Hyperpolarized ^{129}Xe Lung Morphometry Method for Estimation of Xenon Concentration Gradients in Chronic Obstructive Pulmonary Disease

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Introduction: Hyperpolarized xenon-129 (^{129}Xe) pulmonary magnetic resonance imaging (MRI) has become a widely used tool for the observation and earlier detection of human lung diseases (1-2). The hyperpolarized ^{129}Xe method proposed by Sukstanskii (3) was recently demonstrated for lung morphometry of one healthy volunteer and one cystic fibrosis patient (4). Accuracy of morphometric parameters depends on a number of factors including the free diffusion coefficient of xenon (D_0), which is assumed to be the same everywhere in lung. The literature (2, 4) reports a wide range of D_0 estimations (0.1 – 0.221cm^2/s) in human lung. The common assumption that D_0 in the terminal airways of the human lungs corresponds to the diffusion coefficient of xenon measured in the trachea (0.14 cm^2/s) seems reasonable based on geometrical considerations (5), but might depend on the specific gas mixture in the terminal airways due to oxygen uptake, which may depend on COPD. In a recent study (1), it was hypothesized that the xenon dilution effect explained the observed superior-inferior (S/I) ADC gradient. Thus, if the D_0 distribution provides direct information about the gas concentration gradients in the human lung, it may be useful information for lung disease detection. We propose the method of estimation of the nominal xenon free diffusion coefficient based on the Sukstanskii approach (3). In this study, we demonstrate a proposed method in a small group of COPD subjects and healthy volunteers (HV).

Method: Four healthy volunteers and four COPD ex-smokers provided written informed consent to a study protocol approved by Health Canada and a local ethics board. Imaging was performed at 3.0 T (MR750, GEHC, Waukesha WI) using whole-body gradients (5G/cm maximum) and a custom built, rigid quadrature unshielded asymmetrical RF coil. Two interleaved acquisitions (TE = 9.8 msec, TR = 11.0 msec, matrix size = 128 x 128, number of slices = 7; slice thickness = 30 mm, and FOV = 40 x 40 cm) with and without diffusion sensitization were acquired for a given line of k-space to ensure that RF depolarization (5 degree constant flip angle was used) and T_1 relaxation effects (scan time was 2 seconds per slice) were minimal. The diffusion-sensitization gradient pulse ramp up/down time = 500 μs, constant time = 2 ms and diffusion time = 5 ms; providing four b values: 0, 12.0, 20.0, and 30.0 s/cm^2. The diffusion time of 5 ms was used in order to provide ^{129}Xe ADC sensitivity to alveolar length scales based on simulations (3). For all slices, k space was integrated in the complex domain in pairs then Fourier transformed to obtain a single diffusion weighted and a single non-weighted whole lung projection image for each b value. Hyperpolarized ^{129}Xe (86% enriched, polarization ~15-40%) was provided by a commercial xenon polarizer system (XeBox-E10, Xemed LLC, Durham NH). 1L of a 50/50 hyperpolarized ^{129}Xe/^{4}He gas mixture was inhaled by each subject from functional residual capacity (FRC). For each b value, a single 1L mixed dose was inhaled. All imaging was performed 30 minutes post-salbutamol and after spirometry, plethysmography and diffusing capacity of carbon monoxide (D_{LCO}) measurements were performed.

Following the Sukstanskii method (3) external airway radius (R), internal airway radius (r) and D_0 maps were computed from diffusion weighted imaging human data on a pixel-by-pixel basis for all subjects using a custom-built IDL 6.4 algorithm which searched for the global minimum.

Statistical Analysis: A paired Student t-test was performed for statistical comparison of HV and COPD subjects for R, r, and D_0 using IDL 6.4. In all statistical analyses, results were considered significant when the probability of making a Type I error was less than 5% ($P < 0.05$).

Results: Fig. 1a shows representative maps of R respectively for a healthy (left) and a COPD (right) subject. Fig. 1b shows the corresponding nominal D_0 maps for these subjects. Fig.1c shows S/I nominal D_0 gradient for HV and COPD patients obtained from Fig.1b. Table 1 summarizes the pulmonary function measurements, demographic and lung morphometry for all subjects.

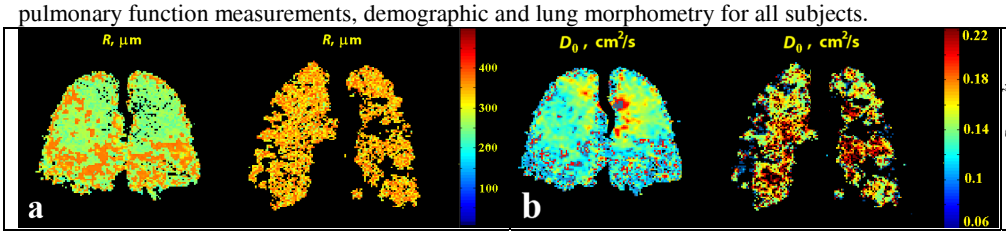

Fig. 1a and b. Representative R and D_0 maps for HV (left hand side image) and for COPD patients (right hand side image). Fig. 1c shows S/I nominal D_0 gradient for HV and COPD patients obtained from Fig.1b.

Table 1. Study Subject Demographic and Lung Morphometry.

	Healthy Never-Smokers					COPD Ex-smokers					Significance of
Parameter	H1	H2	H3	H4	Mean (SD)	C1	C2	C3	C4	Mean (SD)	Difference (p)
Age (yrs)	49	69	79	68	66 (13)	77	68	79	71	74 (5)	-
FEV_1 ($\%_{pred}$)	96	101	96	105	100 (4)	34	59	35	107	59 (34)	-
FVC ($\%_{pred}$)	110	99	95	101	101 (6)	94	86	84	135	100 (24)	-
FEV_1/FVC (%)	69	75	74	79	74 (4)	26	53	31	58	42 (16)	-
D_{LCO} ($\%_{pred}$)	121	101	101	94	99 (4)	17	43	44	42	37 (13)	-
R 10^{-6} (SD)(μm)	290 (53)	282(50)	305(52)	283 (50)	290 (51)	341 (37)	340 (36)	340 (36)	343 (31)	341 (35)	0.0026
r 10^{-6} (SD) (μm)	194 (26)	196 (25)	190 (26)	198 (25)	194 (25)	272 (38)	284 (35)	273 (38)	266 (35)	271 (36)	0.0003
D_0 10^{-1} (SD)	**1.3 (0.2)**	**1.3 (0.2)**	**1.2 (0.3)**	**1.2 (0.2)**	**1.25 (0.2)**	**1.7 (0.4)**	**1.4 (0.2)**	**1.6 (0.3)**	**1.4 (0.2)**	**1.52 (0.2)**	**0.035**

Discussion: We observed significant nominal D_0 ^{129}Xe differences between HV and COPD ex-smokers. Nominal D_0 map obtained for COPD is very heterogeneous in contrast with the corresponding R map. COPD D_0 map shows that there are sites with non-diluted xenon at the lung periphery and significantly diluted xenon at the central part of the lung close to the base of the lung. D_0 map obtained for the HV shows the presence of non-diluted xenon at the bottom of lungs and diluted xenon at the top of the lung. Fig 1c shows S/I nominal D_0 gradient for HV patient and complicate xenon distribution for COPD subject. Ideally, D_0 for each subject should be mapped with a dedicated breath-hold at a sufficiently short value of Δ to ensure unrestricted diffusion in the terminal airways and then results should be compared with D_0 values computed based on the lung morphometry approach. The effect of different gas mixtures and methods (eg. multiple breaths) is another avenue to investigate.

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