THE MEASUREMENT OF REGIONAL VENTILATION IN MAN: A NEW METHOD OF QUANTITATION

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Regional ventilation has been measured in 20 healthy subjects as the fractional exchange of air per breath using radioactive xenon and a gamma scintillation camera interfaced to a small digital computer. Because xenon is slightly soluble in blood and more soluble in fat, a tissue background correction has been incorporated into the calculation so that regional ventilation can be determined from a washout procedure after a washin lasting several minutes. Regional ventilation is determined as the mean fractional exchange of air per breath using the Stewart-Hamilton equation. Figures are obtained for the fractional exchange of air per breath for upper, mid, and lower zones in each lung, and images are produced showing the functional relationships within and between regions. Ventilation in the upright position increased from apex to base in the expected fashion and was slightly more efficient in the left lung than the right, particularly at the left base. No lateral gradient was observed. A good correlation was obtained between tidal volume and the fractional exchange of air per breath ($r = 0.83$). Allowing for differences in tidal volume between the washin and washout parts of the procedure, figures for the regional fractional exchange of air were similar for each part of the study. Thus the tissue background correction allows the washout curves to be used to measure ventilation, and these are a more sensitive indication of impaired ventilation than washin curves.

A large part of our current understanding of regional pulmonary function stems from the introduction of ^{133}Xe by Knipping and his colleagues in 1955 (*1*), and from the extensive use of this gas that was made by the respiratory physiology research groups in Montreal and London (*2–8*). More recently scintillation cameras have been used to assess regional ventilation and perfusion (*9–11*). They offer better spatial resolution than multiple probe systems and when fitted with a diverging collimator can view the whole of each lung from one aspect. They have an additional advantage in that serial images of, for instance, the washout of ^{133}Xe provide visible evidence of the delayed clearance of this gas from poorly ventilated regions. However, for any detailed measurements of ventilation, as distinct from a visual assessment, the data from a scintillation camera must first be recorded in some suitable format and then processed by a computer. A number of systems using off-line computing facilities for the data analysis have been described for this purpose (*12–14*).

This paper describes a new way of measuring regional ventilation from the washout of ^{133}Xe using a gamma scintillation camera interfaced to a small digital computer and also discusses the validity of this method of measuring ventilation. We have chosen to measure ventilation during "natural" respiration so that severely ill patients, unconscious patients, and patients with dyspnea or pleuritic pain could be examined.

METHODS

The equipment used consists of a Nuclear-Chicago Pho/Gamma III scintillation camera interfaced to a Digital Equipment PDP-12 digital computer and a ^{133}Xe delivery system. The computer has 8K 12-bit words of memory, two LINC tape drives, a standard oscilloscope, and a teletype. Photographs of the os-

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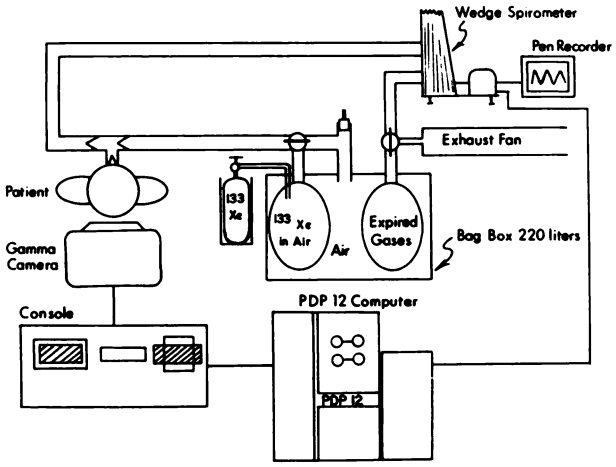

FIG. 1. Diagram of arrangement of apparatus used for ventilation studies.

cilloscope are taken with a Polaroid camera. The interface has a deadtime of 15 μsec, and images from the gamma camera are stored in a 32 $\times$ 32 matrix using the direct memory access function of the PDP-12. The buffered tape system allows continuous data collection while previous input is stored on tape. The construction and function of the interface have been described in detail (*15*).

The ^{133}Xe delivery system consists of a dual bag-box spirometer (constructed by Medical Science, St. Louis) which contains two balloons, each capable of holding 120 liters without tension. The box surrounding these balloons acts as a third compartment. A wedge spirometer is included in the system which is connected together with suitable tubing and valves as shown in Fig. 1. The ^{133}Xe balloon is filled with 50 liters of air (or oxygen) containing 1 mCi ^{133}Xe/liter, immediately before a study.

COMPUTER PROGRAMS FOR DATA COLLECTION AND ANALYSIS

Data collection program. This program starts by collecting an image of a uniform disk source (containing 3–5 mCi ^{99m}Tc) in a 32 $\times$ 32 matrix for 999,000 counts. The pulse-height analyzer of the scintillation camera is then reset for the 81-keV gamma-ray emission from ^{133}Xe with a 25% window. For the examination the patient is seated with his back to the scintillation camera, and after he has become familiar with the system, a background image is collected for 1 min. Xenon-133 is introduced into the inspired line, and serial images, or frames, of the washin of ^{133}Xe are recorded every 6 sec for 90 sec and then every 12 sec for up to 7.5 min. The washout is started when the xenon balloon is exhausted by turning the appropriate valve, so that the air from the third compartment is breathed. Serial images are again collected every 6 sec for 72 sec, every 12 sec for 2 min, and then every 30 sec for up to 10.2 min. An option exists in the data collection program to collect an image of a single breath, and also the washout from such a breath for up to 7 min, before the washin part of the study.

Data correction program. After collection the data are corrected for background, for the nonuniform response of the scintillation camera, and also for the deadtime loss of the computer interface. A decay correction can also be applied if a short-lived radionuclide is used.

Calculation program. The corrected data tape is processed by a special program which requires user interaction. An integrated image of all the washin and washout frames is presented to the user on the computer's oscilloscope and a region between and below the lungs outlined for a tissue background correction as shown in Fig. 2. Regions from each lung are then selected; for studies on the normal subjects, six contiguous regions were chosen in each lung. An activity time plot for both lungs for the entire study appears next, and the user selects those frames that correspond to the end of the washin and the beginning and the end of either the washin and washout curves (Fig. 2).

Ventilation is calculated as the flow of air per unit volume or fractional exchange of air using the Stewart-Hamilton relationship:

$$\frac{F}{V} = \frac{q_0}{\int_0^\infty q(t)dt}.$$

Here q_0 represents the quantity of ^{133}Xe within the lungs at the end of the washin, and the denominator represents the area beneath the washout curve.

Both the height of the curve at the end of the washin and the area under the washin or washout curves are first corrected for the tissue content of ^{133}Xe by subtracting the average counts/cell derived

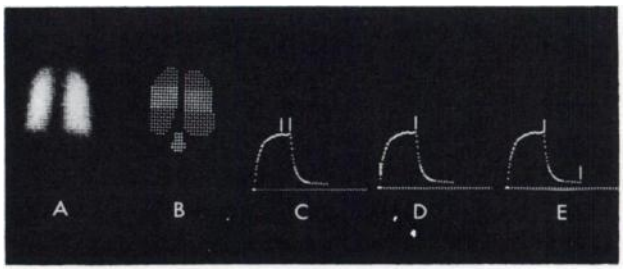

FIG. 2. Several steps in calculation program. (A) image of integrated washin and washout frames, (B) three regions outlined in each lung. Midzones are shown in greater intensity to distinguish them from other regions. In normal subjects discussed in paper, each region was further divided in half vertically. Region beneath lungs is chosen for tissue background correction, (C) two cursors placed over frames chosen for beginning and end of height calculation, (D) two cursors defining area for washin calculation, (E) two cursors defining area for washout calculation.

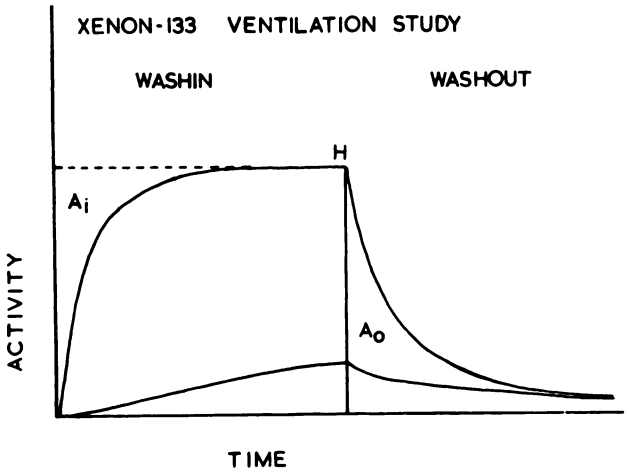

FIG. 3. Activity time curve from ventilation study, showing areas used in calculation—A_i for washin and A_o for washout. H is height of curve at end of washin. Lower tracing indicates changing tissue background activity. For calculation values of H, A_i, and A_o are corrected for tissue background.

from the tissue background region in each frame from each cell in the matrix. For the calculation of ventilation from the washin procedure, A_i is the area above the washin curve (Fig. 3). This area is determined by first constructing a rectangle of height H (corrected for the tissue background) and length, the time to the end of the washin period, and then subtracting the area beneath the washin curve (corrected for the tissue background) from the area of this rectangle. Thus for the washin calculation, $F/V = H/A_i$.

For the washout calculation the area beneath the washout curve, A_o (corrected for the tissue background) is used, so that $F/V = H/A_o$.

The calculations are done automatically for each cell in the outlined regions and then the fractional exchange of air per second for each outlined region is determined and printed out by the teletype, together with the height for each region and the appropriate area. Regions may be summed and figures obtained for each lung or both lungs combined. In addition, gray scale images of the values calculated for each cell in the outlined lungs are presented on the computer's oscilloscope and can be photographed on Polaroid film.

Tidal volume and respiratory frequency are determined from the spirometer tracing and the average time for a breath used to determine the fractional exchange of air per breath from the figures for the fractional exchange of air per second.

The subjects discussed in this paper were healthy physicians and medical students. One had a history of wheezing but was symptom-free at the time of the examination. All were male, and their ages ranged from 22 to 57. All had normal chest radiographs. Routine spirometry was obtained on all but two subjects and the results are shown in Table 1.

Tidal volume and respiratory frequency were determined for the washin and the washout parts of each study.

Total lung volume was calculated from the posterior-anterior and lateral chest radiographs using Barnhard's method (*16*). In two subjects the chest

TABLE 1. SPIROMETRY RESULTS IN 18 HEALTHY VOLUNTEERS

Subject	Age	Height (cm)	Vital capacity (liters)	FEV_1 (liters)	FEV_1/VC (%)	Maximum mid-expiratory flow rate (liters/sec)	Lung volume (liters)*
WJ	28	184	5.30	4.20	79	3.58	5.38
SR	35	184	4.86	3.85	79	3.00	6.84
BM	29	170	4.69	3.73	80	3.52	—
AR	32	185	4.55	4.35	96	8.00	6.98
MB	30	180	4.69	3.24	69	3.70	5.71
LL	27	184	4.90	3.52	72	2.62	6.38
DC	22	180	4.69	4.11	88	4.38	5.15
FH	57	184	4.25	3.45	81	3.42	6.94
SB	27	180	4.15	3.66	88	4.62	5.54
SG	29	184	4.97	3.80	76	2.97	6.19
RL	30	179	3.58	3.34	90	5.10	3.80
SW	36	174	4.84	3.58	74	2.96	5.98
BJ	34	180	5.45	4.49	82	4.21	6.78
EJ	30	191	5.35	5.00	92	5.93	6.94
AD	30	179	3.93	3.52	89	3.66	5.26
FJ	24	175	4.62	3.86	84	4.27	—
FJ	33	180	3.37	3.24	87	3.82	4.03
TS	30	184	5.90	3.50	79	2.33	7.24

* Lung volume was calculated from the postero-anterior and lateral chest radiographs after the method of Barnhard, et al (*16*). Subjects BM and FJ had unsatisfactory films for this determination.

TABLE 2. MEAN FRACTIONAL EXCHANGE OF AIR PER BREATH (±s.e.m.) IN HEALTHY SUBJECTS

Lung zones	Washin n = 20	Washout n = 20	Single breath washout n = 10
LUZ	0.118 ± 0.013	0.129 ± 0.013	0.104 ± 0.009
LMZ	0.137 ± 0.015	0.148 ± 0.015	0.122 ± 0.010
LLZ	0.161 ± 0.018	0.176 ± 0.018	0.165 ± 0.017
Left lung	0.136 ± 0.014	0.149 ± 0.015	0.131 ± 0.001
RUZ	0.116 ± 0.013	0.125 ± 0.013	0.096 ± 0.009
RMZ	0.134 ± 0.013	0.147 ± 0.015	0.117 ± 0.010
RLZ	0.152 ± 0.015	0.161 ± 0.018	0.149 ± 0.014
Right lung	0.134 ± 0.014	0.143 ± 0.014	0.123 ± 0.011
Both lungs	0.135 ± 0.014	0.145 ± 0.014	0.126 ± 0.011

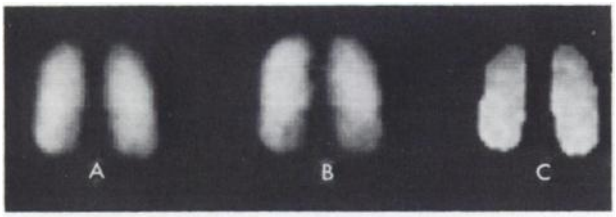

FIG. 4. Computer-generated images from normal subject. (A) Integrated image of frames chosen for height of curve at end of washin, (B) area beneath washout curve, (C) fractional exchange of air obtained by dividing image (A) by image (B).

radiograph was no longer available, and in two others good inspiration films were not available.

To obtain some idea of the magnitude of the tissue background contribution, five patients were examined following pneumonectomy—three between 10 and 14 days after their operation, and the other two at 6 months and 5 years, respectively. In these patients the clearance of ^{133}Xe in the region beneath the lungs, chosen for the tissue background correction, was compared with that in the upper, mid, and lower zones of the side of the pneumonectomy. The tissue background correction was also performed using each of these regions in turn instead of the basal region.

RESULTS

The fractional exchange of air per breath for three large zones in each lung is shown in Table 2, calculated from the washin, the washout, and from the washout from a single breath. An example of the functional images obtained is shown in Fig. 4.

The left lung is ventilated with slightly greater efficiency than the right lung, and this is more apparent at the left lung base, but the difference is not statistically significant ($p > 0.05$). No significant difference was found between the medial and lateral portions of each of the large zones using Student's t-test for paired differences.

Figure 5 shows the relationship between tidal volume and the fractional exchange of air per breath calculated from the washout curves. There is a highly significant correlation between these two measurements ($r = 0.83$, $p < 0.001$).

The figures for lung volume obtained from the chest radiographs have been used to calculate how much air was exchanged per breath (using the calculated fractional exchange of air per breath from the washout for both lungs) and then compared with the measured tidal volume. The difference between the mean estimated exchanged volume and the mean tidal volume was 200 ml for the washin and 250 ml for the washout. The mouthpiece and associated valve chamber had a volume of 80 ml giving a calculated dead space of 120 ml for washin and 170 ml for the washout (Table 3).

TISSUE BACKGROUND

The effect of the ^{133}Xe that enters the tissues on the washout curves has been determined by recalculating the fractional exchange of air per breath for 12 subjects, omitting the tissue background correction. Here the fractional exchange of air calculated without correction from the washout curves averaged 65.2% ± 2.9 (s.e.m.) of that determined from the washin curves. With the tissue background

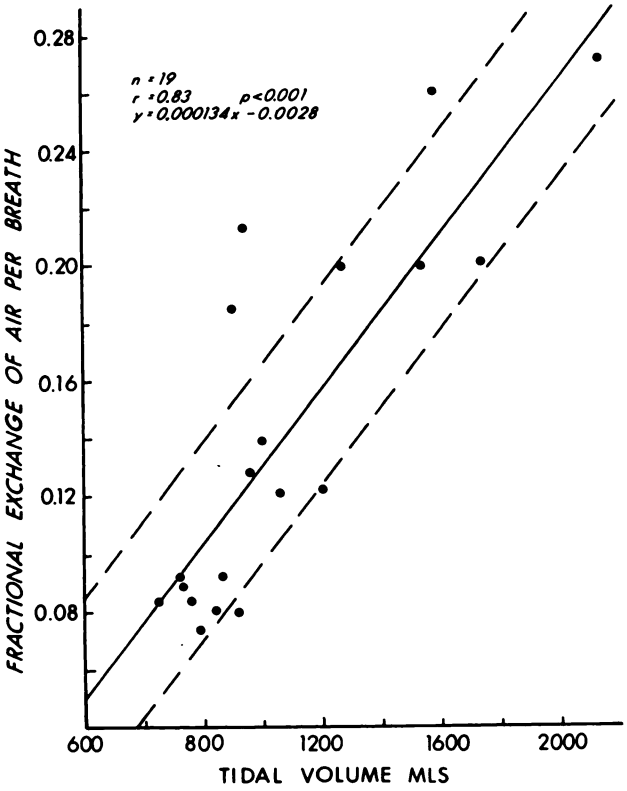

FIG. 5. Relationship between tidal volume and fractional exchange of air/breath in 19 healthy subjects calculated from washout figures.

TABLE 3. WHOLE LUNG FRACTIONAL EXCHANGE OF AIR TIDAL VOLUME AND EXCHANGED VOLUME

	Mean fractional exchange of air per breath (±s.e.m.) both lungs	Mean tidal volume (ml) (±s.e.m.)	Mean exchanged volume (ml) (±s.e.m.)
Washin n = 20	0.135 ± 0.014	999 ± 80	796 ± 92
Washout n = 20	0.145 ± 0.014	1124 ± 106	866 ± 93

correction, the difference was only 7.5% ± 2.5 (s.e.m.) and was comparable to the difference in tidal volumes between the washin and washout parts of the procedure (Table 3).

If the chest wall content of ^{133}Xe has been accounted for by the tissue background correction, then figures for the fractional exchange of air should be unchanged when the washout time is increased beyond the time at which the lungs are clear.

The fractional exchange of air has therefore been determined for two different washout times; one, the full length of the washout, and the other, 1 min less than this. There was no significant difference between these two determinations, suggesting that a reasonable estimate of tissue background has been made. The actual counts per second in the base area have also been compared with counts per second in similar sized areas from three large regions in each lung for the last 24–48 sec of each study, at a time when the lung fields could no longer be distinguished from the tissue background activity. There was no consistent over or under estimate for any of the regions, and the differences between the base area and each of these regions is not statistically significant.

In the five patients who had undergone a pneumonectomy, the fractional exchange of ^{133}Xe per second in the region chosen for the tissue background averaged 0.0048 ± 0.0002 (s.e.m.), whereas in the upper, mid, and lower zones on the side of the pneumonectomy, the figures were 0.0037 ± 0.0002, 0.00038 ± 0.0004 and 0.0035 ± 0.0002, respectively (Table 4).

The fractional exchange of air in the remaining lung has been calculated using both the tissue background region and the corresponding tissue region at the same level (i.e., upper, mid, and lower zones) from the pneumonectomy side instead. The results are shown in Table 4. The use of the tissue background region from below the lungs consistently overestimates the fractional exchange of air when compared with the corresponding zone corrections. The least difference is seen in Patient K who had had his pneumonectomy 5 years before and whose shifted mediastinum was certainly included in the upper and midzone regions used for the tissue correction.

This overestimation results from an average reduction in the height of the activity time curve of 6–8% and in the area under the washout curve of 18–20% compared with the corresponding zone corrections.

TABLE 4. FRACTIONAL EXCHANGE OF ^{133}Xe PER SEC IN LUNGS, CHEST WALL, AND TISSUE BACKGROUND REGION IN FIVE PATIENTS WITH A PNEUMONECTOMY

Patient	Time since operation		Upper zone		Mid zone		Lower zone	
			Base correction	Zone correction	Base correction	Zone correction	Base correction	Zone correction
K	5 years	lung	0.0103*	0.0092	0.0162	0.0156	0.0141	0.0145
		zone	0.0053*	0.0044	—	0.0053	—	0.0038
C	6 months	lung	0.0314	0.0253	0.0419	0.0326	0.0425	0.0329
		zone	0.0054	0.0037	—	0.0033	—	0.0039
F	14 days	lung	0.0302	0.0227	0.0184	0.0159	0.0212	0.0178
		zone	0.0048	0.0038	—	0.0032	—	0.0034
T	10 days	lung	0.0200	0.0156	0.0187	0.0134	0.0169	0.0121
		zone	0.0045	0.0034	—	0.0039	—	0.0027
M	11 days	lung	0.0384	0.0288	0.0286	0.0217	0.0222	0.0185
		zone	0.0041	0.0031	—	0.0031	—	0.0035
		zone	0.0048†	0.0037	—	0.0038	—	0.0035
		mean s.e.m.	±0.0002	±0.0002		±0.0004		±0.0002

* For each patient the top row of figures shows the fractional exchange of air per sec in their remaining lung, while the second row shows fractional exchange of ^{133}Xe in the tissue regions chosen for correction.

† The mean fractional exchange in this zone is significantly greater than the mean of the upper and lower zones, $p < 0.01$. There is no significant difference between the three zones.

DISCUSSION

The original methods of measuring ventilation used quasi-static indices, comparing the distribution of a single breath with the distribution of the tracer after a period of rebreathing (*4,7,8*). Other methods have been used such as the time to 50 or 90% of the equilibrium value or to 50% of the washout curve (*5*). Only recently have functional images been constructed from scintillation camera data (*17*). MacIntyre and his colleagues estimate the regional rate constants of the first 60% of the washout curves that follow an intravenous injection of ^{133}Xe (*18*) while Jones and coworkers do this for both injected and inhaled ^{133}Xe (*19*). Both groups make use of relatively large computers for their data analysis.

The 32 × 32 matrix that we have used to store the data frames represents cells of 0.8 × 0.8 cm on the scintillation crystal and rather larger areas at the front of the diverging collimator. This coarse matrix is a compromise between spatial resolution and temporal resolution. A finer array, such as 64 × 64, would require four times as many counts to give the same statistical accuracy and hence four times as much xenon. In addition, our PDP-12 does not have sufficient core to handle such arrays in a dynamic fashion nor is there sufficient tape to store the 100 or so images that such a study usually requires. The variable time frames for the data collection portray the shape of the curve when the concentration of ^{133}Xe is changing most rapidly, but also, by using longer frames when the counting rate is low, increases the accuracy of this part of the procedure. Using the height-to-area calculation also improves the accuracy of the determination because the height is averaged over several frames to obtain the counts per second, whereas the area beneath the washout curve makes use of all the data points here.

Although the Stewart-Hamilton equation was originally devised to measure cardiac output, Zierler has shown that it applies equally well when measuring blood flow per unit volume using external detectors (*20*). If the system under examination functions as a single exponential process, the height-to-area relationship measures the rate constant of this process or the fractional change with time. If more than one exponential process is involved, as is likely in patients with obstructive airways disease, the height-to-area relationship measures the mean fractional change with time of the various components. By using this approach to measure ventilation, figures are obtained for the mean fractional exchange of air in each cell of the matrix and also in the outlined regions. Flow per unit volume, rate of change per unit volume, and fractional exchange per unit time are different ways of expressing the same idea. In the lungs it is probably more useful to express the results as the mean fractional exchange of air per breath, i.e., a measure of the efficiency of ventilation, than as the mean flow of air per unit lung volume.

TABLE 5. MEAN FRACTIONAL EXCHANGE OF AIR/MIN (±s.e.m.) IN 20 HEALTHY SUBJECTS

Lung zones	Washin N = 20	Washout N = 20
LUZ	1.61 ± 0.14	1.77 ± 0.20
LMZ	1.89 ± 0.16	1.99 ± 0.21
LLZ	2.22 ± 0.22	2.31 ± 0.19
Left lung	1.88 ± 0.15	1.98 ± 0.19
RUZ	1.58 ± 0.15	1.72 ± 0.22
RMZ	1.85 ± 0.15	1.99 ± 0.22
RLZ	2.07 ± 0.16	2.14 ± 0.21
Right lung	1.83 ± 0.15	1.91 ± 0.21
Both lungs	1.85 ± 0.15	1.95 ± 0.20

At the end of the washin period, the activity detected over the lungs represents both the ^{133}Xe within the alveoli and airways and the ^{133}Xe dissolved in the blood and tissues of the chest wall and lung parenchyma. For the tissue background correction, the region between and below the lungs was chosen, as this is the only relatively large area of tissue that can be visualized in the same field of view as the lungs and thus studied simultaneously. We have assumed that the changes in ^{133}Xe concentration in this region reflect those in the blood and tissues within and overlying the lungs. Differences in tissue composition and tissue blood flow per unit volume are likely to exist between the chest wall and the area chosen for the background correction, but we have assumed that these differences are not so large that they invalidate the use of this correction.

In the patients who had undergone a pneumonectomy, the region below the lungs, that was chosen for the tissue background correction, had a significantly greater fractional exchange of ^{133}Xe than the tissue regions overlying the pneumonectomy. The fractional exchange in the upper, mid, and lower zone tissue regions was not significantly different so that it is reasonable to assume a single correction factor for them. The use of the tissue region beneath the lungs to provide this factor seems to work better in practice than the figures from the pneumonectomy patients would suggest. A possible reason for this is that the tissues on the side of the pneumonectomy underestimate the tissue background contribution because no account is taken of the additional ^{133}Xe that would be in the pulmonary vasculature, were there a lung within the chest. Some support for this suggestion is gained from Patient K whose displaced mediastinal structures were asso-

ciated with a greater fractional exchange of ^{133}Xe in the upper and midzones on the side of his pneumonectomy than was seen in the other four patients.

Anthonisen and his colleagues (*21*) assessed the chest-wall contribution in seven patients who had had a pneumonectomy. They used a multiple-probe system and counted a large proportion of scattered radiation. They concluded that the probable errors in their estimation of the chest wall background were not large enough to influence seriously measurement of the intrapulmonary counting rate. If the chest-wall clearance approached or exceeded the pulmonary clearance, then the errors in estimating the chest-wall background by their method would increase. In the five patients studied here, the fractional exchange in the tissues on the side of the pneumonectomy was 2–7 times less than the fractional exchange within the lung but could clearly be similar in patients with more severely disturbed lung function.

The good agreement between the washin and washout figures after the tissue background correction, the similarity between the values for ventilation calculated from both the full washout curve and for the shorter time, the small difference between the tissue background region and the six lung zones at the end of the washout, all suggest that the use of this region provides a reasonable way of subtracting the tissue background contribution from the washout curves.

These healthy subjects showed a gentle gradient of increasing ventilation from apex to base, with the left lung having a slightly greater fractional exchange of air than the right. The smaller gradient in the right lung may be related to the smaller diaphragmatic movement that takes place on this side. The lack of any significant lateral gradient confirms the observations of Newhouse and his colleagues in four normal subjects (*14*).

These results are in general agreement with the pattern of ventilation described by previous investigators (*2,4–7*) but have the advantage that the figures obtained are a measure of the efficiency of ventilation rather than an index of ventilation, whereas the functional images show the relationships between smaller areas of lung. If lung volume is known, then the product of the regional fractional exchange of air per breath, the regional fractional distribution of lung volume, and total lung volume gives the quantity of air exchanged per breath on a regional basis.

When our figures for the fractional exchange of air per breath are converted to fractional exchange of air per minute, they are in good agreement with those found by Matthews and Dollery, who used an analog computer to analyze data from the washin and washout of both ^{133}Xe and ^{13}N (*22*) (See Table 5).

The increase in the fractional exchange of air with increasing tidal volume, and good overall agreement between the volume of air exchanged per breath, calculated from the lung volume figures, and tidal volume suggest that this method of calculating ventilation from the washout curves is a reasonably accurate one. An important additional advantage of using the washout curves, as Matthews and Dollery point out, is that they are more sensitive than the washin curves in revealing small areas of impaired ventilation.

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