On the relationship between 3He ADC and lung morphometrical parameters

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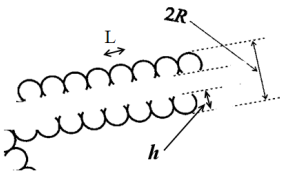
Introduction: After initial publications (1-4), numerous studies have demonstrated that the apparent diffusion coefficient (*ADC*) of hyperpolarized ^{3}He gas in the lungs dramatically increases in emphysema, suggesting a large potential as a diagnostic tool for clinical applications. In attempt to validate this method, several studies demonstrated a correlation between *ADC* and histological parameters of lungs (5-7). Despite a clearly visible correlation, there exists a substantial variation in experimental data. A question arises whether this variation is due to systematic or experimental errors, or if it reflects inherent differences between *ADC* and histological parameters. In the present communication we demonstrate that *ADC* (even aside from its dependence on gas concentration and MRI pulse-sequence parameters) cannot be uniquely related to histological parameters of lungs. As an example, we consider the relationship between *ADC* and mean chord length *Lm*, which is a gold histological standard of emphysema progression.

Materials and Methods: Thirty subjects with significant smoking histories (50 ± 20 pack years, average age 62 ± 3 years, 26 @ GOLD 0, 3 @ GOLD 1, 1 @ GOLD 2) were recruited for hyperpolarized helium-3 MRI from the National Lung Screening Trial (NLST), along with five never-smoking subjects. Axial 2D multi-slice diffusion-weighted ^{3}He FLASH images were acquired during a nine-second breath-hold (resolution = 7 x 7 x 30 mm; TR/TE = 13/8.32 ms; diffusion time = 1.8 ms; 3 slices; *b*-values = 0, 2, 4, 6, 8, 10 s/cm^2). The ^{3}He MRI images were analyzed in the framework of the *in-vivo* lung morphometry technique (8, 9). The technique is based on a theoretical approach that relates MR signal to an accepted geometric model, in which acinar airways are considered as cylinders of radius *R* covered by an alveolar sleeve of depth *h* (Fig. 1) (10). Thus, values of the parameters *R* and *h* can be found from the multi-*b* MRI experiment on a pixel-by-pixel basis (Bayesian probability analysis is used). The mean linear intercept *Lm* is calculated by utilizing a standard relationship to the surface-to-volume ratio: $Lm = 4\cdot(V/S)$. *V* and *S* per 1 alveolus can be readily calculated from *R* and *h* (9):



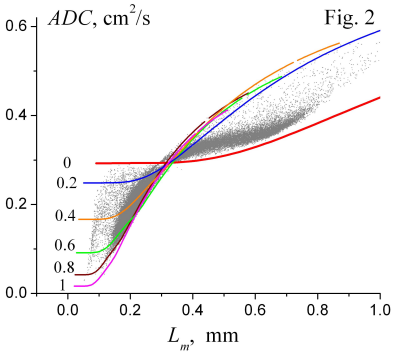
$$V = \pi R^2 L/8, \quad S = \pi RL/4 + \pi h(2R-h)/4 + 2Rh, \quad L = 0.765R \quad . \qquad [1]$$

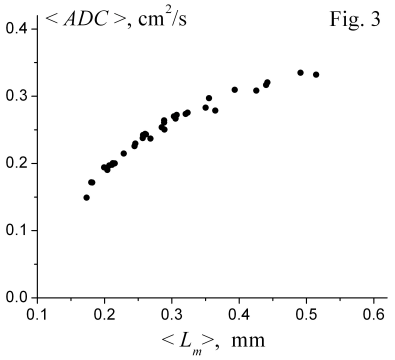
The validation study (9) demonstrated an excellent agreement between *Lm* found by means of *in vivo* lung morphometry technique and *Lm* from direct histological measurements.

ADC is related to the longitudinal (D_L) and transverse (D_T) diffusivities of ^{3}He gas in airways (4): $ADC = (D_L + 2D_T)/3$. In the millisecond range of diffusion time Δ, the parameters D_L and D_T are related to *R* and *h* by the following empirical expressions (8, 9):

$$D_L = D_0\cdot\exp\left(-2.89\cdot(h/R)^{1.78}\right), \quad D_T = D_0\exp\left[-0.73\cdot(L_2/R)^{1.4}\right]\cdot[1+u(h/R)] \qquad [2]$$

Here D_0 is the free diffusion coefficient of ^{3}He gas; $L_2 = (4D_0\Delta)^{1/2}$ is the characteristic free-diffusion length for two-dimensional diffusion and the function *u* is defined in (9).





Results and Discussion: In Fig. 2 we accumulated the results for all 35 subjects and plotted *ADC* vs *Lm* (calculated on a pixel-by-pixel basis) (grey symbols). The color lines represent the dependence of *ADC* as a function of *Lm*, theoretically calculated at fixed values of the ratio *h*/*R* (given by numbers near the lines). All data points are aggregated in two clearly distinguish "pools" separated by a "bottle-neck". Each value of *Lm* can be associated with numerous values of *ADC*, and vice versa. It means that the correlation between these two parameters is very limited. This result should be expected because *Lm* and *ADC* depend on two independent geometrical parameters *R* and *h* in absolutely different ways (Eqs. 1 and 2), and the same values of *Lm* and *ADC* can be achieved at different combinations of *R* and *h*. This effect is especially pronounced in the lower "pool" corresponding to normal lung regions and regions with minor emphysema, for which *Lm* does not exceed 0.3 mm and *ADC* < 0.3 cm^2/s. In the upper "pool", corresponding to airways with substantial degradation of the alveolar sleeve, the alveolar depth does not exceed 0.2*R* and *ADC* > 0.3 cm^2/s. In this "pool", thus, *Lm* and *ADC* mostly depend on only one parameter, *R*. That is why the "scattering" of *Lm* and *ADC* is less than in the lower "pool".

The *average* (over each subject) values of the parameters *ADC* and *Lm*, demonstrate much less variability, however, their dependence is non-linear, as shown in Fig. 3.

Conclusion: Our data demonstrate there is no unique relationship between *ADC* and one of the important histological characteristics of lungs - mean chord length *Lm* - calculated on the pixel-by-pixel basis. This result is due to substantially different dependences of *ADC* and *Lm* on the two main geometrical parameters of acinar airways—*R* and *h*. At the same time, ^{3}He based *in vivo* lung morphometry technique allows quantification of the lung microstructure in terms of *Lm*, surface-to-volume ratio and other standard histological parameters.

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