# A Novel Approach to Measure Regional Lung Ventilation Using Hyperpolarized 3He MRI –Potential in Clinical Studies

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**Introduction:** Pulmonary ventilation is an important marker in lung physiology and sensitive to many obstructive and restrictive pulmonary diseases. Conventional techniques for measuring regional ventilation are based on delivery/clearance rates of radioactive gases, as well as xenon-contrast X-ray CT. These techniques, however, expose patients to radiation and preclude frequent screening necessary for monitoring progression of disease or response to therapy. Hyperpolarized (HP) (HP $^3$He MRI has emerged as a novel technique with unique capabilities in visualizing ventilated airspaces noninvasively. Deninger, *et al.* [1] developed a technique for regional measurement of pulmonary ventilation which was based on HP $^3$He signal buildup in the lung following a sequence of helium breaths. This technique, however, is limited to use in small animals as it requires many HP $^3$He breaths (typically 30~50 breaths) and a relatively long acquisition time. This large number of breaths requires very good accuracy in gas delivery to avoid image misregistration problems. Therefore, we have developed a new technique for measuring regional ventilation that is acquirable over a much shorter period of time and requires a substantially fewer number of helium breaths. These properties allow the new technique to be implemented in humans. Results of the new technique are closely comparable to that of Deninger's method. It is also shown that measurements can be performed with mixtures of helium and oxygen without sacrificing accuracy. This avoids perturbing the physiological state of the subject while measurements are being performed.

**Methods:** Figure 1.a shows a schematic diagram of the new technique entitled *Dynamic Ventilation*. In Deninger's method, each point in the signal buildup curve for a given ROI (Figure 1.b) is acquired separately in Deninger's sequence; e.g. the *n*-th point is acquired during a breath-hold after inhaling *n* helium breaths. The lung is then washed with a sufficient number of air breaths to wash out all the residual helium and provide the subject with oxygen. Deninger's method therefore requires $\Sigma\, j$ ($j$=1→$n$) helium breaths for $n$ points. In contrast, the new approach acquires an image at the end of each inhaled breath and requiring only $n$ polarized breaths for the same number of points. Moreover, the acquisition time of $n$ images in the new technique is only $n.\tau$; this is shorter than Deninger's method by a factor close to $n$. The signal buildup in the dynamic ventilation sequence can be described by the following recursive equation, for the $j$-th breath: $M(j) = M_0 \cdot \exp\left[\frac{\tau}{T_{1,ext}}\right] \cdot r + M(j-1)\cdot(1-r)\cdot \exp\left[N\ln(\cos\alpha) - \frac{\tau}{\xi} P_A O_2 \cdot (1-r)^{washout\cdot(j-1)}\right]$, where $r$ is the fractional ventilation (portion of the gas replaced in a given ROI after inhaling the new gas), $M_0$ is the original magnetization in the helium reservoir. $T_{1,ext}$ and $\xi$ are polarization decay time constants due to interaction with the helium reservoir walls and oxygen, respectively. In practice $T_{1,ext}$ is much longer than the acquisition time and therefore its effect can be neglected. $N$ is the number of phase encoding lines (i.e. imaging resolution). Prior knowledge of $\alpha$, the flip angle, is required. This information is easily obtainable through standardized procedures. The *washout* parameter represents washout of oxygen from the lung airspace; where *washout* = 0 when a mixture of helium and oxygen is inhaled during imaging and $P_AO_2$ is maintained at a constant level, and *washout* = 1 when pure helium is utilized for imaging depleting oxygen from the alveolar spaces after each breath. Effects of oxygen uptake are ignored due to the relatively short timescale of image acquisition. To assess the performance of the new technique, measurements were performed in a group of healthy Sprague-Dawley rats using both techniques. Figure 1.c shows the details of the respiratory cycle. Measurements were performed with pure helium as well as with $^3$He and $O_2$ mixtures that summed to the same tidal volume as pure $^3$He. PFT was performed on animals prior to MRI session and TV was set to 15% of TLC.

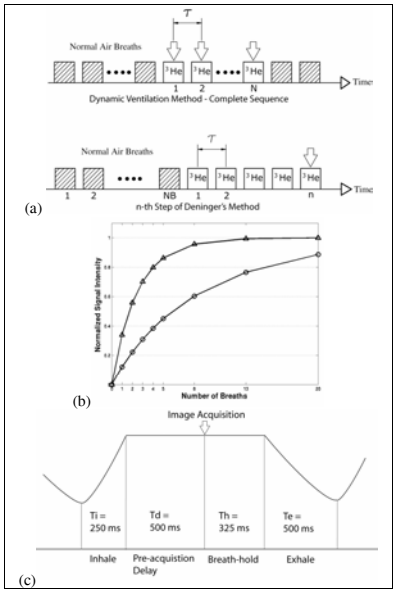
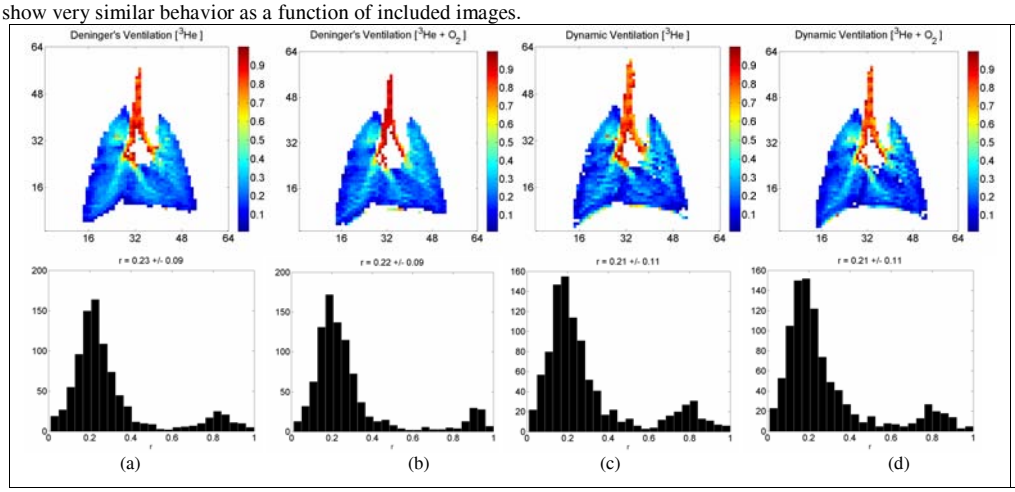
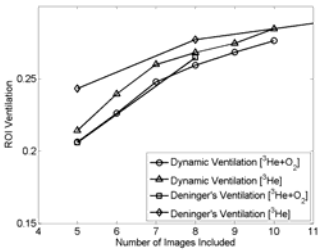



**Figure 1. (a)** Dynamic ventilation sequence compared to *n*-th step of Deninger's ventilation sequence; **(b)** Typical signal build-up for two different $r$ values; **(c)** Details of the breathing cycle for rats.

**Results and Discussion:** Figures 2.a through 2.d show representative maps of fractional ventilation obtained by both techniques, with and without oxygen, and the corresponding distribution histograms. It can be seen that results of both techniques are comparable on a regional basis regardless of the presence of oxygen. High $r$ values are measured in tracheas and conductive airways. The $r$ value in the lung parenchyma is measured at 0.21~0.23 irrespective of the technique used. Similar reproducibility was observed in other healthy rats. To assess the sensitivity of each technique to the number of images acquired/included in analysis, the same dataset was analyzed with a different number of images. Figure 3 shows the mean value of $r$ for an arbitrary region in lung parenchyma. With the exception of Deninger's method with pure helium, the other three methods show very similar behavior as a function of included images.




↑ **Figure 3.** Evolution of calculated $r$ value as a function of number of included images in the representative dataset.

← **Figure 2.** Regional maps of fractional ventilation obtained with Deninger's and the new dynamic ventilation method, with and without oxygen in a rat lung. Pixels with $r$ > 0.6 (corresponding to conductive airways) are excluded in the shown mean and standard deviations

**Conclusion:** The assessment of the new dynamic ventilation technique in rats shows the effectiveness of this method in the measurement of regional fractional ventilation without inherent limitations of the method previously proposed by Deninger *et al.* [1], i.e., high volume of hyperpolarized helium gas and long acquisition time. These key improvements will make it possible to perform such measurements in humans, so that this pulmonary marker can be utilized as a noninvasive regional probe in the early detection and monitoring progression of various lung function disorders

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