are global in nature, this pulsatile blood flow in the pulmonary capillaries has to be sufficiently in phase throughout the pulmonary volume to minimize cancellation effects of the temporal fluctuations. A possible explanation for the disappearance of the global peak pulsations might therefore be that emphysematous lung tissue destruction, or regional pulmonary hypertension, in subjects with severe COPD reduces the coherence of the various regional pulsations. Nevertheless, it is also conceivable that the reduced RBC peak amplitudes that have been observed in COPD subjects (33) reduces the SNR of the measurements to a degree that a reliable detection of the pulsations are no longer feasible. Against this explanation speaks the observation that the pulsations do not appear to be entirely absent but only for part of the measurement (see Figure 8b). Another possibility is that the observability of the cardiac pulsations are age related. Both COPD patients were approximately twice as old as the members of the healthy volunteer group. To at least mitigate this concern we included a 50 year-old, clinically-healthy SHS subject in our studies, who, unlike the 55 and 58 year-old COPD patients, exhibited strong pulsatile xenon uptake throughout the cardiac cycle. Still, given the small number of COPD patients investigated, and the inclusion of only one age-matched control subject, additional subjects will need to be studied before more concrete conclusions can be drawn.

In the studies presented in this work, the pulsatile xenon gas uptake was assessed without external reference. In the future it might be of interest to perform a synchronized recording of the ECG signal as well. This could permit the extraction of a phase difference between the actual heart beat and the arrival of the resulting pressure waves in the pulmonary capillary bed. If such a measurement was coupled with at least a partial spatial encoding, for instance by using an array coil and conducting a CSSR analysis for the data from each individual coil element, a regional lag in pulsation due to pathological changes in vessel compliance might be detectable.

Conclusions

In this preliminary study we have demonstrated that CSSR MR spectroscopy using HXe is sufficiently sensitive to detect the oscillations in the xenon gas uptake rate by the pulmonary circulation associated with the cardiac cycle. In particular, the amplitude pulsations of the RBC peak average 15%. These findings indicate that the existing theoretical models for

xenon uptake by the lung may need to be modified since the physiological parameters extracted by fitting the models to the experimental data could be heavily biased otherwise. Although we were able to reliably detect the RBC oscillations in the healthy subjects, they were at least temporarily absent in the two COPD subjects. Future work that combines partially localized CSSR measurements with ECG signals might provide new insights in the spatial and temporal dynamics of gas uptake in healthy and diseased lungs.

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Figure 1.

Schematic showing the RF and gradient (G) elements of a CSSR spectroscopy pulse sequence. One or more narrow-bandwidth RF pulses are used to saturate the magnetization of HXe dissolved in the lung parenchyma. A gradient spoiler dephases the transverse magnetization. Following a variable delay time τ , a narrow-bandwidth RF excitation pulse centered at the DP resonances creates an FID, which is sampled during the data acquisition period (DAQ). This process is repeated multiple times during the same breath hold either with different or a fixed value of τ and repetition time TR.

Figure 2.

Plot of the measured RBC-to-GP ratio as a function of the delay time from a healthy volunteer (squares). The solid line represents the measurement data fitted to the pulmonary gas-uptake model proposed by Patz et al (35). For delay times longer than approximately 50 ms a non-random oscillation of the measurement points about the fitted curve becomes apparent.

Figure 3.

Areas of the GP (left column), TP (middle column) and RBC (right column) peaks as a function of time at TLC (top row) and RV (bottom row). To correct for the decay of the magnetization due to T1 relaxation and the repeated application of RF pulses, the measured TP peak area was fitted to an exponential decay function. All peak areas (GP, TP and RBC) for the respective lung inflation level were subsequently corrected by the extracted apparent relaxation rate. The measured data is indicated by diamonds while the data corrected by the TP decay is marked by squares. At TLC, this procedure corrects the peak areas from all three compartments almost equally well. However, at RV the GP signal decays at a different rate than the signal from the other compartments.

Figure 4.

Rescaled TP and RBC data from Fig. 3 at TLC (a, b) and RV (d, e) after correction for T1 relaxation. Normalizing the maximum peak area in all plots to 1 illustrates the relative amplitudes of the TP and RBC oscillations (a, d). Scaling the TP (left-hand scale) and RBC (right-hand scale) data separately shows that the oscillations of both signals are synchronized with each other (b, e). Panel (e) further confirms that the signal decay at RV is not well described by a mono-exponential decay function since the corrected curves exhibit a substantial curvature. Two spectra of the dissolved-phase region at TLC (c) and RV (f) are plotted on top of each other to demonstrate that the differences in peak area between a local maximum (dashed line) and a neighboring local minimum (solid line) cannot be attributed to the existence of additional resonances but are solely due to changes in the volume of the existing DP compartments.

Figure 5.

TP (left-hand scale) and RBC (right-hand scale) signal oscillations from three different breath holds in the same subject at TLC (a-c) and the RBC signal from all three measurements combined in a single plot (d). Although in particular the RBC oscillations are clearly discernible in all plots there are apparent differences in the oscillation frequency and of up to 50% in the oscillation amplitude between the three breath holds.

Figure 6.

TP (left-hand scale) and RBC (right-hand scale) signal oscillations for delay times of 50 ms (a), 100 ms (b), 200 ms (c) and 300 ms (d) at TLC. (The time axes are scaled differently for each plot to accommodate the entire breath hold duration). The shorter the delay time, the higher the temporal resolution with which the oscillations are sampled. Longer delay times, on the other hand, result in more periods being sampled and higher signal-to-noise ratios. Given a typical heart rate of approximately 1 Hz, a delay time of 100 ms offers a good compromise.

Figure 7.

(a) Average relative RBC pulsation amplitude at TLC as a function of the delay time in a healthy subject. The measured average amplitude increases only slightly with increasing delay time. (b) Simulations of the RBC-to-GP ratio for three different model scenarios: 1) diastole model with 50% of the normal blood flow rate and normal capillary size (Slow Flow); 2) systole model 1 with the same capillary size as in the diastole model but with twice the normal flow rate (Fast Flow); 3) systole model 2 with a 10% increased capillary size and normal flow rate (Thick Vessels). (c) Predicted change in RBC signal between systole and diastole for the two different systole models. The “Thick Vessels” systole model provides a better match with the measurement results in (a).

Figure 8.

TP (left-hand scale) and RBC (right-hand scale) signal oscillations at TLC for (a) a 51 year-old second-hand smoker, (b) a 55 year-old GOLD stage 3 COPD patient and (c) a 57 year-old GOLD stage 3 COPD patient. All three subjects were of similar age, but while the peak oscillations are clearly discernible in the second-hand smoker they were at least intermittently absent in the two COPD patients.

Table 1.

Subject demographics and study parameters.

Subject	Status	Gender	Age	Inflation	Delay [ms]	TP Pulsation [%]	RBC Pulsation [%]
1	COPD	F	55	TLC	100	-	-
2	COPD	M	58	TLC	100	-	-
3	SHS	F	50	TLC	100	1.9	12.2
4	Healthy	F	21	TLC	100	1.9	19.1
5	Healthy	M	21	TLC	100	-	13.9
				TLC	100	-	14.0
6	Healthy	F	26	TLC	100	1.2	14.6
				TLC	100	-	9.4
				TLC	100	-	12.1
				RV	100	-	7.6
				RV	100	-	-
				RV	100	-	8.3
7	Healthy	F	22	TLC	50	1.4	16.9
				TLC	100	3.2	19.2
				TLC	200	2.9	16.5
				TLC	300	5.5	23.1
8	Healthy	F	32	TLC	100	0.9	10.5
9	Healthy	F	23	TLC	100	1.7	10.3
10	Healthy	F	19	TLC	100	1.2	14.5
11	Healthy	F	50	TLC	100	1.6	24.4
				TLC	100	1.5	16.6
12	Healthy	F	27	TLC	100	1.1	11.4
13	Healthy	F	27	TLC	100	2.2	18.1
				TLC	100	2.7	20.1