Evaluation of Dynamic Lung Function Using Non-Equilibrium Xenon Uptake Spectroscopy (NEXUS)

K. Ruppert[1], J. F. Mata[2], T. Altes[1], J. R. Brookeman[2], K. D. Hagspiel[2], and J. P. Mugler III[2]

[1]Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA, United States, [2]Radiology, University of Virginia, Charlottesville, VA, United States

Introduction: Despite numerous well-known shortcomings, pulmonary function tests based on spirometry are still widely used as the gold standard for evaluating and quantifying lung disease. Although it has been demonstrated that many additional markers of lung function are offered by hyperpolarized-gas MRI, it typically lacks the temporal resolution to obtain anything more than ventilation images during a regular respiratory cycle (1,2). In contrast, we propose that Non-Equilibrium Xenon Uptake Spectroscopy (NEXUS), an extension of a commonly-used hyperpolarized xenon-129 (HXe-129) MRS pulse sequence (3-7), might provide unique insights into the lung-function dynamics of a freely breathing subject that far exceed those of conventional spirometry. In this preliminary work in rabbits, we describe some of the capabilities of this method and discuss potential applications.

Methods: The NEXUS pulse sequence begins with a series of up to three 90° 900-µs Gaussian RF saturation pulses, centered at the xenon dissolved-phase frequency (i.e., 202 ppm downfield from the resonance frequency of the HXe-129 gas residing in the lung airspaces) and separated by gradient spoilers, applied to destroy any xenon signal originating from within the lung parenchyma. After a variable delay time that controls how much HXe-129 gas can enter the lung parenchyma and the blood from the alveolar airspaces, a 900-µs Gaussian RF excitation pulse is applied and a free induction decay is collected (TR 20-100 ms, TE 0.55 ms, bandwidth 65 Hz, 512 data points). At 1.5 T, the RF-pulse bandwidths are sufficiently narrow to only marginally affect the gas-phase magnetization during the saturation segment of the sequence, but wide enough to result in an easily detectable signal from the gas-phase. For each study a total of 256 spectra were collected continuously. Experiments were performed on a 1.5-T commercial whole-body imager (Sonata, Siemens Medical Solutions, Malvern, PA) using a custom-made transmit-receive birdcage RF coil (IGC Medical Advances, Milwaukee, WI). Four New Zealand rabbits (approximately 5 kg each) were anesthetized with a mixture of Xylazine 5 mg/kg and Ketamine 50 mg/kg. The animals were then intubated and placed in the xenon RF coil. Immediately after the pulse sequence had been started the animals were ventilated with 10-50cc of isotopically enriched (85% ^{129}Xe) xenon gas, polarized to approximately 10-15% via spin exchange with an optically pumped rubidium vapor (Model IGI 9600Xe Xenon Polarizer, MITI, Durham, NC). The protocol was approved by our Institutional Animal Care and Use Committee.

Results: Figure 1a shows the behavior of the dissolved- and gas-phase amplitudes, as well as their ratio (DP/GP), over the course of a typical study. Three main respiratory intervals can be identified: 1.) gas administration (RI1); 2.) breath hold (RI2); and 3.) initial expiration followed by free breathing (RI3). During RI1 the gas- and dissolved-phase signals rise in synchrony but at different rates, as indicated by the change in DP/GP. During RI2, DP/GP remains almost constant as the gas magnetization decays away. In the free breathing interval (RI3), the gas is quickly removed from the major airways and continuously diluted in the alveoli. The result is a DP/GP ratio that oscillates in concert with the respiratory cycle. Fig. 1b shows DP/GP during RI1 and the beginning of RI2 for administered gas volumes of 10-50cc.

Conclusion: Most existing techniques that measure HXe-129 uptake by lung tissue operate exclusively within RI2, where they can detect relative changes in the dissolved-phase volume, for instance due to emphysema or cystic fibrosis. However, in particular in conjunction with specific breathing maneuvers that could be performed by human subjects, NEXUS provides a number of additional parameters and time constants to define lung function. For instance, as demonstrated in Fig. 1b, the peak of DP/GP in RI1 indicates the arrival of HXe-129 at the gas exchange sites, which are characterized by having the highest tissue-volume to gas-phase-volume ratio. As the administered gas volume continues to increase, DP/GP decreases as the lung continues to inflate. Combined with a subject performing an inspiratory breathing maneuver similar to the one done for spirometry to measure FIV_1, changes in the gas arrival time might, for instance, become an indicator of small airway disease that restricts gas diffusion towards the gas-exchange sites. Other parameters of potential interest for the detection of pathology may, for instance, include the peak expiratory DP/GP (absolute as well as relative to the value in RI2) and the DP/GP difference between RI2 and the minimum in RI3. Another application for NEXUS might be in form of a free-breathing exam in children who cannot perform forced respiratory maneuvers. Also, with a temporal resolution of 30ms or better, which is much greater than that of any existing technique, not even a breath hold would be required.

References

[1] Saam B, Yablonskiy DA, Gierada DS, Conradi MS. MRM 1999; 42(3):507-14.
[2] Salerno M, Altes TA, Brookeman JR, de Lange EE, Mugler III JP. MRM 2001; 46(4):667-77.
[3] Ruppert K, Brookeman JR, Hagspiel KD, Driehuys B, Mugler III JP. NMR Biomed 2000; 13(4):220-8.
[4] Butler JP, Mair RW, Hoffmann D, Hrovat MI, Rogers RA, Topulos GP, Walsworth RL Patz S. J. Phys.: Condens. Matter 2002; 14:L297-L304.
[5] Mansson S, Wolber J, Driehuys B, Wollmer P, Golman K. MRM 2003; 50(6):1170-9.
[6] Driehuys B, Cofer GP, Pollaro J, Mackel JB, Hedlund LW, Johnson GA. PNAS 2006; 103(48):18278-83.
[7] Abdeen N, Cross A, Cron G, White S, Rand T, Miller D, Santyr G. MRM 2006; 56(2):255-64.

Acknowledgements

This work was supported by NIH grant R01 EB003202 and Siemens Medical Solutions.

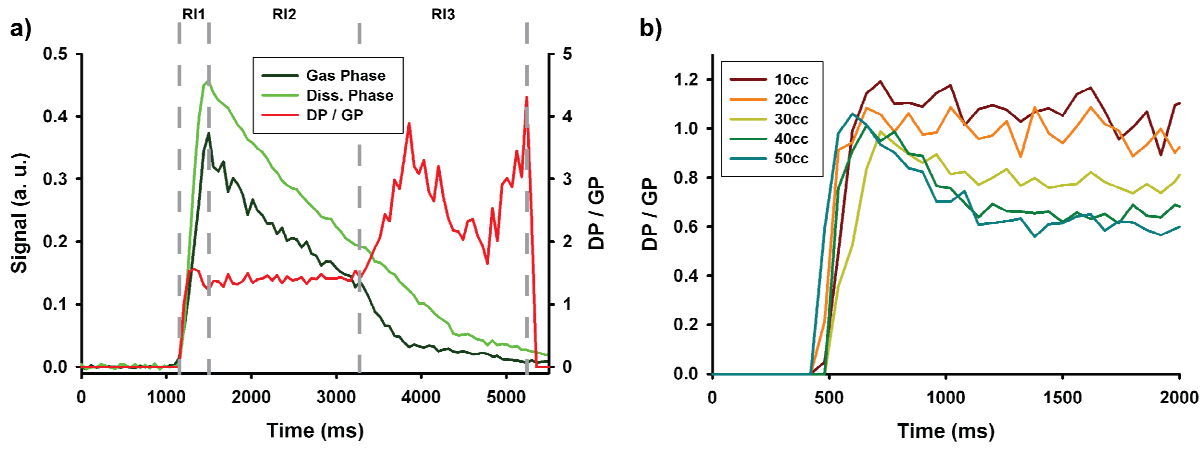

Figure 1. (**a**) Temporal dynamics of the gas- and dissolved-phase signals as well as their ratio, DP/GP, during a NEXUS acquisition for an administered volume of 30 cc. Three characteristic respiratory intervals (RI1, RI2 and RI3) can be distinguished. (**b**) Dependence of the DP/GP ratio on the administered gas volume, which permits the time required for the inspired gas to reach the site of maximum gas exchange to be estimated.