Local Pulmonary Ventilation Using Nonradioactive Xenon-enhanced Ultrafast Computed Tomography*

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Using ultrafast computed tomography, we have developed a technique for measuring local ventilation in a volume of 1 cm³ in the normal supine lung. The technique employs the inert gas xenon in its nonradioactive form and makes use of its radiopaque properties. The inhalation of xenon results in changes in density which can be detected and measured in Hounsfield units using ultrafast computed tomography. Using this property and assuming a monoeXponential form for the washin curve of the inert gas, it is possible to calculate ventilation at a local level. The methodology also permits measurements of minute ventilation during the procedure, thus permitting standardization. Using this technique, we calculated local ventilation in six normal subjects and have demonstrated a minor gradient in ventilation between the dorsal and ventral regions of the lung while in the supine position.

(Chest 1989; 96:799-804)

Methods

The technique used for the measurement of local pulmonary ventilation is based on the original radioactive ¹³³Xe washin technique described by Knipping et al. However, instead of count rate being plotted against time, changes in CT density measurements (Hounsfield units) are plotted against time. A linear relationship exists between CT Hounsfield units and concentration of xenon (Fig 1). The breathing circuit used in the ventilation studies is shown (Fig 2). An open circuit was employed and the subject inspired from a bag containing a mixture of 70 percent oxygen and 30 percent xenon. A bag in the box system with attached spirometer was incorporated into the circuit to permit measurement of minute ventilation and tidal volume, allowing for standardization of these variables.

Mathematical treatment of the washin curve for the inert gas was based on the analysis developed by Kety, which assumes that ventilation is a continuous process, and the inert gas has the solubility of zero, and a constant inspired concentration.

Making these assumptions and treating ventilation as a continuous

**Figure 1.** Linear relationship between change in xenon concentration and enhancement as measured by change in Hounsfield units (or delta CT for the ultrafast CT scanner use) in these experiments.

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process, the equilibrium of an inert gas can be described by the
exponential function \( C_t = C_v (1 - e^{-kt}) \) where \( C_v \) is the concentration
inspired gas at time \( t \) and \( C_v \) is the amount of gas present in the
lungs at time infinity and is related to volume. \( k \) is the rate constant
(the reciprocal of the time constant) — a parameter relating alveolar
ventilation to alveolar volume, \( \frac{\text{v}}{\text{v}} \) with the units \( \text{min}^{-1} \) is time.
The respiratory exchange ratio is assumed to be unity. Since the
equation is of the monoexponential form, calculations of \( k \) can be
simplified using semilog paper. When ventilation is treated as a
continuous process, the lung continuously dilutes inspired gas with
the midinspiratory lung volume, and the volume of distribution of
the inspired gas can be shown to correspond closely with the
functional residual capacity plus one-half the tidal volume.  

In two regions of equal volume \( V \) but with different ventilatory
flows \( \frac{\text{v}}{\text{v}} \) and \( \frac{\text{v}}{\text{v}} \), the region with the least ventilation will have a
slower rise in xenon concentration. However, both regions will
eventually reach the same level of activity, thus there is a finite time
during which differences between well and poorly ventilated regions
will be reflected in the distribution of the inert gas. This time will
be shorter if the difference between regional ventilatory flow rates
are small. The term \( (1 - e^{-kt}) \) reaches 0.95 when \( \frac{\text{v}}{\text{v}} \) is 2.99. For
normal lung, \( \frac{\text{v}}{\text{v}} = 0.035 \text{ s}^{-1} \), and 95 percent of the final concentration
will be reached within 80 s.  

When equilibrium is finally reached, the distribution of concentrations is then proportional to the
distribution of ventilated volumes and not to ventilatory flow rate. The concentration of gas in the alveoli of normal lungs builds up in an exponential fashion which continues for one minute and
beyond (Fig 3). As the total time for washin is limited, the washin
curve is less sensitive than the washout curve to small proportions
of poorly ventilated alveoli. Although there are some disadvantages
to the shorter washin curve, it permits subjects to breathe xenon
for a shorter period, yet allowing calculation of local ventilation
from a minimum number of scans. An open system maintains a
constant inspired concentration of xenon but at the cost of a greater
loss of xenon. As mentioned above, xenon is more soluble in fat
than in water, and accumulation of xenon in chest wall fat results in
a slight error in measurements of local pulmonary ventilation.  

The CT scanning was performed using an ultrafast CT scanner
(Imatron C-100 Scanner) with a scan time of 100 ms. Calibration
was carried out with a water phantom. The scanner can produce
real-time images of the beating heart in 50 ms and stationary images
of the body in 100 ms with 0.75 mm resolution. This scanner
achieves its high speed from a scanning electron beam that replaces

![Diagram](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21602/ on 06/26/2017)
the mechanical motion of the conventional x-ray scanners. This electron beam is directed through a vacuum chamber and magnetically focused over a 210° arc of four tungsten target rings. The electron beam striking these targets produces a fan-shaped x-ray beam that passes through the patient into one of two rings of detector arrays. Output from the detectors is digitized by a data acquisition system.10

In order to detect changes in density due to the inhalation of the radiopaque gas xenon, measurements were made over a region of interest of 121 mm² with a slice thickness of 8 mm, giving a film volume of approximately 1 cm³. Initially, a baseline scan was obtained after the subject had been breathing 100 percent oxygen for seven minutes, and from the derived attenuation coefficients, an average CT number was calculated for regions of interest chosen by the observer to avoid blood vessels. Both dorsal and ventral sites were selected. The subject then inhaled a mixture of 30 percent xenon and 70 percent oxygen for 60 seconds and another scan at the same level and phase of respiration was taken. Finally, oxygen concentration was monitored by an oxygen analyzer.

In the normal subjects, measurements were carried out at a single level. Scans were taken at end-tidal inspiration to standardize lung volume. The total dose of radiation per scan administered to the center of the subject was 330 millirads. Using the two scans, a subtraction image could be generated (Fig 4) permitting the effects of the change in attenuation coefficients, due to the inhalation of xenon, to be measured. From the change in attenuation coefficients detected over the region of interest and knowing xenon enhancement as a function of gas concentration and using the monoeXponential model for the washin curve of the form \( C_v = C_w (1 - e^{-vt}) \), calculation of the rate of constant, \( k \), was made. If \( k \) is given by \( v/s \) and \( v \) is set at 1 cm³, then flow rate per unit volume can be calculated and approximate comparisons made between the ventilation measurements from the dorsal and ventral regions of interest.

The subjects used in this study were six healthy men who, after informed consent, were studied according to a protocol approved by a Committee on Studies in Humans. The subjects undertook a modified Medical Research Council questionnaire on respiratory symptoms12 and also performed pulmonary function tests prior to performing the study. During the study, the ECG and blood pressure were monitored. After the study, each subject reported any side effects experienced. For this particular study, local ventilation is reported in absolute numbers ml/min, i.e., min⁻¹. Measurements were also made in a subject with bullous emphysema for whom whole lung scanning was performed rather than scanning at a single level.

**RESULTS**

Anthropometric data for the six normal subjects is shown in Table 1 and pulmonary function test results are shown in Table 2. Results of the questionnaire revealed that none of the six normal subjects had significant respiratory disease. The results of the change in CT number and the calculated ventilation rates are shown in Table 3. The average change in CT number after inhalation of the xenon-oxygen mixture was 31.08 (±3.8). As can be seen, there is a slight increase in ventilation to the dorsal region. The mean dorsal to ventral ratio is 1.25:1.00.

No significant side effects from inhaling the xenon-oxygen gas mixture were noted. One subject reported anxiety and all subjects described some form of sensation. No blood pressure or electrocardiographic changes were recorded. In the subject with severe bullous emphysema, marked reduction of ventilation to the bulla was observed, with very low ventilation rates being recorded.

**DISCUSSION**

The advent of ultrafast CT has opened a new

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**Table 1—Anthropometric Data (Normal Male Subjects)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>31</td>
</tr>
<tr>
<td>Height, in (cm)</td>
<td>70.5 (176)</td>
</tr>
<tr>
<td>Weight, lb (kg)</td>
<td>175 (79.4)</td>
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**Table 2—Pulmonary Function Tests (Normal Male Subjects)**

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<td>FVC, L</td>
<td>5.53</td>
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<tr>
<td>FVC, %pred</td>
<td>105</td>
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<tr>
<td>FEV₁, L</td>
<td>4.12</td>
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<tr>
<td>FEV₁, %pred</td>
<td>97</td>
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<tr>
<td>FEV₁/FVC%</td>
<td>75</td>
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<tr>
<td>FEF25-75, L/s</td>
<td>3.25</td>
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</table>
Table 3—Results

<table>
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<th>Subjects</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>RNDL Delta CT</td>
<td>42.5</td>
<td>20.8</td>
<td>23.1</td>
<td>28.1</td>
<td>25.6</td>
<td>25.1</td>
</tr>
<tr>
<td>Vml/min/ml</td>
<td>1.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>RDL Delta CT</td>
<td>54.7</td>
<td>31.9</td>
<td>31.1</td>
<td>34.2</td>
<td>29.5</td>
<td>42.8</td>
</tr>
<tr>
<td>Vml/min/ml</td>
<td>3.1</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
<td>1.4</td>
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<tr>
<td>LNDL Delta CT</td>
<td>41.9</td>
<td>16.9</td>
<td>24.9</td>
<td>25.6</td>
<td>8.2</td>
<td>27.9</td>
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<tr>
<td>Vml/min/ml</td>
<td>1.3</td>
<td>0.4</td>
<td>0.6</td>
<td>0.6</td>
<td>0.2</td>
<td>0.7</td>
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<tr>
<td>LDL Delta CT</td>
<td>53.8</td>
<td>34.5</td>
<td>30.4</td>
<td>34.6</td>
<td>12.9</td>
<td>44.8</td>
</tr>
<tr>
<td>Vml/min/ml</td>
<td>2.8</td>
<td>0.9</td>
<td>0.8</td>
<td>0.9</td>
<td>0.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Measured changes in CT number recorded in Hounsfield units after inhalation of the xenon/oxygen mixture for one minute. The calibrated local ventilation rates are shown for comparison.
RNDL, Right nondependent lung; RDL, right dependent lung; LNDL, left nondependent lung; and LDL, left dependent lung.

The major limitation had been that only a few lung slices could be studied due to the relatively long scan times and interscan delays. Scan times for conventional CT have required subjects to hold their breath for as long as 6s during actual scanning. This represents a significant disadvantage when evaluating patients with respiratory disease who have difficulty holding their breath. With short scan times, this disadvantage has been overcome. Whole lung scanning in both normal and abnormal subjects can now be performed in approximately two minutes with the ultrafast scanner.

Radiographic attenuation when measured by CT is proportional to physical density, and thus, varies with lung volume. Also, artefact can affect attenuation measurements. In particular, movement will down-grade images, but rapid scan times tend to reduce this problem. Since the range for mean attenuation is lower during inspiration, standardized lung volume was accomplished by having the subjects hold their breath at the end of an inspiratory tidal volume. Using a “bag in the box” method, it was also possible to standardize tidal volume and maintain a constant end-inspiratory tidal volume during scanning, while allowing measurement of minute ventilation. This combination of traditional pulmonary function measurement techniques with the new ultrafast CT scanning is a new approach to the problem of inconstant volumes during scanning and differs from previous measurements of local ventilation using xenon and CT. Another technique used to standardize the phase of respiration has been to employ a simple strain gauge respiration monitor with or without feedback monitoring.

Since xenon is an attenuator of x-ray films, it has been used as a contrast agent for imaging airways in conventional and digital radiology but has been most effective in CT.

Although washout studies are more sensitive to regional ventilation differences than washin studies, use of the washin curve for analysis permits a reduction in the amount of time that the subject is required to breathe xenon.

With any technique involving CT, the total radiation dosage delivered to the subject is a consideration. Using our ultrafast scanner with two scans, 46 mrad is delivered to the subject. This compares to 1 rad using the conventional nuclear medicine measurement of regional ventilation.

Several authors have studied the anesthetic effects of xenon, and side effects including hallucinations, euphoria, somnolence, and dysesthesias have been reported for inhaled concentrations greater than 30 percent. In our study, no significant side effects were reported by any of the subjects after one minute of inhalation of 30 percent xenon. As the washin curve
reaches 98 percent of equilibrium in two minutes in most normal subjects, it was not necessary to inspire xenon for longer periods.

Using an open system, we have avoided some of the errors inherent in the calculation of local ventilation based on Kety’s model.9 The major problem with closed systems is that the inspired concentration of the inert gas does not remain constant, thereby invalidating the use of the monoexponential equation. Due to the relatively high cost of xenon, some authors have used a closed system to minimize use,23 while others have developed methods of xenon recovery.27

An important factor that must also be considered in these measurements is the tendency for xenon to dissolve in lipids. It has been shown that adipose tissue in the chest wall introduces a 10 percent error in 133Xe studies.11 In our study, density measurements over the axillary fold after breathing 30 percent xenon for one minute revealed a mean change in attenuation of 9.2. This would introduce an error of 16 percent into our calculations.

Measurements of local ventilation derived from calculation of ventilation rate constants using CT have been made by other authors. Gur et al.22,28 carried out animal studies using 80 percent xenon inhaled over a period of six minutes and emphasized the importance of reproducing the same phase of respiration when computed tomograms were serially obtained. Herbert and co-workers29 performed studies on three human subjects obtaining two images from a (voxel) of 1.9 mm3 at end-inspiration at a preselected lung section after inhaling a 45 percent xenon mixture for four to eight breaths.26 These authors emphasized the importance of subtraction artifacts affecting calculations. A further study on one human subject was reported by Snyder et al.40 when the effect of PEEP on local ventilation to apical bullae and atelectatic lung was studied. Our technique extends previous work in this area by controlling and standardizing the lung volume at which scans are taken using spirometric tracings. This also permits measurements of minute ventilation at the time of the study. The applications of this improved technique are several. If one considers the washin curve obtained from measurements over the trachea, then the curve reflects the whole system. If measurements are made at end-tidal expiration, then the time constant is related to the functional residual capacity divided by the alveolar ventilation. Since the technique permits calculation of minute ventilation from the spirometry tracing, correction for dead space ventilation permits calculation of alveolar ventilation, and thus, functional residual capacity.

In the normal subject, equilibrium is reached within a relatively short period. However, in the diseased subject, the inert gas may washin much more slowly. When equilibrium is reached, local flow rate becomes zero and it is then possible to calculate a local static volume: 

\[ V = (\frac{1}{\alpha}) (V_0 - \frac{V}{\alpha}) \]

where \( V \) = volume limit of the unit. Thus, measurements made from the washin curve permit calculation of both static local lung volume and local ventilation for a given region of interest. (Since at the time the study was conducted, the amount of radiation per scan was felt to be too high to permit multiple scans during the washin phase, these calculations were not made.)

The time constant is equal to the product of the resistance and compliance31 of a given lung unit, and for a given subject there will be a whole range of units with varying time constants, some faster than others. A normal distribution will be found in normal subjects and an abnormal distribution in diseased subjects. For any given subject, a range of time constants can be mapped. In the normal state, better ventilation to dependent units in the supine position reflect units with faster time constants.

In our study, we have demonstrated a minor gradient in ventilation between the dorsal and ventral regions of the lungs in the supine position. Using similar techniques, Gur and co-workers32 identified a slight gradient in animals. Using 133Xe in the supine position for measuring regional distribution of ventilation in human subjects, Bryan and co-workers33 showed that the ventilation index gradient present in the upright position was abolished in the supine position but pointed out that failure to identify a ventilation gradient in the supine position could have been due to overlap between the front and back counter-fields that they employed.

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