Comparison of External Lung Monitoring With End-Tidal Air Detection Using the $^{133}$Xenon Inhalation Method

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SUMMARY When the $^{133}$Xe inhalation method is employed for measuring regional cerebral blood flow, the arterial $^{133}$Xe concentration is usually approximated by the end-tidal air concentration. However, this approximation may be invalid in the presence of certain lung pathologies or when the breathing pattern is irregular. Jaggi and Obrist, using an intravenous injection of $^{133}$Xe, suggested that the counts detected by an external lung probe could provide an alternative estimate for arterial blood concentration once the noise produced by $^{133}$Xe in superficial tissues is removed from the signal. A mathematical model, based on hypotheses similar to theirs is presented here together with a new computational procedure for removing the noise. Results from normal rest studies on ten healthy young males indicate that the approximations for arterial blood concentration obtained from end-tidal air and from corrected lung counts are not equivalent when $^{133}$Xe is administered by inhalation. The concentration-time curves have different shapes, and these differences are reflected in blood flow values computed by head channel. However, there is no effect on comparisons between homologous regions of the left and right hemispheres.

PARAMETERS RELATED TO REGIONAL CEREBRAL BLOOD FLOW (rCBF) can be estimated from external monitoring of head regions following the introduction of $^{133}$Xe provided the arterial blood concentration of $^{133}$Xe, $c_a(t)$, is known. With an intra-arterial injection, the $^{133}$Xe can be introduced rapidly at a point which insures that a bolus dose is delivered to the brain with little first passage delivery to extracerebral tissues. Since xenon is removed rapidly through the lungs, there is virtually no recirculation of indicator. Hence, $c_a(t)$ may be assumed to be proportional to the delta function. When $^{133}$Xe is administered intravenously or is inhaled, extracerebral tissues take up substantial amounts of indicator which is, subsequently, recirculated. Since $c_e(t)$ can no longer be approximated with a delta function, it must be measured.

Veall and Mallett suggested estimating $c_e(t)$ with noninvasive measurements of end-tidal air concentration, $c_e(t)$. Obrist et al showed that, under normal circumstances, $c_e(t)$ can be approximated by $c_a(t)$. However, potentially large discrepancies can develop between $c_e(t)$ and $c_a(t)$ when certain lung pathologies are present or when breathing is irregular.

Figure 1 shows the first two minutes of respiratory recordings from two sequential experiments on a single subject. In both cases the subject inhaled $^{133}$Xe mixed with air during the first minute and breathed room air thereafter. Data in figure 1A were recorded with the subject breathing normally at rest. The number of counts accumulated over 0.2 second intervals oscillates with those corresponding to end-tidal air being valleys during the first minute and peaks thereafter. The subject was humming (as dictated by the activation protocol) during the second test (fig 1B). The oscillatory pattern is distorted so severely that valley/peak identification is no longer possible. In such cases external monitoring of the lung may provide a more reliable estimate for $c_a(t)$.

In our experience, valleys and peaks cannot be identified in externally monitored lung data even with rapid sampling at 0.2 second intervals. The signal is probably damped because the lung probe detects emissions from pulmonary dead space as well as from end-tidal air. Jaggi and Obrist have successfully analyzed rCBF data following an IV injection of $^{133}$Xe using the counts accumulated over 0.1 minute intervals by an external lung probe. This effectively smooths the data. Corrections were made for noise superimposed on the lung probe data by radiation emitted from superficial tissues, and these corrected data, together with a proportionality factor, were used to approximate $c_a(t)$.

The experiments reported here were designed to test the feasibility of using externally monitored lung data (counts accumulated over 0.1 minute intervals) in conjunction with $^{133}$Xe inhalation in rCBF studies. A mathematical model based on hypotheses similar to those suggested by Jaggi and Obrist for intravenous injection of $^{133}$Xe is reported here for removing noise superimposed on the lung probe data by radiation originating from superficial tissues. A new computational procedure is presented. A normal rest study was performed on each of ten healthy young subjects using the inhalation method. The results indicate that the approximations for $^{133}$Xe arterial concentration obtained from end-tidal air detection and from external lung monitoring are not equivalent. The shape of the curves is not the same and these differences are reflected in computed blood flow values. However, these
Figure 1. Respired air recordings from a normal subject (first 2.5 minutes shown). A. Subject is at rest; B. Subject is humming.

Differences do not affect comparisons between homologous regions of the left and right hemispheres.

Methods

Measurement of rCBF using computer detected valley/peak count rates of $^{133}$Xe in a continuous respiratory recording to approximate $c_p(t)$ has been described for our system by Wilson et al. In the present study, two additional detectors were positioned over the right lung to monitor $^{133}$Xe over a 20 minute measurement period. These probes were thallium activated sodium iodide crystals, three-fourths inch diameter by three-fourths inch equipped with lead collimators three-fourths inch inside diameter by two inches long. One probe was placed laterally over the third intercostal space approximately one inch anterior to the right mid-axillary line. The axis of this detector made an angle of 25 degrees with the horizontal. The other probe was placed anteriorly over the third intercostal space just below the nipple; its axis was vertical. The positions were chosen to maximize the amounts of lung tissue and minimize other sources of radiation (for example, the heart or the aorta) in each detector’s field of view. Two probes were utilized in order to assess the effects of positioning on the measurements. The counts accumulated during 0.1 minute intervals were transmitted to the computer for subsequent processing. During the first three minutes, counts accumulated by the lateral lung probe over 0.2 second intervals were recorded on a multi-channel analyzer. These data were entered into the computer for subsequent analyses.

Noise is superimposed on the lung data by radiation originating from superficial tissues. This artifact could be removed if certain assumptions similar to those suggested by Jaggi and Obrist for intravenous injection of $^{133}$Xe are valid.

1. Superficial tissue detected by the lung probe can be treated as a single compartment.
2. The rate of clearance from the superficial tissue compartment, $k_s$ (min$^{-1}$), is slow compared to pulmonary clearance, so there is a time period (beginning at $t_m$) during which the data can be adequately represented by a single exponential characterizing superficial tissue clearance.

If these assumptions hold,

$$L(t) = A e^{-kt}, \quad t \geq t_m,$$

where $L(t)$ represents the counts detected by a lung probe and $A$ is an arbitrary constant. If $t_m$ were known, $k_s$ and $A$ could be estimated from data collected between $t_m$ and 20 minutes. For this feasibility study, $t_m$ was set equal to the time beyond which there was no detectable time trend in the respired air recording. At this point, $c_p(t)$, the pulmonary concentration, should not affect the estimates for $k_s$.

The adequacy of the single exponential representation (first assumption) was assessed by fitting

$$L(t) = B + A e^{-kt}, \quad t_m \leq t \leq 20,$$

to these same lung data and testing to see whether $B$ was significantly different from zero.

From the assumptions,

$$c_s(t) = f_s \int_0^t e^{-k_s(t-\tau)} c_p(\tau) d\tau,$$

where $c_s(t)$ is the $^{133}$Xe concentration in superficial tissues at time $t$, and $f_s$ is the blood flow per unit volume of superficial tissue. Combining lung and superficial tissues,

$$L(t) = P_l c_p(t) + P_l' c_s(t),$$

where

$$L(t) = \text{counts detected by a lung probe at time } t,$$

and

$$P_l, P_l' = \text{proportionality constants related to detector efficiency, anatomy of the subject's chest, and the relationship between amount and concentration.}$$

At the beginning of the study, $L(t)$ is approximately equal to $P_l c_p(t)$, the pulmonary contribution, since
very little $^{133}$Xe has been taken up by superficial tissues. Hence, the ratio of $P_L \cdot c_p(t)$ to $P_A \cdot c_a(t)$ can be estimated from the initial ratio of $L(t)$ to $P_A \cdot c_a(t)$, where $P_A \cdot c_a(t)$ represents the counts accumulated by the respired air detector. This ratio should remain constant throughout a given experiment even though it is measurable only at the beginning of the experiment. Since $P_A \cdot c_a(t)$ was observed throughout the experiment, the contribution of $P_L \cdot c_p(t)$ to $L(t)$ in (4) can be assessed. The pulmonary component accounted for less than 2.5 percent of the total lung probe counts after time $t_{m}$ in all but one case.

Substituting (3) into (4) and neglecting $P_L \cdot c_p(t)$ for $t > t_{m}$

$$L(t) = L(t_{m}) e^{-k_{s}(t-t_{m})},$$

Counts are accumulated by the lung probe and entered into the computer at 0.1 minute intervals. Thus, during the interval $(t, t + 0.1)$, the counts observed are

$$\int_{t}^{t + 0.1} L(t) \, dt = A e^{-k_{s}t}, \quad t \geq t_{m},$$

where

$$A = L(t_{m}) \left[1 - e^{-0.1k_{s}}\right] e^{k_{s}t_{m}/k_{s}}.$$  \hspace{1cm} (6)

Using the lung data collected between $t_{m}$ and 20 minutes, least squares estimates can be obtained for $k_{s}$ and $A$.

Counts accumulated over 0.2 second intervals by the lateral lung probe were recorded for the first three minutes of the experiment. The first two minutes of a typical recording are shown in figure 2. It was not possible to identify peaks and valleys either by eye or with a finely tuned computer algorithm in most cases. The minor oscillations seen in the first minute are not correlated in time with the higher amplitude regular oscillations seen in the respired air recordings. Visual scanning of the anterior lung probe analog recording at the time of the experiment revealed similar uninformative patterns. Thus, the analysis was continued on the basis of the working hypothesis that $c_p(t)$ is approximately proportional to $c_a(t)$ with the intent of determining what effect, if any, differences in their shapes would exert on rCBF parameter estimates.

Substituting (3) into (4),

$$L(t) = P_{sf} \int_{0}^{t} e^{-k(t-t')} c_a(t') \, dt' + P_L c_p(t),$$  \hspace{1cm} (7)

where $P_L$ incorporates $P'_s$ and the assumed proportionality between $c_p(t)$ and $c_a(t)$. Taking the Laplace transforms of the terms in (7), solving for the transform of $P_L c_p(t)$ and inverting the transforms yields

$$P_L c_p(t) = L(t) - R \int_{0}^{t} e^{-(k_{s} + R)(t-t')} L(t') \, dt',$$  \hspace{1cm} (8)

where $R = P_{sf}/P_L$.

R can be estimated from (8) by setting $t = t_{m}$.

Then

$$0 = L(t_{m}) - R \int_{0}^{t_{m}} e^{-(k_{s} + R)(t-t')} L(t') \, dt'.$$  \hspace{1cm} (9)

$L(t_{m})$ can be estimated from (6) using $k_{s}$ and $A_{s}$, the least squares estimates obtained from the $t_{m}$ to 20 minute time interval. Since $L(t)$ is observed, (9) is simply a nonlinear equation in $R$ that can be solved by standard methods. Once $R$ has been estimated, (8) can be employed to calculate the desired result for $0 < t < t_{m}$.

The computational steps may be summarized as follows.

1. Determine $t_{m}$ as the time beyond which no time trend can be observed in the respired air data.
2. Estimate $L(t_{m})$ from (6) using the estimates determine in the first step for $k_{s}$ and $A_{s}$.
3. Estimate $R$ from (9) using the above estimates for $k_{s}$ and $L(t_{m})$ together with an algorithm for solving the nonlinear equation.
4. Calculate corrected lung values from (8) for $0 < t < t_{m}$.

Results

A $^{133}$Xe inhalation experiment was performed under normal rest conditions on each of ten healthy young males. Least squares estimates were obtained for the rCBF model parameters ($k_1, k_2, P_1, P_2, S$ and $A$) using 11 minutes of recorded head curve data by total curve analysis as developed by Hazelrig et al. Estimates were obtained using each of the following functions to approximate $^{133}$Xe arterial concentration:

1. $c_a(t) = \text{end-tidal air as determined from computer detection of valley/peak counts in a respiratory recording sampled at 0.2 second intervals (standard method), and}$
2. $P_L c_p(t) = \text{corrected lung counts (both probes) as calculated from (8) at 0.1 minute intervals.}$

![Figure 2. Lateral lung probe recording of counts accumulated over 0.2 second intervals (first two minutes shown).](http://stroke.ahajournals.org/DownloadedFrom.jpg)
TABLE 1  Superficial Tissue Parameters

<table>
<thead>
<tr>
<th>Lateral lung probe</th>
<th>Time Constant (min)</th>
<th>Superficial Clearance Rate (min⁻¹)</th>
<th>Count rate at tₘ (cp)</th>
<th>Maximum Count Rate (cp)</th>
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</thead>
<tbody>
<tr>
<td>14.4</td>
<td>0.0328 ± 0.0089</td>
<td>8.11 ± 1.0</td>
<td>1116 ± 33</td>
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<td>15.3</td>
<td>0.0542 ± 0.0118</td>
<td>11.4 ± 1.0</td>
<td>792 ± 28</td>
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<td>16.0</td>
<td>0.0256 ± 0.0158</td>
<td>5.73 ± 1.06</td>
<td>683 ± 26</td>
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<tr>
<td>15.8</td>
<td>0.0185 ± 0.0139</td>
<td>5.04 ± 0.77</td>
<td>998 ± 32</td>
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<tr>
<td>14.8</td>
<td>0.0167 ± 0.0114</td>
<td>5.64 ± 1.91</td>
<td>1016 ± 32</td>
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<tr>
<td>15.6</td>
<td>0.0015 ± 0.0124</td>
<td>5.26 ± 1.03</td>
<td>718 ± 27</td>
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<td>15.3</td>
<td>0.0294 ± 0.0104</td>
<td>6.80 ± 1.06</td>
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<td>12.5</td>
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<td>16.0</td>
<td>0.0227 ± 0.0140</td>
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<td>15.4</td>
<td>0.0244 ± 0.0110</td>
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<table>
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<tr>
<th>Anterior lung probe</th>
<th>Time Constant (min)</th>
<th>Superficial Clearance Rate (min⁻¹)</th>
<th>Count rate at tₘ (cp)</th>
<th>Maximum Count Rate (cp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.4</td>
<td>0.0301 ± 0.0113</td>
<td>4.48 ± 1.32</td>
<td>1151 ± 34</td>
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<tr>
<td>15.3</td>
<td>0.0373 ± 0.0133</td>
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<td>16.0</td>
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<td>15.8</td>
<td>0.0398 ± 0.0169</td>
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<tr>
<td>14.8</td>
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<td>1047 ± 32</td>
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<tr>
<td>15.6</td>
<td>0.0221 ± 0.0153</td>
<td>4.69 ± 0.92</td>
<td>820 ± 29</td>
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<tr>
<td>15.3</td>
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<td>4.25 ± 1.18</td>
<td>896 ± 30</td>
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<tr>
<td>12.5</td>
<td>0.0336 ± 0.0070</td>
<td>5.15 ± 1.59</td>
<td>1038 ± 32</td>
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<tr>
<td>16.0</td>
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<td>4.54 ± 0.82</td>
<td>1174 ± 34</td>
<td></td>
</tr>
<tr>
<td>15.4</td>
<td>0.0416 ± 0.0136</td>
<td>6.58 ± 0.77</td>
<td>667 ± 26</td>
<td></td>
</tr>
</tbody>
</table>

*ₘ₁ = no detectable time trend in respired air data for t > tₘ

Equation (1) was fitted to the lung data from both probes for each of ten subjects. The single exponential equation was an adequate representation of these data as judged from (2) where B was never significantly different from zero (p < 0.05).

Table 1 presents the superficial tissue parameters. Column 1 shows tₘ. Also shown for the lateral and anterior lung probes are k₁ (the superficial tissue clearance rate), A (the lung probe count rate of tₘ), and the maximum lung probe count rate observed.

A plot of corrected lung counts, calculated from (8), superimposed on end-expired air counts is shown in figure 3 for the first two minutes of a typical recording.

Blood flow parameters were estimated using data collected from the right and left hemispheres of the brain for each of seven head channels (A-E, G-H). Comparisons of f₁ (fast compartment flow), w₁ (relative weight of fast compartment), IS (initial slope of head curve that would be observed following a bolus injection), and CBFₐ (theoretical height/area following a bolus injection) were made using estimates obtained from end-tidal air and from corrected lung probe approximations for ¹³³Xe concentrations of arterial blood. These parameters have been defined by Obrist and Wilkinson. Note that IS is not the initial slope index (ISI) defined by Risberg, but that

\[ IS = FF₁k₁ + FF₂k₂, \]

where FF₁ and FF₂ are the fractional flow to the fast and slow compartments, respectively. Mean hemispheric values are presented in table 2.

The differences between the various estimates obtained from each head probe were analyzed by paired t-tests with the p level being at .05. When the end-tidal air estimates for IS, w₁ and CBFₐ were compared to each of the corrected lung probe estimates, the differences were significant for all three parameters in all 14 head channels. The differences in f₁ estimates were significant in 24 out of the 28 cases tested (14 channels and 2 lung probes). Comparisons between the two corrected lung probes yielded more varied results. The estimates for w₁ and CBFₐ were not significantly different, while those for f₁ and IS were significantly different in more than half of the channels. However, the values estimated from corrected lung probe values were much more similar to each other than to the estimates obtained with end-tidal air values.

The differences between the corresponding left and right channel estimates for f₁, w₁, IS and CBFₐ were tested for all seven regions. There were essentially no significant left-to-right differences between estimates obtained with end-tidal air and estimates obtained with either lung probe (the only exceptions being channel E for f₁ and channel H for IS). No significant left-to-right differences were found when the two corrected lung probe estimates were compared with each other.

**Discussion**

The approximations for ¹³³Xe arterial blood concentration obtained from end-tidal air and from corrected lung counts are not equivalent. The concentration-time curves have different shapes, and these differences are reflected in the blood flow parameters estimated from each head channel. Reexamination of the model assumptions is appropriate.

There is a time period from tₘ to 20 minutes during which the data from each of the 20 lung probe recordings can be adequately represented by a single exponential component. Thus, these data are consistent...
with the first assumption that superficial tissue can be treated as a single compartment. There is no time trend in the respired air data after time \( t_m \). Hence, there should be no time trend in the pulmonary contribution to the lung probe counts, so pulmonary \(^{133}\)Xe should not affect the estimates for \( k_2 \). Further, pulmonary \(^{133}\)Xe accounted for less than 2.5 percent of the lung probe counts after time \( t_m \). The mean estimate for superficial tissue clearance is \(0.028 \text{ min}^{-1} \) which is close to the mean of \(0.033 \text{ min}^{-1} \) reported by Obrist et al\(^8\) for extracerebral tissue in a three-compartment analysis of clearance curves recorded in 15 normal subjects. Thus, the second assumption is plausible.

There was an implicit assumption that the external lung probe was responding primarily to lung tissue. The shape of the lung curve could be influenced by the placement of the external probe if, for example, too much breast tissue or fat tissue is included in the field of view. These problems were minimized by restricting this control study to non-obese males. The influence of probe placement was explored further by obtaining simultaneous recordings from two different lung probes. Since rCBF parameters estimated with the corrected lung probe recordings were far more similar to each other than to the end-tidal air estimates, probe positioning is not the major factor in the discrepancies.

The working hypothesis that \( c_p(t) \) is proportional to \( c_a(t) \) when averaged over 0.1 minute intervals could not be verified in this study. Theoretically, estimates for \( c_a(t) \) based on end-tidal air and on external lung monitoring should differ since the lung probe "sees" all of the air in the lung, not just the end-tidal air. Hence, the lung probe data should overestimate \( c_a(t) \) during \(^{133}\)Xe inhalation and underestimate it thereafter. The expected trends could be clearly seen in most cases as illustrated in Figure 3. Differences in the shapes of the concentration-time curves are reflected in channel estimates obtained for IS, \( f_1 \), \( w_i \), and \( \text{CBF}_m \). However, these differences did not influence comparisons between homologous regions of the left and right hemispheres.

It should be noted that these differences in the input curve would not be anticipated following an intravenous injection of \(^{133}\)Xe since the lung probe should underestimate end-tidal air during both inhalation and clearance. Assuming the end-tidal air counts were under-estimated by a constant percent at all time points, the shape of the curve would not be distorted. Jaggi and Obrist\(^1\) found good comparability between end-tidal and lung probe curves following intravenous injection of \(^{133}\)Xe. The different mode of \(^{133}\)Xe administration (intravenous vs. inhalation) probably accounts for the discrepancy in our findings.

Obrist al\(^7\) have previously shown that the \(^{133}\)Xe concentration in end-tidal air correlates well with that in arterial blood for normal subjects breathing at regular depth and rate. Therefore, the differences seen here suggest that external lung monitoring provides a less accurate approximation for \( c_a(t) \). However this implication cannot be verified for these data since no blood samples were drawn.

Potentially large discrepancies can develop between the end-tidal air and arterial blood concentrations where certain lung pathologies are present or where breathing patterns are highly irregular (such as those induced by experimental protocols requiring verbal responses). Under these circumstances, external lung monitoring might still provide a better estimate for \( c_a(t) \), even when \(^{133}\)Xe is inhaled. End-tidal air and lung monitoring must be combined with arterial blood sampling to test this hypothesis.

### References

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