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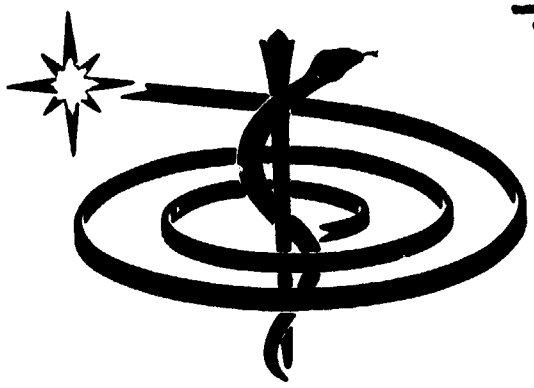
POSITRON EMISSION TOMOGRAPHY OF THE LUNG - INITIAL EXPERIENCES

Per Wollmer



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Positron emission tomography of the lung - initial experiences

Abstract

Positron emission tomography enables the distribution of positron emitting isotopes to be imaged in a transverse plane through the body and the regional concentration of the isotope to be measured quantitatively. This thesis reports some applications of positron emission tomography to studies of pulmonary pathophysiology.

Measurements in lung phantoms showed that regional lung density could be measured from a transmission tomogram obtained with an external source of positron emitting isotope. The regional, fractional blood volume was measured after labelling the blood with carbon-11-monoxide. Regional extravascular lung density (lung tissue and interstitial water per unit thoracic volume) was obtained by subtracting fractional blood volume from lung density.

Measurements in normal subjects revealed large regional variations in lung density and fractional blood volume in the supine posture. Extravascular lung density showed a more uniform distribution.

The technique has been used to study patients with chronic interstitial pulmonary oedema, pulmonary sarcoidosis and fibrosis, pulmonary arterial hypertension and patients with intracardiac, left-to-right shunt.

Tomographic measurements of pulmonary tissue concentration of radionuclides are difficult, since corrections for the blood content and the inflation of the lung must be applied. A simultaneous measurement of lung density and fractional blood volume allows such corrections to be made and the extravascular tracer concentration to be calculated. This has been applied to measurements of the tissue penetration of carbon-11-labelled erythromycin in patients with lobar pneumonia.

Key words

Emission computed tomography, nuclear medicine, pulmonary oedema, pulmonary fibrosis, pulmonary heart disease, pulmonary circulation, sarcoidosis, lung diseases, pneumonia, erythromycin, pulmonary hypertension, heart septal defects

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Per Wollmer, Department of Clinical Physiology, University Hospital, S-221 85 LUND

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POSITRON EMISSION TOMOGRAPHY OF THE LUNG - INITIAL EXPERIENCES

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som med vederbörligt tillstånd av Medicinska Fakulteten vid Lunds universitet för avläggande av medicine doktorsexamen kommer att offentligen försvaras i föreläsningssal 3, Centralblocket, Lasarettet i Lund, fredagen den 10 februari 1984 kl 13.00

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Per Wollmer

From the Department of Clinical Physiology, University of Lund, Sweden
and MRC Cyclotron Unit, Hammersmith Hospital, London, UK

POSITRON EMISSION TOMOGRAPHY OF THE LUNG - INITIAL EXPERIENCES

PER WOLLMER

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To my parents

"Science moves but slowly, slowly, creeping on from point to point"

Lord Tennyson

The present thesis is based on the following papers which will be referred to in the text by their Roman numerals.

I Rhodes CG, Wollmer P, Fazio F, Jones T
Quantitative measurement of regional extravascular lung density using positron emission and transmission tomography
J Comput Assist Tomogr 5:783-791, 1981

II Wollmer P, Rhodes CG, Allan RM, Maseri A, Fazio F
Regional extravascular lung density and fractional pulmonary blood volume in patients with chronic pulmonary venous hypertension
Clin Physiol 3:241-256, 1983

III Wollmer P, Rhodes CG, Hughes JMB
Regional extravascular density and fractional blood volume of the lung in interstitial disease
Thorax. Accepted for publication

IV Wollmer P, Rozkovec A, Rhodes CG, Allan RM, Maseri A
Regional pulmonary blood volume in patients with abnormal pressure or flow in the pulmonary circulation
Submitted for publication

V Wollmer P, Pride NB, Rhodes CG, Sanders A, Pike VW, Palmer AJ, Silvester DJ, Liss RH
Measurement of pulmonary erythromycin concentration in patients with lobar pneumonia by means of positron tomography
Lancet 2:1361-1364, 1982

CONTENTS

INTRODUCTION

Radioactive isotopes offer a means for non-invasive evaluation of lung function. Although the first studies in man utilized the photon emitting isotope ^{133}Xe (Knipping et al 1955), most of the early measurements of regional lung function were made with positron emitting isotopes. The application of these techniques was limited to a few centers with access to a cyclotron, but with the technical and radiochemical development in nuclear medicine during the 1960s, alternative techniques for assessing regional lung function by means of single photon emitting isotopes soon evolved. Lung scintigraphy has proved of great clinical value and is now widely spread (Fazio and Wollmer 1981).

POSITRON EMITTING ISOTOPES

A positron is an elementary particle with the same mass as an electron, but with a positive, rather than negative, electric charge. Positrons may be emitted from an unstable radionuclide with a relative deficiency of neutrons in the nucleus. The kinetic energy of the emitted positron is rapidly absorbed in tissue after a path length of the order of 1 mm in soft tissue. The positron then interacts with an electron (Fig. 1). The two particles annihilate, and their mass is transformed into the energy of a pair of γ-rays. The γ-rays are emitted at 180^{o}, and each has an energy of 511 keV. Some clinically useful positron emitting isotopes are listed in Table 1. It is of particular interest to find positron emitting isotopes of carbon, nitrogen and oxygen, as these can be incorporated into metabolic substrates and pharmaceuticals without changes in the biochemical properties of the compound. Most of the useful istopes are cyclotron produced and have a rather short half-life, which limits their use to institutes with a cyclotron available on site.

Table 1. Some clinically useful positron emitting isotopes.

Isotope	T 1/2
Cyclotron produced	
^{11}C	20.1 m
^{13}N	10.0 m
^{15}O	2.1 m
^{18}F	1.7 h
^{19}Ne	17 s
Generator produced	
^{68}Ga	68 m
from ^{68}Ge	275 d

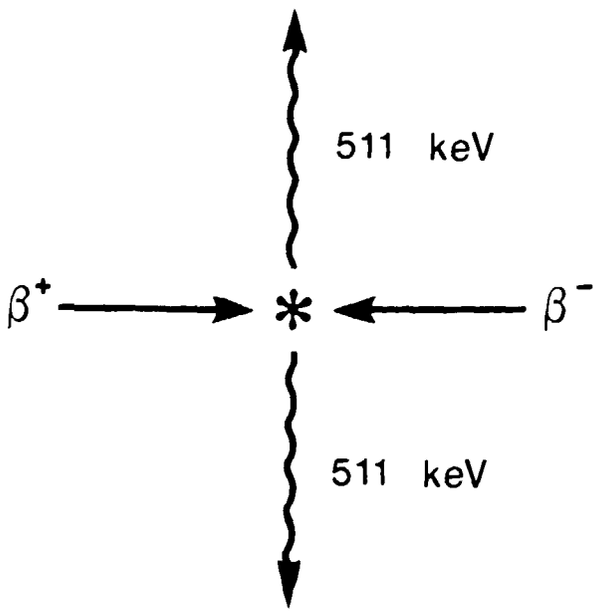

Fig. 1. Positron decay. The positron interacts with an electron, the two particles annihilate and two gamma rays are emitted at an angle of 180°.

COINCIDENCE DETECTION

The positron itself has a short life span and is not readily detected in vivo, but the annihilation γ-rays can be conveniently registered with scintillation counters. The mode of emission of photons in pairs offers considerable advantages. Two detectors placed on either side of an object containing a positron emitting isotope can be connected with an electronic circuit that accepts only pulses which arrive at the two detectors at almost the same time (coincidence detection, Fig. 2A). Such a detection system will only register annihilation events which occur in the space between the two detectors, and thus provides electronic collimation. Another advantage is that the resolution and the sensitivity of the detection system is relatively insensitive to depth. The first pulmonary studies using positron emitting isotopes (Dyson et al 1958) were made with pairs of detectors at the front and the back of the chest. These could be used for coincidence counting or, to obtain higher count rate, parallel counting.

Coincidence detection provides unique possibilities for correction of photon attenuation. If a separate measurement is made with an external source of radiation placed between the object and one detector, one γ-ray will traverse the object. As is illustrated in Fig. 2B, the total path length of the pair of annihilation photons emitted from the external source is identical to that of a pair of photons originating from an annihilation occurring at any depth in the object. The total attenuation of the two gamma rays is thus the same, whether they originate from an organ within the body or from the external source. Furthermore, the photons of different positron emitting isotopes have the same attenuation characteristics. A transmission measurement can thereby be used to measure the tissue attenuation of the annihilation radiation.

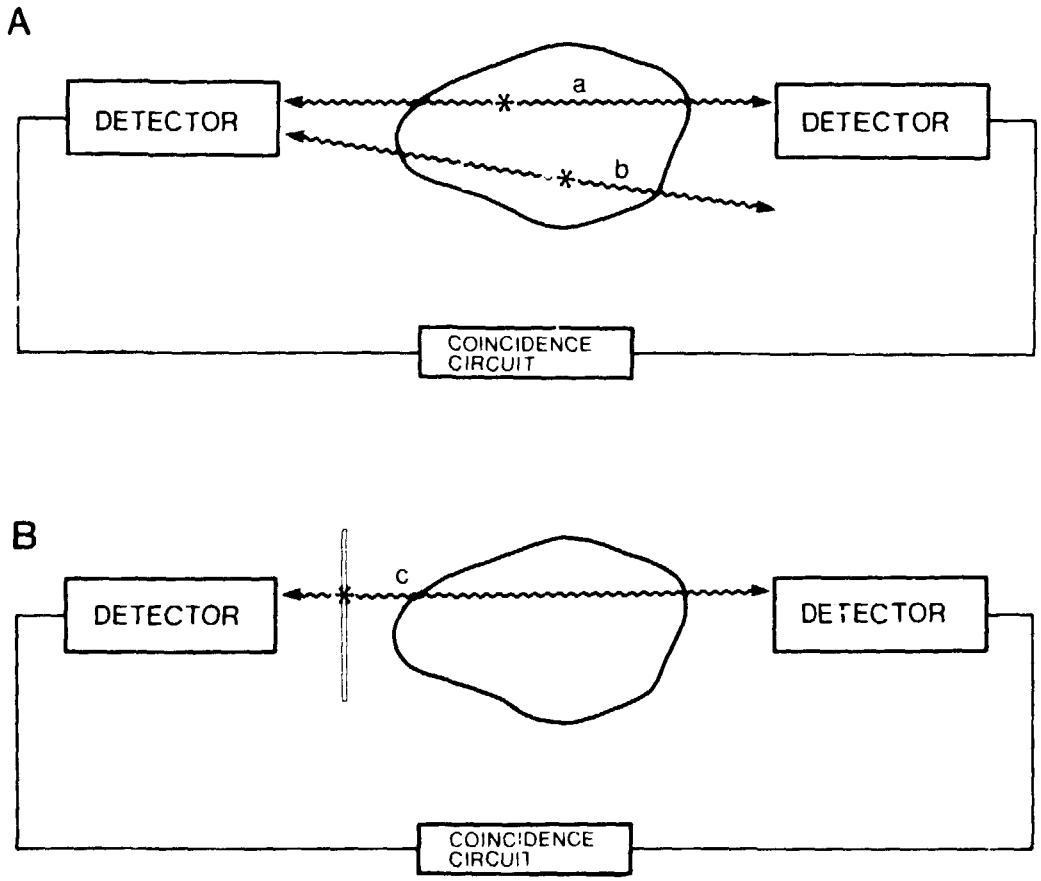

Fig. 2. A. Coincidence detecti . Two detectors placed on opposite sides of an object are connected via a coincidence circuit which accepts only pulses that arrive at the two detectors at almost the same time. Only events occurring between the two detectors (a) are accepted.

B. Attenuation correction. A source containing a positron emitting isotope is placed between the object and one of the detectors. One γ-ray traverses the object before hitting the detector. Note that the total path length through the object is the same for pair a and pair c.

EARLY CLINICAL APPLICATIONS

The first positron emitting isotope to be extensively used for studies of pulmonary physiology was ^{15}O (Dyson et al 1958). West and Dollery (1962) were able to show that inhaled labelled carbon dioxide ($C^{15}O_2$) is taken up exceedingly rapidly in the lung. Through the action of carbonic anhydrase, the oxygen label is exchanged in the water pool in the lung (West and Dollery 1962, Dollery et al 1962). The rate of clearance of the labelled water can be measured with external counters and is linearly related to blood flow (West and Dollery 1960, Dollery et al 1962, Schmidt-Nowara et al 1973). With this technique, West and Dolley (1960) obtained the first regional measurements of pulmonary blood flow in man. They found large regional variations in blood flow in sitting normals, and demonstrated that the distribution of pulmonary perfusion changes with interventions such as changes of posture and exercise. Patient studies revealed profound disturbances of regional pulmonary blood flow in patients with primary lung disease (West et al 1961) as well as in patients with heart disease (Dollery and West 1960, Dollery et al 1961). These findings clearly demonstrated the clinical usefulness of regional measurements of lung function.

Efforts were also made to measure regional oxygen uptake and diffusion properties in the lung using $^{15}O_2$ and $C^{15}O$ (Dyson et al 1958, Dollery et al 1960), but it was soon realized that the clearance of these compounds is heavily influenced by blood flow (West et al 1962, Schmidt Nowara et al 1973).

Some information about regional ventilation in the lung can be obtained from the initial distribution of ^{15}O-labelled compounds (West and Dollery 1960), but more accurate measurements of the regional distribution of ventilation is obtained with poorly soluble gases, such as $^{13}N_2$ (Matthews and Dollery 1965, Rosenzweig et al 1969/70, Ahluwalia et al 1981). Measurements can be made during breath-holding after inhalation of a single breath containing a bolus of $^{13}N_2$, during wash-in of $^{13}N_2$ or during the wash-out after $^{13}N_2$ has been equilibrated in the thoracic gas volume.

Although nitrogen is very poorly soluble, it is possible to produce solutions of $^{13}N_2$ with such high activity that the solution can be used to measure regional blood flow in the lung after intravenous injection (Clark and Buckingham 1975).

Positron emitting isotopes have also been employed for measurements of the extravascular water pool in the lung. The double indicator dilution technique requires the use of one intravascular tracer and one freely diffusible tracer, e.g. radioactive water ($H_2{}^{15}O$). With external detection, information about the regional distribution of extravascular lung water can also be obtained (Fazio et al 1976, Jones et al 1976).

EMISSION COMPUTERIZED TOMOGRAPHY

Detection systems for computerized tomography record disintegrations in one plane (usually transverse) of the body. The thickness of the section studied is dependent on the design of the instrument. The information obtained is fed to a computer and used to reconstruct a tomographic image. In positron emission tomography, photons originating from an annihilation event in the tissue are recorded in coincidence between pairs of detectors organized in a circular or hexagonal array. The reconstructed tomogram shows the distribution of the positron emitting isotope within the plane studied. If an external radiation source containing a positron emitting isotope is placed between the detectors and the object, information about the absorption of γ-rays can be obtained. This can be used to correct the emission tomogram for attenuation, and the corrected emission tomogram then provides quantitative information about the tissue concentration of the isotope (Soussaline et al 1979). The quantitative capability of the positron emission tomograph is related to the finite spatial resolution of the instrument which can be defined by its response (FWHM - full width at half maximum) to a line source of activity. The measured isotope concentration at a given point will be affected, to a varying degree, by surrounding concentration of isotope (partial volume effect) This will result in a loss of accuracy in regions with a size less than twice the FWHM in any direction (Hoffman et al 1979). The resolution of the instrument used in the present studies (ECAT II, EG&G ORTEC; Phelps et al 1978) was 17 mm (FWHM).

POSITRON COMPUTERIZED TOMOGRAPHY OF THE LUNG

MEASUREMENTS OF LUNG DENSITY AND FRACTIONAL BLOOD VOLUME

Development of the technique (I)

Our primary aim of the work with positron tomography of the lung was to develop a technique for measurement of the regional distribution of oedema fluid in man. The regional distribution of extravascular lung water is of interest as regional differences in oedema fluid formation provides information about the relationship between intravascular and interstitial pressure in the lung. Our concept was to measure first the regional density of the lung with a transmission tomogram using an external source of radiation and immediately afterwards the regional blood volume after labelling the blood with ^{11}CO. The difference between these measurements would provide information about the density of the extravascular compartment of the lung.

The relationship between density and picture element counts in the transmission tomogram was studied in a series of phantom studies. We used different materials made up from elements with low atomic numbers to simulate the lung and added water in order to vary the density. The picture element counts were proportional to the density of the phantom in the range 0.02-1 g/ml. Repeated scans were performed in a phantom with a density of 0.28 g/ml to assess the accuracy of the measurement. In a chest phantom with a layer of water simulating the chest wall, we found a small overestimation of lung density, which at least partly can be explained by the partial volume effect.

The fractional pulmonary blood volume was measured after labelling the blood with ^{11}CO by inhalation. An emission scan was obtained, and venous blood was sampled during the measurement. The concentration of ^{11}CO in whole blood was measured in a well counter, and the fractional pulmonary blood volume was obtained by dividing the pulmonary concentration of ^{11}CO (obtained from the picture element counts) with the concentration in whole blood. Lung density and fractional blood volume can be expressed in the same units by taking the density of blood (1.06 g/ml) into account. This allows fractional blood volume to be subtracted from lung density to provide a measurement of extravascular lung density. This reflects the

amount of lung tissue including interstitial water per unit thoracic volume.

Measurements in normal subjects (I, II)

In order to obtain reference values for lung density, fractional blood volume and extravascular lung density, we studied 19 normal volunteers. Illustrative tomograms from one normal subject are shown in Fig. 3.

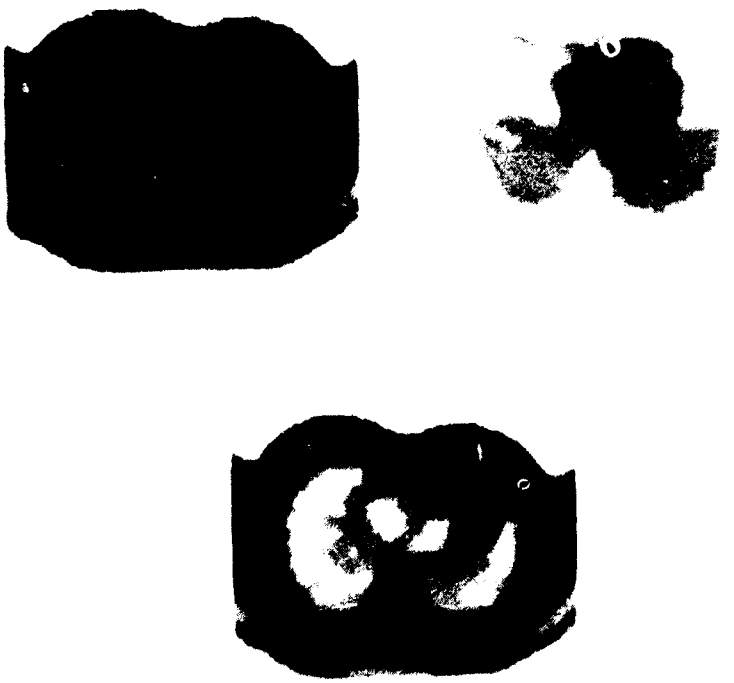

Fig. 3. Tomograms of lung density (top left), fractional blood volume (top right) and extravascular lung density (bottom) from a normal subject.

A constant finding in supine subjects was a ventrodorsal gradient in lung density with mean values of 0.24 g/ml ventrally and 0.40 g/ml dorsally (Fig. 4). The ventrodorsal distribution of fractional blood volume in the supine position is characterized by a ventral plateau at 0.08 ml/ml, which rises steeply in the central part of the lung to a second plateau at 0.21 ml/ml. The distribution of fractional blood volume in normal lung

is mainly determined by the transmural pressure in the vascular bed (i.e. the difference between intravascular and perivascular pressures) and of the elastic properties of the pulmonary vessels. The transmural pressure will vary regionally as a result of hydrostatic effects, whilst the elastic properties are likely to be homogenous in the normal lung. Thus, the observed ventrodorsal gradient of fractional blood volume in normal subjects may be a consequence of the effect of gravity on the transmural pressure.

Most of the ventrodorsal gradient seen in lung density is accounted for by the regional differences in fractional blood volume. The extravascular density shows a minor, uniform ventrodorsal gradient, rising from 0.12 g/ml in the ventral part to 0.16 g/ml in the dorsal part. This gradient could be explained by regional differences in lung expansion due to the influence of gravity (Glazier et al 1967).

Measurements in patients with pulmonary oedema (II)

As a model of pulmonary oedema, patients with cardiomyopathy and chronic pulmonary venous hypertension were studied. We found increased extravascular lung density in the patients. The increase was non-uniform with the greatest abnormalities seen in the dorsocaudal part of the lung (Fig. 4). In this group of patients, increased extravascular lung density not only reflects the accumulation of interstitial or alveolar fluid, but also the structural abnormalities that develop in the lung parenchyma and vasculature with long standing pulmonary venous hypertension (Heath and Edwards 1959). However, without the introduction of an extracellular or cellular marker, it is not possible to differentiate between increased tissue mass and the accumulation of interstitial or alveolar fluid as a cause of increase extravascular lung density.

A problem with the interpretation of changes in extravascular lung density is their relation to lung expansion - since a reduction in lung expansion should automatically be associated with an increase in extravascular lung density. A possible way to account for lung expansion is to take the ratio between extravascular lung density and fractional blood volume, as this ratio is likely to be less affected by moderate changes in lung expansion. Similar ratios have been used by other workers as a measure of pulmonary

oedema (Fazio et al 1976, Binswanger et al 1978, Hales et al 1981). The increase in the ratio of extravascular lung density to fractional blood volume also showed a dependent distribution.

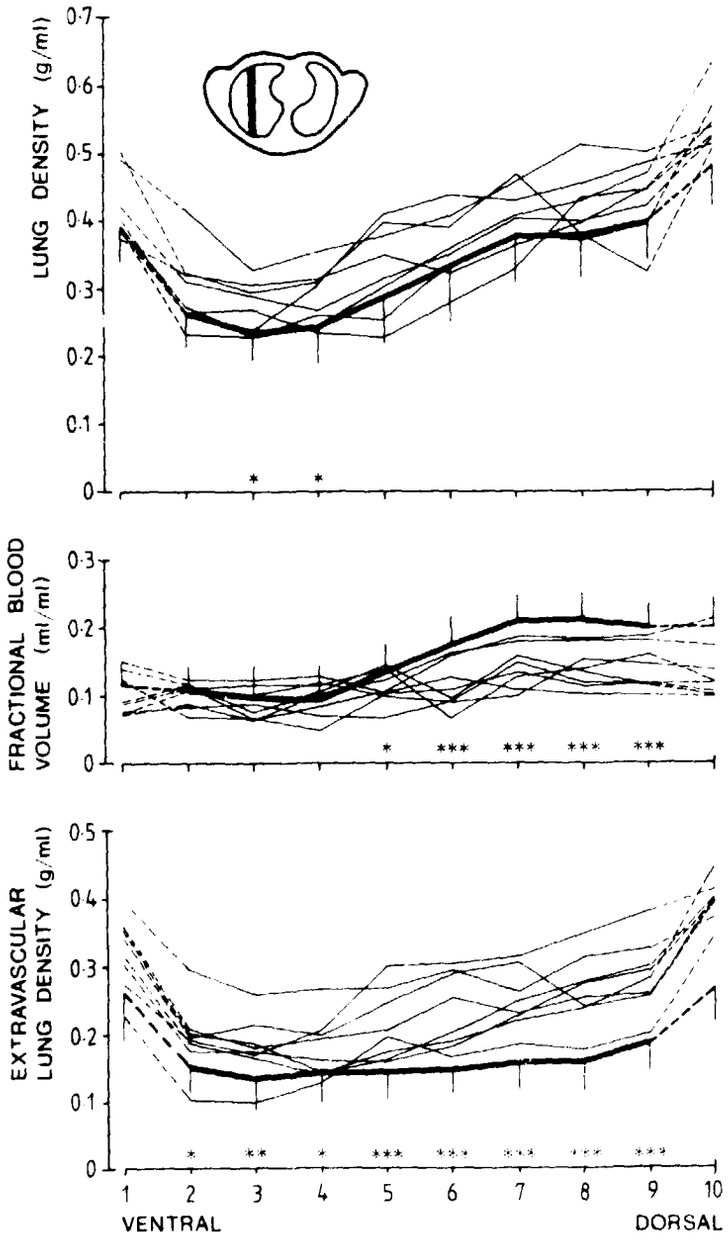

*Fig. 4. Ventrodorsal profiles of lung density, fractional blood volume and extravascular lung density. A 1.7 cm wide region was chosen in the middle of the right lung (inset). Thick lines denote mean of 19 normal subjects and vertical bars one SD. Thin lines represent individual patients with chronic pulmonary venous hypertension. Points 1 and 10 are influenced by "spillover" from the chest wall. Asterisks denote significant deviations from normal: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

The finding of a gravity dependent distribution of regional extravascular lung density may be explained by the relationship between pressure gradients in the lung. It is well established that there is an intravascular pressure gradient down the lung, but regarding perivascular pressure, most of the available information is indirect (Staub 1980). A gravity dependent distribution of oedema fluid implies that net fluid filtration is higher in the dependent parts of the lung. This could be caused by an increase in the perivascular pressure in the direction of gravity that is smaller than the intravascular hydrostatic pressure gradient in the oedematous lung.

Fractional blood volume is a measurement of the volume of blood per unit thoracic volume and includes blood contained in intrapulmonary vessels only. In comparison, measurements of pulmonary blood volume obtained by means of indicator dilution techniques include also extrapulmonary vessels. Measurements of the capillary blood volume of the lung can be obtained from measurements of the transfer factor for carbon monoxide.

Fractional blood volume was reduced in patients with chronic pulmonary venous hypertension (Fig. 4), which may be explained by reactive structural changes in the vessels or reduced transmural pressure due to perivascular oedema.

Measurements in patients with "interstitial" lung disease (III)

Extravascular lung densite encompasses lung tissue as well as interstitial water, and may be used as a measure of the abnormalities occurring in "interstitial" disease - i.e. oedema, accumulation of inflammatory cells, formation of granulomata and fibrosis (Crystal et al 1981). Measurements were performed in one group of patients with sarcoidosis having mild to moderate functional impairment and in one group of patients with pulmonary fibrosis of varying etiology having severe functional impairment. Extravascular lung density was increased in all patients, and large regional variations were observed. In two patients with sarcoidosis, a reduction in extravascular lung density was observed after steroid treatment. This was associated with radiographic and functional improvement and demonstrates the feasibility to measure quantitatively the response to treatment of sarcoidosis.

Fractional blood volume was within normal limits in most patients with sarcoidosis of mild to moderate degree, but was reduced in all patients with pulmonary fibrosis. It is well known that there is a reduction in capillary blood volume in patients with severe fibrosis (McNeill et al 1958, Bates et al 1960, Hamer 1963, Saumon et al 1976). The magnitude of the reduction we observed in fractional blood volume shows that larger vessels as well as capillaries are affected.

Measurements in patients with increased pulmonary blood flow or pulmonary arterial hypertension (IV)

The regional distribution of pulmonary blood flow has been studied extensively in relation to regional vascular pressure (see West 1977 for references). A model has evolved, which relates regional blood flow to arterial, alveolar and venous pressures (Banister and Torrance 1960, Permutt et al 1962, West et al 1964, West and Dollery 1965). Although this model implies regional changes in blood volume with changes in flow and vascular pressure, little information has been obtained about the regional distribution of blood volume in man.

We studied the effect on regional fractional blood volume of chronic increase in flow (patients with intracardiac left-to-right shunt without appreciable pulmonary hypertension) and chronic increase in pressure (patients with Eisenmenger's syndrome or primary pulmonary hypertension). The distribution of fractional blood volume was more uniform in both groups of patients than in normal subjects. This may be explained by recruitment (Maseri et al 1972) and/or distension (Glazier et al 1969) of vascular beds. In patients with chronic increase in flow, we found indications of an over-all increase in intrapulmonary blood volume, whereas patients with severe pulmonary hypertension did not differ from normal subjects in this respect. Longstanding hypertension is likely to be associated with reactive vascular changes reducing the compliance of the vascular bed, and possibly obliteration of capillary beds.

Measurement of tracer concentration in the extravascular compartment of the lung (V)

The isotope concentration measured with a positron tomograph refers to the amount of activity per unit thoracic volume. In the physiological and pharmacological context, the concentration of a tracer must be expressed with respect to its volume of distribution. With the technique for measuring lung density and fractional blood volume, the volume of three compartments can be measured: (i) gas volume (1 - lung density/1.06), (ii) intravascular compartment and (iii) the extravascular lung compartment (which includes the intracellular and interstitial compartment). The distribution of the tracer may not be confined solely to the compartment of interest, and activity in any other compartment then constitutes a background which needs to be subtracted. For this purpose, the background activity must be expressed in terms of thoracic concentration and subtracted from the total thoracic concentration of the tracer. If, for example, the concentration of a tracer in the extravascular compartment is to be measured, the signal from circulating tracer must be subtracted. A measurement of the vascular concentration of the tracer can be obtained from a measurement of pulmonary blood volume and the blood concentration of the tracer, as measured from a blood sample or a sufficiently large region of interest in the heart or the aorta.

This concept has been applied to measurements of the concentration of labelled erythromycin in a pharmacokinetic study in patients with lobar pneumonia. The drug was labelled with ^{11}C without altering its biochemical characteristics (Pike et al 1982). A transmission tomogram provided a measurement of lung density and information for attenuation correction of the ensuing emission scans. Two to four mCi of labelled erythromycin were administered intravenously in a total dose of 270 mg erythromycin lactobionate. The concentration of erythromycin was measured during 60 minutes after the injection. Finally, ^{11}CO was used to obtain a measurement of fractional blood volume. A correction for circulating erythromycin was made by normalizing the blood volume tomogram to the count density of labelled erythromycin in arterial blood as measured from a region in the aorta or the left heart. Normalized in this way, the blood volume tomogram provides a measurement of the intravascular concentration of erythromycin. After subtraction of erythromycin in the vascular pool, a measurement of the amount of erythromycin per unit

thoracic volume was obtained (μCi/ml). By dividing this with extravascular lung density (g/ml), the concentration of erythromycin in the extravascular compartment was obtained (μCi/g). In the pneumonic lung, extravascular lung density includes lung tissue, interstitial fluid and any alveolar fluid.

The mean concentration of erythromycin in the pneumonic lung during the period of measurement was 5.5 μg/g. This was not significantly different from the 6.6 μg/g observed in the control lung. The clearance of activity from the blood, and the accumulation in the pneumonic lung are shown in Fig. 5. Penetration to the extravascular space is rapid, near maximum concentration being reached within 10 minutes after injection. Equilibration between the concentration in blood and in the extravascular space was reached after approximately 45 minutes and thereafter erythromycin was slowly washed out from the extravascular space.

Hence, there is a rapid uptake or erythromycin in pneumonic lung after the intravenous injection of the drug. Moreover, the penetration is as effective in pneumonic regions as in normal lungs. The concentrations achieved in pneumonic regions after injection of 270 mg of erythromycin are well above the minimum inhibitory concentration for most sensitive organisms.

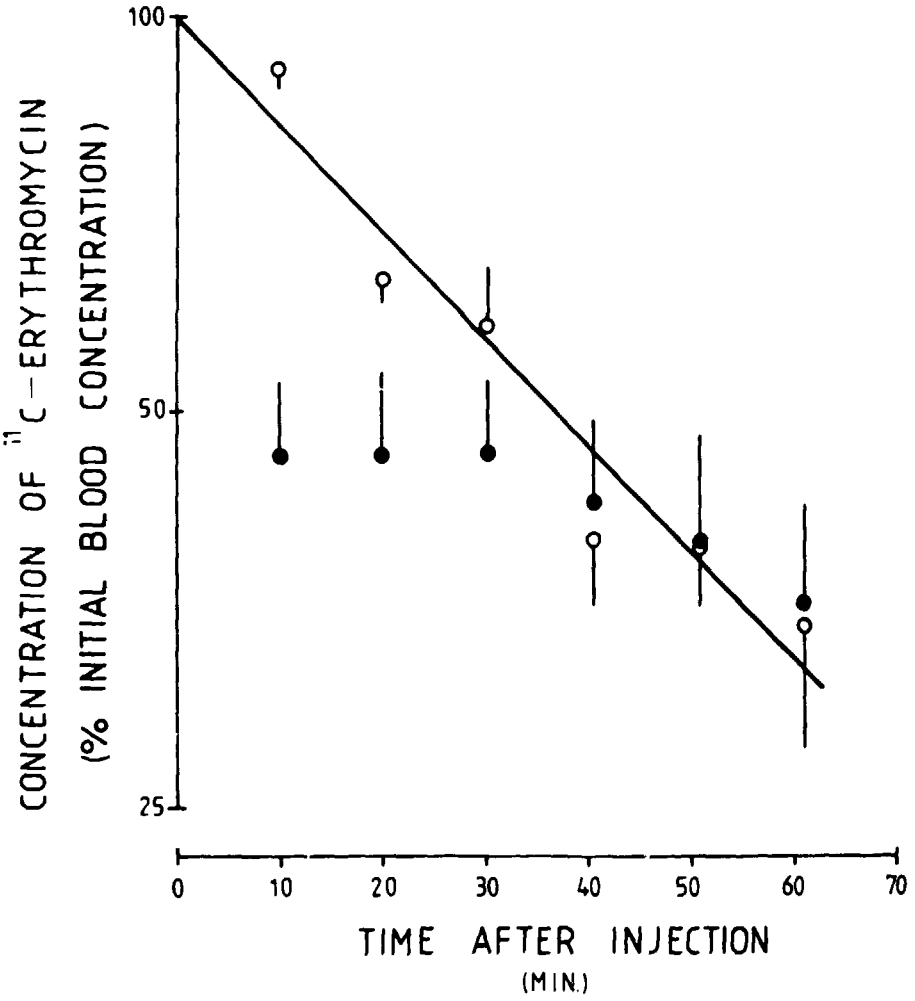

Fig. 5. Blood clearance and uptake of ^{11}C-erythromycin into the extravascular compartment of the pneumonic lung.
Open circles = mean ± SE of arterial blood concentration in five patients.
Equation: ln $y = -0.019x + 4.60$, $r = -0.96$
Closed circles = mean ± SE of extravascular concentration in pneumonic lungs.

CONCLUDING REMARKS

Positron emission tomography enables the regional thoracic concentration of positron emitting isotopes and the regional density of the lung to be measured quantitatively. This concept has been used to measure abnormalities in the lung in terms of extravascular lung density and fractional pulmonary blood volume, providing new clinical information about the pathogenesis of common diseases like pulmonary oedema, "interstitial" lung disease and intracardiac shunt.

Pharmaceuticals as well as metabolic substrates can be labelled with positron emitting isotopes without changing their biochemical characteristics, and their concentration measured in vivo. In combination with measurements of lung density and fractional blood volume, their distribution in different compartments can be measured, as is demonstrated by the study of the pharmacokinetics or erythromycin. The pulmonary handling of certain pharmaceuticals, such as amines, may be interpreted in physiological terms, and studies of their kinetics may provide new information about pulmonary pathophysiology (Pang et al 1982ab, Pascal et al 1982).

The application of positron emission tomography in the lung may also provide a number of other new approaches to the investigation of lung function in health and disease. Radioactive gases are potentially very useful in combination with positron tomography. $C^{15}O_2$ can be used to label the pulmonary water pool (Ahluwalia et al 1980) or to provide information about the ventilation-perfusion relationship in the lung (Nichols et al 1978, Wollmer et al 1982). Quantitative values of regional ventilation-perfusion ratio can be obtained by measurements during continuous infusion of ^{13}N in solution (Wollmer et al 1982) and regional specific ventilation can be measured quantitatively using the short-lived radioisotope ^{19}Ne (Crouzel et al 1980, Valind et al 1982).

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