# Progress in Nuclear Medicine

## Regional Pulmonary Function in Health and Disease

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ISBN 3–8055–1425–5

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61 figures and 13 tables

S. Karger · Basel · München · Paris · London · New York · Sydney 1973

S. Karger · Basel · München · Paris · London · New York · Sydney
Arnold-Böcklin-Strasse 25, CH-4011 Basel (Switzerland)


Printed in Switzerland by Graphische Anstalt Schüler AG, Biel
ISBN 3-8055-1425-5

Distributed exclusively in the USA and Canada by the University Park Press, Baltimore, Md., London, Tokyo
Library of Congress Catalog Card Number 73-12920
ISBN 0-8391-0542-8

# Acknowledgements

The contributors to this volume have been supported by the following grants and contracts which are gratefully acknowledged:

Dr. BASS' work was supported in part by grants from the John A. Hartford Foundation and United States Public Health Service (5-SO1-RR-05489-08).

Drs. SIEGEL and POTCHEN's work was supported in part by National Institutes of Health training grant L TO1 GMO1747-01 and US Atomic Energy Commission grant AT (11-1)-1653.

Drs. TREVES, STRIEDER and ADELSTEIN's work was supported in part by US Public Health Service grant HLI 10436.

Drs. FLETCHER, JAMES and HOLMAN's work was supported in part by National Institutes of Health training grant GMO 2201.

The editors also whish to acknowledge Mrs. SALLY EDWARDS and Miss ELEANOR LIVINGSTON for their kind and generous assistance in editing and preparing this manuscript.

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# Chapter 1

Progr. nucl. Med., vol. 3, pp. 1–9
(Karger, Basel and University Park Press, Baltimore 1973)

## Regional Pulmonary Function in Historical Perspective

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### *The Early Study of Pulmonary Function*

The recognition that the lung is a vital organ performing the function of gas exchange is less than 400 years old. This understanding resulted from observations made independently by HOOK, who demonstrated the necessity of air exchange to sustain life; by HARVEY, who demonstrated the existence of pulmonary blood flow; by LOWER and later MAYOW, who demonstrated the change in blood color between the right and left ventricles; and by MALPHIGI, who demonstrated the proximity of the alveolar wall to the lung capillary and the closed nature of the pulmonary circulation. MAYOW was further instrumental in demonstrating the existence of a vital substance in air, unfortunately named *nitro-aereal particles*, necessary to sustain life.

Subsequent work in pulmonary physiology directed attention to the application of the various gas laws to assess alveolar and intravascular gas partial pressures, to the refinement of the concepts of the lung volumes and lung capacities, to aspects of bronchial resistance, to the significance of thoracic configuration, to the relationship of the respiratory muscles to pulmonary compliance, and to the neuro-control of respiration.

The development of those concepts of pulmonary function related to the partial pressure of oxygen and carbon dioxide were readily accomplished as long as one assumed that each alveolus had the same volume, the same ventilation, the same compliance, the same blood flow, and the same diffusing capacity. As a matter of fact, the experimental model used by BOHR, HALDANE, and others for fractional gas analysis was a 'single compartment' lung-bag breathing system.

But the lung is not such an organ. All physicians have seen evidence of regional variation of pulmonary function clinically in patients with pneumonia, bullous lung disease, asthma, and other pulmonary diseases.

*The Distribution of Ventilation*

Early in the 19th century, DAVEY [11] asked whether ventilated air was uniformly distributed in the lung. There is a simple solution, he thought: measure the time required for hydrogen to equilibrate in a closed lung-bag breathing system. On second thought, he decided that it was intuitively obvious that ventilation in the lung was uniform and that the experiment need not be done. The issue was closed for nearly a century.

Early in the 20th century, physiologists were measuring cardiac output utilizing the Fick principle. Nitrous oxide was inhaled and alveolar gas was sampled before and after a period of breath holding. The method assumed uniformity in distribution of ventilation. There was evidence, however, suggesting that gas distribution was not uniform. KROGH and LINDHARD [16] proposed that regional variation in gas partial pressure in the lung was linear along the branching bronchial system. Gas moved by mass flow in the larger bronchi and by diffusion in the alveolar ducts and alveoli. Thus, rapid changes in gas partial pressure occurred in the bronchi while equilibrium of gas pressure in the alveolar duct and alveoli lagged behind because of the time-consuming process of diffusion. They recognized that gas in the bronchial space represented dead space gas and ascribed the inhomogeneity to the difference in gas partial pressure between the alveolar ducts and alveoli themselves. They termed this 'the stratification theory' of gas distribution.

In the 1930's, ROELSEN [25] observed a progressive fall in the partial pressure of inhaled hydrogen during the course of washout of a single expiration. The gradient in hydrogen concentration between the initial portion of the washout curve and its terminal portion indicated that during inspiration some alveoli received a larger volume of the hydrogen than others. These alveoli apparently emptied first during expiration whereas those which were poorly ventilated washed out last. Subsequently in the 1940s and 1950s much attention was paid to nitrogen washout curves in the assessment of nonuniform ventilation. The validity of the washout curve was established in 1941 by COURNAND *et al.* [10]. Subsequently, COMROE and FOWLER [9] introduced the nitrogen washout curve as a clinical test for assessment of the uniformity of ventilation. Although analysis of washout curves had provided mounting evidence of nonuniform alveolar ventilation during the early portion of the 20th century, the anatomic regions limiting the various compartments remained unknown.

BJORKMAN [5] introduced the technique of bronchospirometry to assess regional ventilation in the lung. He showed that the distribution of ventilation in the right lung was greater than the left in recumbency. Further, he showed that the distribution of ventilation varied with changes in body position and that the dependent lung received a greater portion of ventilation when the experimental subject assumed the decubitus position. BJORKMAN's findings suggested that regional variation in ventilation is not related to the distribution of gas from the alveolar duct to the alveoli as KROGH and LINDHARD had suggested but rather that various regions of the lung were ventilated in series. ROUWERDA [26] published his now famous doctoral thesis entitled 'Unequal Ventilation of Different Parts of the Lung and the Determination of Cardiac Output' which challenged the validity of the stratification theory. The anatomic model ROUWERDA chose was the terminal bronchus and its branches, including alveolar ducts and alveoli. His calculation of gas diffusion in this system was based on the analysis of fractional concentration gradients of nitrogen and oxygen established over time. He was able to show that given an initial gradient in oxygen and nitrogen partial pressure between the alveolar duct and the alveoli at zero time, partial pressure equilibrium occured between the two regions in less than 1 sec. He concluded that the theory of stratification was invalid under normal respiratory conditions and was not responsible for regional variations in ventilation.

The nitrogen washout curve indicated that various units of the lung were ventilated independently in series, supporting BJORKMAN's early conclusions. The stratification theory of KROGH and LINDHARD had been laid to rest as a dominant factor in the nonuniformity of distribution of ventilated air; ROUWERDA's theory was generally accepted by 1950 and is held to this time.

Besides nitrogen, a variety of other insoluble gases have been utilized over the years for the assessment of washout curves, including hydrogen, helium, and radioactive gases. None have shown distinct advantages over nitrogen when the effluent is monitored.

Although the anatomic regions responsible for the shape of washout curve are not clearly defined, factors which affect the shape of such curves are known. In 1958, BATES and COHEN showed that age increased the nonuniformity of washout curves but that alveolar ventilation is constant at varying lung volumes. BOUHUYS *et al.* [6] have shown that exercise does not affect distribution of ventilation.

KNIPPING *et al.* [15] first suggested the use of radioactive xenon and external detectors to assess regional pulmonary ventilation. Subsequently, DYSON *et al.* [12] called attention to oxygen 15 as an agent for the assessment of regional pulmonary function. WEST and DOLLERY [31] described a method for the assessment of regional pulmonary blood flow and regional $\dot{V}/\dot{Q}$ ratios utilizing $^{15}CO_2$. The patient, seated between a series of coincidence counters with a field of view restricted to upper and lower regions of each lung, took a single inspiration of $^{15}CO_2$ with subsequent breath holding. As the gas was distributed into the pulmonary alveoli the count rate increased. The increment increase in count rate at each probe was a measure of regional ventilation. Then during the breath-holding period of 10–15 sec, count rate diminished. The rate of decrement in count rate was a measure of regional pulmonary blood flow. WEST was able to demonstrate a gradient in the distribution of regional ventilation from the diaphragm to the first rib in erect man utilizing this technique. BALL *et al.* [1] demonstrated the usefulness of xenon 133 in assessing regional function and confirmed WEST's observation. Later, BRYAN *et al.* [7] and SUTHERLAND *et al.* [27] were able to assess regional ventilation as a function of regional volume utilizing the same techniques. Knowledge of regional ventilation has subsequently been extended by BATES, WEST, MILIC-EMILI and others. NEWHOUSE *et al.* [20] described the usefulness of the Anger camera to assess regional ventilation using xenox 135. Further, NEWHOUSE *et al.* [20]. KINGABY *et al.* [14], and LOKEN [17] have described effective automated handling of data generated by this system.

The utilization of radioactive gases, especially xenon 133, to assess regional ventilation has become commonplace worldwide. Although the shortlived cyclotron-produced isotopes have been used in some centers, their expense and short half-life precludes popular use at this time.

*Blood Flow Distribution in the Lung*

Early evidence that blood flow, like ventilation, was not evenly distributed in the lung was presented by BJORKMAN [5]. He was able to show that the volume of ventilation and oxygen uptake by the right lung exceeded that of the left in the normal erect subject when measured by bronchospirometry. Furthermore, when the same subject assumed the lateral decubitus position, the volume of ventilation and oxygen uptake in the dependent lung was greatest.

MARTIN *et al.* [18] reported the more selective technique of lobar spirometry. Plastic catheters were inserted into the upper and lower lobe bronchi of a normal erect subject. End-expiratory gas collected from each catheter was assayed for oxygen and carbon dioxide concentrations. The oxygen concentration was highest and the carbon dioxide concentration lowest in gas obtained from the upper lobe. At the same time, oxygen concentration was lowest and carbon dioxide highest in gas obtained from the lower lobe. These results indicated regional variation in the distribution of blood flow as well as ventilation in the single lung, thus extending BJORKMAN's observations.

KNIPPING *et al.* [15] assessed pulmonary function with radioactive gases. Subsequently, WEST and DOLLERY [31] used cyclotron-produced radiounclides of oxygen and carbon dioxide to assess the distribution of regional pulmonary blood flow and ventilation utilizing the instrumentation previously described.

With this technique, WEST and DOLLERY were able to show in normal subjects that the clearance of oxygen-labelled carbon dioxide decreases dramatically from the bottom to the top of the lung in the erect position. Yet in recumbency, clearance rates of the radioactive tracer from various regions of the lung extending from the diaphragm to the first rib were essentially the same, and exercise had a tendency to equalize regional clearance rates. Similar experiments performed by BALL *et al.* [1] utilizing xenon 133 confirmed the observation of WEST that blood flow in the lung is gravity-dependent. BANISTER and TORRANCE [2] presented evidence that regional blood flow is determined by the arterial alveolar pressure gradient when alveolar pressure exceeds pulmonary venous pressure. PERMUTT *et al.* [21] confirmed and extended these data.

Full development of this concept was achieved by WEST *et al.* [33]. They studied the alterations in blood flow distribution in the isolated dog lung resulting from changes in vascular and alveolar pressures. After suspending an isolated dog lung erectly in a lucite box and cannulating the pulmonary artery, pulmonary vein and bronchus, the lung was artificially ventilated and perfused. Gas exchange, pulmonary vascular resistance and compliance remained essentially normal for several hours in this model. The distribution of blood flow in this preparation was measured by injecting xenon 133 into the perfusate. In this model, the distribution of blood flow was essentially the same as the distribution of blood flow in the living erect subject. On the basis of evidence obtained from this model, WEST divided the lung into three horizontal zones according to arteriolar-alveolar-venous pressure gradients. In the upper one third of the lung where alveolar pressure exceeds arteriolar pressure, there is no flow. In the middle third of the lung, where arteriolar pressure is greater than alveolar pressure and venous pressure is less than alveolar pressure, flow increases linearly downward through the region. In the lower third, where arteriolar pressure exceeds venous pressure and venous pressure exceeds alveolar pressure, there is some additional increase in flow. When WEST reduced pulmonary artery pressure, the distribution of blood flow in the mid-lung zone was reduced to zero where pulmonary artery pressure equaled pulmonary venous pressure. Raising pulmonary venous pressure caused a more equal distribution of regional pulmonary blood flow in the lower regions of the lung up to the level at which pulmonary venous pressure equaled pulmonary alveolar pressure. Above that level, blood flow fell rapidly.

Subsequently, BRYAN *et al.* [7] showe that exercise tends to equalize blood flow in the three zones by increasing flow to the upper lung fields. KANEKO *et al.* [13] showed that this vertical zonal distribution persists in all body positions.

WEST [32] has utilized data on the distribution of blood flow and ventilation to describe a lung model which accounts for changes in alveolar and post-capillary oxygen and carbon dioxide partial pressures as one ascends the lung from the diaphragm to the apex, thus providing the dimension of regionality to the concept of the ventilation/perfusion ($\dot{V}/\dot{Q}$) ratio. Yet correlation of $\dot{V}/\dot{Q}$ measurements by external counters with actual gas tensions remains to be accomplished.

*The Clinical Applications of Regional Pulmonary Function*

In 1963, GEORGE TAPLIN [28] was interested in reticuloendothelial function. While confirming previous work indicating that 1-$\mu$m particles