RADIONUCLIDE EVALUATION OF REGIONAL LUNG FUNCTION IN CHILDREN

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A method suitable for the study of regional lung function in children is described. The method is simple to perform, takes only 2 min, and provides pictorial and numerical information on regional ventilation and perfusion and a scaling factor measured after rebreathing to account for regional variation in lung size and shielding. Although the availability of a computer system such as the one described in the text is essential for precise and rapid numerical evaluation, nuclear medicine laboratories that lack this facility but have a gamma camera could use this method to obtain scintigraphic information alone.

Regional lung-function studies with radioactive xenon have a well-established place in the assessment of pulmonary diseases. However, current methods which require the patient to breathe into a spirometer and perform a number of respiratory maneuvers, including breathholding, are inadequate for the study of young children who are unable or unwilling to hold their breath for several seconds or breathe through a mouthpiece for the duration of the study.

The gamma scintillation camera provides better anatomical definition and more precise regional evaluation than multiple-probe detectors used previously (*1*). In addition, the use of on-line digital computer systems allows rapid and accurate evaluation of the massive amounts of data acquired with the gamma camera. These advances in instrumentation, nonetheless, have not been accompanied by the development of pediatric applications for evaluation of regional lung function.

We have developed a method to assess regional lung function in infants and children of all ages using ^{133}Xe and the gamma scintillation camera which does not require patient cooperation. The test is without risk and simple to perform and provides morphologic and quantitative information of quality and accuracy concerning regional lung function equal to that achieved with adults.

MATERIALS AND METHODS

The gamma scintillation camera (Searle Radiographics Pho/Gamma HP) is equipped with a parallel or converging multihole collimator, as preferred for the size of the patient. The on-line digital computer system (Digital Equipment Corp., PDP 11/20, "Gamma-11") with 16,000 words of core memory and 1.2 million words of magnetic disk capacity acquires and stores the camera output in the form of sequential matrices at a variable number of frames per unit of time. At the end of the study, the data are displayed as single or accumulated frames on a persistence oscilloscope. Frame algebra, contrast enhancement, and smoothing routines are available for visual analysis. Regions of interest can be defined over the lung fields from which histograms of activity compared with time may be generated. Numerical analysis of the data proceeds directly from disk without the need to extract and reenter information for processing. Results are available shortly after the examination.

A short-tube pediatric scalp vein set, inserted beforehand in a superficial vein, is connected to a small disposable injection system with a one-way valve which facilitates the delivery of small volumes of radiopharmaceutical in solution followed by a rapid saline flush (*2*). The patient is examined in the supine or seated position and centered in front of the camera with help of a shielded syringe containing the radioactive xenon held perpendicular to the pa-

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tient's chest over the suprasternal notch and the xiphoid process.

Xenon-133 gas dissolved in saline is injected into an 800-ml plastic bag filled with oxygen, closed with a surgical clamp, and shielded in a lead box (Fig. 1). In the bag the gas diffuses out of solution and a gauze absorbs the saline, preventing accidental swallowing. The final concentration of xenon gas in the bag is 10–20 μCi/ml.

The xenon bag is attached to an anesthesia mask which is placed firmly over the nose and mouth of the patient. The clamp is released and the patient is allowed to rebreathe into the bag (washin) until constant activity levels indicate that equal concentrations of xenon prevail in lungs and bag (equilibration). The mask is then withdrawn and the patient is allowed to breathe room air and exhale into the exhaust system (washout). Washout is continued until radioactivity levels are close to background or less than 10% of the equilibration activity.

Xenon-133 in saline in a dose of 300 μCi/kg with a specific activity of 10–40 μCi/ml is then injected as an intravenous bolus for evaluation of pulmonary perfusion. A minimum of 2 mCi is necessary to achieve reasonable counting statistics. Washout of the perfused lung is allowed to continue until background levels are reached.

The entire study is recorded on videotape and in the computer on magnetic disk at a frame rate of 1 frame/sec in a matrix of 64 $\times$ 64 cells and lasts approximately 2 min except in patients with obstructive airway disease for whom longer time is needed for equilibration and washout. The estimated absorbed radiation dose (*3*) for an infant under 1 year of age is 5 mr (gamma radiation) to the whole body and 90 mr (beta radiation) to the lungs, slightly higher in patients with delayed washout due to obstruction of airways or to the right-to-left intracardiac shunting.

At the end of the test, serial scintigraphs are obtained from the gamma camera at 5-sec intervals. Computer-displayed images of equilibration and perfusion are generated and enhanced by background subtraction and nine-point weighted smoothing. The perfusion image is normalized to the equilibration frames by comparison of total counts, and computer images of equilibration minus perfusion and of perfusion minus equilibration are displayed to depict any areas of mismatch between equilibration and perfusion.

An image of lung radioactivity during equilibration is then displayed on an oscilloscope and regions of interest, identical in size, are marked over each lung field. To demonstrate vertical gradients of ventilation or perfusion, three or more regions may be marked over each lung although for comparison of right and left lung function alone, one region of interest over each lung is sufficient. Histograms of activity as a function of time are generated and stored for each region of interest.

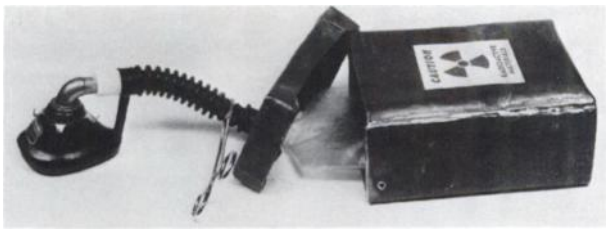

FIG. 1. Inhalation system—plastic bag containing xenon–oxygen mixture housed in protective lead box is connected to pediatric anesthesia mask.

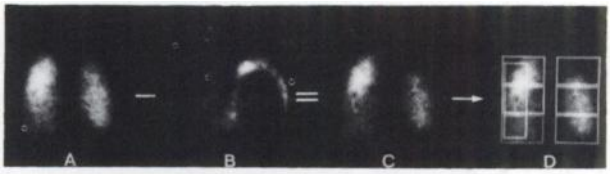

FIG. 2. Image of radiopharmaceutical in SVC and right heart (B) is subtracted from equilibration image (A); the regions of interest (D) including reference region are placed over subtracted image (C).

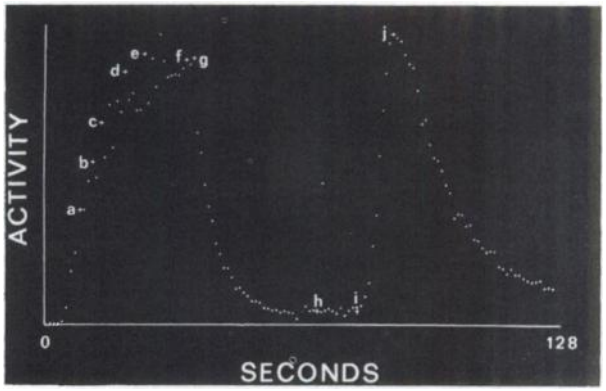

FIG. 3. Time-activity histogram as seen on computer oscilloscope with points A to J (crosses) selected by interactive program.

An additional region of interest is marked over the lung away from the superior vena cava and the heart (Fig. 2); this region is taken as reference for the time course of the study, uncontaminated by the injection. The histogram of the reference area is displayed on the oscilloscope (Fig. 3) and by means of an interactive computer program various points are marked with a light cursor to indicate the exact time of the first inspirations during washin (Fig. 3, points A-C), the end of washin (D), the boundaries of equilibration (E-F), the start of washout following equilibration (G), the background activity prior to perfusion (H-I), and the perfusion peak (J).

Identical points in time are automatically marked by the computer on the histograms corresponding to other lung regions. The histograms are then analyzed to determine regional distribution of the radioactivity representing ventilation, perfusion and equilibration, the rate of washin, and the rate of washout recorded after the equilibration and perfusion measurements.

Regional distributions of single-breath ventilation ($\dot{V}_{SB}$) and of perfusion ($\dot{Q}$) are calculated with the formula:

$$D_i \text{ (percent)} = \frac{A_i \times 100}{\sum_{i=1}^{N} A_i}$$

where D_i is the regional distribution expressed as percent of the total ventilation or perfusion, A_i is the regional activity measured at the appropriate time (end of single breaths during washin, plateau of equilibration, and peak of perfusion) and N is the number of regions (exclusive of the region of reference). Results are given as percent of total lung ventilation, perfusion, and equilibration.

Regional distribution of ventilation is also calculated from washin and washout of equilibrated lung and washout of perfused lung according to an extension of the mean clearance rate formula (*4*):

$$D_i \text{ (percent)} = \frac{\frac{\bar{A}_i}{T_{1/2_i}} \times 100}{\sum_{i=1}^{N} \frac{\bar{A}_i}{T_{1/2_i}}}$$

where D_i is the regional distribution, $\bar{A}_i$ is the mean regional activity during the equilibration plateau or the perfusion, $T_{1/2_i}$ is the half-time of washin or washout in that region, and N is the number of regions, exclusive of the representative region.

Distribution ratios of ventilation/equilibration ($\dot{V}/E$) and ventilation/perfusion ($\dot{V}/\dot{Q}$), are calculated with each estimate of regional ventilation and the distribution ratio of perfusion/equilibration ($\dot{Q}/E$) is derived from regional perfusion.

RESULTS

Out of 258 studies performed to date only six patients had normal lungs by clinical and radiological examinations. Four had a left-to-right shunt due to a small atrial or ventricular septal defect (ASD or VSD), one was examined after closure of a VSD, and another because of suspected pulmonary embolism, later disproved. These six children were all studied in the supine position. A series of 5-sec scintigraphs obtained in the study of one patient with a small ASD (Fig. 4) shows the gradual buildup of inhaled radioxenon in the lungs, followed by equilibration and washout, and the rapid appearance of intravenously injected radioxenon, similarly followed by washout. The time to half-equilibration varied from 5 to 11 sec. The half-disappearance time of xenon following equilibration ranged from 5 to 11 sec and 6 to 12 sec following perfusion.

Numerical analysis revealed slight assymmetry in the distribution of function between right and left lung, slightly more marked for equilibration activity than for perfusion and washin ventilation and for single-breath and washout ventilation (Table 1). Consequently, the distribution indices which appreciate ventilation and perfusion per unit of lung volume ranged from 1.02 to 1.04 for the left lung and from 0.96 to 0.98 for the right lung. Ventilation/perfusion ratios were nearly one (Table 2).

The estimates of regional ventilation derived from washout following perfusion may be markedly different from those calculated by inhalation methods.

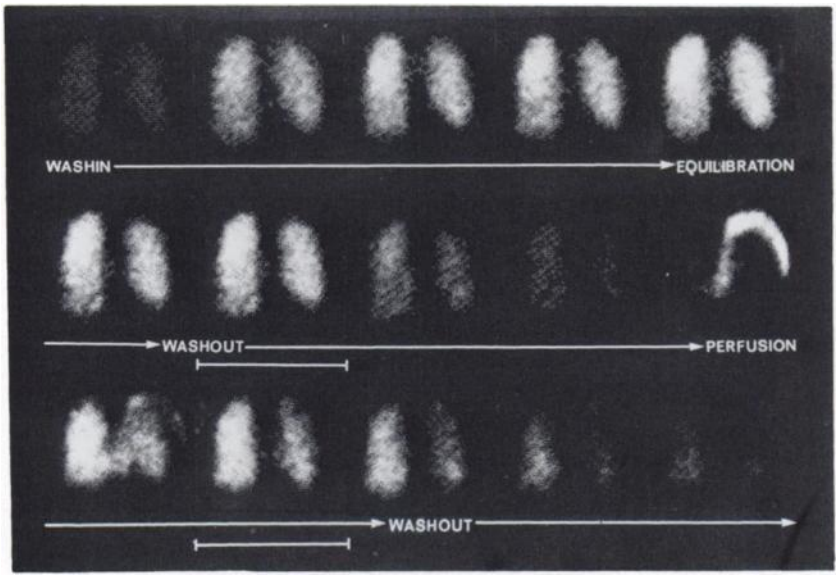

FIG. 4. Series of 5-sec computer images in 3-year-old patient with very small atrial septal defect. Gradual buildup of activity (washin) is seen to reach maximum (equilibration) followed by gradual disappearance of activity (washout). Following intravenous injection of radionuclide there is distribution of activity throughout lung fields followed by gradual disappearance (washout).

For example, in a patient with agenesis of the left pulmonary artery (Fig. 5), the left-lung ventilation calculated from inhalation data was 35% of total and that calculated from perfusion washout was 0%. Even in less extreme cases, inhalation of xenon is the best method for determining the distribution of ventilation and the distribution of aerated lung volume. Estimation of ventilation by washout of perfused lung evaluates those parts of the lung which are perfused by the pulmonary artery and therefore defines areas of regional gas exchange but fails to reveal other areas of aerated lung.

A much more detailed evaluation of the regional ventilation perfusion balance can be obtained by subtraction of normalized images of inhalation and perfusion as seen in Figs. 6, 7, and 8. Areas of ventilation/perfusion imbalance can be portrayed rather dramatically with this maneuver that adds fine detail to the numerical evaluation from the entire lung zones.

TABLE 1. NUMERICAL ANALYSIS OF DISTRIBUTION OF FUNCTION BETWEEN RIGHT AND LEFT LUNG

Patient	Age (yr)	Diagnosis		Percent distribution $\dot{V}1$	$\dot{V}2$	$\dot{V}3$	$\dot{V}SB$	$\dot{Q}$	$\bar{E}$
1	9	VSD, postclosure	LL	50	48	51	49	52	49
			RL	50	52	49	51	48	51
2	5	VSD 1.9*	LL	48	51	56	49	51	48
			RL	52	49	44	51	49	52
3	1	ASD 2.0*	LL	48	53	48	53	47	48
			RL	52	47	52	47	53	52
4	8	? PE†	LL	47	45	52	49	50	47
			RL	53	55	48	51	50	53
5	2	VSD 2.1*	LL	45	47	46	47	44	43
			RL	55	53	54	53	56	57
6	3	ASD 1.5*	LL	47	47	41	47	42	47
			RL	53	53	58	53	58	53
		MEAN‡	LL	48	49	49	49	48	47
			RL	52	51	51	51	52	53

$\dot{V}1$ = Ventilation calculated from washin
$\dot{V}2$ = Ventilation calculated from washout of equilibrated lung
$\dot{V}3$ = Ventilation calculated from washout of perfused lung
$\dot{V}SB$ = Ventilation calculated from single-breath distribution
$\bar{E}$ = Equilibration (volume)
$\dot{Q}$ = Perfusion

* Pulmonary-to-systemic flow ratio (Qp:Qs).
† Pulmonary embolism.
‡ S.E.M. ranges from 1 to 2%.

TABLE 2. RANGE OF DISTRIBUTION INDICES FOR THE RIGHT AND LEFT LUNG

Patient		Regional ventilation $\dot{V}1/E$	$\dot{V}2/E$	$\dot{V}3/E$	$\dot{V}SB/E$	Perfusion $\dot{Q}/E$	Ventilation/perfusion $\dot{V}1/\dot{Q}$	$\dot{V}2/\dot{Q}$	$\dot{V}3/\dot{Q}$	$\dot{V}SB/\dot{Q}$
1	LL	1.02	0.98	1.04	1.00	1.06	0.96	0.92	0.98	0.94
	RL	0.98	1.02	0.96	1.00	0.94	1.04	1.08	1.02	1.06
2	LL	1.00	1.06	1.17	1.02	1.06	0.94	1.00	1.10	0.96
	RL	1.00	0.94	0.85	0.98	0.94	1.06	1.08	0.90	1.04
3	LL	1.00	1.10	1.00	1.10	0.98	1.02	1.13	1.02	1.13
	RL	1.00	0.90	1.00	0.90	1.02	0.98	0.89	0.98	0.89
4	LL	1.00	0.96	1.11	1.04	1.06	0.94	0.90	1.04	0.98
	RL	1.00	1.04	0.91	0.96	0.94	1.06	1.10	0.96	1.02
5	LL	1.05	1.09	1.07	1.09	1.02	1.02	1.07	1.05	1.07
	RL	0.96	0.93	0.95	0.93	0.98	0.98	0.95	0.96	0.95
6	LL	1.00	1.00	0.87	1.00	0.89	1.12	1.12	0.98	1.12
	RL	1.00	1.00	1.11	1.00	1.09	0.91	0.91	1.02	0.91
Mean	LL	1.02	1.02	1.04	1.04	1.02	1.00	1.00	1.02	1.02
	RL	0.98	0.98	0.96	0.96	0.98	1.00	1.00	0.98	0.98

LL = Left lung.
RL = Right lung.

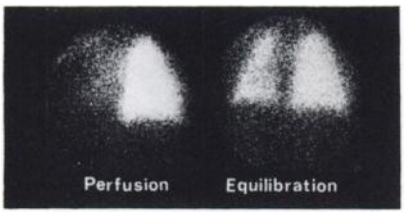

FIG. 5. Agenesis of left pulmonary artery. These are Polaroid images obtained using converging collimator in 2-year-old girl. There is no perfusion of left lung which contributes to about 35% of total ventilation.

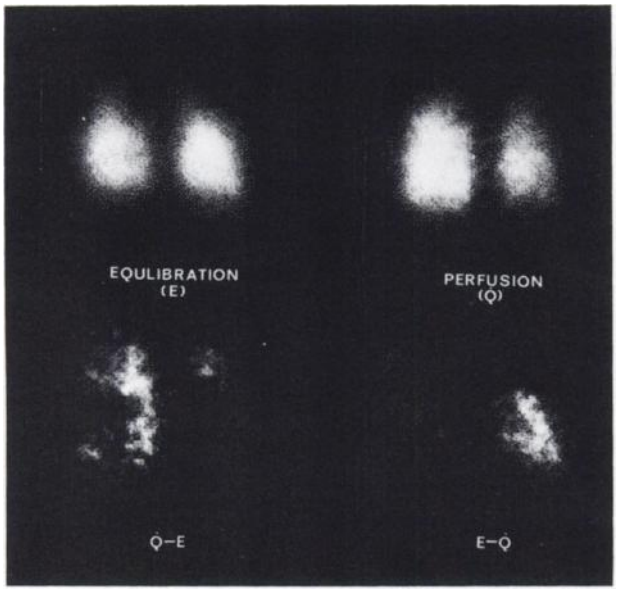

FIG. 6. Ten-year-old boy with cystic fibrosis lung disease. Diffuse imbalance between ventilation and perfusion can be seen. Right lower lung field appears relatively hyperventilated whereas left appears to have more perfusion than ventilation over an irregular area.

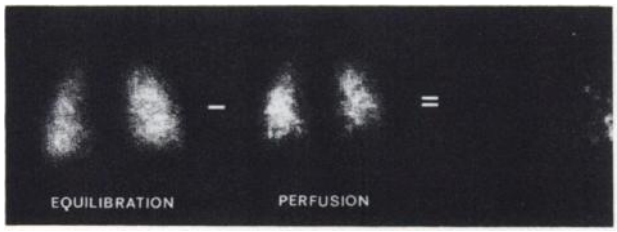

FIG. 7. Seven-year-old boy with pulmonary artery banding reveals relative hyperperfusion of left lung creating area of relative hyperventilation over periphery of right lung field since ventilation balance between left and right lungs is preserved.

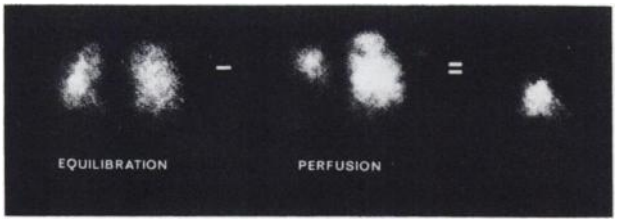

FIG. 8. Pulmonary embolism in 8-year-old boy with fractured leg. (Left) image representing equilibrated lung space from which image representing perfusion (center) is substracted results in image (right) that portrays area of perfusion deficit and preserved ventilation over left lower lung field.

DISCUSSION

Knipping, et al (*5*) in 1955 were the first to attempt measurements of regional lung function through the use of radioactive gases and external detection systems. In 1962, Ball, et al (*6*) described a more informative method using gaseous and dissolved ^{133}Xe for measurements of ventilation and perfusion during breathholding. However, Miörner (*7*) has compared measurements of regional pulmonary blood flow during breathholding and during steady-state breathing in man and Jones, et al (*8–10*) made the same comparison in isolated lung preparations. Both studies showed that regional perfusion measured during uninterrupted respiration accurately reflects known values of perfusion when ventilation is evenly distributed. Jones (*8*) and Goodrich (*11*) further determined that open system washout data correlate well with known ventilation.

With uneven distribution of ventilation, an error arises from the uneven rate of washout superimposed upon the peaks of perfusion activity. The error is proportional to the regional differences in ventilation and to the rising time of the radioactivity pulse generated by the bolus of intravenous xenon. The latter component is reduced by using a small bolus of high specific activity. The component due to ventilation inequality cannot be avoided. Theoretically an appropriate correction can be applied when the washout rate of perfused lung is known. Such a correction could be needed in diseases causing extreme differences in regional ventilation such as lobar emphysema.

Other sources of error are circumvented in the present method. Most importantly, the equilibrium activity provides a normalizing factor which accounts for relative size of right and left lungs or of the various regions of interest as well as for unequal distance from the camera face or unequal shielding by the chest wall. In the original method of Ball this scaling factor was provided by rebreathing into a spirometer; in the present method this is replaced by rebreathing in a bag.

Conversely, the inhalation test allows us to determine the distribution of ventilation even in the presence of gross perfusion abnormalities. With impaired regional perfusion as caused by obstruction or agenesis of large pulmonary arteries, the involved areas of the lung receive little or no xenon. Then ventilation, even if it is relatively preserved, cannot be measured from postperfusion washout. With a right-to-left shunt, a fraction of intravenous xenon reaches the systemic circulation, diffuses into all tissues of the body, and returns progressively to the lung where washout proceeds at a slow rate, inde-

pendent of lung function. In these conditions, ventilation distribution can be assessed only by an inhalation test which in the present method is carried out in a fashion comparable to the original method of Ball.

The gamma camera contributes to the accuracy of the results because it allows visual detection of small defects and monitoring of the whole lung fields for numerical analysis. Visual and numerical data are used together as complementary information. Small defects of perfusion or ventilation defects can be detected visually but are lost in numerical information generated from relatively large zones or regions of interest over the lung. Conversely, a mild change in the gradient of distribution of perfusion or ventilation not sufficiently large to be appreciated visually may only become apparent in the numerical readout. Subtraction of normalized images of equilibration and perfusion serve to depict areas of mismatch in greater detail than numerical information generated from large regions of interest. Such rapid, versatile, and accurate analysis is necessary if quantitation of regional lung function is to become clinically useful.

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