Measurement of p_AO_2 with Hyperpolarized ^{129}Xe: Correction for Signal Decay due to Gas Exchange.

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TARGET AUDIENCE: Pulmonary researchers and clinicians.

INTRODUCTION: Obtaining regional alveolar oxygen tension p_AO_2 is a coveted goal in pulmonary medicine. It is dependent on both ventilation (V) and perfusion (Q); pulmonary disease is associated with deterioration of either or both; differential diagnosis requires quantifying these changes. V/Q can be measured with Nuclear Medicine techniques at the cost of ionizing radiation exposure. Deninger [1] originally proposed a noninvasive MRI method to map p_AO_2 with hyperpolarized (HP) ^3He and there has been some follow up work in humans also primarily with ^3He [2-5]. Since ^3He is expensive and in short supply, ^{129}Xe is desirable as it is naturally occurring and far less costly. The calculation of p_AO_2 is based on the effect of O_2 on T_1 relaxation [6, 7]. For ^3He this is straightforward as helium is virtually insoluble in tissue and thus remains in the alveolar space. Xe, however, dissolves into tissue and blood and is carried away from the alveolar space [8]. This, along with T_1 decay, contributes to the loss of the ^{129}Xe MRI signal. There are initial reports of using HPXe for p_AO_2 mapping [8-12], but to date no attempt has been made to address this issue, mostly because only a small fraction of Xe is lost. However, this small amount (~3-5% in the timeframe of the measurement), translates into a significantly larger effect on T_1 calculation and can thus affect the estimation of p_AO_2. Here we report a novel use of the single-breath xenon transfer contrast (SB-XTC) [13] to measure p_AO_2 while simultaneously measuring and taking into account xenon gas exchange on the signal decay.

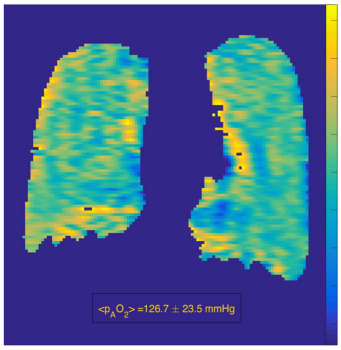

Figure 1. pAO2 map of a healthy subject, calculated from SB-XTC data after inhalation of HPXe containing 21% O_2. Mean pAO_2 before correction for Xe exchange was 127 Torr. After correction (estimated from this subject's measured global xenon septal uptake curve), the mean p_AO_2=97 Torr.

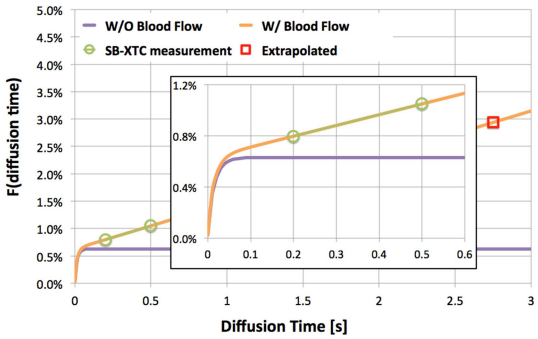

Figure 2. Simulated Xe uptake curve based on the mean values of S/V, gas-blood barrier thickness, and blood transit time in healthy volunteers.

METHODS: Here we present a new analysis of the data from a previously published study [13]. In short, in SB-XTC, 4 gas phase images are collected. During the time interval between images 1 and 2, RF pulses are applied at -205ppm separated by a diffusion time t_{diff}. while between images 2 and 3, identical RF pulses are applied at +205ppm (the dissolved state frequency) separated by the same t_{diff}. Image 4 is acquired immediately after image 3. The ratio I_3/I_2 is used to calculate the Fractional gas transport $F(t_{diff})$, while I_2/I_1 is dependent on the effect of the RF pulses and T_1 relaxation of the gas state signal; I_4/I_3 serves for flip angle calibration and mapping its distribution. We have estimated p_AO_2–equivalent before [8]: if in vivo T_1 is calculated from I_2/I_1, then p_AO_2 can be estimated using the linear relationship between $1/T_1$ and p_AO_2. However we did not account for the off-resonance RF pulse effect on the gas signal, assuming it was negligible. As a result, the T_1 values were underestimated and p_AO_2 values - overestimated.

In our data reanalysis, we accounted for the off-resonance pulse effect obtaining a mean p_AO_2=127.0±17.4Torr (mean ± standard deviation) in 17 volunteers. Since in all our experiments F_iO_2 = 0.21, we estimate the initial p_AO_2 ~100Torr. The time delay between the images is slightly under 2.75sec. To estimate the amount of xenon lost during this time due to gas exchange and blood flow, we used data from the xenon uptake curve studies in healthy volunteers: [14-16]. It has been shown that for diffusion times over ~100ms the tissue is saturated with xenon and the assumption of linear bulk blood flow is supported by the in vivo data. Figure 2 shows a simulated xenon uptake curve using the mean values of the surface area per unit volume available for gas exchange, tissue thickness and pulmonary blood transit time measured on healthy volunteers. We used this curve to estimate F(2.75sec)~0.03, i.e. in a healthy volunteer ~3% of xenon is taken away from the pulmonary region by the blood. When that loss is accounted for, the corrected mean p_AO_2=101.7±13.9Torr in 17 volunteers and is in agreement with expected values.

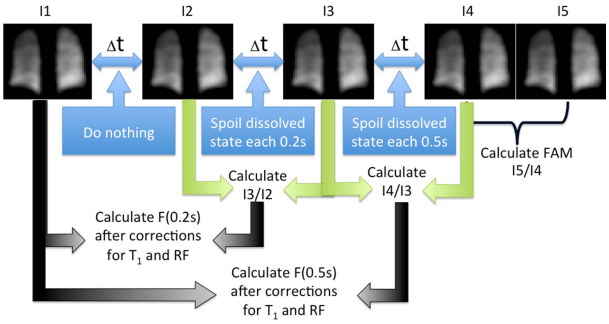

Figure 3. A schematic of the proposed SB-XTC approach to p_AO_2 measurement. If shorter breath-holds are necessary, one can separate the measurement into 3: during the 1st images 1, 2 and 3 will be collected, during the 2nd – images 1,2 and 4, and during the 3rd breath-hold - images 1,2 and 5. Thus 1st breath-hold will provide F(200ms), 2nd one – F(500ms), 3rd one – FAM; all of them have a pair of images that can be used to calculate T_1, and thus p_AO_2.

RESULTS AND DISCUSSION: From the reanalysis of the data above, it is apparent that although only ~3% of Xe reaches blood and leaves the pulmonary region, it results in a significant change in pAO_2 values, lowering the mean from 127.0±17.4 to 101.7±13.9 Torr, more than a 25% change. Of course, this is not a desired approach for p_AO_2 mapping – one needs simultaneous estimation of F during the same experiment, and not an ad-hoc correction using estimated values from an "average human volunteer". One way to accomplish this would be to use SB-XTC to measure F at both Δt_{23} =200 and Δt_{34} =500ms (green circles in Fig.2) while keeping the inter-image delay Δt constant (Fig.3). Again I_2/I_1 will be used to calculate T_1; between I_2 and I_3 a number $N_{23}=\Delta t/t_{23}$ (rounded to an integer) of 90° RF pulses are applied at +205ppm to measure F(200ms); between I_3 and I_4 $N_{34}=\Delta t/t_{34}$ 90° RF pulses are applied at +205ppm to measure F(500ms). Similar to SB-XTC, images 1 and 2 will be used to correct for all signal loss mechanisms not related to the gas exchange in estimation of F; further, using the linearity argument of the blood flow, the value of F will be extrapolated for Δt greater than 500ms (see red open square in Fig.2). N_{23} and N_{34} are determined by the overall delay time Δt, as this time is kept constant. Further, it is necessary to ensure that the saturation pulses at the dissolved state are wide enough to saturate all the dissolved frequencies (span of ~20ppm), but narrow enough not to affect the gaseous xenon at 0ppm. Otherwise, an extra calibration step will be necessary for the correction of the RF pulse effects on the gas phase signal (as was necessary in our current data).

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