Indicator Dilution Measurements of Lung Volumes and
Alveolar Air Exchange During Breathing

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ABSTRACT A new triple tracer indicator dilution technique has been used to measure alveolar ventilation as well as air and tissue volumes in the lungs of experimental animals and man. The tracers indocyanine green, [133Xe]antipyrine and xenon-133 were rapidly injected into the right atrium, while sampling was carried out from a peripheral artery.

Blood flow and tissue volumes were obtained by classical analysis of the indocyanine green and antipyrine concentration-time curves. A double exit-port, constant air flow model was used to analyze the xenon curves, because ventilatory loss led to incomplete recovery of the gas tracer in effluent blood. Uniform ventilation and perfusion were assumed. This analysis permitted calculation of alveolar ventilation (VAx) and functional residual capacity (FRCx) during normal breathing.

In control studies, VAx was similar to VACO2, obtained with the steady-state CO2 method (r = 0.87), while in critically ill patients the xenon measurement was significantly lower, averaging 54% of VACO2. In theory, underestimates in VAx and decrease in the ratio VAx/VACO2 relate to nonuniformity in regional ventilation and perfusion. The effect is greatest for the slightly soluble gas, xenon. The significant inverse correlation between VAx/VACO2 and the physiologic shunt is consistent with this postulate.

FRCx was similar to the predicted FRC in animals but was 76% of the helium measured FRC in patients. FRCx was significantly lower than the xenon measured air volumes during breath-holding when nonuniformity of ventilation was not operative. Lung tissue volumes in animals were 83% of gravimetric lung weights, while in patients the volumes were much lower than predicted. Nonhomogeneous lung function, including failure to perfuse the entire capillary bed, with resultant incomplete penetration of tracers into all segments of lung air and tissue, may explain these findings. The resultant errors can be significant in sick patients, and may themselves be used to study nonhomogeneities in the distribution of ventilation and volume.

INTRODUCTION

Alveolar ventilation and the functional residual capacity (FRC) are two indices of pulmonary function which have proven useful in the understanding and treating of abnormalities in respiratory gas exchange. The significance of these flows and volumes, lies both in their absolute values as well as in the uniformity of distribution.

Symbols used in this paper: C (amount/ml), concentration; f (breaths/min), respiratory frequency; FAna (ml gas/ml alveolar air), alveolar fraction of a gas, FRC (ml air), functional residual capacity during breathing; M (mass), amount of indicator injected; Q (ml/s), blood flow; R (dimensionless), fraction of injected tracer recovered in effluent blood; S, saturation of hemoglobin; t (s), time; t(s), transit time parameter, reduces to classic mean transit time when R = 1; τ (s), total transit time from site of injection to site of sampling; Δ(t), difference in transits time parameters; T(s), time of one complete respiratory cycle; VA (ml air/s), alveolar ventilation —air flow through the control volume effective in tracer removal via the airway; VA (ml air), gas volume at end-expiration bounded by the “control surface”, during breath-holding; VA (ml air), mean gas volume during breathing contained within the control surface; if VP = 0, VA = FRCx + VT/2; Vd (ml), volume penetrated by tracer particles which leave the lung via effluent blood—the control volume; Vd (ml air), dead space—air volume contained within the lung, but outside the control surface; VT (ml air/breath), tidal volume; Vv, Vr (ml), tissue or capillary blood volume; λa, λc (dimensionless), gas partition coefficient between tissue or blood and air at 37°C; Z (ml/sec), diffusional clearance. Subscripts: Ap, iodantipyrine, tissue tracer; c, capillary blood; g, gas tracer; G, indocyanine green; H, helium; i, input of the control surface; Kr, krypton-85; o, output of the control surface via effluent blood; r, reference tracer; t, tissue; Xe, xenon-133; 1, vascular segment from injection site to (i); 2, vascular segment from (o) to sampling site.
The study of the ventilated lung with gas tracers requires special consideration. Under such circumstances two exit-ports exist. Tracer gas injected as a bolus into input blood may leave the lung through either of two parallel flow channels, blood vessels and airways. In theory, the fraction of gas tracer injected which is recovered in effluent blood is defined by solubility, blood flow, ventilation, and diffusional clearance. Measurement of the recovery fraction may in turn be used to determine these flows or clearances. The mean transit time of gas tracer particles recovered in effluent blood is defined by the ratio: volume of tracer distribution/sum of the parallel flows or clearances. Measurement of the mean transit time therefore provides sufficient additional information to measure the volume of gas tracer distribution.

**THEORETICAL CONSIDERATIONS**

The general lung model is shown in Fig. 1. The control volume includes the perfused capillary bed which permits diffusion of blood-born tracers into the surrounding tissue Vt, and alveolar air spaces Va. Nonperfused regions (anatomic and physiologic dead space) lie outside the control volume and are excluded from this analysis. The model assumes that the ventilation/perfusion ratio is uniform throughout the lung. Time 无可 occurs when the tracer crosses the control surface at point (i) (input) as C(i). Tracer leaves the control surface at (o) (output) as C(o). The tissue and air space components are limited to those regions into which tracer can both penetrate and return to capillary blood to exit via port (o).

In the case of the inert gas xenon, we assume that there is no diffusion limitation between alveolar gas and blood (7). Therefore the capillary blood (c) concentration at the output (o) is Cxoe(t) = λXeoFAXeo, where λXeo is the partition coefficient between blood and gas and FAeo is the fraction of xenon in the control air volume. Blood flow is assumed to be constant since observations of tracer concentration are made over many cardiac cycles. Tissue and capillary blood volume are also considered constant.

Let us assume that tracer is rapidly injected at (i). C(t) is monitored at point (o) as C(o)(t). Delays t1 and t2 are considered later. The mean transit time parameter is defined as

\[ i = \frac{\int_{0}^{\infty} tC_{eo}(t) dt}{\int_{0}^{\infty} C_{eo}(t) dt}. \]  

When all injected tracer leaves the control volume by way of (o), the transit time parameter becomes the “classic” mean transit time and

\[ i = \frac{V_{d}}{\lambda \hat{Q}} \]  

Blood flow \( \hat{Q} \) is defined as

\[ \hat{Q} = \frac{M_{r}}{\int_{0}^{\infty} C_{rev}(t) dt} \]
where $M_g$ is milligrams indocyanine green and $C_{con}(t)$ is the concentration of reference tracer at the output at time $t$. Tracer recovery must be complete.

**THEORETICAL RESULTS**

**Breath-holding, $R_g = 1$.** General indicator dilution theory is directly applicable to this single exit-port model (5). The air volume $V_{a}$, is assumed constant, therefore the respiratory quotient is 1. Tracer gas is distributed according to its solubility coefficient $\lambda$, in air, tissue, and blood. The volume equation 2 which relates the control volume to the product of blood clearance $\lambda_{gc}\dot{Q}$, and mean transit time is

$$VA + \lambda_{gc} V_t + \lambda_{gc} V_e = \lambda_{gc} \dot{Q} t.$$  \hspace{1cm} (4)

The blood volume $V_e$, an element of the control volume, is defined by the reference tracer as

$$V_e = \dot{Q} t,$$  \hspace{1cm} (5)

where $t$ is the transit time through lung capillaries.

The general lung model (Fig. 1) assumes that tracer injection and sampling are remote from the control surface. The absolute values of $t_1$, $t_2$, or $t$, the mean transit times in the control volume, cannot be measured directly. This is so because the mean intravascular transit delays from injection site to (i) $t_1$ and from (o) to the sampling site $t_2$ are unknown. Therefore, $t = 0$, when tracer enters the control surface is not defined. It may be stated that the total mean transit time of the reference indicator ($\lambda$) from the site of injection to the site of sampling is

$$t_{TOT} = t_1 + t_2.$$  \hspace{1cm} (6)

Further, it is reasonable to assume that $t_1 = t_1^o$ and $t_2 = t_2^o$. It has been found that in the dog lung, the mean transit time of red cells is 0.3 s shorter than plasma (8). Knowing that xenon is two times more soluble in red cells than plasma (9), the error incurred by assuming that the transit times 1 and 2 are the same for xenon and indocyanine green, is 0.2 s. Since the average experimental $\Delta t_{Xe}$ exceeds 20 s (Tables II, III) there will be an underestimation of $\Delta t_{Xe-o}$ of approximately 10% when (o) is indocyanine green.$^3$

Therefore

$$t_{TOT} = t_1 + t_2$$  \hspace{1cm} (7)

and

$$t_2 = t_{TOT} - t_1 - t_2.$$  \hspace{1cm} (8)

Equation 5 becomes:

$$V_e = \dot{Q} (t_{TOT} - t_1) - t_2.$$  \hspace{1cm} (9)

Equation 4 becomes:

$$VA + \lambda_{gc} V_t + \lambda_{gc} V_e = \lambda_{gc} \dot{Q} (t_{TOT} - t_1 - t_2).$$  \hspace{1cm} (10)

Multiplying equation 9 by $\lambda_{gc}$ and subtracting from equation 10 gives

$$VA + \lambda_{gc} V_t = \lambda_{gc} \dot{Q} \Delta t_{gc-o},$$  \hspace{1cm} (11)

where we define

$$\Delta t_{gc-o} = t_{TOT} - t_{TOT}.$$  \hspace{1cm} (12)

$^3$ In a strict sense, precise measure of $\Delta t_{Xe-o}$ requires a reference tracer which is distributed in red cells and plasma exactly as xenon. An alternative is the use of both a plasma and red cell indicator (8).

**Breath-holding and constant ventilation, $R_g < 1$.** Under most circumstances tracer gas recovery in effluent blood is $< 1$. The remaining tracer may diffuse or be transported by ventilation from the control volume through a second parallel flow channel, and exit the lung through a port other than (o). Diffusion is defined as a flow or clearance, $\dot{Z}$. It is the volume of air completely cleared of tracer per second and is assumed constant. This requires that there be a steady-state flux, without back diffusion, across a fixed barrier such as the pleural surface. $\dot{Z}$ is determined by the diffusion constant and geometric parameters of the system, which include the area and thickness of the barrier. Ventilatory clearance $V_{a}$, is assumed to be constant. This requires that there be continuous and uniform air flow through the control volume at a rate $V_{a} \text{ml/s}$. Since the control volume contains no dead space, all air entering this region will be effective in tracer removal. The average size of the control volume will be $V_{a}$ plus the tissue and blood components.

The total mass of gas tracer leaving the control volume will be the sum of tracer mass leaving from the two exit-ports, measured over the time period required for washout. Providing tracer is not entrapped within the control volume, the mass exiting will be equal to $M_{g}$, the mass injected. For the purposes of this discussion, $M_{g}$ is defined by the units, milliliters of gas at 1 atm pressure and 37°C. $C_{con}$ is milliliters of gas dissolved in 1 ml blood at the same temperature and pressure. If at any time $t$, there is concentration equilibrium, then $\lambda_{gc} F_{ag}(t) = C_{con}(t)$. The mass flow at time $t$ may therefore be defined for both exit ports as the product of the respective flows and concentrations: $\lambda_{gc} F_{Ag}(t) = 2 F_{Ag}(t)$, and $\dot{V}_{A} F_{Ag}(t)$. Summing these mass flows over a very long period of time yields: tracer mass recovered in effluent blood, $\lambda_{gc} \dot{Q} F_{Ag}(t) / M_{g}$; and that not recovered in blood, $\dot{V}_{A} F_{Ag}(t)$ and $\dot{V}_{A} F_{Ag}(t)$. Therefore

$$M_{g} = \lambda_{gc} \dot{Q} \int_{0}^{\infty} F_{Ag}(t) dt + \dot{Z}$$

$$\times \int_{0}^{\infty} F_{Ag}(t) dt + \dot{V}_{A} \int_{0}^{\infty} F_{Ag}(t) dt$$  \hspace{1cm} (13)

Dividing by $M_{g}$, the fraction of injected tracer recovered in blood is

$$R_{ag} = \lambda_{gc} \dot{Q} \int_{0}^{\infty} F_{Ag}(t) dt / M_{g}.$$

$$\dot{V}_{A} + \dot{Z} = \frac{1}{R_{ag}} - \frac{1}{\lambda_{gc} \dot{Q}}.$$  \hspace{1cm} (16)

During breath-holding when $\dot{V}_{A} = 0$, equation 16 may be used to define diffusional clearance. During breathing, evidence indicates that $\dot{V}_{A} \gg \dot{Z}$ (10). Therefore equation 16

\begin{verbatim}

1 In Methods, $M_{g}$ is counts per minute. $C_{con}$ is counts/min per milliliter of blood; $F_{Ag}$ becomes a concentration term, counts/min per milliliter alveolar air.

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\end{verbatim}
reduces to
\[ \dot{V}_A = \left( \frac{1}{R_g} - 1 \right) \lambda_{ge} \dot{Q} \]  
(17)

or
\[ R_g = \frac{1}{\frac{\dot{V}_A}{\lambda_{ge} \dot{Q}}} \]  
(17a)

for constant ventilation.

The mean transit time for a single exit-port system is equal to the ratio: volume/flow or clearance (5). Equation 2 is applicable to the lung when an intravascular reference tracer is used. In this case the denominator of equation 2 is blood flow, \( \dot{Q} \). If a gaseous tracer gains entry to the extravascular space and still exits the lung through port (o), the denominator of equation 2 is modified by \( \lambda_{ge} \) in order to describe the flow effective in tracer washout or clearance, \( \lambda_{ge} \dot{Q} \). When a second parallel flow channel washes tracer from the control volume, equation 2 will hold if the two flow channels mix at port (o). In this case the parallel flows are summed by the system. However, when the parallel flows exit through separate ports, equation 2 must be rewritten
\[ \dot{I}_g = \frac{V_d}{\text{flow } 1 + \text{flow } 2} \ldots . \]  
(18)

If there is concentration equilibrium in the control volume, such that \( \lambda_{ge} \) describes the tracer partition coefficient between blood and air, then the flows or clearances in the denominator of equation 18 become
\[ \dot{I}_g = \frac{V_d}{\lambda_{ge} \dot{Q} + \dot{V}_A + \dot{Z}}. \]  
(19)

The denominator of equation 19 will now be examined with respect to tracer recovery in effluent blood. Flow which is effective in removing the intravascular tracer from the control volume is defined by equation 3. In an analogous equation, the flows clearing tracer gas from \( V_d \) are
\[ \dot{Q} + \frac{\dot{V}_A + \dot{Z}}{\lambda_{ge}} = \frac{M_g}{\int_0^\infty C_{geo}(t)dt}. \]  
(20)

Rewriting equation 14
\[ R_g = \dot{Q} \frac{\int_0^\infty C_{geo}(t)dt}{M_g} \]  
(14a)

and combining with equation 20 yields
\[ \frac{\lambda_{ge} \dot{Q}}{R_g} = \frac{\lambda_{ge} \dot{Q} + \dot{V}_A + \dot{Z}}{R_g} \]  
(21)

which states that blood clearance divided by the fractional recovery of tracer gas in effluent blood equals the sum of the flows or clearances acting on tracer in the control volume. \( V_d \) is defined in Fig. 1. Equation 19 becomes
\[ \dot{I}_g = \frac{V_d + \lambda_{ge} \dot{V}_t + \lambda_{ge} \dot{V}_e}{\lambda_{ge} \dot{Q}/R_g} \]  
(22)

for breath-holding, and
\[ \dot{I}_g = \frac{V_d + \lambda_{ge} \dot{V}_t + \lambda_{ge} \dot{V}_e}{\lambda_{ge} \dot{Q}/R_g} \]  
(23)

for constant ventilation.

Multiplying equation 9 by \( \lambda_{ge}/R_g \) and subtracting from equations 22 and 23 yields equations 24 and 25.

\[ V_A + \lambda_{ge} \dot{V}_t + \lambda_{ge} \dot{V}_e \left( 1 - \frac{1}{R_g} \right) = \frac{\lambda_{ge} \dot{Q} \Delta E - \tau}{R_g} \]  
(24)

\[ V_A + \lambda_{ge} \dot{V}_t + \lambda_{ge} \dot{V}_e \left( 1 - \frac{1}{R_g} \right) = \frac{\lambda_{ge} \dot{Q} \Delta E - \tau}{R_g} \]  
(25)

where \( \Delta E \) is equivalent to the difference in transit times of gas and reference tracers from the site of injection to site of sampling (equation 12). Since \( \lambda_{ge} = 0.18 \) (9), \( R_g \) averages 0.23 (Table 11), and \( V_d \) is approximately 4% of the air volume of the normal lung: \( V_A \) or \( V_d \) \( \gg \lambda_{ge} \dot{V}_e \left( 1 - \frac{1}{R_g} \right) \). Therefore, the term \( \lambda_{ge} \dot{V}_e \left( 1 - \frac{1}{R_g} \right) \) may be eliminated from equations 24 and 25 such that
\[ V_A + \lambda_{ge} \dot{V}_t = \frac{\lambda_{ge} \dot{Q} \Delta E - \tau}{R_g}. \]  
(26)

The average air volume \( V_A = F R C_g + V_T/2 \) when \( V_D = 0 \). Since the tidal volume is normally distributed both to areas of dead space as well as to the control volume, \( T V_A/2 \) is substituted for \( V_T/2 \). The equation describing constant ventilation becomes
\[ F R C_g + \lambda_{ge} \frac{T V_A}{2} = \frac{\lambda_{ge} \dot{Q} \Delta E - \tau}{R_g}. \]  
(27)

**Oscillatory ventilation.** The normal respiratory pattern is periodic ventilation. Classical indicator dilution theory assumes constancy of flow and constancy of the control volume (5). Oscillatory ventilation appears to violate these assumptions. Fortunately however, air flow and volume changes vary together. Under these conditions, and especially if the changes in flow and volume are rapid and phasic, the oscillatory ventilation model will reduce to constant ventilation. The maximum error in \( F R C_g \) using equation 27 will occur when respiratory cycling is extremely slow, and the entire indicator dilution curve is drawn during one respiratory phase. Thus, during the phase end-exhalation \( F R C_g \) will equal the true FRC but during end-inhalation \( F R C_g \) will overestimate true FRC by the factor \( T V_A \). The percentage volume error will be reduced as the ratio \( V_T/V_A \) or more exactly \( T V_A/V_A \) becomes small. Under most circumstances \( T V_A \) is much less than the volume of air contained within the lung. For this reason as well as the fact that respiratory frequency is relatively rapid, our choice of the continuous flow model appears to be a reasonable approximation.

**METHODS**

**Animals.** Mongrel dogs and monkeys were anesthetized with sodium pentobarbital, intubated, and placed on their backs. Control experiments were conducted during spontaneous breathing as well as during mechanical ventilatory assistance with a piston pump.

Two dogs were bled into a reservoir and their arterial pressures maintained at 50 mm Hg. After 1 h of hypotension, indicator dilution studies were done. Another two animals were kept hypotensive for 2 h. They were studied 1 h after the reinfusion of shed blood. Autopsies were conducted at the termination of all animal experiments. The blood drained lungs were weighted, dried to constant weight and examined histologically.
Richard A. Dunlop, James W.  

TABLE I  
Patient Studies

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Age</th>
<th>Body surface area m²</th>
<th>Diagnosis</th>
<th>Operation</th>
<th>Condition</th>
<th>Autopsy lung wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>49</td>
<td>1.59</td>
<td>Hepatoma</td>
<td>Right hepatic lobectomy</td>
<td>Uneventful recovery</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>1.48</td>
<td>Embolus to superior mesenteric artery; 90% small bowel infarction</td>
<td>Emboleectomy; bowel resection</td>
<td>Septic</td>
<td>1,500</td>
</tr>
<tr>
<td>16</td>
<td>58</td>
<td>1.76</td>
<td>Reflex esophagitis</td>
<td>Esophagogastrctomy</td>
<td>Mediastinitis, acute tubular necrosis</td>
<td>1,700</td>
</tr>
<tr>
<td>17</td>
<td>41</td>
<td>1.94</td>
<td>Coronary insufficiency; severe congestive failure</td>
<td>Attempted coronary bypass</td>
<td>Slow recovery</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>59</td>
<td>1.88</td>
<td>Coronary insufficiency; compensated congestive failure</td>
<td>Coronary bypass graft</td>
<td>Arrhythmia</td>
<td>No autopsy</td>
</tr>
<tr>
<td>19</td>
<td>51</td>
<td>1.38</td>
<td>Mitral stenosis and insufficiency</td>
<td>Mitral valve replacement</td>
<td>Uneventful recovery</td>
<td>—</td>
</tr>
</tbody>
</table>

Five anesthetized dogs were given succinylcholine and their ventilation controlled. Indicator studies were done in rapid sequence during breath-holding at end-expiration and during breathing. The order of this sequence, breath-holding or breathing was varied.

Three in vitro studies were conducted in the left lower lobe of a dog at 37°C, during breath-holding at end-expiration and during breathing. Recirculation was eliminated during indicator runs. Details of the perfusion apparatus have been described (11).

Patients were selected for study, either because they were suffering acute arterial hypoxemia, or because their disease or the major surgical procedure indicated for its treatment, made the patient vulnerable to pulmonary complications (Table I). Most patient studies were conducted during mechanical ventilatory assistance with an endotracheal tube in place. Control of the airway in the one patient without an endotracheal tube was accomplished with nose clips and a mouthpiece (ex. 14).

Respiratory measurements. A 71 spirometer (Warren E. Collins, Inc., Braintree, Mass.) was used to measure tidal volume \( V_t \) and respiratory frequency. The functional residual capacity \( FRC_{fr} \), was determined by helium dilution after switching the subject from the respirator to the Collins spirometer circuit. All patients demonstrated adequate ventilatory exchange during the several minutes required to reach helium equilibrium. Expired air was collected in small meteorologic balloons and analyzed for \( CO_2 \) tension with the Severinghaus electrode.

Hemodynamic measurements. All subjects had right atrial and either carotid or brachial arterial catheters. The brachial artery was utilized in patients. In addition, all patients had a balloon-tipped catheter (Swan-Ganz, Edwards Laboratory, Santa Ana, Calif.) positioned in a distal pulmonary artery. On occasion this catheter was coupled to a strain gauge transducer to give pulmonary arterial and wedge pressures.

Physiologic shunt \( Q_S / Q \). The partial pressures of oxygen and carbon dioxide were measured with Clark and Severinghaus electrodes (II. 213, Instrumentation Laboratories, Lexington, Mass.), in blood drawn from arterial and right atrial (animals), or pulmonary arterial (patients) catheters. Arterial \( C_A \) and mixed venous \( C_V \) oxygen contents were then calculated from the hemoglobin concentration measured by oximetry and the derived value for hemoglobin saturation. The latter was obtained from standard nomograms describing the oxygen hemoglobin dissociation curve. The alveolar gas equation was used to calculate end-capillary oxygen content \( C_c \). The fraction of blood flow passing through the lungs, having the same oxygen content as mixed venous blood, was obtained from the formula

\[
\frac{Q_S}{Q} = \frac{C_{O_2} - C_{O_2}}{C_{O_2} - C_{O_2}}. 
\]

Indicator dilution studies. The three tracers employed were: indocyanine green as the intravascular marker; indantipyrine \( [131] \) antipyrine, 20 \( \mu \)Ci, Amersham/Searle Corp., Arlington Heights, Ill.) for the extravascular tissue space; and a saline solution of xenon-133 (200 \( \mu \)Ci, New England Nuclear Corp., Boston, Mass.) for both the extravascular tissue and air spaces. An isosmotic tracer mixture was prepared anerobically and a portion saved for analysis (12). The mass of tracer injected was expressed as milligrams indocyanine green and counts per minute of \( [131] \) and \( [18] \)Xe. Patients were pretreated with 200 mg sodium iodide to block \( [131] \) uptake by the thyroid. A rapid injection of 1–2 ml of tracer mix was made into the right atrial catheter, followed by a 5 ml flush of blood. Arterial sampling was started at the moment of injection, at a rate of 25 ml/min. In small monkeys, the rate was reduced to 11.6 ml/min. Mercury spacers were used to separate samples at 1–2-s intervals (12). The concentration of indocyanine green (milligrams per milliliter) was measured spectrophotometri-
Calculations. A typical set of indicator dilution curves is illustrated for experiment 16d (Fig. 2). All tracer downslopes were monoexponential and were extrapolated by the method of least squares to ordinate values which were 1% of peak height. The integrals \( \int_0^t C_{\text{int}}(\theta) d\theta \) and \( \int_0^t C_{\text{int}}(\theta) d\theta \) were calculated according to the method of Chinard et al. (6). The mean transit time parameters \( t_0, t_{\text{Ap}}, \) and \( t_{Xe} \) were derived from equation 1 while blood flow \( Q \) was derived from equation 3.

Tissue volume \( V_t \) is:

\[
V_t = Q \Delta t_{\text{Ap}-0},
\]

where \( \Delta t_{\text{Ap}-0} \) is the difference in mean transit times between antipyrine and indocyanine green. The partition coefficient for indocyanine green between tissue and blood is assumed to be 1.0.4

Alveolar ventilation. \( V_{\text{Alveol}} \) (milliliters per second) was calculated from the xenon and indocyanine green data using the continuous air flow model of the lung (equation 17). The partition coefficient \( \lambda_{\text{Xe-xe}} \) was modified for changes in hematocrit (Hct) (13), which was measured by the capillary tube technique. The fractional recovery of injected xenon in effluent blood \( R_{\text{Xe}} \) was calculated from the normalized indicator curves by means of

\[
R_{\text{Xe}} = \frac{\text{area}_{\text{xe}}}{\text{area}_{\text{Xe}}},
\]

where “area” is that described under the normalized concentration time curves of xenon (Xe) and indocyanine green (G).

Alveolar ventilation (milliliters) was also derived from measurements of tidal volume \( V_T \), mixed expired carbon dioxide tension \( P_{ECO_2} \) and arterial carbon dioxide tension \( P_{ACO_2} \).

\[
V_{\text{ACO}_2} = \frac{V_T (P_{ECO_2})}{T (P_{ACO_2})}
\]

End-expiratory air volume. FRC\( _{\text{x}} \) (milliliters) during breathing was calculated from the constant airflow model (equation 27). The solubility coefficient of xenon between tissue and air \( \lambda_{\text{Xe}} \approx 0.1 \) (9).

RESULTS

Alveolar ventilation was measured in all subjects: 2 rhesus monkeys, 11 mongrel dogs and 6 patients (Table II). \( V_{\text{Alveol}} \) was calculated from equation 17 and \( V_{\text{ACO}_2} \) from equation 31. A comparison of these measurements is given in Fig. 3. The six closed circles refer to dogs which had been subjected to hemorrhage while the 11 closed triangles refer to patients who were critically ill at the time of the study (Table I, exps. 15–18). The remaining 28 runs in control animals, and patients who made uneventful recoveries are described by the regression equation \( TV_{\text{Alveol}} = (0.87) TV_{\text{ACO}_2} + 12.8 \) (\( r = 0.87 \)). Alveolar ventilation calculated from xenon was 93.8% of that calculated from CO2. During and after hemorrhagic hypotension the percentage was 77.4% (\( n = 6 \)).5 In the seriously ill patients \( V_{\text{ACO}_2} \) was

1. Since the partition coefficient is assumed, \( V_t \) is strictly defined as an \([^{131}I]\) antipyrine volume of distribution.

2. \( n \) refers to the number of runs.
significantly lower than $\dot{V}_{\text{A}CO_2}$ averaging 53.9% of $V_{\text{A}CO_2}$ ($P < 0.01$). The pulmonary tissue volume $V_t$ in dogs, measured with the antipyrene tracer using equation 29, averaged 8.86 ml/kg ± 3.10 SD in 22 control runs (Table II). This was significantly lower than weights of the blood drained lungs, which averaged 10.7 ml/kg ($P < 0.05$). During hemorrhagic hypotension, the average of three runs was 5.70 ml/kg, while after the reinfusion of shed blood, the average was 12.9 ml/kg ($n = 3$). The results in these three groups demonstrate a wide scatter from the mean. The fractional recovery of antipyrene was 0.986 ± 0.088 SD for all 28 runs.6

The patients also showed wide variations in the measured tissue volume. The four patients (exp. 15–18) who were seriously ill averaged 7.52 ml/kg ± 2.51 SD, or 274 ml/m² ($n = 11$), while the two patients who made uneventful recoveries (exp. 14, 19), averaged 4.70 ml/kg or 144 ml/m² ($n = 2$). The fractional antipyrene recovery was 0.886 ± 0.158 SD for all patient runs ($n = 13$).

Air volumes. FRC$_{xe}$, measured by the tracer technique using equation 27, averaged 34.8 ml/kg ± 14.5 SD in the control dogs ($n = 22$), 23.3 ml/kg in the two hypotensive animals ($n = 3$), and 15.3 ml/kg in the two animals who had their shed blood reinfused ($n = 3$) (Table II).

A tissue tracer was not used in the two monkey experiments nor in the first two patient runs (exp. 14a, b). In these runs the volume calculated from equation 27 is $\text{FRC}_{xe} + \lambda_{gt} V_t$. The overestimate in $\text{FRC}_{xe}$ by assuming $\text{FRC}_{xe} \gg \lambda_{gt} V_t$ is between 3 and 4%, since the ratio $\text{FRC}_{xe}/\lambda_{gt} V_t = 39.3$. For the 22 control runs and 28.2 for all patient runs other than 14a and b. If the assumption $\text{FRC}_{xe} \gg \lambda_{gt} V_t$ is permitted, then $\text{FRC}_{xe}$ averaged 27.8 ml/kg for the two monkey runs. The two patients who made uneventful recoveries had an average $\text{FRC}_{xe}$ of 35.6 ml/kg ($n = 4$). In the four critically ill patients where the assumption was not necessary, $\text{FRC}_{xe}$ was 18.2 ml/kg ($n = 11$). The $\text{FRC}_{he}$ was 63.3 ml/kg and 24.7 ml/kg, respectively, in these two patient groups. The $\text{FRC}_{he}$ in exp. 17b is not included in these results. A prolonged delay occurred in this run, in switching the patient from the respirator to the Collins spirometer.

Five dogs were made to breath-hold at the end of a normal tidal volume (Table III). The average air volume $V_{\text{Ax}}$ was 32.9 ml/kg (equation 26). Breathing $\text{FRC}_{xe}$ and breath-holding volumes $V_{\text{Ax}}$ were compared in sequential runs in four dogs and in three pump perfused lobes. $\text{FRC}_{xe}$ was lower than $V_{\text{Ax}}$ ($P < 0.05$), averaging 87.6% of $V_{\text{Ax}}$. In comparing $\text{FRC}_{xe}$ and $V_{\text{Ax}}$, the small error due to the tissue factor $\lambda_{gt} V_t$, tends to cancel out.

$^6$ $R_A = \frac{\text{area}_{ap}}{\text{area}_{G}}$, cf. equation 30.

$^7$ $\text{FRC}_{xe}$ and $V_{\text{Ax}}$ include air volume and the tissue factor, $\lambda_{gt} V_t$.
TABLE II

Lung Volumes and

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* Volume cycled respirator.
‡ Prolonged time to switch into spirometer circuit; result suspiciously low.
§ \( FiO_2 = 50\% \); unmarked signifies room air.
|| Bracketed runs were done within 30 min of each other.

H. B. Hechtman, M. H. Reid, B. C. Dorn, and R. D. Weisel
**Alveolar Ventilation**

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DISCUSSION

Alveolar ventilation measured by the xenon method correlated well with $\dot{V}_{\text{ACO}}$ ($r = 0.87$) in control animals and patients who made uneventful recoveries. $\dot{V}_{\text{AX}}$ tended to be slightly but not significantly lower than $\dot{V}_{\text{ACO}}$ in this group. The average was 93.8%. A highly significant difference in the measured alveolar ventilations occurred in the critically ill patients where $\dot{V}_{\text{AX}}$ averaged 53.9% of $\dot{V}_{\text{ACO}}$. The two factors that may account for this discrepancy are diffusion and non-uniform ventilation-perfusion ratios.

In normal lungs, where there is minimal or no diffusion limitation across the pulmonary membrane, it is probable that tracer gases, including CO$_2$, diffuse beyond alveoli and enter the distal conducting airways (14). Air exchange in these distal airways effectively removes tracer, and therefore, is included in the measured "alveolar ventilation". The rate of gas diffusion will determine the depth of tracer penetration into the conducting airways. As the rate of diffusion increases, there will be an apparent decrease in wasted, dead space ventilation and an increase in $\dot{V}_A$. Carbon dioxide is lighter than xenon-133 and therefore diffuses more rapidly in air. These considerations are consistent with the findings that $\dot{V}_{\text{AX}} < \dot{V}_{\text{ACO}}$. Similar results have been reported using steady state techniques for the calculation of $\dot{V}_{\text{AX}}$ and $\dot{V}_{\text{ACO}}$ (10). Although the findings are consistent with diffusion effects, it has been observed experimentally that during the period of a normal respiratory cycle, there is insufficient time for the diffusion separation of the gases krypton-85 and CO$_2$ (10).

Another possible mechanism that may produce this disparity in $\dot{V}_A$, relates to regional variations in the ventilation-perfusion ratio. The ventilation equation

\[ \frac{1}{\text{density}} \]

*Graham's law states that the rate of diffusion is proportional to $\frac{1}{\text{density}}$. 

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17 assumes a single compartment lung with a uniform 
\( \frac{V_A}{Q} \) ratio. Under such circumstances \( V_{AXe} \) will be 
equal to \( V_{ACO_2} \). As the distribution of ventilation-perfusion ratios around the average ratio becomes 
wider, tracer recovery in effluent blood will, in theory 
increase. This leads to a calculated \( V_A \) which is lower 
than the single compartment lung (10). A theoretical 
example of a two compartment lung is given in Fig. 4.

Despite inhomogeneities, as long as the gas tracers 
have equal blood solubilities, there should be no dis-
parity in their measured \( V_A \)’s; although they will be 
lower than those measured in the homogeneous lung.

The critical issue involves the use of tracers of different 
solubilities in a lung with nonuniform ventilation per-
fusion ratios. In theory, this will lead to discrepancies 
in the calculated alveolar ventilation (15). The lower 
the solubility, the lower the calculated \( V_A \). The 
experimental observation that \( V_{AXe} < V_{ACO_2} \) is in keeping with 
the fact that CO₂ is much more soluble in blood 
than xenon. The theoretical calculations illustrated in 
Fig. 4 shows that a 20% anatomic shunt will lead to 
reductions in \( V_{AXe} \) to 42% of true ventilation while 
\( V_{ACO_2} \) is minimally reduced to 97.3%. The striking re-
duction in \( V_{AXe} \) relates to the low solubility of xenon. 
Only 15% of xenon entering the lung via input blood is 
recovered in the venous effluent. A 20% anatomic shunt 
results in 30% recovery. In the case of the 
highly soluble gas CO₂, 90.00% is normally recovered, 
(\( \frac{VA}{Q} = 1, \lambda = 9 \)) whereas a 20% shunt leads to a 
minimal increase in recovery to 90.24%. Thus, although 
the absolute mass of xenon cleared by ventilation may 
be far greater than CO₂, the reduction in the efficiency 
of this ventilatory clearance is more marked for 
xenon in the presence of shunting. The reduced effi-
ciency of gas exchange due to \( \frac{VA}{Q} \) inhomogeneities may be 
described by the ratio \( \frac{V_{AXe}}{V_{ACO_2}} \).

Nonuniformity in perfusion also results in \( \frac{VA}{Q} \) 
imbalance and again leads to greater underestimates in 
\( V_{AXe} \) than \( V_{ACO_2} \) (Fig. 5). When regional perfusion is 
completely interrupted, that region is no longer in-
cluded within the control volume. Ventilation to the 
region (dead space ventilation) is then unmeasured 
regardless of the tracer used.

These theoretical considerations demonstrate that 
although \( V_A \) is unchanged, the effective ventilation 
depends on both gas solubility and the degree of non-
homogeneity in the \( \frac{VA}{Q} \) ratios. Experimental evidence 
supports this postulate. A significant correlation exists 
between \( \frac{V_{AXe}}{V_{ACO_2}} \) and \( \frac{Q_{8}}{Q} \) measured during room 
air breathing (\( r = -0.54, P < 0.001 \)). If the calculated 
shunt \( \frac{Q_{8}}{Q} \), represents anatomic shunting (flow 
through nonventilated lung regions), then the exper-
imental ratio \( \frac{V_{AXe}}{V_{ACO_2}} \) should be the same as the 
ratio predicted from the two-compartment lung model 
when \( V_{A1} = 0 \) (anatomic shunt). It may be seen how-
ever, that the data points fall to the right of the theo-
retical curve (Fig. 6). Agreement is somewhat better 
when \( \frac{Q_{8}}{Q} \) is calculated during 50% oxygen breathing. 
These observations are in accord with the fact that 
\( \frac{Q_{8}}{Q} \) becomes a better index of anatomic shunting when 
high concentrations of oxygen are inspired.

The shunt fraction \( \frac{Q_{8}}{Q} \), calculated from equation 28 
is conceptually the same as the recovery fraction 
\( R_{xe} \) (16, 17). Oxygen contents however, are primarily 
determined by a chemical union with hemoglobin and 
not by \( \lambda_{CO_2} \). This explains the fact that disparities exist 
between \( R_{xe} \) and \( \frac{Q_{8}}{Q} \) (Table II) and make it unlikely

\[ R_x = \frac{1}{\frac{V_{A1}}{\lambda Q_1} + 1} \frac{Q_1}{Q} + \frac{1}{\frac{V_{A2}}{\lambda Q_2} + 1} \frac{Q_2}{Q} \]

\( V_A \) gas is then calculated by substituting \( R_x \) into equation 17. 
Xenon is a poorly soluble gas and \( R_{xe} \) is normally about 0.15. 
As \( V_A \), and therefore \( \frac{V_{A1}}{Q} \), decrease to zero, \( R_{xe} \) will 
increase substantially. Since \( V_A, Q, \) and \( \lambda \) are constant \( V_{AXe} \) 
will decrease dramatically (solid line). The greatest rate 
of increase in \( R_{xe} \) (and therefore decrease in \( \frac{V_{AXe}}{V_{ACO_2}} \)) will be when 
the \( \frac{VA}{Q} \) ratio deviates from a mean \( \lambda_{xe} = 0.181 \) 
(9). In the case of the very soluble gas CO₂ where \( \lambda \sim 9 \) (10), 
recovery is usually very high (~0.90). Therefore \( V_{ACO_2} \) is 
relatively unaffected by low \( \frac{VA}{Q} \) ratios. The minimal fall in 
\( V_{ACO_2} \) leads to use of the ratio \( \frac{V_{AXe}}{V_{ACO_2}} \) as an index of 
nonuniformities in regional \( V_A/Q \).

![Figure 4 Alveolar ventilation measured with \( V_{AXe} \) under-
estimates true ventilation when there are ventilation-perfusion 
inhomogeneities. This is shown in a two-compartment lung 
model where compartment 1 receives 20% of blood flow \( Q_1 \), 
and from 20% to 0% of the ventilation \( V_A \). Total flow \( Q \), and 
ventilation \( V_A \) are constant. Tracer recovery \( R_x \) is the sum of 
the recovery fractions from each compartment, weighted by 
flow to that compartment, and is calculated from a modifica-
tion of equation 17a:

\[ R_x = \frac{1}{\frac{V_{A1}}{\lambda Q_1} + 1} \frac{Q_1}{Q} + \frac{1}{\frac{V_{A2}}{\lambda Q_2} + 1} \frac{Q_2}{Q} \]
that xenon can provide an accurate reflection of the efficiency of oxygen exchange.

**Pulmonary tissue volume.** In control dogs the lung tissue volume, $V_t$, was 8.86 ml/kg. The tritiated water volume in dogs, reported in three series, averaged 3.81 ml/kg (18–20). After a correction factor was applied to account for water volume in blood, Goresky found that he was able to measure between 50–61% of the lung weight (8). $V_t$ was 82.8% of the weight of the blood-drained lung.

The differences in the water and antipyrine measured volumes, might be due to the fact that antipyrine has access to a larger extravascular lung volume than tritiated water. The moderate fat solubility of antipyrine argues for its distribution into a larger extravascular space. If the density of the lung is one, $V_t$ then should approach the weight of the blood drained lung.

Comparison of the volumes accessible, and those actually measured, results in better agreement. Antipyrine measures 82.8% of the lung weight while tritiated water measures 64–78% of lung water (28). The failure to measure 100% of the respective volumes is probably due to incomplete perfusion of the pulmonary capillary bed (21).

The data in patients is also consistent with this perfusion hypothesis. In the two patients who made uneventful recoveries, $V_t$ was found to be 144 ml/m², while in five comparable individuals, the tritiated water space after correction for water in blood was 112 ml/m² (20). The predicted normal parenchymal volume is 259 ml/m² (22). The group of patients who were critically ill had an enlarged $V_t$ of 274 ml/m². Without knowledge of the size of the perfusion bed, a precise estimate of lung weight cannot be given.

**Air volumes.** In control dogs, $FRC_{Xe}$ was found to be 34.8 ml/kg while the predicted $FRC$ is 33.1 ml/kg (23, 24). In the complete patient series, $FRC_{Xe}$ was significantly lower than the helium measured $FRC$, averaging 76.5% ($P < 0.05$). Several factors may be responsible for this discrepancy in $FRC_{Xe}$ and $FRC_H$. These are: (i) regional variations in the $VA/Q$ ratio, (ii) restriction in the volume available to xenon because of (a) diffusion limitations and (b) contraction of the perfusion bed.

**Nonhomogeneous lung function.** Since both the ventilation and volume equations (17 and 27) assume a single compartment lung, it might be argued that $VA/Q$ variations will lead to underestimates in both $VAXe$ and $FRC_{Xe}$. The simulated two-compartment lung model shows that this is not necessarily true.

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**Figure 5** The two-compartment lung described in Fig. 4 is used to illustrate the effect of decreasing blood flow to compartment I from 20% to 0%, while $V_{A1}$ remains at 20%. Total flow and ventilation are constant. $VAXe$ and $VACO2$ are calculated by the method described in Fig. 4. As $Q_1$ decreases, tracer measured $V_{A1}$ underestimates true ventilation. The error is greatest with xenon, the least soluble gas. When $Q_1 = 0$, the air spaces (physiologic dead space) are no longer within the control volume and $V_{A1}$ is unmeasurable. In this example $VACO2$ is reduced to a greater extent than when inhomogeneities are due to very low $VA/Q$ ratios. In theory, the most pronounced changes in $VACO2$ will occur when the $VA/Q$ ratios vary about $k_{CO2}$. As $Q_1$ is reduced $VA1/Q1$ becomes very high and equals or exceeds $k_{CO2}$.

**Figure 6** Anatomic shunting will cause the ventilation ratio $VAXe/VACO2$ to decrease. This is shown by the simulated two compartment lung model (see Fig. 4). In this case $V_{A1} = 0$ while $Q_{1}$ was increased from 0 to 30% of total flow (solid line). The data from Table I are also plotted using $Q_{1}/Q \times 100$ as the abscissa. The closed circles represent the physiologic shunt calculated during room air breathing while the closed circles represent $Q_{1}/Q$ at 50% inspired oxygen. Most data points fall to the right of the theoretical curve which represents anatomic shunting. This is probably a reflection of the fact that $Q_{1}/Q$, the physiologic shunt is very sensitive not only to anatomic shunts but also to other $VA/Q$ imbalances. The ventilation ratio $VAXe/VACO2$ is probably less sensitive to these other $VA/Q$ imbalances.
In the presence of large intrapulmonary shunts, FRC$_{Xe}$ may increase or decrease depending upon the distribution of air volume. On the other hand, it may be shown that if ventilation and perfusion are uniform, air volume inhomogeneities will not lead to errors in FRC$_{Xe}$.

In the case of acute bronchial obstruction, right-to-left shunts may occur through nonventilated but air-containing lung. This leads to an overestimate in FRC$_{Xe}$ but an underestimate in FRC$_{He}$ since the air distal to the obstructed airway will not equilibrate with helium. The volume ratio FRC$_{Xe}$/FRC$_{He}$ will increase even though the ventilation ratio has been shown to decrease (Fig. 6). The data in the seriously ill patients show that V$_{AXe}$/V$_{ACO2}$ = 0.539 while FRC$_{Xe}$/FRC$_{He}$ = 0.737. This is consistent with intrapulmonary shunting occurring, at least in part, through regions with entrapped air. In the case of perfused atelectatic or airless lung segments, both FRC$_{Xe}$ and V$_{AXe}$ will decrease. V$_{ACO2}$ and FRC$_{He}$ will continue to approximate true ventilation and volume. Therefore, both the ventilation and volume ratios will fall. The use of more soluble gas tracers will reduce these ventilation and volume errors.

A third common example of combined ventilation and volume inhomogeneity is under perfusion or complete failure to perfuse portions of the lung. This will lead to identical underestimates in both V$_{AXe}$ and FRC$_{Xe}$. When regional flows cease, neither ventilation nor volume will be measured. FRC$_{He}$ is unaffected. Therefore, while the ventilation ratio remains constant, the volume ratio falls.

These three common examples of ventilation-perfusion inhomogeneity, bronchial obstruction, atelectasis, and physiologic dead space, lead to different effects on the V$_{AXe}$/V$_{ACO2}$ and FRC$_{Xe}$/FRC$_{He}$ ratios. Since these pathologic events often occur together, and in varying degree, it is not surprising that there is no significant correlation between the volume ratio and either Q$_{S}$/Q or the ventilation ratio (Table II).

Comparison of air volumes measured during breathing and breath-holding demonstrate that FRC$_{Xe}$ was consistently lower than V$_{AXe}$, averaging 87.6% (Table III). During breath-holding, V$_{AXe}$ should be virtually insensitive to inhomogeneities in the distribution of volume and of course ventilation. This is true, particularly as xenon recovery approaches unity. Under these circumstances, the volume measured is simply the sum of the regional volumes (equation 4). In theory therefore, the ratio FRC$_{Xe}$/V$_{AXe}$ should reflect the nonhomogeneous V$_{A}$/Q distributions present during the breathing phase of these experiments. Experimental data in Fig. 5 (Table II) show that a 5% error in FRC$_{Xe}$ is the same as V$_{AXe}$ illustrated in Fig. 5.

**Figure 7** Combined inhomogeneities in the distribution of V$_{A}$/Q and air volumes lead to errors in FRC$_{Xe}$. The simulated two-compartment lung was used to demonstrate the effects of right-to-left shunts. Total V$_{A}$, Q, and FRC were maintained constant. Ventilation to compartment one V$_{AXe}$ was zero while Q$_{AX}$ was increased from 0 to 20% of total flow. The air volume in compartment one FRC$_{1}$, was either kept constant at zero (atelectasis), or varied with Q$_{AX}$ such that FRC$_{AXe}$/FRC$_{1}$ = Q$_{AX}$/Q (entraped air). The latter case exemplifies airways obstruction, where there is perfusion of non-ventilated but air-containing lung regions. $\Delta Q_{AXe}$ was calculated from a modification of equation 19:

$$\Delta Q_{AXe} = \frac{Q_{AXe}}{Q_{AXe}} \left( \frac{Q_{AXe}}{Q_{AXe} + Q_{AXe}} \right) \left( \frac{R_{1}}{R_{1} + R_{2}} \right)$$

where the difference in gas and reference tracer transit times in each compartment was weighted by tracer recovery from that compartment. FRC$_{AX}$ was then derived from a modification of equation 27:

$$FRC_{AX} = \frac{\lambda Q_{AXe} \Delta Q_{AXe}}{R_{e}}$$

Elimination of the terms $\tilde{Z}$, $\lambda_{ax} V_{ax}$, and $TV_{ax}$/2 from these equations leads to small errors. The curves show that right-to-left shunts occurring through air containing lung, result in overestimates of FRC$_{AXe}$. The same shunts through regions of atelectasis result in underestimates in FRC$_{AXe}$. The errors are minimized if a very soluble gas is used. The changes in FRC$_{CO2}$ are illustrated. These curves are entirely theoretical since $\lambda_{ox}$ cannot be measured without using labeled CO$_2$.

25% shunt measured during room air breathing corresponds to a V$_{AXe}$/V$_{ACO2}$ ratio of 0.6 to 0.7. The FRC$_{Xe}$/V$_{AXe}$ fell only to 0.876. These considerations indicate that the right to left shunts, which were ob-
served in the experiments of Table III, occurred through lung regions containing entrapped air.

**Diffusion.** In addition to nonhomogeneities in lung function, diffusion may be a factor in the underestimation of \( \text{FRC}_{\text{x}e} \). In theory, volumes measured by indicator techniques are those into which tracer has penetrated before returning to exit the lung via effluent blood. Since the air spaces are large, and many of them are distant from the perfusion bed, the short time available for diffusion interchange during breathing will limit the volumes measured. During breath-holding, there is sufficient time for xenon to evolve into airways distant to alveolae. In one second, xenon diffuses approximately 1.4 cm in air.\(^{10}\) Therefore over the 1–3 min period required for washout of xenon from the breath-holding lung, it is probable that diffusion interchange occurs with the entire FRC. These differences in the volume accessible to xenon during breathing and breath-holding may in part account for the finding \( \text{FRC}_{\text{x}e} < \text{VAX}_{\text{x}e} \). Membrane diffusion limitations will accentuate the underestimate in \( \text{FRC}_{\text{x}e} \). The relative importance of this membrane phenomenon in sick patients is uncertain.

During breathing, there is no direct data to resolve the question as to how much airway volume is contained within the control volume. In theory, during one normal respiratory cycle there are no oxygen concentration gradients from respiratory bronchialies to alveoli (14). Therefore, the minimum volume included in \( \text{FRC}_{\text{x}e} \) encompasses those distal conducting airways, contiguous and in concentration equilibrium with perfused alveoli. If the entire lung is perfused and \( \text{VA}/\dot{Q} \) ratios are uniform, \( \text{FRC}_{\text{x}e} \) should approach \( \text{VAX}_{\text{x}e} \) and \( \text{FRC}_{\text{He}} \) under these circumstances will be due to anatomic dead space.

**Perfusion bed.** Regional inhomogeneities in blood flow result in underestimates in both \( \text{VAX}_{\text{x}e} \) and \( \text{FRC}_{\text{x}e} \) (Fig. 5). The effect is most pronounced when flow is completely interrupted. All ventilation to, and volume contained in this region of physiologic dead space will be excluded from tracer measurement.

**Application of indicator method.** Tracer measurements of extravascular tissue volumes, alveolar ventilation, and air volumes must be interpreted in light of the distribution of blood flow, ventilation, and air volumes. Failure to perfuse lung segments will result in underestimates of \( \text{Vt} \), \( \text{VA} \), and FRC. Nonuniform distribution of ventilation will lead to underestimates in \( \text{VA} \) and either under or overestimates in FRC depending upon the distribution of volume. These errors are significant, particularly in sick patients, and limit the independent use of indicator methods.

Combination of tracer techniques with other measurements may circumvent these problems. Thus, if it can be shown that the \( \text{VAX}_{\text{x}e}/\text{VACO}_{2} \) ratio is unity, \( \text{FRC}_{\text{x}e} \) will be a precise estimate of the volume of air surrounding the perfusion bed. This bed can also be described by the ratio \( \text{FRC}_{\text{x}e}/\text{Vt} \) (Table II). In addition, \( \text{FRC}_{\text{x}e}/\text{FRC}_{\text{He}} \) will provide an estimate of the size of the perfusion bed, and when divided into \( \text{Vt} \) will yield total tissue volume.

The errors inherent in these indicator methods can be used to advantage to provide information concerning nonhomogeneity. The simultaneous use of gases of different solubilities may permit understanding of the type and degree of maldistributions of volume and ventilation which occur in pulmonary disease (15–17). Interpretation of such data can offer insights into pathophysiologic mechanisms. The ability to distinguish flow through nonventilated but air-containing regions, from flow through regions of alveolar collapse may serve to identify airway obstructions or alveolar instability as a cause of right-to-left shunting.

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**REFERENCES**


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\(^{10}\) Based on the relationship \( (\bar{x})^2 = \sqrt{2D}\bar{t} \), where \( (\bar{x})^2 \) is the root mean square diffusional displacement, \( D \) is the diffusion coefficient and \( \bar{t} \) is time in seconds (6).


