^{129}Xe Dynamic Spectroscopy and Modelling: A Repeatability and Method Comparison Study

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Target Audience: Respiratory clinicians and physiologists; hyperpolarized gas MRI community.

Introduction & Purpose: NMR spectroscopy methods have been developed to quantitatively examine pulmonary gas exchange in humans with hyperpolarized (HP) ^{129}Xe, exploiting the solubility of xenon in bodily tissues and blood, and the chemical shift sensitivity of ^{129}Xe dissolved in lung tissue and blood plasma (T/P) and red blood cells (RBCs) in vivo – these are well separated from the ^{129}Xe gas resonance (~ 200 ppm). One such method – dubbed chemical shift saturation recovery (CSSR) [1] – involves dynamic monitoring of the RBC and T/P signals after selective saturation and a variable wait period during which gas exchange occurs. An alternative method involves measuring the ratio of signals from ^{129}Xe in RBCs to that in the T/P compartment after one particular wait period (exchange time) [2]. Both methods have been shown to be clinically useful, particularly in interstitial lung disease (ILD) [1], including idiopathic pulmonary fibrosis (IPF) [2, 3], wherein gas exchange efficiency is impaired. However these studies were small, with limited patient numbers and the repeatability of these techniques in single subjects is yet to be assessed. The repeatability of metrics derived from these methods is critical to determining their sensitivity and clinical robustness as quantitative markers of early stage ILD – a clinical issue for which there is currently no diagnostic tool. In this work, the intra-subject repeatability of two different implementations of the CSSR method and the quantitative parameters derived from them – including RBC-T/P ratio – was assessed in healthy normal volunteers.

Methods: Five healthy volunteers, 24 – 63 yrs (2 female, 3 male) and with no history of respiratory disorders, were recruited. Each subject was scanned on three separate days over a period of 1-3 weeks on a 1.5 T (GE HDx) whole-body MR system. The MR protocol consisted of running the ^{129}Xe CSSR spectroscopy sequence in two manners that have been used in the literature [3, 4] (see Figure 1). In both cases, binomial-composite radiofrequency pulses were utilized for selective saturation of dissolved ^{129}Xe [5] and 64 or 128 sampling points were acquired for a bandwidth of 12 kHz. CSSR data were fitted with the models of Patz et al. [1] and Chang [4] in order to quantify parameters of lung microstructure and function including alveolar septal thickness (ST), surface-area-to-volume ratio (S/V) and RBC capillary transit time (CTT). Finally, the RBC-T/P ratio was estimated from multi-sweep CSSR data by numerical integration of the ^{129}Xe signal intensities in each compartment from spectra acquired at a TR value of 1 s. To appraise the repeatability of a specific parameter, the within-subject standard deviation (SD) and the "repeatability coefficient", $R = 1.96 \times 2^{1/2} \times SD$, was calculated. R represents the value for which 95% of repeat measurements for a given subject will lie within R of the mean [6].

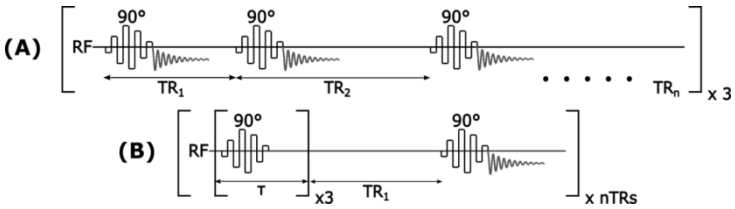

Figure 1: (A) "Multi-sweep" CSSR sequence with a single saturation pulse followed by a variable wait time (TR). 25 TRs from 20 ms to 1 s were swept through sequentially and the sequence was repeated 3 times (total breath-hold 15 s). (B) "Multi-sat" CSSR with multiple pulses before each "TR", to ensure total saturation. 21 TRs (20 ms – 1 s) were used and the sequence was only repeated once (total breath-hold 7 s).

Results & Discussion: Figure 2 depicts example Bland-Altman plots [7] showing the intra and inter-subject variations of three parameters derived from ^{129}Xe CSSR experiments; the ST and S/V (from Patz et al. model fits) and the RBC-T/P ratio. The intra-subject variability (repeatability) is represented by the standard deviation (y-axis). The mean intra-subject SDs of the ST parameter (0.45 µm, multi-sweep; 1.17 µm, multi-sat) were found to be significantly lower than the average difference in septal thickness between healthy normal and IPF subjects (~ 7 µm) as reported earlier [3], and for the multi-sweep implementation, the mean repeatability coefficient (1.24 µm) was also considerably less than this value, whilst the mean multi-sat R value was 3.23 µm. The mean repeatability coefficient for the RBC-T/P ratio was 0.08, compared with the ~ 0.40 difference in this parameter reported between IPF and normal subjects [2]. However, repeatability coefficients of derived CTT and S/V parameters from CSSR modelling were of the same order or larger than the measured parameters themselves, indicating that

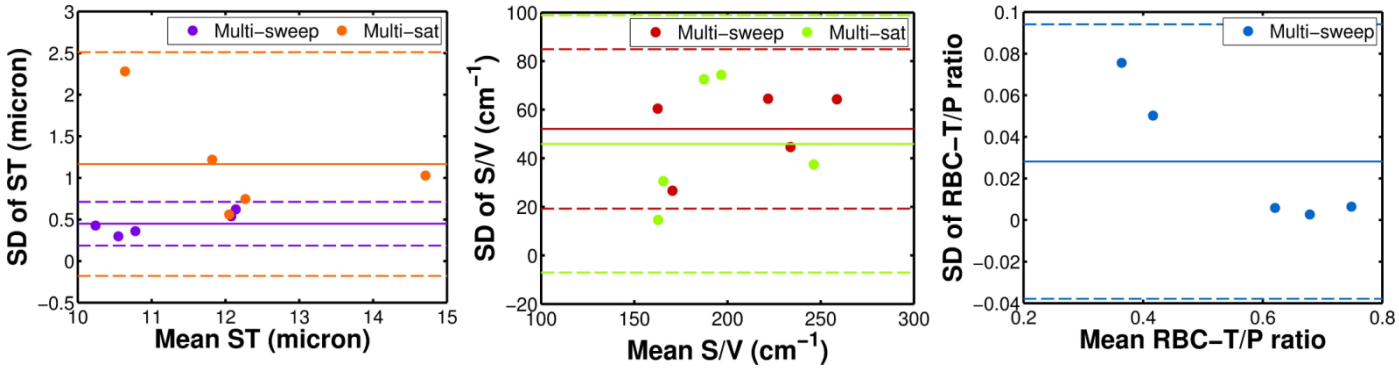

Figure 2: Left – Bland-Altman plot of the within-subject standard deviation (SD) in septal thickness (ST) against the mean value for each subject, including multi-sweep (purple) and multi-sat (orange) CSSR data. Middle – Bland-Altman plot depicting within-subject repeatability against between-subject variations for CSSR-derived surface-area-to-volume ratio (S/V). Right – Repeatability of the RBC-T/P ratio at a 1 s TR as derived from multi-sweep CSSR data. In each case, solid lines represent the mean intra-subject SD value for each parameter and the dashed lines denote ± 2 standard deviations from the mean SD.

the CSSR modelling process is not particularly sensitive to changes in these parameters introduced by lung pathology. Furthermore, comparing different implementations of the CSSR technique, the mean SD of each parameter derived from CSSR modelling was typically higher for the multi-sat compared with the multi-sweep sequence, indicative that the reduction in variance due to multiple averaging directly reduces the variance in fitting parameters. The Bland-Altman plots show that the SD of ST does not change with the mean ST value itself for either method; however there is evidence of a systematic bias tending towards higher ST values for the multi-sat implementation. Nevertheless, this may be an artefact induced by the complex modelling of multiple interrelated parameters.

Conclusion: In conclusion, it has been demonstrated that the septal thickness values derived from ^{129}Xe CSSR data are repeatable within subjects measured on three different scan sessions. However, the model-derived surface-area-to-volume ratio and capillary transit time values were found not to be repeatable and therefore cannot be considered as robust quantitative markers for use in future clinical studies.

References: [1] S. Patz et al., New J Phys. 2011;13:015009. [2] S. S. Kaushik et al., J Appl Physiol. 2014; doi:10.1152/japplphysiol.00326.2014. [3] N. J. Stewart et al., MRM. 2014; doi:10.1002/mrm.25400. [4] Y. V. Chang et al., MRM. 2013;69:884-890. [5] G. Leung et al., MRM. 2014; doi:10.1002/mrm.25089. [6] J. W. Bartlett, C. Frost. Ultrasound Obstet Gynecol. 2008;31:466-475. [7] J. M. Bland, D. G. Altman. Lancet. 1(8476).307-310.