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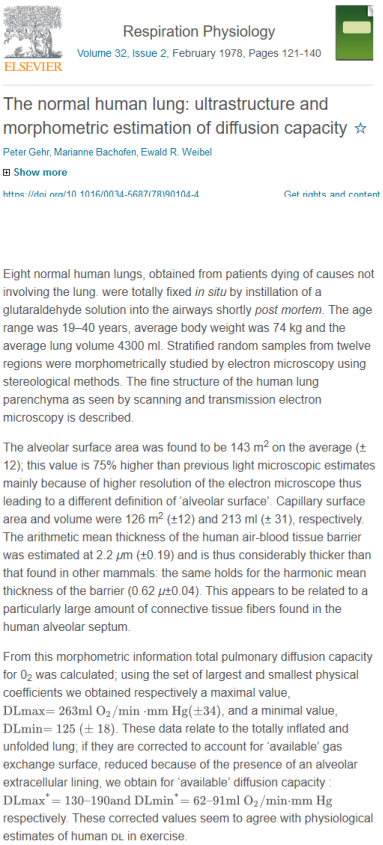

Respiration Physiology

Volume 32, Issue 2, February 1978, Pages 121-140

ELSEVIER

The normal human lung: ultrastructure and morphometric estimation of diffusion capacity ☆

Peter Gehr, Marianne Bachofen, Ewald R. Weibel

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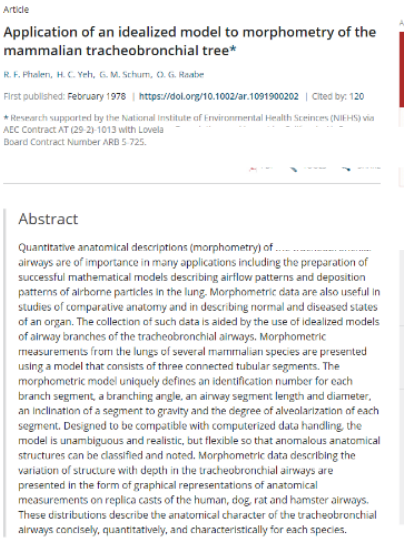
Eight normal human lungs, obtained from patients dying of causes not involving the lung. were totally fixed *in situ* by instillation of a glutaraldehyde solution into the airways shortly *post mortem*. The age range was 19–40 years, average body weight was 74 kg and the average lung volume 4300 ml. Stratified random samples from twelve regions were morphometrically studied by electron microscopy using stereological methods. The fine structure of the human lung parenchyma as seen by scanning and transmission electron microscopy is described.

The alveolar surface area was found to be 143 m^2 on the average (± 12); this value is 75% higher than previous light microscopic estimates mainly because of higher resolution of the electron microscope thus leading to a different definition of ‘alveolar surface’. Capillary surface area and volume were 126 m^2 (±12) and 213 ml (± 31), respectively. The arithmetic mean thickness of the human air-blood tissue barrier was estimated at 2.2 μm (±0.19) and is thus considerably thicker than that found in other mammals: the same holds for the harmonic mean thickness of the barrier (0.62 μ±0.04). This appears to be related to a particularly large amount of connective tissue fibers found in the human alveolar septum.

From this morphometric information total pulmonary diffusion capacity for 0_2 was calculated; using the set of largest and smallest physical coefficients we obtained respectively a maximal value, $\mathrm{DLmax} = 263\mathrm{ml\ O_2/min \cdot mm\ Hg}(\pm 34)$, and a minimal value, $\mathrm{DLmin} = 125\ (\pm\ 18)$. These data relate to the totally inflated and unfolded lung; if they are corrected to account for ‘available’ gas exchange surface, reduced because of the presence of an alveolar extracellular lining, we obtain for ‘available’ diffusion capacity : $\mathrm{DLmax}^* = 130\text{–}190\mathrm{and\ DLmin}^* = 62\text{–}91\mathrm{ml\ O_2/min \cdot mm\ Hg}$ respectively. These corrected values seem to agree with physiological estimates of human D_L in exercise.

Ref. 4



Article

Application of an idealized model to morphometry of the mammalian tracheobronchial tree*

R. F. Phalen, H. C. Yeh, G. M. Schum, O. G. Raabe

First published: February 1978 | https://doi.org/10.1002/ar.1091900202 | Cited by: 120

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Board Contract Number ARB 5-725.

Abstract

Quantitative anatomical descriptions (morphometry) of
airways are of importance in many applications including the preparation of successful mathematical models describing airflow patterns and deposition patterns of airborne particles in the lung. Morphometric data are also useful in studies of comparative anatomy and in describing normal and diseased states of an organ. The collection of such data is aided by the use of idealized models of airway branches of the tracheobronchial airways. Morphometric measurements from the lungs of several mammalian species are presented using a model that consists of three connected tubular segments. The morphometric model uniquely defines an identification number for each branch segment, a branching angle, an airway segment length and diameter, an inclination of a segment to gravity and the degree of alveolarization of each segment. Designed to be compatible with computerized data handling, the model is unambiguous and realistic, but flexible so that anomalous anatomical structures can be classified and noted. Morphometric data describing the variation of structure with depth in the tracheobronchial airways are presented in the form of graphical representations of anatomical measurements on replica casts of the human, dog, rat and hamster airways. These distributions describe the anatomical character of the tracheobronchial airways concisely, quantitatively, and characteristically for each species.

Ref. 5

Respiratory System

Postnatal enlargement of human tracheobronchial airways and implications for particle deposition

Robert F. Phalen, Michael J. Oldham, Christine B. Beaucage, T. Timothy Crocker, Jd Mortensen

First published: August 1985

Abstract

In support of predictions for inhaled particle deposition, morphometric measurements were taken on 20 replica airway casts of people aged 11 days to 21 years. Measurements of right upper lobe airway lengths, diameters, and branching angles were made such that a growth model suitable as input to predictive equations for particle deposition efficiency was obtained. The tracheobronchial airways growth was describable by linear regressions on body length. The length-to-diameter ratio of growing airways did not change in any simple way as a function of airway generation. Airflow rates for a given state of physical activity for various ages were found from previously published data to be describable by linear regressions on body mass. Three states of physical exertion–low activity, light exertion, and heavy exertion–were used for modeling purposes. The computed particle deposition efficiencies indicate that under most circumstances smaller (younger) people will have greater tracheobronchial deposition efficiencies than larger (older) people. For example, tracheobronchial dose on a per kilogram body mass basis for 5-μmdiameter particles may be more than 6 times higher in the resting newborn than in the resting adult assuming equivalent deposition efficiencies above the larynx.

Ref. 6

KEITH HORSFIELD, GLADYS DART, DAN E. OLSON,
GILES F. FILLEY, AND GORDON CUMMING
Department of Medicine, Queen Elizabeth Medical Centre, Edgbaston, Birmingham B15 2TH, England; and Webb-Waring Institute, University of Colorado Medical Centre, Denver, Colorado 80220

HORSFIELD, KEITH, GLADYS DART, DAN E. OLSON, GILES F. FILLEY, AND GORDON CUMMING. *Models of the human bronchial tree.* J. Appl. Physiol. 31(2): 207–217. 1971.—A resin cast of a normal human bronchial tree was prepared and all structures down to branches of 0.7-mm diameter were measured. A sample of structures smaller than 0.7-mm diameter was broken off and measured down to and including respiratory bronchioles. A silicone rubber cast of the trachea and larger bronchi was prepared and the morphology of dichotomous branching studied. The data were punched on cards and analyzed using a computer. Information obtained both from the original measurements and the subsequent analysis was used to construct two mathematical models of the bronchial tree. Asymmetry is stressed in both models; in model 1 each lobe was considered separately, as was each bronchopulmonary segment in model 2. The models permit calculation of physiologic variables to be made while taking asymmetry into account.

lung anatomy; bronchial tree morphology; mathematical models

DIRECT MEASUREMENTS of pressure and flow in the bronchial tree of living man are difficult to obtain, especially in the smaller airways. Techniques of bronchial catheterization to measure flow in the larger airways have been developed (13) but the presence of the catheter distorts that which is being measured. Because of these difficulties convective flow and gaseous diffusion in the airways are being increasingly studied by mathematical analysis (2, 3, 12, 14). The techniques employed are of such complexity that simplified models of airways anatomy have to be used, most commonly Weibel's symmetrical model A (23) or some modification of it. Analysis of such models may or may not give reasonable estimates of mean values for gas flow and diffusion, but certainly cannot give information on the effects of anatomic asymmetry.

In some circumstances consideration of airways asymmetry may be important, for example, when analyzing flow to different regions of the lung or studying the effects of gravity. Although an account which stresses the asymmetry of bronchial anatomy has been published (8) the data are difficult to use in practice. It is the purpose of this paper to describe two models of the bronchial tree which include some of the asymmetry of the real structure and yet at the same time permit physiologic calculations to be made. In addition, some morphologic details of bronchial bifurcations are given because these are important parameters in fluid flow calculations.

DEVELOPMENT OF THE MODELS

The models are based on data obtained from measurement of a resin cast of a normal human bronchial tree. The preparation of the cast (9) and its measurement (7, 8, 15) have been described elsewhere. Data obtained from these studies were punched on computer cards and then transferred to electromagnetic tape, thus facilitating further analysis using a computer. Both the original data and that obtained from subsequent analysis were utilized in the development of the models.

Before proceeding with the models some concepts relating to branching systems require discussion. When a branch, termed the "parent" branch, divides into two, it branches by "dichotomy." The two branches to which it gives rise are termed "daughter" branches. These daughter branches may in turn divide, and the process can be repeated any number of times to form a "dichotomous" branching system. The one original branch from which all the others arise is termed the "stem." Figure 1*A* shows a dichotomously branching system in which each branch is numbered according to how many dichotomous divisions it is situated from the stem branch, which is itself numbered 0. The simple term "divisions" is now preferred to "divisions down" used previously (8) since in some branching systems, such as rivers and trees, the divisions would in fact be upward.

In Fig. 1*B* the same system has been numbered in a different way, starting at the periphery and working toward the stem. In this case the numbers define the "order" of each branch, previously termed "divisions up" (8). The term order is now preferred because this was used originally by Horton (10) to describe branching in rivers. There are several different ways of counting orders, including those of Horton (10), Strahler (21), Scheidegger (16), and Horsfield and Cumming (8), so that if there is doubt about which is being used the appropriate name should be used as a prefix, e.g., "Horton orders." The type of order we shall use is that previously defined as divisions up, in which the most distal branches comprise the first order, two of these meet to form a second-order branch, and so on. Where branches of different order meet, the order of the parent branch is one greater than the higher of the two daughter branches.

When the numbers of divisions from the stem branch to every first-order branch are equal the system is "symmetrical." In such a symmetrical branching system each parent branch divides into two daughter branches of the

Ref. 7

Respir Physiol. 1984 Mar;55(3):317-24.

Axial pathways compared with complete data in morphological studies of the lung.

Horsfield K.

Abstract

Morphometric studies of pulmonary airways and arteries can be laborious and time consuming. In order to see whether the effort involved could be reduced in some cases, data obtained from axial pathways of bronchopulmonary segments or lobes were compared with the mean total data obtained from four lungs. It was concluded that axial pathway data classified by generations could be compared between lungs only if the same segment or lobe was used from each individual. Such data are usually not representative of the total structure. Data from axial pathways of segments or lobes which have been classified by Horsfield orders can be pooled, and the mean values thus obtained are fairly close to the mean values obtained from the total data.

Ref. 8

Anat Rec. 1988 Apr;220(4):401-14.

Morphometry of the human pulmonary acinus.

Haefeli-Bleuer B[1], Weibel ER.

Abstract

The geometry and morphometry of intraacinar airways in human lungs were studied on silicone rubber casts from two adult lungs. We defined acini as the complex of alveolated airways distal to the terminal bronchioles--that is, beginning with the first-order respiratory or transitional bronchiole. The morphological properties of pulmonary acini are described. The acinar volume averages 187 mm3 (SD +/- 79 mm3). Intraacinar airways branch dichotomously over about 9 generations (range 6-12). The internal airway diameter falls from 500 micron to 270 micron between acinar generations 0 and 10, whereas the outer diameter (including the sleeve of alveoli) remains constant at 700 micron. Towards the periphery the size of alveoli increases and clusters of alveoli become more numerous. The longitudinal path length of acinar airways (defined as the distance along the ducts from the transitional bronchiole to the alveolar sacs) averages 8.8 mm (+/- 1.4 mm). The morphometric data collected in this study are used to construct an idealized model of human acinar airways that can be related to existing models of the human bronchial tree.

Ref. 9

Am Rev Respir Dis. 1975 Apr;111(4):489-95.

Interacinar pathways in the human lung

Raskin SP, Herman PG

Abstract

Normal lung specimens from patients 18 to 86 years of age were inflated, fixed, and cleared. After micropuncture of the distal airspaces and injection of silicone rubber, the dissemination pattern was studied by cinematography. Free interacinar flow was commonly observed. The major pathways of spread among adjacent acini were the interacinar ducts. These were short, tubular structures 200 mum in diameter that were continuous with respiratory bronchioles and alveolar ducts. The flow of silicone rubber was impeded only by the septa of the secondary lobule of Miller. Our finding support the view that the smallest morphologic unit of airspace disease is more likely to be the secondary lobule than the acinus.

Ref. 10

Radiology VOL. 239, NO. 2
Reviews and Commentary

Thin-Section CT of the Secondary Pulmonary Lobule: Anatomy and the Image—The 2004 Fleischner Lecture

W. Richard Webb

Published Online: May 1 2006

Abstract

The secondary pulmonary lobule is a fundamental unit of lung structure, and it reproduces the lung in miniature. Airways, pulmonary arteries, veins, lymphatics, and the lung interstitium are all represented at the level of the secondary lobule. Several of these components of the secondary lobule are normally visible on thin-section computed tomographic (CT) scans of the lung. The recognition of lung abnormalities relative to the structures of the secondary lobule is fundamental to the interpretation of thin-section CT scans. Pathologic alterations in secondary lobular anatomy visible on thin-section CT scans include interlobular septal thickening and diseases with peripheral lobular distribution, centrilobular abnormalities, and panlobular abnormalities. The differential diagnosis of lobular abnormalities is based on comparisons between lobular anatomy and lung pathology.

Ref. 11

Is the Lung Built Reasonably?[1–3]

The 1983 J. Burns Amberson Lecture

EWALD R. WEIBEL

It is now two dozen years since I entered, as a young postdoctoral fellow, the Cardiopulmonary Laboratory at Bellevue Hospital, then headed by Drs. André Cournand and Dickinson W. Richards, in order to start, as it turned out, a career in the study of lung design in relation to its gas exchange function. Dr. Amberson had just recently retired, but the Grand Old Man could still be seen around on occasion. I feel particularly honored to have been invited to pay my tribute to Dr. Amberson by reporting to the scientific society he has so decisively influenced where we have gone since those early days. The story I shall expose to your critique has been brought about by the work of a large number of excellent collaborators, but it is also the offshoot of a particularly privileged training by great teachers whom I had the good fortune to experience, and those who taught me at Bellevue rank at the top of this list.

The story has its origin during my first weeks at Bellevue. Having brought with me from Switzerland a good training in the meticulous morphologic sciences of the time, I was assigned the task "to do anything on the structure of the lung that was of interest to physiology." The environment offered by the Cardiopulmonary Laboratory of Drs. Cournand and Richards was ideal for taking up this challenge, and it was under the guidance of Dr. Domingo Gomez that I started to look at the architecture of the lung in a new way, seeking numbers rather than pictures, looking for structural traits that are determinants of function. The first question was how many alveoli were needed to make a human lung; but this quickly led to more sophisticated questions on the size and dimensions of the apparatus that allows efficient O_2 uptake in the lung.

Combining modern methods of microscopy with sound methods of morphometry produced a basic knowledge of the principal design features of the lung, namely: (*1*) that the walls between alveoli are densely populated with blood; (*2*) that the tissue barrier separating air and blood is exceedingly thin—50 times thinner than a sheet of air mail stationery—and is yet tightly organized into 3 basic layers; (*3*) that the surface of contact between air and blood is very large, approaching in humans the square footage of a tennis court; (*4*) that the airways and blood vessels are designed in such a way as to allow efficient ventilation and perfusion of the gas exchange units that number some 300 million in humans. It is intuitively plausible that these features establish favorable conditions for gas exchange.

If I now ask the question whether the lung is built reasonably, intuitive reasoning is no longer sufficient; we need a sound rational approach based on hard data. Also, I introduce a value judgment for which we need some valid criteria. Reasonable with respect to what, we must ask. Reasonable with respect to solving the mechanical problem of maintaining such a large surface exposed to air using a minimum of tissue; or reasonable with respect to solving the metabolic problems of maintaining a healthy living lung despite the need to reduce the metabolically active cell mass to nearly vanishing dimensions? All such questions are valid, but they are, in some way, secondary to the main question: whether the lung is built reasonably in view of its central function: the supply of O_2 to the cells of the body at the rate they need it to do work.

Thus, in asking this question, we cannot look at the lung alone but must rather consider it as merely a part of the respiratory system that conducts O_2 from outside air to the mitochondria in the cells, using the lung and the circulation of blood as intermediates (figure 1). The pattern of this model is familiar

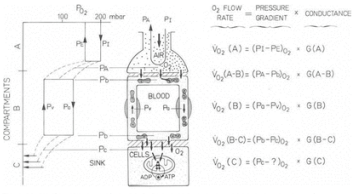

Fig. 1. Model of respiratory system with O_2 flow rates from lung to mitochondria driven by P_{O_2} cascade. Modified from Reference 4.

[1] From the Department of Anatomy, University of Berne, Bern, Switzerland.
[2] Supported by Grant No. 3.128.81 from the Swiss National Science Foundation.
[3] Requests for reprints should be addressed to Ewald R. Weibel, M.D., Department of Anatomy, University of Berne, CH-3000 BERN 9, Switzerland.

Ref. 12

JOURNAL OF APPLIED PHYSIOLOGY
Vol. 24, No. 3, March 1968. *Printed in U.S.A.*

Morphology of the bronchial tree in man[1]

KEITH HORSFIELD[2] AND GORDON CUMMING
Department of Medicine, Queen Elizabeth Hospital, University of Birmingham, Birmingham, England

HORSFIELD, KEITH, AND GORDON CUMMING. *Morphology of the bronchial tree in man.* J. Appl. Physiol. 24(3): 373–383. 1968.—The anatomical arrangements of the air passages in the human lung have been studied by preparing a cast with a thermosetting resin, followed by measurement of all the structures so delineated. The airways larger than 0.7 mm in diameter have been measured individually; those smaller have been measured by a sampling technique. The data obtained from all these measurements and some derived quantities are presented. A method for numbering the generations of branches counting up the bronchial tree is described.

bronchial anatomy; gas flow; morphometry

THE PART PLAYED by the structure of the lungs in determining their function has been the subject of recent work (4, 11, 13, 14). The interpretation of a variety of physiological tests is assisted by a knowledge of structure, and recent papers concerning the rate of gas mixing by diffusion serve to emphasize the importance of a knowledge of the geometrical arrangement of the air passages in the lung.

The transfer of a molecule of oxygen to its final destination in a biochemical reaction within a living cell is complex and, so far as the process of ventilation is concerned, involves two distinct processes—gas transport down the airways and gas mixing within them.

Gas transport is concerned with the characteristics of flow in branching tubes where mass movement is the dominant process. Gas mixing occurs in the terminal airways and here the physical process involved is gaseous diffusion so that understanding involves the application of physical knowledge to the biological situation. It is in these areas that quantitative measurements of the anatomy of the airways can be most helpful.

Other authors have undertaken this task of measurement (5, 12, 13). Ross (13) stressed the importance of asymmetry in the production of inequality of ventilation in the dog's lung and calculated the effect of such asymmetry in producing regional inequality of ventilation.

An analysis of the human bronchial tree has been made by Weibel (16). Using a resin cast of the larger airways he measured completely only as far as generation 5 and incompletely down to generation 10. The smaller structures were examined by conventional histological techniques.

The area between, involving the smaller bronchioles, was difficult and this he overcame by making the assumption of regular dichotomy and predicting therefrom the missing measurements. This approach has been valuable but suffers from the defect that inhomogeneity due to asymmetrical bronchial anatomy is automatically excluded.

The purpose of the study reported in this paper was to make measurements of the human bronchial tree as nearly complete as possible so that the functional effects of asymmetry could be studied. Before embarking on a description of the techniques of measurement and computation several points of principle should be discussed.

PATTERNS OF BRANCHING IN BIOLOGICAL SYSTEMS

Branching systems may be organized in various patterns. At each node the parent branch may divide to produce two (dichotomy), three (trichotomy), or many (polychotomy) daughter branches. Another type of branching occurs when a lateral branch arises from a main stem, this being termed monopody. In dichotomy the growing point divides into two while in monopody a separate growing point arises on a branch which has been formed previously.

Apparent trichotomy may be found in a dichotomous system due to shortening of a branch to zero length.

Number of Branches

Symmetrical dichotomy. In this system each parent branch gives rise to two daughter branches of the same length and diameter. If the initial member of the system is designated as generation zero, then the total number of branches at any given generation is 2^w, where w is the generation considered. Since this is an exponential statement, a plot of the logarithm of the number of branches against w will be linear.

Received for publication 12 June 1967.
[1] This study was supported by the Aerospace Medical Research Laboratories under Contract AF 61 (052)-775 through the European Office of Aerospace Research (OAR), United States Air Force.
[2] Recipient of a British Heart Foundation grant.

Ref. 13

NOBEL PRIZE SYMPOSIUM

Structure and Function Relationships in Diseases of the Small Airways

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Abstract

It is well known that particulate matter suspended in the earth's atmosphere generated by tobacco smoke, automobile exhaust, industrial processes, and forest fires has been identified as a major risk factor for chronic lung disease. Particulate matter can be divided into large, intermediate, and fine particulates. When inhaled, large particulates develop sufficient momentum to leave the flowing stream of inhaled air and deposit by impaction in the nose, mouth, nasopharynx, larynx, trachea, and central bronchi. Intermediate-sized particulates that develop less momentum deposit in the smaller bronchi and larger bronchioles, and the finest particulates that develop the least momentum make it to the distal gas-exchanging tissue, where gas moves solely by diffusion. On the basis of Einstein's classic work on Brownian motion that showed particles suspended in a gas diffuse much more slowly than the gas in which they are suspended, we postulate that the small airways that accommodate the shift from bulk airflow to diffusion become the major site for deposition of fine particles, resulting in a host immune response. Much remains to be learned about the interaction between the deposition of fine particulates and the host immune and tissue responses; the purpose of this review is to examine the hypothesis that the smallest conducting airways and proximal gas-exchanging tissue are the primary sites for the deposition of the finest particulates inhaled into the lungs.

Keywords: small airways disease; chronic obstructive pulmonary disease; particulate matter; host response; tertiary lymphoid follicles

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Author Contributions: J.C.H and T.-L.H. drafted and edited the manuscript.

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DOI: 10.1513/AnnalsATS.201710-808KV
Internet address: www.atsjournals.org

This review provides a hypothesis for why the small airways are so susceptible to disease in the setting of inhaled particulate matter, especially in individuals with chronic obstructive pulmonary disease (COPD). An overview of the lung anatomy and how changes from bulk airflow in the conducting airways to diffusion at the gas-exchanging tissues affect the deposition of inhaled particulates is provided. Furthermore, the mechanisms of the host response to inhaled particulates and the subsequent effects on tissue remodeling and destruction are discussed. This discussion was previously presented in part at a public symposium dedicated to the life and work of Dr. André Gourmand entitled "A Celebration of Cardiopulmonary Physiology from the Nobel Prize to the Modern Era," held on January 17, 2017, at New York University.

Functional Lung Anatomy

Figure 1A shows the bronchogram of a normal lung, where the peripheral conducting airways end in clusters (highlighted by white boxes in the figure) which are surrounded by fibrous connective tissue septa that define the secondary lung lobules (Figure 1B). The secondary lobules, in turn, contain both the pericentrilobular and terminal bronchioles which supply the individual acini containing the respiratory bronchioles, alveolar ducts, and sacs that contain the individual alveoli where gas exchange occurs (1) (Figure 1C). Although the human lung is most often described as a dichotomous branching system of approximately 23 generations, where all the pathways are exactly the same length and each generation of branching contains airways uniform in size, this type of model is in fundamental conflict with the anatomic facts. Simple inspection of a normal human bronchogram (Figure 2A) shows very substantial differences in the pathway lengths between the trachea and the distal gas-exchanging surface in the upper and lower lobes. The difference in pathway length was first reported by Horsfield and Cumming (2) (Figure 2B), who observed that the number of divisions between the lobular branches and the trachea is actually normally distributed between the 8th and 22nd generations of airway branching. Furthermore, an earlier analysis of a human airway cast by Weibel (3) (Figure 2C) showed that conducting airways 2 mm in diameter are spread out between the 4th and 14th generations of conducting airway branch points.

Ref. 14

Bulletin of Mathematical Biology, Vol. 42, pp. 461–480
Pergamon Press Ltd. 1980. Printed in Great Britain
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MODELS OF HUMAN LUNG AIRWAYS AND THEIR APPLICATION TO INHALED PARTICLE DEPOSITION

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Models of the human respiratory tract were developed based on detailed morphometric measurements of a silicone rubber cast of the human tracheobronchial airways. Emphasis was placed on the "Typical Path Lung Model" which used one typical pathway to represent a portion of the lung, such as a lobe, or to represent the whole lung. The models contain geometrical parameters, including airway segment diameters, lengths, branching angles and angles of inclination to gravity, which are needed for estimating inhaled particle deposition. Aerosol depositions for various breathing patterns and particle sizes were calculated using these lung models and the modified Findeisen–Landahl computational scheme. The results agree reasonably well with recent experimental data. Regional deposition, including lobar deposition fractions, are also calculated and compared with results based on the ICRP lung deposition model.

1. Introduction. Knowledge of initial deposition pattern of inhaled particles is of interest in toxicology studies using laboratory animals and in assessing hazards to people from airborne toxicants present in the environment. One approach to understanding the deposition of inhaled particles is the use of mathematical models.

The geometry of the tracheobronchial airways is one of the factors influencing particle deposition during inhalation. Airway structure parameters which influence particle deposition include airway segment diameters, lengths, branching angles and angles of inclination to gravity (Yeh *et al.*, 1976). Because of the complexity of lung anatomy and the mathematical calculations involved in particle deposition, most of the lung models have had fairly simple simulated lung structures (Davies, 1961; Findeisen, 1935; Horsfield *et al.*, 1971; Landahl, 1950; Olson *et al.*, 1970;

†Present address: Department of Biology, San Diego State University, San Diego, CA, U.S.A.

Ref. 15

J Thorac Imaging. 1993 Summer;8(3):176-88.

Diffuse lung disease: pathologic basis for the high-resolution computed tomography findings.

Itoh H[1], Murata K, Konishi J, Nishimura K, Kitaichi M, Izumi T.

⊕ Author information

Abstract

High-resolution computed tomography (HRCT) allows accurate assessment of the pattern and distribution of diffuse lung diseases. Optimal interpretation of the HRCT images requires understanding of some basic concepts of normal anatomy, as well as the pathologic basis for the HRCT findings in diffuse lung disease. This review summarizes our experience with over 400 radiologic-pathologic correlations in diffuse lung disease. These correlations include contact radiography with stereo views and stereomicroscopic images of lung specimens. We describe our technique to inflate and fix the lung specimens and illustrate normal and abnormal lung morphology.

Ref. 17

Thorax (1958), **13**, 103.

THE PERIPHERAL PATTERN IN THE NORMAL BRONCHOGRAM AND ITS RELATION TO PERIPHERAL PULMONARY ANATOMY*

BY

LYNNE REID AND G. SIMON

From the Institute of Diseases of the Chest and Brompton Hospital, London

(RECEIVED FOR PUBLICATION OCTOBER 19, 1957)

The appearances in a bronchogram of the more proximal branches of the bronchial tree are well known and have been fully described (Huizinga and Smelt, 1949; Twining and Kerley, 1951; Fischer, 1953; Brock, 1954; Ritvo, 1956). This is not so in regard to the more distal and final branches, and there is, moreover, some confusion as to which structures are outlined by the contrast medium at the periphery of a well-filled clinical bronchogram. The earlier belief that the rather woolly shadows sometimes seen in a well-filled bronchial tree, and illustrated in Fig. 4, represented alveolar filling is to-day thought unsatisfactory (Twining and Kerley, 1951; Fischer, 1953), but the term "peripheral filling," which is tending to replace the earlier description, does not give an exact indication of the structures outlined. Twining suggests, as the result of stereoscopic examination of a lung specimen injected with "lipiodol," that an appearance "like a tree in bud" was the result of filling of respiratory bronchioles, and Ritvo describes a similar granular appearance as being characteristic of filling of respiratory bronchioles.

A more detailed description of the normal appearances of the distal part of the bronchial tree would be of value both in the detection and localization of abnormalities of the peripheral bronchi and bronchioles, such as are seen in chronic bronchitis (Simon and Galbraith, 1953), and in the localization in relation to the peripheral bronchi of small abnormal shadows such as are seen in tuberculosis and sarcoidosis. Several hundreds of apparently normal clinical bronchograms were therefore examined, and these form the basis for the description of the normal pattern of the peripheral part of the bronchial tree given in Part I of this paper. Part II describes how, by histological examination of injected specimens, the exact anatomical site of certain of these shadows was demonstrated.

* A communication based on this paper was delivered to the Thoracic Society in July, 1957.

PART I: STUDY OF THE PERIPHERAL PATTERN IN NORMAL CLINICAL BRONCHOGRAMS

The word "peripheral" or "distal" is used here to describe those parts which are toward the end of the pattern of branching of the bronchial tree. In this sense, a structure may be peripheral or distal and yet deep in the lung's substance, and central in a radiograph. Although the same peripheral pattern is seen throughout the lung, it is easier to study its details in the subpleural region than in the central part where it is apt to be obscured by overlying shadows.

The bronchograms studied were taken as part of the examination of patients, many being rejected because they showed obvious pathological changes or because the contrast medium did not fill the peripheral bronchi. Those showing adequate peripheral filling, and thought to be normal in at least one lobe, were then examined in detail. When possible, the shadow cast by a filled air tube was examined in two planes by identifying it both in the postero-anterior and in the lateral or oblique view. In several cases tomograms were available so that even in well-filled bronchograms it was possible to study the shadow of a bronchus or bronchiole deep in the lung without its being obscured by overlying bronchi. A similar peripheral pattern was shown whether the contrast medium used was iodized oil or oily or watery propyliodone, and whatever the method of introduction.

THE SHAPE OF THE LUMEN.—The pattern of the bronchi when traced from the hilum to the periphery is essentially that of frequently branching line shadows, progressively decreasing in width. Whereas in the larger proximal bronchi it is sometimes possible to see the shadow of the contrast

Thorax (1958), **13**, 110.

Ref. 18

THE SECONDARY LOBULE IN THE ADULT HUMAN LUNG, WITH SPECIAL REFERENCE TO ITS APPEARANCE IN BRONCHOGRAMS *

BY

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From the Institute of Diseases of the Chest, Brompton Hospital, London

(RECEIVED FOR PUBLICATION NOVEMBER 19, 1957)

Anatomical descriptions of the peripheral part of the lung are varied and inconsistent. They are difficult to relate to bronchographic and radiographic appearances (Twining and Kerley, 1951; Fischer, 1953) or to morbid anatomy.

The units in which the periphery has been described may broadly be grouped into two types. The smaller units, measured in millimetres, include those described as the acinus and the primary lobule, and the larger, measured in centimetres, has usually been known as the secondary lobule. To date, attempts to define the secondary lobule have been especially unsatisfactory and, although this paper is concerned primarily with this unit, some preliminary consideration must be given to the smaller units of which it is composed. This smaller unit is concerned with respiratory tissue lying beyond the bronchial tree (Fig. 1), i.e., the alveolar region of the lung.

SMALLER PERIPHERAL UNIT

Confusion here arises mainly from the variety of ways in which respiratory tissue has been subdivided for purposes of description. Some of the many names by which this part of the lung has been described are shown in Table I. Because these subdivisions are anatomical they are intrinsically accurate, but misunderstanding arises because the same unit is variously described and the same term applied to different units (see Table I). Perhaps the most useful term is "acinus" (Rindfleisch, 1878; Loeschke, 1921), used here to embrace all the respiratory tissue (including respiratory bronchioles, since these have alveoli opening into the lumen) beyond a terminal bronchiole. Lung tissue can thus be divided into the bronchial tree and acini.

* A communication based on this paper was delivered to the Thoracic Society in July, 1957.

TABLE I
EXAMPLES OF PREVIOUSLY DEFINED UNITS OF PERIPHERY OF LUNG

Structure Supplying Unit	Name Applied to Unit	Author by Whom Name Used
Terminal bronchiole	Acinus	Rindfleisch (1878) Loeschke (1921)
Respiratory bronchiole—first order of generation	Primitive lobule Acinus	Cournellman (1900) Husten (1921)
Alveolar duct	Primary lobule	Miller (1947)

LARGER PERIPHERAL UNIT

The previously accepted definition of the secondary lobule is that it is the unit demarcated by septa of connective tissue passing into the lung from the pleura. This simple definition has given rise to the assumption that throughout the lung the septa are uniformly and regularly present; nevertheless various authors in applying the definition have given widely differing estimates of the number of acini which a secondary lobule contains. Rindfleisch (1878) thought that the lobule might include as few as two acini or as many as 30, Berdal (1903) estimated 15 to 18, Braus (1924) 12 to 18, while Laguesse and d'Hardivillier (1898), whose diagram is still included in current textbooks, gave as wide a range as 36 to 100. Perhaps because of this embarrassing diversity in the number of acini, more modern accounts (Miller, 1947; Birnbaum, 1954) make no reference to them, but describe the lobule in terms of septa only.

The need for applying these anatomical descriptions to radiographs and particularly bronchograms has made radiologists especially conscious of these inconsistencies and of the difficulty of relating the number of acini included to the volume of the secondary lobule. Twining and Kerley (1951) have emphasized how unfortunate

Ref. 20

Pulmonary Tuberculosis: CT and Pathologic Correlation

Lee, Ji Yeon; Lee, Kyung Soo; Jung, Kyung-Jae; Han, Joungho; Kwon, O Jung; Kim, Jhingook; Kim, Tae Sung

Journal of Computer Assisted Tomography: September-October 2000 - Volume 24 - Issue 5 - p 691-698
THORACIC IMAGING: Pictorial Essay

Abstract | Author Information

Typical CT findings of active postprimary pulmonary tuberculosis include centrilobular nodules and branching linear structures (tree-in-bud appearance), lobular consolidation, cavitation, and bronchial wall thickening. The CT findings of inactive pulmonary tuberculosis include calcified nodules or consolidation, irregular linear opacity, parenchymal bands, and pericicatricial emphysema. The typical appearance of primary tuberculosis on CT scans is homogeneous, dense, well-defined segmental or lobar consolidation with enlargement of lymph nodes in the hilum or the mediastinum. Miliary nodules may be seen in primary and postprimary tuberculosis. On CT, tuberculomas appear as a nodule with surrounding satellite nodules and internal cavitation on CT. Atypical radiologic manifestations of tuberculosis, encountered in as many as one third of the cases of adult-onset tuberculosis, are single or multiple nodules or masses, basilar infiltrates, miliary tuberculosis with diffuse bilateral areas of ground-glass opacity, and reversible multiple cysts. Underlying histopathologic findings of typical and atypical CT findings of tuberculosis are caseating granulomas or pneumonia in the active phase and fibrosis and dystrophic calcification in the inactive phase.

Ref. 21

ARTICLES

Branching pattern of airways and air spaces of a single human terminal bronchiole

J. E. Har

1 JUN 19

TOOLS SHARE

Abstract

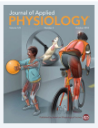
A polyurethane-foam enlarged reconstruction was made from serial sections of a portion of young adult human lung parenchyman. Study of the progeny of a terminal bronchiole disclosed three generations of respiratory bronchioles and an irregular branching pattern of eight generations of alveolar ducts. Sacs and alveoli arose from the lateral and distal aspects of all generations of ducts. There were an average of 3.5 alveoli per sac. Considering the terminal bronchiole as the first generation branch of the acinus, over 60 per cent of the alveoli counted and predicted were members of the 10–12th generations. The acinus contained one terminal bronchiole and approximately 14 respiratory bronchioles, 1,200–1,500 ducts, 2,500–4,500 sacs, and 14,000–20,000 alveoli.

Ref. 22

ARTICLES

Model analysis of gas distribution within human lung acinus

M. Paiva, and L. A. Engel



Volume 56, Issue 2
February 1984
Pages 418-425

Abstract

Alveolar gas concentrations were simulated in an asymmetrically branching model of a human lung acinus based on morphometric measurements. The structure was expansile so that convective flow into and out of every part was proportional to its volume. Despite the homogeneous volume change solution of a differential equation for simultaneous convection and molecular diffusion following a 1-liter breath of O2 at 0.5 l/s predicted substantial inhomogeneity of O2 concentrations. This was reflected in a twofold range of inspired gas per unit volume computed from O2 concentrations averaged throughout expiration. Even a 10-s breath hold at end inspiration did not result in uniform concentrations. Larger breaths, corresponding to a ventilation of 60 l/min, increased the degree of inhomogeneity 50%. Diffusive pendelluft at intra-acinar branch points during expiration produced a sloping alveolar plateau of 0.53% N2/l, i.e., much smaller than that measured from the whole lung in vivo. Similarly, an estimate of single-breath mixing efficiency also indicated a much smaller degree of inhomogeneity than inferred from measurements of expired gases at the mouth. The model analysis suggests that if anatomical data used are representative of a normal lung, then the intra-acinar gas inhomogeneity, although substantial, constitutes a small fraction of the overall impairment in gas mixing.

Ref. 23

JOURNAL OF APPLIED PHYSIOLOGY
Vol. 28, No. 3, March 1970. Printed in U.S.A.

Diffusional transport in the human lung

RICHARD CONLEY LA FORCE AND BENJAMIN M. LEWIS
Mayo Foundation, Rochester, Minnesota 55901; and Wayne State University School of Medicine, Detroit, Michigan 48207

LA FORCE, RICHARD CONLEY, AND BENJAMIN M. LEWIS. *Diffusional transport in the human lung.* J. Appl. Physiol. 28(3): 291–298. 1970.—Calculations of the time for gaseous diffusion were made by finite difference techniques in a dichotomously branched model of the human lung. The lengths and cross-sectional areas of the branches were derived from anatomical data and the diffusion coefficient was that of O_2 diffusing into N_2. Finite difference equations for treating diffusion at a branch point were developed. If the diffusion front was established at the terminal bronchioles, O_2 concentration in the terminal alveoli rose to a plateau value in 2 sec which was maintained for 50 sec. A diffusion front in the alveolar ducts led to a plateau in 1 sec. Critical examination of the assumptions made in this model (axial diffusion, a square, stationary front, and symmetrical branching) does not affect the conclusion that no significant concentration gradient exists between gas in the terminal bronchioles and gas distal to this point during the normal respiratory cycle. Physiological data on the reason for the slope of the alveolar plateau are briefly reviewed.

computers; distribution of ventilation; single-breath nitrogen test; mechanics of lung

THIS PAPER ATTEMPTS to explain a fact observed by Krogh and Lindhard in 1914 (8) and confirmed by innumerable subsequent investigators: "The distribution of a gas in the alveolar air after one inspiration of it is not uniform. The last portion of an expiration will contain less of a gas than the earlier." In 1946 Rauwerda (12) summarized the possible explanations of this fact: *a*) stratified inhomogeneity (i.e., the gas inspired fails to equilibrate by diffusion with that already present), *b*) regional inhomogeneity (different areas of the lung are more or less well ventilated than others), or *c*) a combination of both. He made a major contribution toward deciding which explanation was correct: the calculation of the time for diffusion in lung models based on anatomical data. He used two models, a cylinder and a cone with a globular end (rather like a filled ice cream cone). In each case the system was closed and the distance for axial diffusion 0.7 cm (a distance equal to that from the beginning of a respiratory bronchiole to a terminal alveolus, according to the data of Weibel (14). He found that diffusion was more rapid in the cone than in the cylinder and in each case was fast, equilibration being attained in less than 0.5 sec. He concluded that stratified inhomogeneity was not significant after an inspired breath and that regional inhomogeneity was the proper explanation of Krogh and Lindhard's observations. This view was reinforced by the conclusion of Otis and co-workers (11), that the mechanical properties of the lung were not uniform and until recently Rauwerda's interpretation was generally accepted.

In 1966, however, Cumming and his associates (3) criticized Rauwerda's models on the obvious grounds that they were closed at both ends while the terminal airways of the lung are open proximally. They proposed instead a larger right circular cone, having a length for axial diffusion of 2.1 cm. They found that it made little difference over several seconds whether this larger cone was open or closed at its apex and further that an appreciable diffusion gradient persisted in this cone for 5 sec or more after an interface between inspired gas and alveolar air was established 0.2 cm from the distal end. Cumming and another set of coworkers (4) put the theoretical conclusion that a diffusion gradient existed in the terminal airways after an inspired breath to an experimental test using a mixture of sulfur hexafluoride (molecular weight 146) and neon and felt that experiment confirmed theory. Shortly before, Sikand, Cerretelli, and Fahri (13) concluded that all parts of the lungs emptied simultaneously, which would render regional inhomogeneity undetectable during expiration. The combined effect of arguments for stratified inhomogeneity and against regional inhomogeneity has brought stratified inhomogeneity into favor again, more than half a century after Krogh and Lindhard proposed it as an explanation of their results.

The reason for this change is basically the differing results of diffusion calculations in two models of the terminal portions of the human airway. While the criticism of Rauwerda's models by Cumming and co-workers is valid, their model, in its turn, is open to criticism on two grounds. If the terminal airways are to be treated as a solid figure, the appropriate one is not a cone but a golf tee, since most of the volume of the airways is concentrated near their termination. Even if this objection were met, the further one that the airways are not a solid figure but a succession of dichotomous branches would remain.

The work which follows frees the problem from the Procrustean bed which distorts the finer airways into some sort of solid figure, by the development of finite difference equations which treat diffusion at a branch point. With these equations calculations were made on a dichotomously branched model having the lengths and cross-sectional areas proposed by Weibel (14). Weibel's values are obtained from empirical equations fitted to actual anatomical measurements. Although the model assumes symmetrical dichotomy it is clearly a closer approximation to the real lung than any previously used.

Ref. 26

Respiratory System

Morphology of the guinea pig respiratory tract

Jay P. Schreider, John O. Hutchens

First published: March 1980 |

Abstract

A morphologic description of the airways of the guinea pig was developed from measurements of casts of the lungs and nasal cavity and from measurements of frozen sections of the lungs. The lengths, diameters, branching pattern, and numbers of elements of the respiratory tract formed the basis for a representative model of the system. The brainching pattern is irregular to the pulmonary region but regularly dichotomous thereafter. The nasopharyngeal-tracheobronchial region contributes 2.64 cm^3 of the total respiratory volume of 21.62 cm^3. The alveoli contribute 16.31 cm^3 of the 18.98 cm^3 pulmonary region. The nasal region consist of convoluted and irregular airways with a functional volume of 0.48 cm^3.

Ref. 28

J Pathol Bacteriol. 1955 Oct;70(2):311-4.

Accessory bronchiolealveolar communications.

LAMBERT MW

No abstract

Ref. 29

J Pathol Bacteriol. 1964 Oct;88:389-403.

THE PATHOGENESIS OF COAL MINER'S PNEUMOCONIOSIS.

DUGUID JB, LAMBERT MW.

No abstract

Ref. 30

Respiratory bronchioles as the pathway for collateral ventilation[1]

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MARTIN, H. B. *Respiratory bronchioles as the pathway for collateral ventilation.* J. Appl. Physiol. 21(5): 1443–1447. 1966.—Left upper lobes from the dog were subjected to three different procedures to study the pathways for collateral ventilation. The first procedure involved measuring the pressure required to initiate collateral ventilation in a completely collapsed lobe. In the second procedure, polystyrene spheres between 60 and 710 μ in diameter were passed through the lobe and an estimate made of the size of the largest to pass through. Finally, in a third lobe aerosolized India ink was deposited along the pathways of flow which later served to outline them for identification in histological sections. The pressure required to start collateral ventilation in six collapsed lobes varied from 17 to 28 cm of water. Polystyrene spheres as large as 120 μ were able to pass through to the outflow side of the lobe. Serial sections from the aerosolized material indicated respiratory bronchioles connecting terminal bronchioles from adjacent lung segments. The data thus obtained from three experimental procedures indicate that collateral respiration occurred through respiratory bronchioles but not through smaller pathways such as the alveolar pores of Kohn.

pathways for collateral ventilation in dog lung; respiratory bronchioles and collateral ventilation in the dog; dog lung

IT HAS PREVIOUSLY been assumed (3) that collateral ventilation in mammalian lungs occurred by way of the alveolar pores of Kohn. Certain theoretical considerations based on recent findings with respect to the surface tension values of the alveolar lining have caused a re-evaluation of this assumption. The need for further evidence resulted in the following studies.

METHODS

Dogs sacrificed by intravenous injection of Nembutal were used in all experiments. The left upper lobe was used, the first two bronchial branches were dissected free, and each was cannulated. The lobes were then subjected to three different procedures to study the pathways for collateral ventilation, a different lobe being used for each procedure.

The first procedure involved measuring the pressure required to cause collateral ventilation to begin in a completely collapsed lung. This entailed degassing of the lung by placement in a vacuum desiccator and lowering of the absolute pressure to 25 mm Hg. The vacuum was broken and the collapsed lobe removed and connected by its first two bronchi to the apparatus shown in Fig. 1. The pressure was raised in 1-cm steps and held for 3 min at each pressure until a pressure was reached where air bubbled out of the outflow side.

In the second procedure, polystyrene spheres of diameters from 60 to 710 μ were suspended in saline and allowed to flow through the pathways of collateral ventilation as diagramed in Fig. 2. At no time was the pressure of the saline on the inflow side allowed to exceed 4 cm of water. The outflow was collected and allowed to settle for 24 hr. Most of the saline was gently pipetted off and the sediment examined with a microscope equipped with a micrometer eyepiece to estimate the size of the largest sphere which had passed through.

In the final procedure, aerosolized India ink was allowed to flow under controlled pressure through the lobe for 2 min by use of the apparatus shown in Fig. 3. After 2 min the direction of flow was reversed by connecting the lobe so that the previous outflow bronchus was now the inflow bronchus. By this means the ink was partially deposited along the pathways of flow and served to outline the pathways of collateral ventilation for later identification in sections. To control the pressure a 20 cm of water blowoff was used between the India ink solution and the lobe and to prevent gross collapse of the outflow segment of the lobe an outflow blowoff was set at 8 cm under water. The lobe was then fixed in the inflated state with intrabronchial perfusion of 4 % formaldehyde under a pressure of 10 cm of water. Following this, the area involving the intersegmental plane of the lobe was dissected out, embedded in paraffin, serially

Received for publication 3 September 1965.
[1] This investigation was supported by National Heart Institute Research Grant H-6993.
[2] Deceased.
[3] Late author's department, and mailing address for reprints. Attn.: E. S. Boatman.

Ref. 31

Article

The structure of the pulmonary acinus in a child of six years and eight months**

Edward A. Boyden

First published: November 1971

* Supported by Research grant HD-00656, National Institutes of Health, U. S. Public Health Service.
* See page 2.

Abstract

So far as known this is the first portrayal of the detailed structure of a pulmonary acinus as seen both from within its cavities and from without. Some 200 serial sections (× 50) were traced upon transparent plastic plates and then viewed as translucent objects in packets of ten. This method was supplemented by wax-plate and graphic reconstructions of the whole and of its parts.

The pulmonary acinus is a terminal bronchiole and all its branches. In this example there were three generations of respiratory bronchioles and from two to five generations of alveolar ducts ending in saccules. This acinus had a volume of 15.6 mm^3, comparable to a cube measuring 2.5 mm on each side. The two halves (medial and lateral semiacini) interdigitated. Only the lateral, forming 53.4% of the whole, was analyzed in detail. It consisted of a *roof* having three portions with varying patterns (namely a proximal wing, a distal wing extending to the connective tissue septum, and a rudimentary lateral component); a *septal portion* resting on the septum and consisting of four pairs of alternating small and large clusters of alveolar ducts, to the lower half of which a *cluster of vesicles* was appended; and a *paired lateral envelope* of ducts which in one place communicated with an adjacent acinus, thereby revealing a third mode of collateral ventilation.

This acinus, reconstructed over a period of three years, is replete with numerous variations such as dilated atria and saccules, supernumerary structures, recurrent ducts, irregular branches and differing lengths of airways. Thus, it records the "fight for space" in earlier periods of growth. Knowing the pattern of this particular acinus, it has been possible to calculate the rate of diffusion of gases between the terminal bronchiole and the peripheral saccules, and *vice versa*. Yet the impression persists that no two acini are alike in either proximal or distal portions; therefore, it is questionable whether diffusion of gases in the peripheral airways of the living individual are really subject to precise mathematical measurement.

Ref. 32

Am Rev Respir Dis. 1975 Apr;111(4):489-95.

Interacinar pathways in the human lung.

Raskin SP, Herman PG.

Abstract

Normal lung specimens from patients 18 to 86 years of age were inflated, fixed, and cleared. After micropuncture of the distal airspaces and injection of silicone rubber, the dissemination pattern was studied by cinematography. Free interacinar fl ow was commonly observed. The major pathways of spread among adjacent acini were the interacinar ducts. These were short, tubular structures 200 mum in diameter that were continuous with respiratory bronchioles and alveolar ducts. The flow of silicone rubb er was impeded only by the septa of the secondary lobule of Miller. Our finding support the view that the smallest morphologic unit of airspace disease is more likely to be the secondary lobule than the acinus.

Ref. 33

Microvascular Research
Volume 19, Issue 2, March 1980, Pages 217-233

Topology of pulmonary arterioles, capillaries, and venules in the cat ☆

Sidney S. Sobin [1, 2, 2], Yuan-Cheng Fung [1, 2], Roberta G. Lindal [1, 2], Herta M. Tremer [1, 2], Linda Clark [1, 2]

Abstract

It is shown in this paper that each alveolus is not a unit of microcirculation: It is not supplied by one arteriole and one venule; each arteriole supplies several alveoli, which are connected to other alveoli before draining into venules. The spatial relationship among the arterioles, venules, and capillaries in the lung is not clear in the literature. To clarify the topology, we developed a special method of particulate polymer casting of the vascular tree, and four criteria to decide whether a noncapillary vessel is arterial or venous. Then on each histological cross section of the lung parenchyma, we marked all arteries with white dots, and all veins with red dots, and covered the area of white dots with one color, and the area of red dots with another. A two-colored map emerged. A two-colored cartographic map can only show islands in an ocean. Our histological maps of the cat lung show that the arterial zones are islands, and the venous zone is the ocean. From these maps quantitative information about the arterial and venous zones in the lung is obtained by stereological methods, and the data for the cat are presented. A morphological definition of the average length of capillary blood vessels connecting arterioles and venules is proposed. The average morphological length of capillary blood vessels in cat lung was found to be 556 ± 286 (SD) μm when the transpulmonary pressure was 10 cm H_2O. The average length of capillaries (L) is an important determinant of pulmonary blood flow: for given arterial and venous pressures, the flow rate is inversely proportional to L^2, the square of the average length; the transit time (time available for diffusion and oxygenation) varies directly with L^2; the regional difference of blood flow also depends on L.

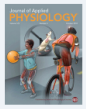
Ref. 34

ARTICLES

Demonstration of pulmonary vascular perfusion by electron and light microscopy

M. F. Konig, J. M. Lucocq, and E. R. Weibel

01 OCT 1993 //



Volume 75, Issue 4
October 1993
Pages 1877-1883

Abstract

To estimate the fraction of dense pulmonary capillary network that is perfused under physiological conditions, we developed a new method for the demonstration of in vivo capillary perfusion by light and electron microscopy. Blood plasma was labeled by 8-nm colloidal gold particles coated with rabbit serum albumin. In anesthetized rabbits, 4#x2013;5 ml of this tracer were injected into the right atrium. Two and 15 min later, the circulation was interrupted by a snare around the heart, and the lung was fixed by instillation with glutaraldehyde. Gold particles were found in the plasma space of alveolar capillaries as well as in other organs. A random sample of thin sections studied by electron microscopy revealed that the entire capillary bed of the lung was perfused at least with plasma within 2 min after tracer infusion. Light microscopy of silver-enhanced sections showed areas with different staining intensities but no obviously unperfused capillaries. The concept of capillary recruitment, which would require a significant fraction of capillaries unperfused at rest, may have to be reassessed to consider time factors as well as the two-phase nature of blood; red blood cells and plasma may take different paths.

Ref. 35

Article | Published: 18 February 1967

Design of the Bronchial Tree

THEODORE A. WILSON

Nature volume 213, pages 668–669 (18 February 1967) | Download Citation

Abstract

The bronchial tree is so designed that the functions of the lung can be carried out with minimum entropy production.

Ref. 36

Research

Cite this article: Al Mukahal FHH, Duffy BR, Wilson SK. 2017 Advection and Taylor–Aris dispersion in rivulet flow. *Proc. R. Soc. A* **473**: 20170524.
http://dx.doi.org/10.1098/rspa.2017.0524

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mathematical modelling, applied mathematics, fluid mechanics

Keywords:
advection, Taylor–Aris dispersion, rivulet

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Motivated by the need for a better understanding of the transport of solutes in microfluidic flows with free surfaces, the advection and dispersion of a passive solute in steady unidirectional flow of a thin uniform rivulet on an inclined planar substrate driven by gravity and/or a uniform longitudinal surface shear stress are analysed. Firstly, we describe the short-time advection of both an initially semi-infinite and an initially finite slug of solute of uniform concentration. Secondly, we describe the long-time Taylor–Aris dispersion of an initially finite slug of solute. In particular, we obtain the general expression for the effective diffusivity for Taylor–Aris dispersion in such a rivulet, and discuss in detail its different interpretations in the special case of a rivulet on a vertical substrate.

1. Introduction

One of the ongoing challenges in microfluidics is that of controlling and optimizing the transport (i.e. the mixing and dispersion) of solutes at small length scales and low Reynolds numbers (see, e.g. the reviews in [1–3]). The dispersion (i.e. the combined effect of advection and diffusion) of a solute in a steadily flowing fluid is a classical problem in fluid mechanics which arises in numerous practical situations (such as the spread of pollutants in rivers, chromatographic separation, and the transport of dissolved drugs in the bloodstream) and has been the subject of a huge body of theoretical and experimental research, the vast majority of it originating from the pioneering papers by Taylor [4,5] and Aris [6] published in this journal. The key insight of this pioneering work was that after a sufficiently long time the mean concentration of solute adopts a symmetric

THE ROYAL SOCIETY PUBLISHING

Ref. 37

THE JOURNAL OF CHEMICAL PHYSICS 139, 084101 (2013)

Aris-Taylor dispersion with drift and diffusion of particles on the tube wall

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A laminar stationary flow of viscous fluid in a cylindrical tube enhances the rate of diffusion of Brownian particles along the tube axis. This so-called Aris-Taylor dispersion is due to the fact that cumulative times, spent by a diffusing particle in layers of the fluid moving with different velocities, are random variables which depend on the realization of the particle stochastic trajectory in the radial direction. Conceptually similar increase of the diffusivity occurs when the particle randomly jumps between two states with different drift velocities. Here we develop a theory that contains both phenomena as special limiting cases. It is assumed (i) that the particle in the flow can reversibly bind to the tube wall, where it moves with a given drift velocity and diffusivity, and (ii) that the radial and longitudinal diffusivities of the particle in the flow may be different. We derive analytical expressions for the effective drift velocity and diffusivity of the particle, which show how these quantities depend on the geometric and kinetic parameters of the model. [http://dx.doi.org/10.1063/1.4818733]

I. INTRODUCTION

The increase of the diffusivity of Brownian particles due to a radial gradient of advection velocity (often referred to as the Aris-Taylor or shear dispersion[1–5]) is of a significant importance in a number of fields of science and technology covering many practical applications. Examples include chemical engineering (microfluidics,[4] chromatography,[5,6] heterogeneous catalysis[7]), biophysics (vascular flow,[7] airflow in lungs,[8] targeted drug delivery[9]), and transport processes in geophysical systems (capillary flows in fractures,[10] colloid filtration,[11] mixing in rivers[12]). Starting with the seminal works of Taylor,[13,14] who calculated the diffusivity of a passive tracer in the Poiseuille flow (laminar flow in a cylindrical tube), followed by a more rigorous derivation of Aris,[15] this problem has been in the focus of both theoretical and experimental studies for the last six decades. There is a vast amount of literature devoted to this subject (see Refs. 1–3, 16, and 17 and references therein). Although the Aris-Taylor dispersion is nowadays discussed in textbooks,[1,2,16,17] it is still the area of active research.[18–23]

The celebrated result obtained by Taylor[13,14] can be summarized as follows. Consider a laminar stationary flow of viscous fluid in a cylindrical tube of radius a (Fig. 1). The velocity profile of the Poiseuille flow is given by the well-known expression

$$v_f(r) = 2\overline{v}_f\left(1 - \frac{r^2}{a^2}\right), \tag{1.1}$$

where $\overline{v}_f$ is the velocity averaged over the tube cross-section, $\overline{v}_f = (2/a^2)\int_0^a v_f(r)r\,dr$. Taylor showed that the effective diffusivity of a point Brownian particle along the tube axis is given by

$$D_{\text{eff}} = D_f + \frac{\overline{v}_f^2 a^2}{48 D_f}, \tag{1.2}$$

where D_f is the particle diffusivity in the absence of the flow.

Since the pioneering work of Taylor this problem has been extended to cover more complicated settings including various geometrical complexities,[24,25] oscillating flows,[7,26] transient phenomena,[18] effects of chemical reactions,[27–29] and many others (see, for instance, books[1,2] and recent papers[30,31]). An important generalization of the problem is to account for the "effect of wall" (absorption and desorption, as well as diffusion of the particle on the wall). The "wall effect" is especially important for the design of microfluidic devices (so-called "Lab-on-a-Chip"[11,30]). It has been studied theoretically in a number of recent publications (see Refs. 20, 22, 27, 31, and 32 and references therein).

When a Brownian particle is advected by a laminar flow, its reversible binding to the tube wall can be described by the kinetic scheme

$$\text{flow} \underset{k_u}{\overset{\kappa}{\rightleftharpoons}} \text{wall}, \tag{1.3}$$

where κ and k_u are the intrinsic rate constants (see Fig. 1). Let p_f^{eq} and p_w^{eq} be the equilibrium probabilities of finding the particle on the wall and in the flow, $p_f^{\text{eq}} + p_w^{\text{eq}} = 1$. As follows from the principle of detailed balance the ratio of these probabilities is

$$\frac{p_w^{\text{eq}}}{p_f^{\text{eq}}} = \frac{2\kappa}{a k_u} = K, \tag{1.4}$$

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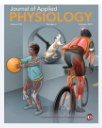
Ref. 38

ARTICLES

Measurement of axial diffusivities in a model of the bronchial airways

P. W. Scherer, L. H. Shendalman, N. M. Greene, and A. Bouhuys

01 APR 1975 // https://doi.org/10.1152/jappl.1975.38.4.719



Volume 38, Issue 4
April 1975
Pages 719-723

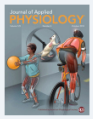
Values for the effective axial diffusivity D for laminar flow of a gas species in the bronchial airways have been obtained as a function of the mean axial gas velocity u by experiment measurements of benzene vapor dispersion in a five generation glass tube model of the bronchial tree. For both inspiration and expiration D is seen to be approximately a linear function of u over the range of Reynolds' numbers 30–2,000 corresponding to peak flows in bronchial generations 0–13 under resting breathing conditions. The diffusivity for expiration is seen to be approximately one-third that for inspiration due presumably to increased radial mixing at bifurcations during expiration. The effective diffusivities relative to the molecular diffusivity can be expressed by the formulas D/Dmol = 1 + 1.08 NPe for inspiration and D/Dmol = 1 + .37 N-Pe for expiration. These velocity dependent diffusivities help to explain the short transit times of gas boluses from mouth to alveoli and will aid in the analysis of airway gas mixing by mathematical transport equations.

Ref. 39

ARTICLES

Augmented diffusion in the airways can support pulmonary gas exchange

J. J. Fredberg



Volume 49, Issue 2
August 1980
Pages 232-238

Abstract

Bohn et al. (J Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48: 710-716, 1980) reported that paralyzed beagle dogs maintained normal gas exchange for 6 h or more when small tidal volumes at high breathing rates were maintained at the airway opening (15 ml tidal volume at 15 breaths/s). These tidal volumes were 25% of dead space and thereby were too small to permit convective gas exchange with pulmonary air spaces. I have used a semiempirical analysis to show that augmented diffusion in the central airways, akin to Taylor's turbulent dispersion (Proc. R. Soc. Ser. A 223: 446-468, 1954) combined with molecular diffusion in the periphery of the lung, can account for most if not all of the observed gas transport during small tidal volume, high-frequency ventilation. Ventilation efficiency (alveolar ventilation/minute ventilation) is approximately 2-5% and is insensitive to the combination of frequency and tidal volume giving rise to the minute ventilation.

Ref. 40

ELSEVIER

Respiration P

Volume 25, Issue 2, Novembe 157-173

Transport of H_2 and SF_6 in t

Ludovic M. Lacquet [a], Leo P. Van Der Linden [b], Manuel Paiva [a]

Abstract

The dead spaces for hydrogen and sulfur hexafluoride are predicted from the solution of a partial differential equation, applied to Weibel's morphometric data of the lung, and including longitudinal convection and diffusion coupled with instantaneous radial diffusion. Traces of H_2 and SF_6 were washed in and out of the lungs of two normal subjects. Dead spaces for both gases were calculated from the wash-out curves by a least squares analysis. Prediction and experiment agree in the case of H_2. The model overestimates the dead space for SF_6 particularly for large tidal volumes and for high breathing frequencies.

Several factors which can contribute to this disagreement are considered. From simulation experiments it is evident, that the dead space for SF_6 is highly sensitive to factors which influence molecular dispersion in the region of respiratory bronchioles. Cardiogenic mixing and some sort of flow-dependent mixing in this zone cannot be ruled out. However, the experimental data can also be explained by choosing another set of morphometric data for the alveolated airways.

Ref. 41

Mathematical Bic
Volume 29, Issues 3–4, 197(349

A theoretical discussion of diffusion and convection in the lung

David B. Chang, Steven M. Lewis, Allan C. Young *, †, ‡

Abstract

A differential equation is derived to describe the effects of diffusion and convection on gas concentrations in the lung. The terms in this equation are discussed. Attention is drawn to the effect of the changing cross-sectional area of airways. This leads to an effect called "pseudoconvection", which causes a peak in gas concentration to move toward the mouth. A Green's-function solution is presented for conditions of zero flow and end exponential growth of cross-sectional area. A similar differential equation is derived for total gas as a function of distance and time. For the static exponential lung model, a Green's function solution is derived. The effects of convective dispersion are discussed and found to be relatively minor over most of the respiratory tree at physiological flows. Finally, the effect of protrusions into a tube, such as alveolar walls in an alveolar duct down which a gas diffuses, is discussed, and an analytical expression is derived to describe their effect on the rate of diffusion.

Ref. 42

Respiration Physiology
Volume 29, Issue 1, February 1977, Pages 101-123

A computational model of pulmonary gas transport incorporating effective diffusion

A. Pack [2, 1], M.B. Hooper [3], W. Nixon [3], J.C. Taylor [4]

Abstract

A computational model of gas transport in the lung is described which remedies many of the deficiencies of previous models, as listed by Chang and Farhi (1973), in that it allows for fluctuating lung dimensions, gas exchange, simultaneous convection and diffusion, and the enhanced effective diffusion that occurs when convective flow is also present. The results of calculations using the model are presented, showing the maximum effect of Taylor diffusion. The actual magnitude of Taylor diffusion, suitably modified to allow for the disturbed conditions within the lung, is considered in the light of recent experiments.

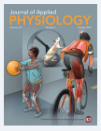
Ref. 43

ARTICLES

Penetration of inhaled He and SF6 into alveolar space at low tidal volumes

H. Worth, F. Adaro, and J. Piiper

01 SEP 1977 //



Volume 43, Issue 3
September 1977
Pages 403-408

Abstract

To study mixing of inspired gas with lung gas, penetration of simultaneously inspired helium (He) and sulfur hexafluoride (SF6) into alveolar space was determined in normal subjects at low tidal volumes (from 50 to 500 ml) and at varied lung volumes and speeds of inspiration/expiration. The volume of inspired gas reaching the alveolar space, termed alveolar-tidal volume, VTA, was calculated from preinspiratory lung volume, inspired volume, and inspired and expired alveolar test gas concentrations. The difference between the VTA values calculated for He and SF6, VTA(He) - VTA(SF6), was influenced by tidal volume, lung volume, and the speed of inspiration/expiration, but it was always positive. The results are qualitatively explainable on the basis of easier diffusive mixing of He in lung airways compared with SF6. Since Taylor dispersion would produce deeper penetration, and therefore higher VTA, for a less diffusible gas the results provide no evidence for its implication in pulmonary gas exchange.

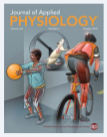
Ref. 44

ARTICLES

Effect of altered gas diffusivity on alveolar gas exchan theoretical study

W. Nixon, and A. Pack

01 JAN 1980 // h



Volume 48, Issue 1
January 1980
Pages 147-153

Abstract

Experimental studies have established that alveolar gas exchange is inversely relation to the molecular diffusivity of gas in the lung airways. The mechanism underlying this relationship is, however, unclear. To investigate this phenomenon, the conditions relevant to the experimental studies are simulated using a computational model of pulmonary gas transport. Results from these simulations suggest that the inverse relationship found experimentally can largely be explained on the basis of the intra-acinar stratification of blood flow and gas concentrations. Gas having a relatively low molecular diffusivity is not transported as far into the acinus as gas having a higher diffusivity. When these relative intra-acinar gas distributions interact with the blood flow distribution, which has been shown experimentally to be weighted towards the proximal alveoli, more gas exchange occurs in the low molecular diffusivity mixture. Consideration of the various other mechanisms that have been proposed to explain the experimental findings.he inverse dependence suggests that they are of little significance. In particular, our studies remove the need to invoke Taylor diffusion to explain the experimental findings.

Ref. 45

Respiration Physiology
Volume 12, Issue 3, August 1971, Pages 329-345

Diffusion equilibrium in the lungs examined by nodal analysis

Gordon Cumming, Keith Horsfield, Stuart B. Preston [1]

Abstract

The time course of gaseous diffusion in a model of the human lung has been investigated using the relaxation method of nodal analysis. The model of the lung used takes account of known information about alveolar geometry and airways branching, but the asymmetrical characteristics of bronchial branching have not been considered. Analysis has been done using different sets of boundary conditions — in the first an interface between inspired and residual gas has been instituted at two appropriate volumes within the lung, and in the second the interface has been moved into and out of the lung model whilst diffusion continued. The two boundary conditions give entirely different results in respect of the gradient of concentration within the alveolar gas. The analysis permits a precise definition in mathematical terms of dead space and this suggests a clinical application. The conclusion drawn from the analysis is that the computed time course of diffusive mixing in a given lung model, and its effects on the concentration gradients in the alveolar gas, are crucially dependent upon the boundary conditions employed. It is possible to obtain a horizontal or sloping concentration gradient at will by inserting appropriate boundary conditions. Both the anatomy of the terminal airways and the boundary conditions obtaining within the lungs must be accurately defined before a realistic mathematical analysis is possible. It is likely that no analysis yet published has satisfactorily defined these parameters.

Ref. 46

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 34, 1972

SIMULTANEOUS DIFFUSION AND CONVECTION IN SINGLE BREATH LUNG WASHOUT

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New Haven, Connecticut 06510

Two mathematical models of pulmonary single breath gas washout (one analytic, one numerical) are developed and their predictions compared with experimental data on human subjects. Weibel's 23 generation symmetric anatomical model is used as a guide to bronchial tree geometry. Experimental plots of nitrogen concentration versus volume expired, dead space versus breath holding time, and dead space versus tidal volume are compared with plots predicted by the models. Agreement is good. A plot of nitrogen concentration in the airways as predicted by the numerical model at different times during inhalation and exhalation of a single breath of oxygen is shown. Model predictions for changes in dead space with changes in washout gas and expiratory flow rate are discussed. Use of the analytic model for obtaining average values of the path length from mouth to alveoli in a given subject is discussed. To the extent of their agreement with experiment, the models provide a sound physical basis for the correlation of airway structure and function.

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Ref. 47

Gas transport in the human lung

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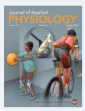

Volume 35, Issue 3
September 1973
Pages 401-410

PAIVA, MANUEL. *Gas transport in the human lung*. J. Appl. Physiol. 35(3): 401–410. 1973.—We have solved the transport equation in a model built from the anatomical data of Weibel. The transport equation (simultaneous diffusion and convection) can be solved numerically. Moreover, our formulation of the problem enables us to take into account the influence of the alveolar septa upon the diffusion rate. The solution of the transport equation can be verified experimentally by analysis of the nitrogen washout and particularly by the single-breath test. We have analyzed the solution of the transport equation as a function of the following factors: shape of the flow, tidal volume, and period of the respiratory movements. We have shown the incidence of the ventilation distribution in these curves. The analysis of the solutions of our equation leads us to the conclusion that: *1*) during inspiration the convection movement favors the stratification which exists in the very last generations and favors its elimination during expiration, the stratification being then entirely negligible at the end of the expiration; and *2*) the final part of the classical single-breath test (alveolar plateau) is due essentially to phenomena other than the gas transport by diffusion and convection in the series spaces.

transport equation; nitrogen washout single-breath test; stratified inhomogeneity; alveolar plateau; distribution of ventilation; alveolar septa

RECENTLY THERE HAVE BEEN several attempts to solve the diffusion equation in models approaching the pulmonary structure. The aim of these papers was often to elucidate the controversy about whether inhomogeneity of alveolar gas is stratified, or regional, or both, and to elucidate the meaning of the plateau in the single-breath test.

Krogh and Lindhard (16) observed, half a century ago, that after one inspiration of a gas, its distribution in the alveolar air is not uniform. Rauwerda (28) basing his study on calculations made in a conical model concluded that stratified inhomogeneity was not significant after an inspired breath and that the alveolar plateau was due to the distribution of the ventilation (regional inhomogeneity).

Cumming and associates (1) have analyzed solutions of the diffusion equation in several conical models and have concluded that stratified inhomogeneity within the lung was likely. Later on, Cumming et al. (2) concluded that the alveolar plateau results in the main from stratified inhomogeneity. La Force and Lewis (17) were the first to build a model whose structure corresponds closely to the anatomical structure of the lung, or at least to the anatomical description of Weibel (31). They concluded that no significant stratification exists. It is evident that there always exists a certain stratification in the bronchial tree because neither the period of respiratory cycle nor the diffusion coefficient is infinite. We have decided that the stratification is negligible if the difference in fractional concentration between the beginning of the 20th and the end of the 23rd generation of the Weibel model is less than 2%. (We attribute concentration 1 to inspired gases and concentration 0 to residual gases.)

In the previous studies two important factors have been neglected, as has been pointed out by Piiper and Scheid (27). The first consists not taking into account that convection and diffusion occur simultaneously in the movement of gases. The second is failure to consider the role played by the alveolar septa in the stochastic movement of the molecular diffusion. Simultaneously and independently, Cumming et al. (3), on the one hand, and Scherer et al. (29), on the other, and we ourselves (21–23, 26) have built models which take these two factors into account. We will summarize in the APPENDIX their difference from the mathematical point of view and will merely point out here that Scherer et al. have by different reasoning arrived at a transport equation equivalent to ours. The main object of their paper was not to elucidate problems of pulmonary physiology. However, it appears from the analysis of the published figures (we only refer to the numerical model presented), and particularly that of the single-breath test, that there is a surprisingly good agreement with our previous conclusions (22, 23) and those of this paper. In both studies the slope of the alveolar plateau is negligible. Cumming, Horsfield, and Preston (3) now come to the conclusion that diffusion plays no part in the production of the experimentally observed slope of the plateau and on this point they join La Force and Lewis (17), but they again found a slope of 1.1% if the computations are made with a moving interface. It is therefore the convection term which again introduces a non-negligible slope in the alveolar plateau.

We think, however, that it is essential to separate two distinct phenomena: one, the stratification, the other, the alveolar plateau. It would only be possible to calculate the slope of the alveolar plateau from the stratification if there was no diffusion during expiration. Thus it is that the mere solution of a diffusion equation can show a nonnegligible stratification without there being a nonnegligible slope of the alveolar plateau. We have previously solved the diffusion equation (26) with boundary conditions similar to those of La Force and Lewis (17), but by introducing the delay due to the existence of the alveolar septa. Contrary to La Force and Lewis (17) and to Cumming et al. (3), we have found a nonnegligible stratification which agrees qualitatively with the first results of Cumming and co-workers (1). However,

Ref. 48

Respiration Physiology
Volume 18, Issue 3, September 1973, Pages 386-397
ELSEVIER

A model study of gas diffusion in alveolar sacs ☆

Hsin-Kang, Chang, Ralph T. Cheng, Leon E. Farhi

Abstract

Models of alveolar sacs with individual alveoli attached have been studied for their diffusion properties Radial as well as axial diffusion are considered. The axisymmetric diffusion equation is solved numerically by finite element method.

Paramciric studies are made to determine the effects of the individual alveoli on the equilibrium time. For the models used, the results differ by about 70%. The diffusion equilibrium time for an interface 0.48 cm away from the terminal alveolar wall is between 2.4 and 3.1 sec, for the models used, which are likely to be lower estimates than the real case. Based on these numbers and arguments, it is felt that the stratification of alveolar air during quiet breathing is a definite possibility.

Ref. 49

BULLETIN OF
MATHEMATICAL BIOLOGY
VOLUME 36, 1974

TRANSPORT OF O_2 ALONG A MODEL PATHWAY THROUGH THE RESPIRATORY REGION OF THE LUNG

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University of Queensland, Australia

A pathway through the system of branching in the respiratory region of the lung is modelled by a circular cylinder, closed at one end, with partitions which define the component respiratory units. In this model the transport of O_2 during inspiration, generated by diffusion is compared with that produced by diffusion together with convection and the importance of convection in the respiratory region in promoting oxygen uptake at the alveolar wall is discussed. For this discussion it is only necessary to consider inspiration. The equations are solved numerically for flow rates of 10, 85 and 200 liters/min. O_2 uptake at the wall and curves of constant O_2 concentration are shown to illustrate the influence of convection. It is found that after a 2 sec inspiration from an O_2 tension of 98 mm Hg and a lung volume of 2300 ml, convection is about 12 per cent as important as diffusion at a flow rate of 85 liters/min, whereas at 10 liters/min convection is only about 0.4 per cent as important as diffusion.

I. Introduction. *1. Physiological Considerations.* While gas transport in the lung occurs by both convection and diffusion simultaneously, the relative importance of these two mechanisms varies throughout the lung. Convection dominates in the larger airways (trachea and bronchi) and mixing occurs in the secondary flows at branchings. As inspired gases move further into the lung, total cross-sectional area increases, velocities correspondingly decrease, and diffusion becomes increasingly important until finally, in the alveoli, diffusion dominates completely. Gas exchange occurs at the alveolar walls; O_2 diffuses through the walls into the blood while CO_2 diffuses out of the blood into the alveoli.

The extent to which bulk flow contributes to the transport of gas from inhaled

Ref. 50

BULLETIN OF
MATHEMATICAL BIOLOGY
VOLUME 37, 1975

LUNG GAS MIXING DURING EXPIRATION FOLLOWING AN INSPIRATION OF AIR

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University of Queensland,
Australia

The airway system of the lung from the mouth to the pulmonary membrane is modelled by matching a cylindrical model of a pathway through the respiratory region of the lung onto a one-dimensional trumpet model for the conducting airways. The concentration of O_2 in gas expired from this model airway system is investigated following an inspiration of air at two different flow rates (10 litres/min and 85 litres/min). In each case, expiration occurs at the same constant flow rate as that during the previous inspiration. The inspirations, which are studied in an earlier paper, are each of 2 sec duration and begin at a lung volume of 2300 ml and a lung oxygen tension of 98 mm Hg. The equations are solved numerically and plots of expired O_2 concentration against time and against expired volume are shown. It is found that at 85 litres/min, gas mixing in the lung is complete after about 0.7 sec of expiration whereas at 10 litres/min, about 2.6 sec of expiration is required for complete equilibration. It is suggested that the experimental alveolar plateau slope is not in general caused by a slow approach to equilibrium of gas concentrations; except at very low flow rates in the early part of the concentration/time plateau.

1. Introduction. In 1917, Krogh and Lindhard observed that, after a single inspiration of a gas, the concentration of the gas in the latter part of the subsequent expiration continued to decrease—a phenomenon which is still not completely understood. Krogh and Lindhard contended that, while new air is entering the lung, there are always longitudinal concentration differences in the terminal airways (stratified inhomogeneity) and that these differences are reflected at the mouth during the following expiration.

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Ref. 51

BULLETIN OF
MATHEMATICAL BIOLOGY
VOLUME 39, 1977

THE INFLUENCE OF GAS EXCHANGE ON LUNG GAS CONCENTRATIONS DURING AIR BREATHING

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New South Wales, Australia

A model study is made of the contribution that continuing respiratory gas exchange makes to the alveolar plateau slope for O_2 during air breathing. Calculations in the model of the O_2 concentration appearing at the mouth during expiration, are performed for single breaths of air at constant flow rates 18 litres/min and 120 litres/min. At 18 litres/min the breathing period is 5 sec, the initial lung volume is 2300 ml, and the O_2 uptake rate is 300 ml STPD/min; whereas at 120 litres/min these parameters are 4 sec, 1200 ml, and 1800 ml STPD/min respectively. In each case the initial lung O_2 tension is taken to be 98 mm Hg. It is found that at 18 litres/min, the O_2 concentration difference on the alveolar plateau over the last second of expiration is 0.4 mm Hg when gas exchange is omitted and 1.2 mm Hg when gas exchange is included in the model. At 120 litres/min, this difference is zero and 5.0 mm Hg respectively. The gas exchange component predicted from a corresponding well-mixed compartment model is the same at 18 litres/min (0.8 mm Hg) but is 6.0 mm Hg at 120 litres/min.

1. Introduction. After an inspiration of air, the concentration of O_2 appearing at the mouth during the subsequent expiration does not approach some uniform value but continues to decrease. Similar behaviour is observed for a foreign, insoluble gas following inspiration of a gas mixture containing it. In the single-breath N_2 washout experiment, the N_2 concentration at the mouth is measured following an inspiration of pure O_2. It rises rapidly to a plateau, then continues to increase gradually. Since end expiration gas comes from the alveoli, the corresponding part of a concentration curve is called the alveolar plateau for that gas species.

A considerable amount of attention has been focused on mechanisms

Ref. 52

Respiration Physiology
Volume 44, Issue 3, June 1981, Pages 325-337

The anatomical basis for the sloping N_2 plateau ☆

M. Paiva [a, b], L.A. Engel [a, b]

Abstract

We examined the influence of asymmetry on the interaction of convection and gas-phase diffusion within the acinus of the lung. Single breaths of O_2 were simulated by solving a differential equation for gas transport in two trumpet shaped units which were joined at a branch point and whose relative lengths and volumes were made to vary. Despite synchronous bulk flow to and from the units, in proportion to their relative volumes, the shorter unit always reached a higher O_2 concentration (F_{O_2}) at end inspiration. Interdependence of gas transport at the branch point resulted in a falling F_{O_2} within the shorter unit during expiration. The F_{O_2} at the exit of the model therefore decreased progressively throught expiration, simulating a sloping alveolar plateau. The simulations suggest that despite the relatively short distances separating parallel intra-acinar pathways, convective-diffusive interactions in the presence of asymmetry may produce substantial inhomogeneity in alveolar gas concentrations. Furthermore, the slope of the N_2 plateau in the normal mammalian lung is explicable on the basis of the asymmetrical airway anatomy and well defined physical processes.

Ref. 53

THE THEORY AND APPLICATIONS OF THE EXCHANGE OF INERT GAS AT THE LUNGS AND TISSUES[1]

SEYMOUR S. KETY, M.D.

From the Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania

The respiratory and circulatory systems of the higher animals constitute a single homeostatic complex whose chief function is the maintenance of an optimal molecular concentration of oxygen and carbon dioxide about each cell. This is accomplished by a highly effective combination of physical diffusion and transport together with reversible chemical reactions. The process of diffusion, which alone is sufficient for the metabolic exchange of unicellular organisms, operates in higher animals only across the microscopic spaces between the blood and pulmonary alveoli or peripheral cells. Between the lungs and the body tissues the molecules of gas are transported by the circulating blood in physical solution and, in the case of oxygen and carbon dioxide, in loose chemical combination with certain blood constituents.

The relative magnitudes and time relationships of these various processes are not obvious in the steady state of metabolic exchange. They become apparent, however, when a new molecular species is introduced into the atmosphere which the organism breathes, and, if the new substance happens to be an inert gas, its behavior in the organism may be explained and predicted on the basis of relatively simple physical laws. For the purpose of this discussion an inert gas will be defined as one which dissolves in the blood and tissues in a manner that can be described by Henry's Law, which suffers no change in chemical identity during its passage through the organism, and which is therefore quantitatively recoverable from the organism at any time (54, 105). This definition would include those volatile anesthetic agents which are not chemically altered in the body even though they produce definite physiological effects.

When an inert gas in abruptly introduced at a constant partial pressure into the inspired air, the tissues of the body do not suddenly acquire the gas at this partial pressure. A number of physical processes intervene, each with its own time rate of change, to delay the eventual saturation of the tissues. First, by means of pulmonary ventilation the gas is inspired, diluted with the functional residual air and distributed to the alveolar membrane. Here diffusion occurs and alveolar gas is equilibrated with pulmonary blood which is then distributed via the peripheral arteries to the individual tissues. A second diffusion step now occurs across the capillary membrane, interstitial fluid and cellular membrane and through the intracellular fluid itself. The venous blood from all the tissues returns to the lungs carrying some fraction of its original gas concentration which is thus contributed to the equilibration process occurring at the alveoli. In this manner the alveolar, arterial, tissue and venous tensions of the inert

[1] Original work reported in this review was supported, in part, by a grant from the National Heart Institute, U. S. Public Health Service.

1

Ref. 54

Respiration Physiology
Volume 3, Issue 1, August 1967, Pages 1-11

Elimination of inert gas by the lung ☆

L.E. Farhi

Abstract

When an inert gas G which is not part of the inspirate is present in the mixed venous blood at a partial pressure PV_G, the partial pressure of G in an alveolus, Pa_G, or in the blood returning from this alveolus will be governed by several factors. These are λ, the Ostwald partition coefficient for that gas, A, the ventilation of the alveolus, and , its perfusion, according to the equation $\mathrm{Pa} = \mathrm{rmP\bar{r}mV} \cdot \lambda/\lambda + \mathrm{Va/Q}$. The clearance of such a gas, Cl, is given by (A .)/(A + λ), indicating that when A/ is much higher than λ, the clearance is dictated mainly by the ventilation, while at A/ considerably lower than γ, the perfusion is the determining factor. The fractional elimination of the gas is given by Cl/, and increases with A/ but decreases with an increase in λ. As a result, the lung acts as a filter, retaining selectively the gases having a high solubility. When chemical transport of O_2 and CO_2 is taken into account, the behavior of these gases follows the same general pattern of inert gas exchange.

Ref. 56

Respiration Physiology
Volume 13, Issue 3, December 1971, Pages 292-304

Oncepts and basic quantities in gas exchange physiology

J. Piiper [a, d, b, c], P. Dejours [a, b, c], P. Haab [a, b, c], H. Rahn [a, b, c]

Abstract

1. 1) The amount of a gas species is dimensionally considered not as a volume, but as a quantity of substance M, expressed in moles, but also, less appropriately, in volumes stpd. The transfer rate of a gas species (), with dimension (quantity of substance)·(time)$^{-1}$, may thereby be clearly distinguished from the volume flow rate () which has the dimension (volume).(time)$^{-1}$.

2. 2) The concentration (C), defined as quantity of substance per volume, is used for all media (blood, water and gas). For the gas phase, C is proportional to the fractional concentration, F, and is dependent on temperature, pressure and water vapor pressure.

3. 3) For the increment of concentration in liquid or gas phase of a gas species per increment of its partial pressure, $\mathrm{sol}\Delta\mathrm{C}\Delta\mathrm{P}$, the term "capacitance coefficient" is proposed. In respect to gas transfer, it is a measure of the carrying capacity of a medium for a given gas species. It is usefully applied not only to water and to blood (slope of CO_2 and O_2 dissociation curves), but also to the gas phase, for which it is identical for all ideal gases at a given temperature.

   Some basic equations of gas transfer by blood, air and water convection and by diffusion have been rewritten according to these concepts.

Ref. 57

JOURNAL OF APPLIED PHYSIOLOGY
Vol. 36, No. 5, May 1974. Printed in U.S.A.

Measurement of continuous distributions of ventilation-perfusion ratios: theory

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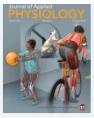

Volume 36, Issue 5
May 1974
Pages 588-599

WAGNER, PETER D., HERBERT A. SALTZMAN, AND JOHN B. WEST. *Measurement of continuous distributions of ventilation-perfusion ratios: theory.* J. Appl. Physiol. 36(5): 588–599. 1974.—Most previous descriptions of the distribution of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) divide the lungs into only two or three uniform compartments. However, an analysis which would result in definition of the position, shape, and dispersion of the distribution would be more realistic. We describe here such a technique, applicable both in health and disease, in which the characteristics of distributions containing up to three modes can be determined. In particular, areas with low but finite $\dot{V}_A/\dot{Q}$ ratios are separated from areas whose $\dot{V}_A/\dot{Q}$ ratio is zero (shunt), and regions with high $\dot{V}_A/\dot{Q}$ ratios are differentiated from regions that are unperfused (dead space). To perform the measurement, dextrose solution or saline is equilibrated with a mixture of several gases of different solubilities and then infused into a vein. After a steady state has been established, the concentrations of each gas are measured in the mixed arterial blood and mixed expired gas. The curve relating arterial concentration and solubility is transformed into a virtually continuous distribution of blood flow against $\dot{V}_A/\dot{Q}$, using techniques of numerical analysis. The relation between expired concentration and solubility is similarly converted into the distribution of ventilation. The numerical analysis technique has been tested against many artificial distributions of $\dot{V}_A/\dot{Q}$ ratios and these have all been accurately recovered.

blood flow; gas exchange; hypoxemia; inert gas

IT IS GENERALLY ACCEPTED that the major cause of hypoxemia in most types of lung disease is the existence of an uneven distribution of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratios. However, in spite of a large variety of experimental approaches, the shapes of the distributions of $\dot{V}_A/\dot{Q}$ ratios remain virtually unknown, both in health and disease.

Most investigators have characterized the lung as if it consisted of two or three compartments. Thus, Riley and his colleagues (27, 28) used a combination of P_{O_2} and P_{CO_2} in arterial blood and mixed expired gas to divide the lung into three functional compartments: one ideal, one unventilated, and the third unperfused. Briscoe and his coworkers (3–5) divided the lung into two ventilated compartments on the basis of gas washout rate, and then calculated the blood flow to each compartment. A related method was described by Finley (10). Lenfant (17) measured the alveolar-arterial difference for O_2, CO_2, and N_2 with increasing $F_{I_{O_2}}$ and proposed the existence of $\dot{V}_A/\dot{Q}$ distributions with two modes, the majority of alveoli having a $\dot{V}_A/\dot{Q}$ ratio slightly above the mean, and the rest having a very low $\dot{V}_A/\dot{Q}$ ratio.

Lenfant and Okubo (19, 25) have derived continuous distributions of $\dot{V}_A/\dot{Q}$ ratios, using the change in arterial O_2 saturation with increasing $F_{I_{O_2}}$ during a nitrogen washout. Their method has been criticized on theoretical grounds (26), and in addition the distributions were assumed not to change with $F_{I_{O_2}}$, which as Lenfant (18) showed may be unjustified and lead to errors. It is also possible that when room air is breathed, some of the hypoxemia results from diffusion impairment rather than $\dot{V}_A/\dot{Q}$ inequality.

If inert gas techniques are used in place of the oxygen methods described, both of the above-mentioned objections are circumvented. Kety (13), Norhren (24), and Farhi (9) have given theoretical equations relating inert gas exchange in the lungs to the ventilation-perfusion ratio and the solubility of the gas. Measurements with several foreign inert gases such as krypton and xenon (29) and methane, ethane, and nitrous oxide (34) have been used to gain information about distributions of $\dot{V}_A/\dot{Q}$ ratios. However, these analyses, as with the oxygen methods, have been limited to a small number of compartments.

Measurements with radioactive tracers (2, 6, 14, 22, 32) have yielded useful topographical information about ventilation and blood flow in normal lungs. However, even in normal, but especially in diseased lungs, these techniques lack resolution because of the large tissue volumes that must be averaged. It is unlikely that the differences of ventilation and blood flow detected by external counters in patients with lung disease throw much light on the $\dot{V}_A/\dot{Q}$ distributions responsible for their impaired gas exchange.

This paper describes a method for determining virtually continuous distributions of $\dot{V}_A/\dot{Q}$ ratios. The resolution of the technique is sufficient to describe smooth distributions containing blood flow to unventilated regions (shunt), ventilation to unperfused regions (dead space), and up to three additional modes over the range of finite $\dot{V}_A/\dot{Q}$ ratios. In particular, areas whose $\dot{V}_A/\dot{Q}$ ratios are low can be separated from unventilated regions and those whose $\dot{V}_A/\dot{Q}$ ratios are high can similarly be distinguished from unperfused areas. The technique has been developed using inert gases as the forcing function, both because of the simple relationship governing inert gas exchange, and because of the objections to the oxygen method outlined above.

Ref. 58

Continuous Distributions of Ventilation-Perfusion Ratios in Normal Subjects Breathing Air and 100% O_2

PETER D. WAGNER, RAYMOND B. LARAVUSO, RICHARD R. UHL, and JOHN B. WEST

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ABSTRACT A new method has been developed for measuring virtually continuous distributions of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) based on the steady-state elimination of six gases of different solubilities. The method is applied here to 12 normal subjects, aged 21–60. In nine, the distributions were compared breathing air and 100% oxygen, while in the remaining three, effects of changes in posture were examined. In four young semirecumbent subjects (ages 21–24) the distributions of blood flow and ventilation with respect to $\dot{V}_A/\dot{Q}$ were virtually log-normal with little dispersion (mean log standard deviations 0.43 and 0.35, respectively). The 95.5% range of both blood flow and ventilation was from $\dot{V}_A/\dot{Q}$ ratios of 0.3–2.1, and there was no intrapulmonary shunt ($\dot{V}_A/\dot{Q}$ of 0). On breathing oxygen, a shunt developed in three of these subjects, the mean value being 0.5% of the cardiac output. The five older subjects (ages 39–60) had broader distributions (mean log standard deviations, 0.76 and 0.44) containing areas with $\dot{V}_A/\dot{Q}$ ratios in the range 0.01–0.1 in three subjects. As for the young subjects, there was no shunt breathing air, but all five developed a shunt breathing oxygen (mean value 3.2%), and in one the value was 10.7%. Postural changes were generally those expected from the known effects of gravity, with more ventilation to high $\dot{V}_A/\dot{Q}$ areas when the subjects were erect than supine. Measurements of the shunt while breathing oxygen, the Bohr CO_2 dead space, and the alveolar-arterial oxygen difference were all consistent with the observed distributions. Since the method involves only a short infusion of dissolved inert gases, sampling of arterial blood and expired gas, and measurement of cardiac output and minute ventilation, we conclude that it is well suited to the investigation of pulmonary gas exchange in man.

INTRODUCTION

It has been known for many years that the distribution of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) is uneven in the lungs of normal subjects. The work of Martin, Cline, and Marshall (1) in 1953 and of Mattson and Carlens (2) in 1955 demonstrated interlobar differences in O_2 and CO_2 concentrations best explained by regional differences in ventilation and blood flow. Measurements using radioactive gases (3) demonstrated uneveness of both ventilation and blood flow topographically from apex to base, and indicated a range of $\dot{V}_A/\dot{Q}$ of from approximately 3 at the apex to 0.6 at the base in 16 seated normal volunteers. Since external counting methods cannot cover all regions of the lungs, and in addition represent averages in those areas within the counting fields, this range of $\dot{V}_A/\dot{Q}$ is likely to be an underestimate of the actual degree of ventilation-perfusion inequality. Thus radioactive gas measurements do not permit accurate definition of the shape, position, or dispersion of the distribution of $\dot{V}_A/\dot{Q}$ in normal subjects, and certainly in lung disease where the inequality is more marked, external counting gives little information on the distribution.

Several workers, notably Riley, Cournand, and Donald (4, 5) and Briscoe (6) have developed methods for quantifying the degree of $\dot{V}_A/\dot{Q}$ inequality in terms of two or three parallel $\dot{V}_A/\dot{Q}$ compartments. Riley and Cournand, for example, divided the lungs into three units on the basis of the arterial and expired pressures of O_2 and CO_2. One unit was unventilated, one unperfused, and the third was the ideal compartment. The amount of blood flow in the unventilated unit was termed venous admixture and the ventilation in the unperfused unit was called physiological dead space,

This work was presented in part at the national meeting of the Federation of American Societies for Experimental Biology, April 1973.
Received for publication 30 November 1973 and in revised form 18 February 1974.

Ref. 61

Respiration Physiology
Volume 35, Issue 1, October 1978, Pages 27-42

Analysis of the effects of pulsatile capillary blood flow and volume on gas exchange ☆

A. Bidani [a, b, 3], R.W. Flumerfelt [a, b], E.D. Crandall [a, b] 2

Abstract

Blood flow into the pulmonary capillaries and the volume of blood within the capillary bed are both pulsatile with the cardiac cycle. We have developed a quantitative model of diffusional gas exchange in the lung to investigate the effects of coupling between these tow time-varying parameters on lung O_2 and CO_2 exchange. For normal man breathing room air at rest, the computed results agree well with previous predictions for the constant flow and volume case, and for the case of pulsatile flow alone. When coupled time-varying pulmonary capillary blood flow and volume are included, using the best data available in the literature to define these parameters, diffusional O_2 exchange is improved over the cases of pulsatile flow or volume alone, and closely approximates that obtained for hypothetical constant flow and volume case. CO_2 exchanges, O_2 exchange during hypoxia, are not affected by pulsatile flow and/or volume. These results suggest that O_2 exchange is efficient in the presence of coupled blood flow and blood volume pulsations as they exist in the lung capillaries. and that these conditions may be optima lfor gas exchange under certain physiological (or pathological) conditions.

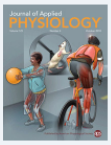
Ref. 63

ARTICLES

A method for dealing with data concerning uneven ventilation of the lung and its effects on blood gas transfer

William A. Briscoe

01 MAY 1959 //



Volume 14, Issue 3
May 1959
Pages 291-298

Abstract

This is a consideration of the relationships between the uneven ventilation of the lung and the arterial oxygen saturation and CO_2 tension. In the simplest case, the lung is considered to contain only two differently ventilated and perfused components. Graphic methods are developed for dealing with situations of this type and illustrated by application to the data obtained in a normal subject. Some of the methods outlined here can be applied in situations where the lung is composed of three or more differently ventilated and perfused components. In the normal subject considered here, the uneven ventilation of the lung is compatible with A-a gradients of 6 and 0.8 mm for O2 and CO2, respectively.

Submitted on October 3, 1958

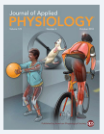
Ref. 64

ARTICLES

Effect of intrapulmonary hematocrit maldistribution on O2, CO2, and inert gas exchange

I. H. Young, and P. D. Wagner

01 FEB 1979 // I



Volume 46, Issue 2
February 1979
Pages 240-248

Abstract

The potential effect of intrapulmonary variations in hematocrit on gas exchange has been studied in theoretical models of the lung containing maldistribution of both hematocrit (Hct) and ventilation-perfusion (VA/Q) ratio. Hematocrit inequality enhanced gas exchange when units of low VA/Q were given a low Hct, arterial PO2 rising by as much as 14 Torr and PCO2 falling by up to 2 Torr depending on the particular distributions of Hct and VA/Q, whereas gas exchange was depressed when units of low VA/Q had a high Hct. After measuring inert gas solubilities in both dog and human blood of different Hct, the effect of Hct inequality on inert gas exchange was similarly assessed. Solubility was found to increase with HCT for less soluble gases. Because of this, conditions for enhancement of inert and O2 exchange by HCt inequality coincided, and it was found that in general the effects on O2 and inert gas transfer were quantitatively internally consistent. Even when Hct inequality was extreme, the resulting perturbation of inert gas concentrations was sufficiently small that the main features of the recovered VA/Q distributions were unaltered.

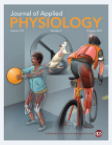
Ref. 65

ARTICLES

Effects of pH and SO2 on solubility coefficients of inert gases in human whole blood

K. Yamaguchi, M. Mori, A. Kawai, K. Asano, T. Takasugi, A. Umeda, T. Kawashiro, and T. Yokoyama

01 FEB 1993 // I

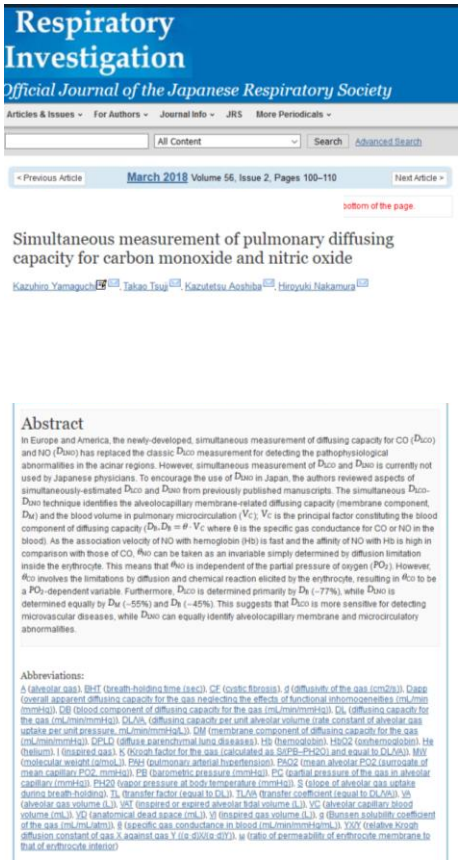


Volume 74, Issue 2
February 1993
Pages 643-649

Abstract

We systematically investigated the quantitative importance of pH and O2 saturation (SO2) of hemoglobin on the solubility coefficients (alpha) for six inert gases: sulfur hexafluoride, N2, ethane, cyclopropane, halothane, and diethyl ether. Measurements of alpha were made at 37 degrees C with SO2 of 0–1.0 and pH of 7.2–7.7 by use of whole blood obtained from three healthy subjects. No significant dependence of alpha on pH was demonstrated for sulfur hexafluoride, N2, halothane, or diethyl ether, but an appreciable augmentation of alpha with increasing pH was found for ethane and cyclopropane. No alpha value obtained for oxygenated blood differed statistically from that for deoxygenated blood. In addition to the basic findings on the effects of pH on alpha values of ethane and cyclopropane with the multiple inert gas elimination technique (data obtained from 22 patients with either interstitial pneumonia or chronic obstructive pulmonary disease), we also found that dependence of alpha on blood pH exerted no significant influence on the recovery of ventilation-perfusion distribution in the lung. We concluded that: 1) pH plays an appreciable role in determining gas solubilities in blood, 2) SO2 is not a decisive factor for gas solubilities in blood, and 3) the influence of various pH values in pulmonary capillaries on inert gas exchange is negligible.

Ref. 66



Respiratory Investigation
Official Journal of the Japanese Respiratory Society
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< Previous Article · March 2018 Volume 56, Issue 2, Pages 100–110 · Next Article >
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Simultaneous measurement of pulmonary diffusing capacity for carbon monoxide and nitric oxide

Kazuhiro Yamaguchi, Takao Tsuji, Kazutetsu Aoshiba, Hiroyuki Nakamura

Abstract

In Europe and America, the newly-developed, simultaneous measurement of diffusing capacity for CO (D_{LCO}) and NO (D_{NO}) has replaced the classic D_{LCO} measurement for detecting the pathophysiological abnormalities in the acinar regions. However, simultaneous measurement of D_{LCO} and D_{NO} is currently not used by Japanese physicians. To encourage the use of D_{NO} in Japan, the authors reviewed aspects of simultaneously-estimated D_{LCO} and D_{NO} from previously published manuscripts. The simultaneous D_{LCO}-D_{NO} technique identifies the alveolocapillary membrane-related diffusing capacity (membrane component, D_M) and the blood volume in pulmonary microcirculation (V_C); V_C is the principal factor constituting the blood component of diffusing capacity (D_B, $D_B = \theta \cdot V_C$ where θ is the specific gas conductance for CO or NO in the blood). As the association velocity of NO with hemoglobin (Hb) is fast and the affinity of NO with Hb is high in comparison with those of CO, θ_{NO} can be taken as an invariable simply determined by diffusion limitation inside the erythrocyte. This means that θ_{NO} is independent of the partial pressure of oxygen (PO_2). However, θ_{CO} involves the limitations by diffusion and chemical reaction elicited by the erythrocyte, resulting in θ_{CO} to be a PO_2-dependent variable. Furthermore, D_{LCO} is determined primarily by D_B (~77%), while D_{NO} is determined equally by D_M (~55%) and D_B (~45%). This suggests that D_{LCO} is more sensitive for detecting microvascular diseases, while D_{NO} can equally identify alveolocapillary membrane and microcirculatory abnormalities.

Abbreviations:

A (alveolar gas), BHT (breath-holding time (sec)), CF (cystic fibrosis), d (diffusivity of the gas (cm2/s)), Dapp (overall apparent diffusing capacity for the gas neglecting the effects of functional inhomogeneities (mL/min/mmHg)), DB (blood component of diffusing capacity for the gas (mL/min/mmHg)), DL (diffusing capacity for the gas (mL/min/mmHg)), DLVA (diffusing capacity per unit alveolar volume (rate constant of alveolar gas uptake per unit pressure, mL/min/mmHg/L)), DM (membrane component of diffusing capacity for the gas (mL/min/mmHg)), DPLD (diffuse parenchymal lung diseases), Hb (hemoglobin), HbO2 (oxihemoglobin), He (helium), I (inspired gas), k (Krogh factor for the gas (calculated as S/PB–PH2O) and equal to DL/VA), MW (molecular weight (g/mol)), PAH (pulmonary arterial hypertension), PAO2 (mean alveolar PO2 (surrogate of mean capillary PO2, mmHg)), PB (barometric pressure (mmHg)), PC (partial pressure of the gas in alveolar capillary (mmHg)), PH2O (vapor pressure at body temperature (mmHg)), S (slope of alveolar gas uptake during breath-holding), TL (transfer factor (equal to DL)), TLVA (transfer coefficient (equal to DL/VA)), VA (alveolar gas volume (L)), VAT (inspired or expired alveolar tidal volume (L)), VC (alveolar capillary blood volume (mL)), VD (anatomical dead space (mL)), VI (inspired gas volume (L)), α (Bunsen solubility coefficient of the gas (mL/mL/atm)), θ (specific gas conductance in blood (mL/min/mmHg/mL)), YXY (relative Krogh diffusion constant of gas X against gas Y ((α·dX/(α·dY)), ω (ratio of permeability of erythrocyte membrane to that of erythrocyte interior)

Ref. 67

ELSEVIER

Respiration Physiology

Volume 98, Issue 2, October 1994, Pages 165-177

Ventilation-perfusion inequality and diffusion impairment in acutely injured lungs

Kazuhiro Yamaguchi, Masaaki Mori, Akira Kawai, Tomoaki Takasugi, Kochiro Asano, Yoshitaka Oyamada, Takuya Aoki, Hirofumi Fujita, Yukio Suzuki, Fumihiro Yamasawa, Takeo Kawashiro

Abstract

To assess the significant role of diffusion impairment and its unequal distribution in acutely injured lungs with alveolar flooding, oleic acid was intravenously injected into twenty-five mongrel dogs. The animals were divided into two groups, A and B. 0.1% CO in air was delivered, as an inspired gas, to the animals of group A. Simultaneously, saline containing a trace amount of six foreign inert gases was infused through a peripheral vein. While allowing the animals in group B to breathe air, saline containing ethylene, acetylene and freon 22 was infused. After injection of oleic acid, group A revealed increase in intrapulmonary shunt accompanied by a marked broadening of ventilation-perfusion ($\dot{V}A/\dot{Q}$) and diffusing capacity-perfusion ($G/\dot{Q}$) distributions. A considerable amount of total cardiac output was received by the lung areas with low $G/\dot{Q}$ ratios where significant diffusion limitation was predicted to occur. Group B showed that excretion of freon 22 (gas with lower diffusivity) in injured lungs was considerably distorted as compared to those of ethylene and acetylene (gases with higher diffusivities), again ascertaining the importance of diffusion limitation in lungs with exudate in alveolar regions.

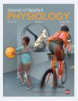
Ref. 68

ARTICLES

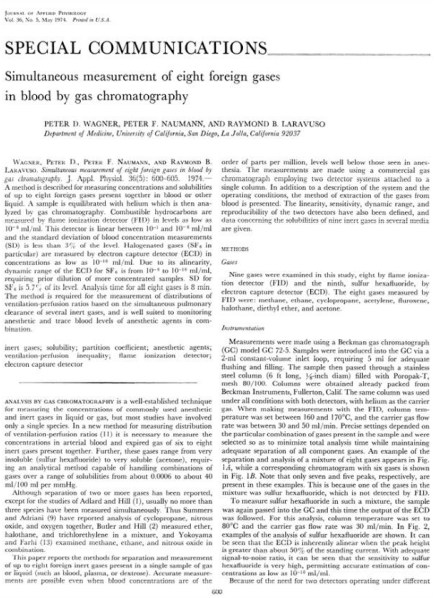
Simultaneous measurement of eight foreign gases in blood by gas chromatography

P. D. Wagner, P. F. Naumann, and R. B. Laravuso

01 MAY 1974 // htt



Volume 36, Issue 5
May 1974
Pages 600-605



SPECIAL COMMUNICATIONS

Simultaneous measurement of eight foreign gases in blood by gas chromatography

PETER D. WAGNER, PETER F. NAUMANN, AND RAYMOND B. LARAVUSO

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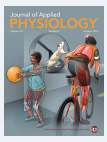
Ref. 71

ARTICLES

Limits on VA/Q distributions from analysis of experimental inert gas elimination

J. W. Evans, and P. D. Wagner

01 JUN 1977 //



Volume 42, Issue 6
June 1977
Pages 889-898

Abstract

Distributions of ventilation-perfusion ratios (VA/Q) actually present in the lung cannot be exactly recovered using current inert gas elimination methods, principally because of the limited number of gases and errors in their measurement. The amount of information that can be gained is studied here. When six gases are used the results are difficult to visualize so that a graphical analysis is first given for only two gases. Methods are proposed for 1) the probabilistic description of retentions compatible with a set of measured values of all six gases, and 2) the placing of limits on the associated VA/Q distributions. It is found that the variability among distributions with compatible retentions depends greatly on the particular set of data. Distributions consisting of a single or of two separated narrow modes can be identified reliably.

Ref. 72

Physiologist. 1977 Feb;20(1):18-25.

A general approach to the evaluation of ventilation-perfusion ratios in normal and abnormal lungs.

Wagner PD

Ref. 74

Respiration Physiology
Volume 49, Issue 3, September 1982, Pages 293-313

Resolution of the multiple inert gas method for estimating $\dot{V}_A/\dot{Q}$ maldistribution

Edward R. Ratner, Peter D. Wagner

Abstract

During steady-state infusion of a mixture of dissolved inert gases, their elimination by the lung depends on the distribution of ventilation/perfusion ($\dot{V}_A/\dot{Q}$) ratios. Thus, certain features of the $\dot{V}_A/\dot{Q}$ distribution can be inferred from inert gas measurement. Because of the: (1) complexity of the lung, and (2) experimental errors, the ability of such a technique to describe the shape and position of the $\dot{V}_A/\dot{Q}$ distribution accurately is limited. In this report we present an analysis of the resolution of the method for 9 representative sets of inert gas data, taking account of both of the above factors. These 9 sets span the range of commonly observed data, both in health and in diseases such as asthma, interstitial fibrosis, chronic obstructive lung disease and respiratory distress syndromes. Both error-free and error-containing data are studied and by linear programming methods, bounds are placed on maximum and minimum possible perfusion in several regions of the $\dot{V}_A/\dot{Q}$ spectrum. Modality is also studied by linear programming. The results show that the resolving power of the method depends greatly on the specific case under study. When groups of units are separated in $\dot{V}_A/\dot{Q}$ by a decade, this can be determined with considerable confidence. Shunt and low $\dot{V}_A/\dot{Q}$ areas can generally be well resolved, but when distributions are very broad, resolution is limited.

Ref. 75

Distribution of Ventilation-Perfusion Ratios in Patients with Interstitial Lung Disease*

P. D. Wagner, M.D.; D. R. Dantzker, M.D.; R. Dueck, M.D.; J. L. dePolo, M.D.; K. Wasserman, M.D.; and J. B. West, M.D.

Ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) distributions were measured in eight patients with stable chronic interstitial lung disease using our previously described technique of multiple inert gas elimination. Six patients had diffuse interstitial fibrosis of various causes, and two had biopsy-proved pulmonary alveolar proteinosis. All were characterized by resting hypoxemia, static and dynamic lung volumes showing restrictive disease without appreciable obstruction, a greatly reduced $D_{L_{CO}}$ (mean 40 percent of normal, range 23 to 60 percent) and a chest x-ray film with diffusely distributed increased markings. In each patient, duplicate measurements of the distribution were made first at rest, then during exercise, again at rest, and finally after breathing 100 percent oxygen for 30 minutes. The results at rest before and after exercise were similar, and revealed most of the ventilation and blood flow in a relatively narrow mode centered on a

*From the Department of Medicine, University of California, San Diego, and the Division of Respiratory Physiology and Medicine, University of California, Los Angeles-Harbor General Hospital.
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Ref. 76

Ventilation-Perfusion Inequality in Chronic Obstructive Pulmonary Disease

P. D. WAGNER, D. R. DANTZKER, R. DUECK, J. L. CLAUSEN, and J. B. WEST

From the Department of Medicine, University of California, San Diego, La Jolla, California 92093

ABSTRACT A multiple inert gas elimination method was used to study the mechanism of impaired gas exchange in 23 patients with advanced chronic obstructive pulmonary disease (COPD). Three patterns of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality were found: (*a*) A pattern with considerable regions of high (greater than 3) $\dot{V}_A/\dot{Q}$, none of low (less than 0.1) $\dot{V}_A/\dot{Q}$, and essentially no shunt. Almost all patients with type A COPD showed this pattern, and it was also seen in some patients with type B. (*b*) A pattern with large amounts of low but almost none of high $\dot{V}_A/\dot{Q}$, and essentially no shunt. This pattern was found in 4 of 12 type B patients and 1 of type A. (*c*) A pattern with both low and high $\dot{V}_A/\dot{Q}$ areas was found in the remaining 6 patients. Distributions with high $\dot{V}_A/\dot{Q}$ areas occurred mostly in patients with greatly increased compliance and may represent loss of blood-flow due to alveolar wall destruction. Similarly, well-defined modes of low $\dot{V}_A/\dot{Q}$ areas were seen mostly in patients with severe cough and sputum and may be due to reduced ventilation secondary to mechanical airways obstruction or distortion. There was little change in the $\dot{V}_A/\dot{Q}$ distributions on exercise or on breathing 100% O_2. The observed patterns of $\dot{V}_A/\dot{Q}$ inequality and shunt accounted for all of the hypoxemia at rest and during exercise. There was therefore no evidence for hypoxemia caused by diffusion impairment. Patients with similar arterial blood gases often had dissimilar $\dot{V}_A/\dot{Q}$ patterns. As a consequence the pattern of $\dot{V}_A/\dot{Q}$ inequality could not necessarily be inferred from the arterial P_{O_2} and P_{CO_2}.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is classically associated with abnormalities of pulmonary gas exchange. In the past these abnormalities have most often been characterized by the alveolar-arterial P_{O_2} difference ($A_aD_{O_2}$), venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$), and physiologic deadspace ($\dot{V}_D/\dot{V}_T$). However, characterization by these indices cannot provide a complete picture of the physiological abnormalities that are present.

An unresolved issue is whether diffusion impairment contributes to the hypoxemia in these patients. It has been known for many years that they may have a low diffusing capacity for carbon monoxide but this measurement is notoriously difficult to interpret in patients with large amounts of uneven ventilation (1). More recently King and Briscoe (2) have argued on the basis of two-compartment models that some of the hypoxemia may be caused by failure of P_{O_2} equilibration between alveolar gas and end-capillary blood.

Consequently there are numerous unanswered questions concerning both the nature of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality and the mechanism of hypoxemia in COPD: (*a*) the shape, position, and dispersion of the distribution of $\dot{V}_A/\dot{Q}$ ratios remain essentially undefined; (*b*) to what extent shunting and diffusion impairment are responsible for the hypoxemia are unresolved issues; (*c*) it is also not known to what degree there is impaired gaseous diffusion in the alveoli and airways as a result of the structural changes in the lungs; (*d*) the effects of breathing 100% oxygen are important but poorly understood because of uncertainty about how completely poorly ventilated areas have their nitrogen washed out; (*e*) the relationships between the pattern of $\dot{V}_A/\dot{Q}$ abnormalities, the mechanical properties of the lung, and the clinical picture are not well understood. It

Presented in part at the American Thoracic Society Annual Meeting, Cincinnati, Ohio, May 1974. (*Am. Rev. Respir. Dis.* 109: 706.)

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[1] *Abbreviations used in this paper*: $A_aD_{O_2}$, alveolar-arterial P_{O_2} difference; BTPS, body temperature, pressure, saturated with water; COPD, chronic obstructive pulmonary disease; $D_{L_{CO}}$, diffusing capacity for carbon monoxide (single breath); FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; $F_{I_{O_2}}$, fractional concentration, inspired gas; $\dot{V}_A/\dot{Q}$, ventilation-perfusion; VC, vital capacity.

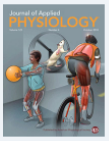
Ref. 78

ARTICLES

Variations of ventilation and diffusing capacity to perfusion determining the alveolar-arterial O_2 difference: theory

Johannes Piiper

01 MAY 1961



Volume 16, Issue 3
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Abstract

The factors determining the alveolar-arterial O_2 pressure difference, AaD, have been theoretically reinvestigated, taking into account the effect of unequal distribution of pulmonary diffusing capacity, D, to pulmonary perfusion, Q. It is shown that, for a given inspired gas and a given mixed venous blood, the AaD is determined by two parameters, the ratios diffusing capacity :perfusion, D/Q, and alveolar ventilation :perfusion, Va/Q. Two characteristics of both of these ratios, the mean value and the variation, affect the AaD.

Submitted on May 23, 1960

Ref. 79

CONTINUOUS DISTRIBUTIONS OF VENTILATION AND GAS CONDUCTANCE TO PERFUSION IN THE LUNGS

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INTRODUCTION

Overall gas transfer in the lung under a steady state is commonly considered to be limited mainly by uneven distribution of ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$) and by diffusion impairment (Wagner, 1977). Although remarkable methods allowing one to know the distribution of $\dot{V}_A/\dot{Q}$ in the lung have recently been developed (Yokoyama and Farhi, 1967; Wagner et al., 1974; Evans and Wagner, 1977), no reliable tool has been introduced for directly solving the issue of whether diffusion impairment across the blood-gas barrier contributes significantly to determining the efficiency of pulmonary gas exchange. In 1961, Piiper theoretically analyzed the importance of $\dot{V}_A/\dot{Q}$ and diffusion impairment in terms of "$\dot{V}_A/\dot{Q}$-D/$\dot{Q}$ field",but rigorous method to realize his theory has not been accomplished. The present study was, therefore, undertaken to develop a new method for detection of distribution of $\dot{V}_A/\dot{Q}$ and diffusing capacity in the lung using nine gases as indicator gases. Applying the present procedure to patients with interstitial lung disease, the importance of $\dot{V}_A/\dot{Q}$ inequality and of diffusion impairment will be discussed.

METHODS

Indicator gases. In order to assess a quantitative significance of maldistribution of $\dot{V}_A/\dot{Q}$ as well as of diffusion impairment for the gas exchange in the lung, nine gases with varied diffusivity and solubility were used for analysis. Among them, sulfur hexafluoride (SF_6), ethane, cyclopropane, halothane, diethyl ether and acetone are physiologically inert gases. The remainder are O_2, CO_2 and CO, all of which combine chemically with hemoglobin molecules (Hb) in red cells. The reason why these gases are used in the present study will be discussed in detail later (see below).

Diffusive conductance. The gas transfer efficiency at each lung unit was taken to be limited both by $\dot{V}_A/\dot{Q}$ and by $G/\dot{Q}$, G is diffusive conductance for a given indicator gas (i.e. diffusing capacity) defined in a certain lung unit. Gas transfer between alveolar gas and pulmonary capillary blood may be perturbed by several factors such as diffusion limitation in gas phase, in alveolar-capillary membrane including plasma layer and

Oxygen Transport to Tissue XII, Edited by J. Piiper *et al.*
Plenum Press, New York, 1990

Ref. 80

Respiration Physiology
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Distribution of ventilation and of diffusing capacity to perfusion in the lung

Kazuhiro Yamaguchi, Akira Kawai, Masaaki Mori, Kohichiro Asano, Tomoaki Takasugi, Akira Umeda, Takeo Kawashiro, Tetsuro Yokoyama

Abstract

We developed a method for estimating the distribution of ventilation VA) and of diffusing capacity (G) to perfusion (Q) in the lungs. We used O_2, CO_2 and CO together with six inert gases of widely differing solubility and assumed that mass transfer efficiency of each gas in a gas exchange unit is limited by both $\dot{V}A/\dot{Q}$ and $G/\dot{Q}$ ratios. The underlying lung model comprised 20 units along both the $\dot{V}A\dot{Q}$ and $G/\dot{Q}$ axes. Using numerical analysis, we transformed the data into a virtually continuous distribution of $\dot{Q}$ in the $\dot{V}A/\dot{Q}$-$G/\dot{Q}$ field. We tested the precision of the numerical procedure by examining the recovery of various artificial distributions, and found that distributions with up to two modes could be recovered with reasonable accuracy. Analytical results from 15 patients with interstitial pneumonia of unknown etiology (IPF) revealed the following features. (1) In an early disease stage, most of the lung was operating in the range of normal $\dot{V}A/\dot{Q}$, without a significant contribution of diffusion limitation. (2) An advanced stage of the disease exhibited a widening of $\dot{V}A/\dot{Q}$ distribution and either broad unimodal or bimodal distribution of $G/\dot{Q}$, extending to $G/\dot{Q}$ below 10^{-3} ml (STPD)/(ml·Torr) with diffusion-limited O_2 exchange. (3) Severe diffusion limitation causing disequilibrium of inert gas across the blood-gas barrier was observed in three (far advanced fibrosis; active interstitial inflammation) out of 15 patients. These findings suggest that inhomogeneity of $G/\dot{Q}$ does exist and may play an appreciable role in causing impairment of gas exchange in patients with interstitial pneumonia.

Ref. 81

American Journal of Respiratory and Critical Care Medic

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Inhomogeneities of Ventilation and the Diffusing Capacity to Perfusion in Various Chronic Lung Diseases

KAZUHIRO YAMAGUCHI , MASAAKI MORI , AKIRA KAWAI , TOMOAKI TAKASUGI , YOSHITAKA OYAMADA , and EIICHI KODA

Abstract

Although impairment of gas exchange caused by ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch has been extensively analyzed, there have been no systematic studies focused on determining the distributions of diffusion properties in close connection with those of $\dot{V}_A/\dot{Q}$. We attempted to clarify the simultaneous distributions of $\dot{V}_A/\dot{Q}$ and diffusion capacity to perfusion ($D/\dot{Q}$) in patients with idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD). To assess pathologic determinants causing functional abnormalities, we compared $\dot{V}_A/\dot{Q}$ and $D/\dot{Q}$ distributions with the findings on high-resolution computed tomography. O_2, CO_2, and CO together with six foreign inert gases were used as indicator gases. We transformed the measured data on indicator gases in arterial blood into a continuous distribution of $\dot{Q}$ in the $\dot{V}_A/\dot{Q}$-$D/\dot{Q}$ field. In IPF, active alveolitis or acinitis played a major role in producing low $D/\dot{Q}$ regions impeding gas exchange via a diffusion limitation, whereas extensive fibrosis with minimal inflammation accounted for low $D/\dot{Q}$ as well as low $\dot{V}_A/\dot{Q}$ regions. In COPD, no regions with low $D/\dot{Q}$ ratios were observed, but an abnormality in the $\dot{V}_A/\dot{Q}$ distribution with low or high $\dot{V}_A/\dot{Q}$ ratios was identified. Emphysematous lesions produced high $\dot{V}_A/\dot{Q}$ regions, whereas peripheral airway involvement yielded low $\dot{V}_A/\dot{Q}$ regions. These findings suggest that hypoxemia in patients with IPF is caused by inhomogeneous distributions of $D/\dot{Q}$ in combination with those of $\dot{V}_A/\dot{Q}$. Hypoxemia in patients with COPD is attributable primarily to inhomogeneities in $\dot{V}_A/\dot{Q}$ rather than in $D/\dot{Q}$ distributions.

Ref. 82

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The volume of the dead space in breathing and the mixing of gases in the lungs of man

A. Krogh, J. Lindhard

First published: 20 March 1917 | Cited by: 55

THE VOLUME OF THE DEAD SPACE IN BREATHING AND THE MIXING OF GASES IN THE LUNGS OF MAN. By A. KROGH and J. LINDHARD.

(*From the Laboratory of Zoophysiology, Copenhagen University.*)

The problem concerning the volume of the dead space in the air passages of man has been much debated of late years. Up to 1904 the measurements of Zuntz and Loewy(1) on the bronchial tree of a corpse were generally accepted as giving at least a good approximation to the volume, and by the Zuntz school of physiologists and many others the figure found (140 c.c.) was used for calculating the composition of the alveolar air from that of the mixed expired air. When Haldane and Priestley(2) had invented the direct method of taking samples of alveolar air they utilised this also for determining the volume of the dead space, comparing the CO_2 percentage of the alveolar air with that of the total expired air according to the formula[1]

$$EC_e = (E - D)\,C_a.$$

They measured and analysed the whole of the air expired in one deep expiration and determined the composition of the alveolar air in separate experiments. The results varied by about 30 % on either side of the mean, which was 142 c.c. for one subject and 189 for the other.

In 1911 Siebeck(3) introduced a new modification of the method invented by Haldane and Priestley which gave much more consistent results. He took an inspiration of between 500 and 1000 c.c. pure hydrogen and made an expiration of similar depth into a small spirometer. At the end of the expiration a sample of alveolar air was drawn, and the air in the spirometer as well as the alveolar sample were analysed for hydrogen. By a special series of experiments

[1] In the following E means the volume of the expiration, D the personal dead space, and d the additional instrumental dead space, C, O and H percentages of CO_2, O_2 and H_2 respectively, while the indices i, e and a mean inspired air, expired air and alveolar air respectively.

Ref. 83

A British Medical Association Lecture

ON

SOME RECENT ADVANCES IN THE PHYSIOLOGY OF RESPIRATION, RENAL SECRETION, AND CIRCULATION.*

BY

J. S. HALDANE, M.D., F.R.S.,

OXFORD.

In this lecture I shall endeavour to summarize the results of a number of recent investigations, with most of which I have been closely associated, on respiration, renal excretion, and circulation, and to point out, as far as I am able, their significance in helping us to understand the symptoms of disease and the real characters of that marvellous living body with which our profession has to deal. I will begin with respiration, as it was from the side of respiration that I myself, in conjunction with Professor Lorrain Smith, Professor Pembrey, Dr. Priestley, Professor Boycott, Dr. Douglas, and others who worked along with me, approached the subjects of this lecture.

REGULATION OF CO_2 PRESSURE IN ARTERIAL BLOOD.

The rate, depth, and regularity of breathing vary greatly at different times. A graphic record of my breathing while I am giving this lecture would, for instance, present an apparent picture of hopeless irregularity in every direction. If, however, we collect the expired air minute by minute we find that the samples obtained do not vary very much in composition. This suggests underlying regulation; and in order to test this more closely Priestley and I, about eighteen years ago, investigated the air present in the lung alveoli, of which we found that a sample can easily be obtained by catching the last parts of the air expired in a deep expiration. This investigation showed that whether the breathing was rapid or slow, provided only that there was no voluntary interference with its depth, the mean percentage of CO_2 in the alveolar air was maintained extraordinarily steady—far more steady than in the expired air, which is, of course, a variable mixture of the alveolar air with air contained in the air passages at the beginning of expiration.

Addition of moderate amounts of CO_2 to the inspired air, or moderate increases, owing to muscular exertion, of the amount of CO_2 produced in the body, hardly altered the alveolar CO_2 percentage except momentarily. The breathing was simply increased sufficiently to keep the alveolar CO_2 percentage almost exactly the same. Nor did great increases or moderate diminutions in the oxygen percentage of the inspired air alter the CO_2 percentage. By varying the barometric pressure we showed also that it is the partial pressure or concentration of CO_2 in a given volume of air that is kept so constant. At a barometric pressure of two atmospheres, for instance, the percentage of CO_2 which is maintained in the alveolar air is only half that at one atmosphere; but this means that the partial pressure or concentration of CO_2 is the same.

Now the arterial blood leaving the lungs is saturated with CO_2 at the same partial pressure as exists in the alveolar air; and this arterial blood in its turn saturates the respiratory centre at a similar partial pressure, and by so doing stimulates it to activity. The latter saturation, however, takes a little time, since the capacity of the body liquids for holding CO_2 in combination and simple solution is relatively large. The breathing, therefore, responds gradually and smoothly to any change in the alveolar CO_2 pressure, just as if the respiratory governor was associated with a fly-wheel; and at the same time the vagus reflex which governs the depth of breathing is accurately adjusted so that depth and frequency harmonize with one another. The response is extremely delicate. We found that in most persons there is about 5.6 per cent. of CO_2 in the alveolar air. If, by adding sufficient CO_2 to the inspired air, this percentage was raised by 0.2, the breathing during rest was doubled. If, on the other hand, the mean percentage was lowered by 0.2 by voluntary forced breathing, natural breathing ceased for the time, a temporary apnœa being produced.

Calculation shows that the corresponding increase or diminution in the free CO_2 contained in the arterial blood was only two parts by weight in a million of blood. This at once affords an idea of the astounding delicacy of physiological regulation. Physiology is an exact quantitative science, and for the purpose of these investigations I had to improve the existing methods of gas analysis. But what we are really measuring in physiology is the accuracy of maintenance of organic regulation, and this is something very different from what the physicist or chemist is engaged in measuring.

REGULATION OF THE REACTION OF ARTERIAL BLOOD.

Now, when carbon dioxide goes into solution in water it acts as an acid, though a very weak or feebly ionized one. Hence its old name, carbonic acid. Since an investigation by Walter, from Schmiedeberg's laboratory, in 1877, it has been known that in poisoning by dilute acids the breathing is greatly increased, and that accompanying the increased breathing there is greatly increased excretion of ammonia in the urine. It appeared, also, that the increased formation of ammonia in the body was a compensatory process, tending to neutralize the acid. It was the presence of a great excess of ammonia in the urine in diabetic coma that caused von Jaksch to suspect that diabetic coma is a state of acid poisoning or acidosis, and so led to the discovery that aceto-acetic and oxybutyric acids are formed within the body in large amounts in diabetic coma. Shortly after Priestley and I published our work on the alveolar air Pembrey and Haldane found that in diabetic coma the alveolar CO_2 percentage falls to less than a third of normal, but returns towards normal when the symptoms are relieved by sodium bicarbonate. This and various other pieces of evidence led us to conclude that it is probably as an acid, and in conjunction with other acids, that CO_2 acts in the regulation of breathing. But this theory was first established on a quantitative basis by the investigations of Hasselbalch of Copenhagen. He found that by taking an alkali-forming or acid-forming diet he could alter distinctly the percentage of CO_2 to which the alveolar air is regulated during rest, but that the alteration was just such as to keep the reaction or hydrogen ion concentration of the arterial blood steady in so far as the available physical and chemical methods enable us to estimate the steadiness. Putting together Hasselbalch's results and our own, we were able to conclude that the reaction of the blood is regulated with a delicacy which is almost inconceivable,[1] and which can only be followed very roughly by existing physical and chemical methods, though much more closely by the observation and interpretation of symptoms—by "diagnosis." Every normal response of the breathing to increased muscular exertion or other causes leading to increase in alveolar CO_2 percentage betokens a temporary acidosis or diminution in the blood's alkalinity. Calculation shows that a deficiency of one part by weight of ionized hydrogen in about one million million parts of blood suspends completely the activity of the respiratory centre.

Let us glance very shortly at the means by which the blood reaction is regulated. The first means is by regulation of the breathing so as to vary the amount of carbonic acid in the arterial blood. This process of regulation acts very rapidly, but, of course, cannot in the long run deal with the non-volatile acids in the blood. The temporary acidosis of muscular exertion, or the temporary alkalosis of forced breathing, is rapidly compensated approximately by variations in the breathing. Another interesting form of compensation has quite recently been demonstrated by Dodds.[2] When food is taken there is a rapid secretion of dilute HCl into the stomach, followed about an hour later by alkaline secretion into the small intestine. The gastric secretion of HCl leaves, of course, a temporary excess of alkali in the blood, and this promptly produces a quite marked compensatory rise in the alveolar CO_2 percentage, followed, about an hour later, by an equally marked fall while the alkaline secretion is being produced. A large dose of sodium bicarbonate will also produce a marked compensatory rise in the alveolar CO_2.

The second means of regulation is by varying the excretion of acid or alkali by the urine. Compared with variations in reaction of the blood, which is always slightly alkaline, the variations in reaction of normal urine are enormous. The acidity of average human urine

* Delivered before the Edinburgh Branch of the British Medical Association, March 9th, 1921.

Ref. 84

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A THEORETICAL STUDY OF THE COMPOSITION OF THE ALVEOLAR AIR AT ALTITUDE[1]

WALLACE O. FENN, HERMANN RAHN AND ARTHUR B. OTIS

From the Department of Physiology, The School of Medicine and Dentistry of the University of Rochester, Rochester, N. Y.

Received for publication March 7, 1946

In our studies of high altitude physiology we have found an oxygen-carbon dioxide diagram a very great aid to accurate thinking. It has been useful in so many different problems that we consider it worth while to describe it in this paper so that it can be made available to others.

1. *Breathing pure oxygen.* In this diagram the alveolar tensions of carbon dioxide are plotted as ordinates against the alveolar tensions of oxygen as abscissae as in figure 1, which represents the situation when an aviator ascends to high altitudes breathing pure oxygen. At any altitude, breathing pure oxygen,

$$pCO_2 + pO_2 = p'O_2 \qquad (1)$$

where $p'O_2$ refers to the tension of oxygen in the inspired air (BTPS or body temperature, saturated, ambient pressure) and the other tensions refer to alveolar air (BTPS). This equation gives a family of parallel diagonal lines on the chart each of which represents a given altitude such that $B - 47 = p'O_2$. The intercepts of these diagonals on the X axis represent therefore values of $B - 47$. With the aid of Henderson's nomogram for the blood of A.V.B. or any other similar data it is possible to assign a given percentage saturation of the arterial blood to every point on the chart. Thus lines of equal arterial saturation can be drawn. To indicate the location of such a family of curves the 65, 75, 85 and 95 per cent saturation lines have been drawn. When the saturation becomes less than about 65 per cent the subject is almost certain to lose consciousness very soon and this region of the chart has therefore been labelled "anoxia."

To show the normal behaviour of an aviator in going to progressively higher altitudes the line marked "alveolar air" has been drawn to indicate the successive positions of the alveolar air composition as the altitude is increased from ground level to above 43,000 feet. The curve bends downward after passing the 95 per cent saturation line because of the hyperventilation caused by the stimulus of anoxia. Hyperventilation at 43,000 feet moves the alveolar point

[1] This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

Ref. 85

'Ideal' Alveolar Air and the Analysis of Ventilation–Perfusion Relationships in the Lungs[1]

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THE ANALYSIS OF BLOOD-GAS RELATIONSHIPS in the lungs is handicapped by ambiguity regarding the concept of alveolar air (1). It is well known that patients suffering from pulmonary diseases may have alveolar air which varies in composition in different parts of the lungs (2, 3), yet there has been no adequate way of defining the composition of alveolar air under such circumstances. Furthermore, the relationships between alveolar ventilation and alveolar perfusion with blood, which are primary factors in determining the composition of the alveolar air, have been dealt with only in general terms. The purpose of this paper is to discuss a specific definition of alveolar air which is applicable to both normal and pathological conditions, and, with the help of this concept, to outline a system of analysis of ventilation-perfusion relationships in health and disease.

SCHEMATIC REPRESENTATION OF VENTILATION, PERFUSION AND GAS EXCHANGE

The cyclic nature of the ventilatory process tends to obscure certain fundamental relationships between alveolar air and the blood in the alveolar capillaries. Let us therefore consider a schematic representation of ventilation, perfusion and gas exchange in which these processes are conceived of as continuous (fig. 1). Inspired air and mixed venous blood pass into the alveoli where they approach equilibrium with respect to partial pressures of oxygen and carbon dioxide by diffusion of gases across the pulmonary membrane. The blood leaving the alveolar capillaries is modified slightly by the admixture of a small amount of venous blood which can be thought of as a shunt. The alveolar air leaving the alveolar spaces is modified by the admixture of dead space air, which has the composition of inspired air and may also be thought of as a shunt.

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[1] Under grants from the Life Insurance Medical Research Fund and the Commonwealth Fund.

Ref. 86

A CONCEPT OF MEAN ALVEOLAR AIR AND THE VENTILATION—BLOODFLOW RELATIONSHIPS DURING PULMONARY GAS EXCHANGE[1]

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IN THE past many different methods have been employed for the direct sampling of alveolar air. A sound criticism of the validity of the technique has usually been futile since one was at loss to define or determine mean alveolar composition. The ease with which alveolar air composition can be altered by the slightest change in ventilation is very impressive and makes one aware of the possibility of unequal ventilation in various parts of the lung and the consequential regional variability of gas concentration. The concept of unequal bloodflow to the various alveoli has received less attention, although this factor is equally important in altering the gas composition.

It is the purpose of this paper *1)* to define the alveolar air composition in terms of alveolar ventilation and pulmonary bloodflow which allow one to define a concept of mean alveolar gas composition; *2)* to discuss a method for the direct sampling of mean alveolar air; *3)* to compare this with the Haldane technique of sampling alveolar air; *4)* to predict on the basis of the ventilation-bloodflow equations the effect of unequal ventilation and bloodflow upon the alveolar-arterial oxygen gradient.

A Concept of Mean Alveolar Air. The alveolar air equation and the alveolar ventilation equation have given us a theoretically precise definition of the relation of the alveolar-gas concentrations and the ventilation (1). When this equation is combined with the Fick equation, it allows one to express the alveolar gas concentration in terms of bloodflow and ventilation (2).

Let

F = bloodflow in liters/min.
Va = alveolar ventilation in liters/min. B.T.P.S.
$(A\text{-}V)O_2$ = arterial-venous oxygen difference in ml/l.
X_o = oxygen intake in ml/min. S.T.P.
Q = respiratory quotient
pC = partial pressure of CO_2 in alveolar air.

then the bloodflow according to the equation of Fick is

$$X_o = F(A\text{-}V)O_2 \qquad (1)$$

and the alveolar ventilation according to Fenn *et al.* (1) is

$$X_o = \frac{Va \times pC}{.864Q} \qquad (2)$$

Combining the equations and eliminating X_o we have

$$pC = \frac{F}{Va}(A\text{-}V)O_2(.864Q) \qquad (3)$$

Received for publication March 14, 1949.
[1] Work done under contract with the Air Materiel Command, Wright Field.

Ref. 87

ON THE DETERMINATION OF THE PHYSIOLOGICALLY EFFECTIVE PRESSURES OF OXYGEN AND CARBON DIOXIDE IN ALVEOLAR AIR[1]

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Received for publication March 25, 1946

Although studies of the composition of alveolar air have been invaluable to the advance of respiratory physiology a precise definition of alveolar gas pressures and the accurate sampling of alveolar air have proved elusive goals (1). Owing to the cyclic nature of the ventilatory process the partial pressures of O_2 and CO_2 in the alveoli are changing continually (time factor) (9), and, owing to inequalities in intrapulmonary ventilation and circulation, the partial pressures in different parts of the lungs may differ significantly (space factor) (10, 15). Therefore, the concept that a single value represents the partial pressure of an alveolar gas requires the assumption that the spot sample of alveolar air be representative with respect to both time and space.

There are cogent reasons for believing that the two principal methods for sampling alveolar air (the single complete expiration method of Haldane and Priestley and the fractional sampling technic of Sonne and Nielsen) do not guarantee that the sample always is, in fact, representative. Neither method insures that the sample contains proportional contributions of alveolar air from all portions of the lung (space error), nor that the sample obtained has not lost O_2 and gained CO_2 during the brief period of stasis within the alveoli (time error). For example, the partial pressures of O_2 and CO_2 in samples of alveolar air obtained by the Haldane-Priestley technic vary with respect to the timing of the expiratory effort (end-inspiration or end-expiration) (5, 6). And again, fractional sampling of the alveolar air by the Sonne-Nielsen technic has yielded evidence that successive samples of alveolar air taken at different stages during expiration vary appreciably with respect to gaseous composition (14).

Despite these limitations many fundamental contributions to an understanding of respiratory mechanisms have come from studies of the composition of alveolar air at rest (4, 7). However, during even moderate exercise the rate of evolution of CO_2 into and the escape of O_2 out of the alveoli may be increased tenfold or more so that the slight delay necessary to expel the alveolar sample is sufficient to permit radical changes to develop. This failure of the direct sampling technics to provide reliable data during exercise has led us to measure alveolar gas pressures by an indirect method now to be described.

The indirect measurement of alveolar gas pressures. Indirectly determined alveolar CO_2 and O_2 pressures are calculated from the arterial pCO_2 and the

[1] The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

[2] Present address: the Johns Hopkins Hospital, Baltimore, Md.

Ref. 89

Respiration Physiology
Volume 70, Issue 1, 1987, Pages 113-120

Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurements of NO and CO transfer

Author links open overlay panel H.Guenard
N.Varene P.Vaida

Abstract

NO and CO lung transfer values (Tl) were measured separately in 14 healthy subjects (7 men, 7 women), using the single breath technique. Five repetitive maneuvers were performed by each subject for Tl_{NO} and Tl_{CO} determinations. The inspired mixture contained either 8 ppm NO or 0.25% CO, with 2% He, 21% O_2 in N_2. In order to measure an appreciable fraction of NO in the alveolar gas it was necessary to shorten the breath holding time to 3 sec. Tl_{NO} was about five times greater than Tl_{CO}. This result suggests that the specific conductance of blood (ϑ) for NO is very high and that the second term of the second member of the equation $1/Tl_{NO} = 1/Dm_{NO} + 1/(\vartheta_{NO} \cdot Qc)$ is therefore negligible. Dm_{CO} and Qc values can thus be computed from Tl_{NO} and Tl_{CO} measurements. The results obtained with this method are very close to those reported in the literature; for men $Dm_{CO} = 79.0 \pm 14.3$ ml $\cdot$ $min^{-1} \cdot Torr^{-1}$, $Qc = 78.0 \pm 13.2$ ml and for women $Dm_{CO} = 59.0 \pm 10.1$ ml $\cdot$ $min^{-1} \cdot Torr^{-1}$, $Qc = 59.5 \pm 11.6$ ml.

Ref. 90

Eur Respir J. 1989 Jan;2(1):56-63.

A simultaneous single breath measurement of pulmonary diffusing capacity with nitric oxide and carbon monoxide.

Borland CD, Higenbottam TW.

Abstract

Pulmonary diffusing capacity (DL) for carbon monoxide (CO) and nitric oxide (NO) were simultaneously measured in man using the single breath method, by adding 4O ppm of NO to the inspired gas and analysing the expirate for NO by a chemiluminescent method. The mean ratio of DLNO to DLCO in thirteen subjects was 4.3 (SD 0.3), mean DLNO = 49 mmol.min-1.kPa-1 (SD 10) and mean DLCO = 11 mmol.min-1.kPa-1 (SD 2). An increase in alveolar oxygen concentration from a mean of 18 to 68% in five subjects was associated with a 54% fall in DLCO but no change in DLNO. A reduction of lung volume from total lung capacity (TLC) (mean of 7 l) to a mean volume of 3.9 l in five subjects caused a fall in both DLNO (by 34%) and DLCO (by 8%). With 175 watts cycle exercise in three subjects the DLCO rose by 45% and DLNO by 25%. Since NO reacts much faster with haemoglobin than CO, DLNO should be influenced much less by reaction with haemoglobin, and perhaps represents a better index for the diffusing capacity of the alveolar-capillary membrane (Dm) than DLCO.

Ref. 91

THE DIFFUSION OF GASES THROUGH THE LUNGS OF MAN. By MARIE KROGH, M.D.

(*From the Laboratory of Zoophysiology, University of Copenhagen.*)

The problem concerning the forces by which oxygen is transported from the alveolar air into the blood has resolved itself into two distinct questions. The first is whether the tension of oxygen in the blood is always lower than in the alveolar air, or whether it may in certain circumstances become higher. If the latter alternative is true, as maintained by Haldane and his collaborators, there can be no doubt that forces other than diffusion must come into play. If on the other hand the tension of oxygen in the blood is always lower than in the air, as found by A. Krogh and the writer(1) and also by Hartridge(2), the second question arises: Is diffusion quantitatively sufficient to explain the intakes of oxygen measured under the most adverse conditions and especially during muscular work at low oxygen pressures. The present paper deals with the second question, but as this is worth dealing with only in so far as diffusion cannot *à priori* be ruled out as being unable to explain the transport of oxygen, it is necessary to consider very briefly the evidence on which the assumption is based of a higher O_2 tension in the arterial blood than in the alveoli.

Without entering upon a discussion of the CO method of tension determination or the carmine titration as worked out by Haldane and Douglas(3), I wish to point out the discrepancy which is apparent in several cases between the arterial O_2 tension as determined by these methods and the symptoms of oxygen want simultaneously observed. In their series of investigations carried out on Pike's Peak, Douglas, Haldane, Henderson and Schneider(4) found that acclimatisation to the low oxygen pressure took place after a few days and they ascribe this to the high arterial O_2 tensions observed, which were on an average about 35 mm. higher than the alveolar or from 85 to 100 mm. (corresponding to percentage saturation of the blood with oxygen of 92 to 96 %). Nevertheless they point out that "excessive breathlessness on any considerable exertion remained a prominent

Ref. 92

A STANDARDIZED BREATH HOLDING TECHNIQUE FOR THE CLINICAL MEASUREMENT OF THE DIFFUSING CAPACITY OF THE LUNG FOR CARBON MONOXIDE [1]

By C. M. OGILVIE,[2] R. E. FORSTER,[3] W. S. BLAKEMORE,[4] and J. W. MORTON [5]

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(Submitted for publication April 16, 1956; accepted August 13, 1956)

Previous publications from this laboratory have described (1, 2) a modification of the Krogh breath holding technique for measuring the pulmonary diffusing capacity for carbon monoxide (D_L).[6] This test can be performed quickly and simply and does not require arterial blood analyses. It has recently (2) been shown to provide an index of pulmonary diffusing capacity similar to that given by the $D_{L_{O_2}}$ method of Lilienthal, Riley, Proemmel, and Franke (3) and the "steady state" method of Filley, MacIntosh, and Wright (4). The purpose of the present report is to enumerate some of the factors that affect D_L, to describe a standardized technique for its measurement, and to present normal values of D_L as well as values in patients with various chest diseases.

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[6] Since the combination of CO with intracellular hemoglobin occurs at a rate that offers an appreciable, and under some conditions the major, part of the resistance to the uptake of CO in the lungs (5, 6) it is desirable to distinguish between the "true" diffusing capacity, or that of the pulmonary capillary membrane alone (D_m), and the apparent diffusing capacity of the whole lung (D_L). These are related by the equation $1/D_L = 1/D_m + 1/\theta V_c$ where θ is the rate of combination of CO with intracorpuscular hemoglobin in ml. per min. per mm. Hg CO tension per ml. blood, and V_c is the volume of blood in the pulmonary capillaries at any instant. θ decreases as O_2 tension increases (7), causing D_L to decrease, since D_m and V_c are presumably relatively independent of alveolar O_2 tension (8). Normally a further subscript of CO or O_2 would be used to indicate the gas to which the measurement applies. However, in this article, which is mainly concerned with CO, the subscript is omitted and can be assumed to be "CO" unless otherwise stated.

METHODS

The technique for the measurement of D_L, which has been reported before (1, 2), consists essentially of having the subject make a maximal inspiration of a gas mixture containing 10 per cent helium (He), 0.3 per cent CO and approximately 21 per cent O_2 in N_2 from the level of his residual volume, hold it for a measured time, and then rapidly expire. All of this expiration except the first liter is collected in a bag by the operator and analyzed as alveolar gas. The CO concentration which was present in this sample before any CO had been absorbed in the lungs is calculated from the dilution of the inspired He according to the equation,

$$\text{Initial CO concentration in the expired alveolar sample} = \frac{\text{He concentration in the expired alveolar sample}}{\text{Inspired He concentration}} \times \text{Inspired CO concentration} \quad (1)$$

Knowing the change in CO concentration in the alveolar sample during the period of breath holding, D_L can be calculated from Krogh's equation (9).

$$D_L \left[\frac{\text{In ml. CO STPD}}{\text{Min.} \times \text{mm. Hg CO tension}}\right] = \frac{\text{Alveolar volume (STPD) 60}}{\text{Time in seconds} \times (\text{barometric pressure} - 47)} \times \text{Natural logarithm} \left[\frac{\text{Initial CO concentration in the expired alveolar sample}}{\text{Final CO concentration in the expired alveolar sample}}\right] \quad (2)$$

The apparatus used for the test is illustrated in Figure 1. It differs from that reported previously (1, 2) mainly in its greater simplicity; in these previous communications the expired alveolar He and/or CO concentrations were measured at the mouth by recording analytical instruments. The circuit is closed, permitting inspiration from the bag of the Donald-Christie apparatus and expiration into the space around the bag, a spirometer recording the change in respiratory volumes. Tap (A) is used by the operator for collecting the expired alveolar sample. Since the gas mixture is inspired from the level

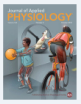
Ref. 93

| ARTICLES

Relative Importance of Diffusion and Chemical Reaction Rates in Determining Rate of Exchange of Gases in the Human Lung, With Special Reference to True Diffusing Capacity of Pulmonary Membrane and Volume of Blood in the Lung Capillaries

F. J. W. Roughton, and R. E. Forster

01 SEP 1957 //



Volume 11, Issue 2
September 1957
Pages 290-302

Abstract

An equation, $i/D_m + i/\theta V_c = i/Dl$, has been derived which relates the measured pulmonary diffusing capacity (Dl), the true diffusing capacity of the pulmonary membrane (Dm), the rate of uptake of CO by the red cells per mm Hg CO tension (θ) and the blood volume of the pulmonary capillary bed (V_c). By making measurements of Dl at different alveolar O_2 tensions, thereby causing to vary, this equation can be solved graphically for Dm and V_c, which are assumed to be independent of O_2 tension. Calculations of Dm and V_c were made utilizing *a*) values of θ previously obtained from the *in vitro* rates of CO uptake of suspensions of human red cells at 37°C and *b*) values of Dl in normal resting subjects at alveolar O_2 tensions from about 100 mm Hg to over 600 mm Hg measured by both steady state and breath holding CO techniques. Dm is about twice the value of Dl measured in subjects breathing air at sea level. V_c is about 75 ml in approximate agreement with the previously reported estimate of Roughton. Similar results were obtained using values of Dl at different alveolar O_2 tensions reported in the literature. This means that, in determining the rate of CO absorption in the lungs, the resistance of the red cell to the uptake of CO is of the same order of importance as the resistance of the pulmonary membrane to the diffusion of gas across it. Arguments are advanced to show that red cell resistance is of at least equal importance in the case of O_2 uptake.

Submitted on February 15, 1957

Ref. 94

TASK FORCE REPORT
ERS TECHNICAL STANDARDS

Standardisation and application of the single-breath determination of nitric oxide uptake in the lung

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Pulmonary diffusing capacity for nitric oxide is standardised by a panel of experts for use around the world http://ow.ly/Tp9Y1300Y5p

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ABSTRACT Diffusing capacity of the lung for nitric oxide (D_{LNO}), otherwise known as the transfer factor, was first measured in 1983. This document standardises the technique and application of single-breath D_{LNO}. This panel agrees that 1) pulmonary function systems should allow for mixing and measurement of both nitric oxide (NO) and carbon monoxide (CO) gases directly from an inspiratory reservoir just before use, with expired concentrations measured from an alveolar "collection" or continuously sampled via rapid gas analysers; 2) breath-hold time should be 10 s with chemiluminescence NO analysers, or 4–6 s to accommodate the smaller detection range of the NO electrochemical cell; 3) inspired NO and oxygen concentrations should be 40–60 ppm and close to 21%, respectively; 4) the alveolar oxygen tension (P_{AO_2}) should be measured by sampling the expired gas; 5) a finite specific conductance in the blood for NO (θ_{NO}) should be assumed as 4.5 mL·min^{-1}·mmHg^{-1}·mL^{-1} of blood; 6) the equation for θ_{CO} should be [0.0063.P_{AO_2})–1.16]×(ideal haemoglobin/measured haemoglobin) based on breath-holding P_{AO_2} and adjusted to an average haemoglobin concentration (male 14.6 g·dL^{-1}, female 13.4 g·dL^{-1}); 7) a membrane diffusing capacity ratio (D_{MNO}/D_{MCO}) should be 1.97, based on tissue diffusivity.

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Ref. 96

Respiration Physiology
Volume 1, Issue 1, 1966, Pages 75-87

Determination of D_{CO} by the single breath method in inhomogeneous lungs: Theory ☆

J. Piiper, R.S. Sikand

Abstract

The effects of functional inhomogeneities in the lungs upon the single breath CO diffusing capacity were studied in theory. Non-uniform distribution of the alveolar tidal volume to the alveolar volume and unequal distribution of the diffusing capacity to the alveolar volume or to the pulmonary capillary flow were found to reduce the apparent single breath $_{CO}$, i.e. the D_{CO} calculated ignoring the presence of such unequal distributions. The characteristic feature in the presence of unequal distributions of the diffusing capacity is a decrease of the apparent D_{CO} with increasing times of apnoea. Approaches are described to arrive at the true D_{CO} in presence of functional inhomogeneities in the lungs from data obtained from measurements of D_{CO} by the single breath method.

Ref. 97

Respiration Physiology
Volume 1, Issue 2, 1966, Pages 172-192

Pulmonary diffusing capacity for co in dogs by the single breath method ☆

R.S. Sikand, J. Piiper

Abstract

In order to determine the diffusing properties of the lung an attempt was made to take into account the disturbing effects of functional inhomogeneities upon determinations of Dco. Dco was measured by the single breath method in 21 anaesthetised dogs weighing on the average 25 kg. The Dco values decreased considerably as the time of apnoea was increased from 3–30 sec, indicating presence of unequal distribution of Dco in the lungs. For an apnoea time of 10 sec a mean Dco value of 25 ml/min. mm Hg in hypoxia (Flo_2 = 0.12) was obtained, on the assumption of a homogeneous lung. When the effects of unequal distribution of inspired volume and of Dco were taken into account, the value increased to 52 ml/min. mm Hg. Using data from CO uptake of human red blood cells, the membrane component of Dco was estimated from measurement of Dco at varying inspired O_2 concentrations to be 80 ml/min. mm Hg and the pulmonary capillary volume, to 100 ml.

Ref. 98

Examination of the Carbon Monoxide Diffusing Capacity ($D_{L_{CO}}$) in Relation to Its Kco and VA Components

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The single-breath carbon monoxide diffusing capacity ($D_{L_{CO}}$) is the product of two measurements during breath-holding at full inflation: (1) the rate constant for carbon monoxide uptake from alveolar gas (kco [minute^{-1}]) and (2) the "accessible" alveolar volume (Va). kco expressed per mm Hg alveolar dry gas pressure [PB] as kco/PB, and then multiplied by Va, equals $D_{L_{CO}}$ thus, $D_{L_{CO}}$ divided by Va ($D_{L_{CO}}$/Va, also called Kco) is only kco/PB in different units, remaining, essentially, a rate constant. The notion that $D_{L_{CO}}$/Va "corrects" $D_{L_{CO}}$ for reduced Va is physiologically incorrect, because $D_{L_{CO}}$/Va is not constant as Va changes; then, the term Kco reflects the physiology more appropriately. Crucially, the same $D_{L_{CO}}$ may occur with various combinations of Kco and Va, each suggesting different pathologies. Decreased Kco occurs in alveolar-capillary damage, microvascular pathology, or anemia. Increased Kco occurs with (1) failure to expand normal lungs to predicted full inflation (extrapulmonary restriction); or (2) increased capillary volume and flow, either globally (left-to-right intracardiac shunting) or from flow and volume diversion from lost or damaged units to surviving normal units (e.g., pneumonectomy). Decreased Va occurs in (1) reduced alveolar expansion, (2) alveolar damage or loss, or (3) maldistribution of inspired gases with airflow obstruction. Kco will be greater than 120% predicted in case 1, 100–120% in case 2, and 40–120% in case 3, depending on pathology. Kco and Va values should be available to clinicians, as fundamental to understanding the clinical implications of $D_{L_{CO}}$. The diffusing capacity for nitric oxide ($D_{L_{NO}}$), and the $D_{L_{NO}}/D_{L_{CO}}$ ratio, provide additional insights.

Keywords: diffusing capacity for carbon monoxide ($D_{L_{CO}}$); diffusing capacity for nitric oxide ($D_{L_{NO}}$); $D_{L_{CO}}$/Va (Kco); pulmonary function tests; alveolar gas exchange

The single-breath diffusing capacity for carbon monoxide ($D_{L_{CO}}$) (known in Europe as the transfer factor, $T_{L_{CO}}$) is, after spirometry and lung volumes, the most clinically useful routine pulmonary function test. The $D_{L_{CO}}$, as pointed out by its originator, Marie Krogh (1), is the product of two separate but simultaneous measurements (Figure 1): the rate constant kco (the rate of uptake of CO from alveolar gas), and the alveolar volume (VA). The important point is that Kco (kco renormed per mm Hg alveolar Pco) is linearly related to the alveolar uptake efficiency for carbon monoxide (2, 3). Because of the special properties of carbon monoxide, Kco directly reflects the quality of alveolar–capillary gas uptake. Many articles and pulmonary function testing (PFT) laboratories do not quote VA and Kco from which the $D_{L_{CO}}$ is derived; this may result in significant loss of clinical information.

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Internet address: www.atsjournals.org

MEASUREMENT OF Kco AND VA

Rate of Uptake of Alveolar Carbon Monoxide (kco)

During breath holding in the single-breath $D_{L_{CO}}$, CO is removed from alveolar gas at an exponential rate [$\log_e$(FCO_A/FCO_A)/BHT], where FCO_A and FCO_A are the alveolar concentrations at the start and finish of the breath-holding time (BHT). This expression is a rate constant with units of minute^{-1} or second^{-1}; in Figure 1 it is represented by the slope, kco.

Alveolar Volume (VA)

The $D_{L_{CO}}$ is measured during breath holding at full inflation; in absolute terms, this represents total lung capacity (TLC). The lung volume during breath holding is measured simultaneously by dilution of any nonabsorbable gas, most commonly helium (He) (Figure 1), at the same time as the kco is measured (4). The alveolar volume (VA) is an "accessible" volume, that is, that seen by the gas exchanging surface, derived from the single-breath helium dilution volume after subtracting an "estimated" anatomic dead space ($V_{D anat}$) from the inspired volume (Vi) (Figure 1). The Vi starts from residual volume and finishes at maximal inflation (~TLC); the inspiration should be made as rapidly as possible. In normal subjects, VA is within 10% of TLC, with a mean VA/TLC ratio (combining men and women) of 93.5% ± 6.6 (1 SD) (5); the VA/TLC ratio has no significant dependence on age, sex, height, or weight (5), but decreases substantially when there is intrapulmonary airflow obstruction and maldistribution of ventilation. $V_{D anat}$ represents 2–3% of the TLC in normal subjects, the remaining 4% of the VA/TLC difference occurring because gas mixing in the 10-second breath hold is incomplete. In disease, the difference between the single-breath VA and the multibreath or plethysmographic TLC, and the VA/TLC ratio, deserves more study (3) as an index of gas mixing efficiency.

Combining VA and kco

Equation 1 is the first step in the calculation of the $D_{L_{CO}}$:

$$V_A \times kco = V_{CO} \qquad (1)$$

$$\text{ml (STPD)} \times \text{min}^{-1} = \text{ml min}^{-1},$$

where kco is the fractional change in CO concentration, expressed in minute^{-1}, and V_{CO} is the uptake of CO from alveolar gas during breath holding at TLC. Equation 1 gives a large value for V_{CO} because, as pointed out by Marie Krogh (1), the calculation implies that all alveolar gas is pure CO. For the second step, to obtain $D_{L_{CO}}$, both sides of the equation are divided by P_B, where P_B is

Ref. 99

Alveolar-capillary membrane diffusion measurement by nitric oxide inhalation in heart failure.

Magini A[1], Apostolo A[1], Salvioni E[1], Italiano G[1], Veglia F[1], Agostoni P[2].

Author information

Abstract

BACKGROUND: In heart failure, lung diffusion is reduced, it correlates with prognosis and exercise capacity, and it is a therapy target.

DESIGN: Diffusion is measured as CO total diffusion (DL(CO)), which has two components: membrane diffusion (Dm) and capillary volume, the latter related to CO and O2 competition for hemoglobin. DL(CO) needs to be corrected for hemoglobin. Diffusion can also be measured with NO (DL(NO)), which has a very high affinity for hemoglobin, and thus, the resistance of hemoglobin being trivial, it directly represents Dm. Therefore, Dm is directly calculated from DL(NO) through a correction factor. DL(NO) has never been measured in heart failure. The study aims at determining, in heart failure, DL(NO), Dm correction factor, and whether Dm(NO) provides Dm estimates comparable to Dm(CO).

METHODS: We measured DL(CO), Dm(CO) by multi-maneuver Roughton-Forster method, and DL(CO) and DL(NO) by single-breath maneuver in 50 heart failure and 50 healthy subjects.

RESULTS: DL(CO) was 21.9 ± 4.8 ml/mmHg per min and 16.8 ± 5.1 in healthy subjects and heart failure subjects, respectively ($p < 0.001$). DL(NO) was 88.6 ± 20.5 ml/mmHg per min and 72.5 ± 22.3, respectively ($p < 0.001$). The correction factors to obtain Dm from DL(NO) were 2.68 (entire population), 2.63 (healthy subjects) and 2.75 (heart failure subjects). Dm(CO) and Dm(NO) were 34.7 ± 10.9 ml/mmHg per min and 33.8 ± 7.6 in healthy subjects and 25.9 ± 2.0 and 26.4 ± 8.1 in heart failure subjects.

CONCLUSIONS: DL(NO) and Dm(NO) measurements are feasible in heart failure. Dm(CO) and Dm(NO) provide comparable results. The correction factor to calculate Dm from DL(NO) in heart failure is 2.75, which is little different from the 2.63 value we observed in healthy subjects.

KEYWORDS: Oxygen consumption; gas exchange; lung diffusion

Comment in

Reply to commentary on: confusion in reporting pulmonary diffusion capacity for nitric oxide and the alveolar-capillary membrane conductance for nitric oxide. [Eur J Prev Cardiol. 2015]

Confusion in reporting pulmonary diffusing capacity for nitric oxide and the alveolar-capillary membrane conductance for nitric oxide. [Eur J Prev Cardiol. 2015]

Ref. 100

Confusion in reporting pulmonary diffusing capacity for nitric oxide and the alveolar-capillary membrane conductance for nitric oxide

Gerald S Zavorsky, Colin Borland,

First Published March 27, 2014 Editorial

We read with interest the paper by Magini and colleagues on the measurement of pulmonary diffusing capacity for nitric oxide in patients with heart failure (ejection fraction<40%).1 In their study they report pulmonary diffusing capacity and the individual components of pulmonary diffusing capacity in 50 patients with heart failure (65 years of age), and 50 control subjects (61 years of age). We feel that there are two problems with this paper that warrant discussion. First, the mean values for pulmonary diffusing capacity for nitric oxide (DLNO) for the healthy subjects are too low, and second, both their alveolar-membrane conductances (DmNO and DmCO) and pulmonary capillary blood volume (Vc) calculations, and hence conclusions, are incorrect.

First, the values for DLNO for the healthy volunteers appear too low. If we assume that the women's and men's mean height in the healthy volunteers was 163 and 173 cm, respectively, then the mean DLNO values should be 96–113 and 140–154 ml/min/mm Hg, for women and men, respectively.2,3 The combined average for DLNO should be then 118–133 ml/min/mm Hg. The author's mean values of 89 ml/min/mm Hg for the healthy volunteers are 25–33% lower than predicted. However, their values for pulmonary diffusing capacity for carbon monoxide (DLCO) were correct and the healthy volunteers was close to 100% of that predicted.2,3 Thus, if the mean DLNO in the control group is under-predicted by at least 25%, then the DLNO values in the heart failure patients could be under predicted by ≥25% too. Since DLNO and DLCO are measured simultaneously, and DLCO values were appropriate (close to 100% of those predicted), there must be some mathematical error in the calculation of DLNO and/or their breath-hold time was too short. The breath-hold time should be 5–10 s,4 and it seems that their breath-hold time varied between 2–4 s.

Ref. 101

Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion

The syndrome of "alveolar-capillary block"

Robert Austrian, M.D.[1], John H. McClement, M.D.[1,†], Attilio D. Renzetti Jr., M.D.[1], Kenneth W. Donald, M.D. Richard L. Riley, M.D.[1], André Cournand, M.D.[1]
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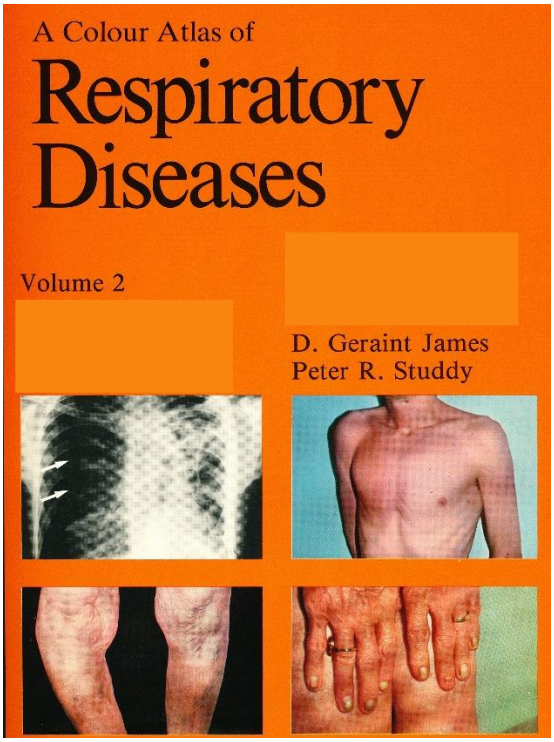
Abstract

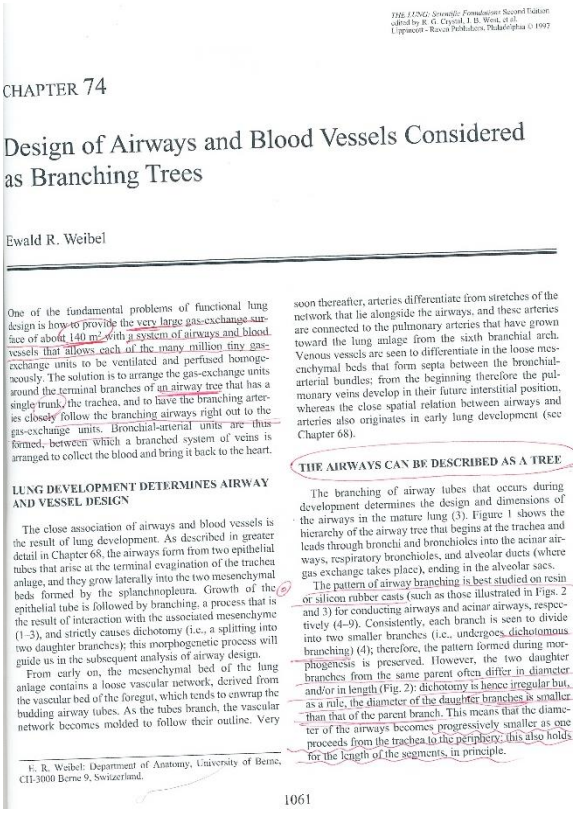
1. 1. Twelve additional cases with various diffuse diseases of the lungs characterized physiologically principally by interference with the diffusion of oxygen across the alveolar-capillary septum have been studied.
2. 2. The patients in this group included two with pulmonary granulomatosis following exposure to beryllium; one with pulmonary granulomatosis of the Boeck's sarcoid type; one with pulmonary granulomatosis of undetermined etiology, in which the granulomatous lesion contained unusually large numbers of foreign body-type giant cells and bi-refractile crystals; one patient with scleroderma; three patients with pulmonary fibrosis of unknown etiology (in one case after exposure to beryllium, in two cases associated with granulomas in other organs), and four cases in which a diagnosis could not be made.
3. 3. The pattern of pulmonary dysfunction consisted of (1) reduced lung volumes, (2) maintenance of a large maximum breathing capacity, (3) hyperventilation at rest and during exercise, (4) normal or nearly normal arterial oxygen saturation at rest but a marked reduction of the arterial oxygen saturation after exercise, (5) normal alveolar oxygen tension, (6) a reduced oxygen diffusing capacity and (7) pulmonary artery hypertension.
4. 4. In some severe cases the dead space-like ventilation and the venous admixture-like perfusion was increased. These findings have been interpreted as an indication of the inhomogeneous nature of the pathologic process.
5. 5. The clinical findings have been analyzed in the light of the physiologic data and the evolutionary trends, both clinical and physiologic, have been described.
6. 6. Because the major pathologic changes are localized in the alveolar capillary septa and because the major physiologic defect is a reduction of the permeability of the alveolar capillary membrane for oxygen, the name "alveolar-capillary block" has been tentatively offered to describe this syndrome.

Fist-page copies of Books used for references

Ref. 1



Ref. 2



THE LUNG: Scientific Foundations Second Edition edited by R. G. Crystal, J. B. West, et al. Lippincott - Raven Publishers, Philadelphia © 1997

CHAPTER 74

Design of Airways and Blood Vessels Considered as Branching Trees

Ewald R. Weibel

One of the fundamental problems of functional lung design is how to provide the very large gas-exchange surface of about 140 m² with a system of airways and blood vessels that allows each of the many million tiny gas-exchange units to be ventilated and perfused homogeneously. The solution is to arrange the gas-exchange units around the terminal branches of an airway tree that has a single trunk, the trachea, and to have the branching arteries closely follow the branching airways right out to the gas-exchange units. Bronchial-arterial units are thus formed, between which a branched system of veins is arranged to collect the blood and bring it back to the heart.

LUNG DEVELOPMENT DETERMINES AIRWAY AND VESSEL DESIGN

The close association of airways and blood vessels is the result of lung development. As described in greater detail in Chapter 68, the airways form from two epithelial tubes that arise at the terminal evagination of the trachea anlage, and they grow laterally into the two mesenchymal beds formed by the splanchnopleura. Growth of the epithelial tube is followed by branching, a process that is the result of interaction with the associated mesenchyme (1–3), and strictly causes dichotomy (i.e., a splitting into two daughter branches); this morphogenetic process will guide us in the subsequent analysis of airway design.

From early on, the mesenchymal bed of the lung anlage contains a loose vascular network, derived from the vascular bed of the foregut, which tends to enwrap the budding airway tubes. As the tubes branch, the vascular network becomes molded to follow their outline. Very soon thereafter, arteries differentiate from stretches of the network that lie alongside the airways, and these arteries are connected to the pulmonary arteries that have grown toward the lung anlage from the sixth branchial arch. Venous vessels are seen to differentiate in the loose mesenchymal beds that form septa between the bronchial-arterial bundles; from the beginning therefore the pulmonary veins develop in their future interstitial position, whereas the close spatial relation between airways and arteries also originates in early lung development (see Chapter 68).

THE AIRWAYS CAN BE DESCRIBED AS A TREE

The branching of airway tubes that occurs during development determines the design and dimensions of the airways in the mature lung (3). Figure 1 shows the hierarchy of the airway tree that begins at the trachea and leads through bronchi and bronchioles into the acinar airways, respiratory bronchioles, and alveolar ducts (where gas exchange takes place), ending in the alveolar sacs.

The pattern of airway branching is best studied on resin or silicon rubber casts (such as those illustrated in Figs. 2 and 3) for conducting airways and acinar airways, respectively (4–9). Consistently, each branch is seen to divide into two smaller branches (i.e., undergoes dichotomous branching) (4); therefore, the pattern formed during morphogenesis is preserved. However, the two daughter branches from the same parent often differ in diameter and/or in length (Fig. 2): dichotomy is hence irregular but, as a rule, the diameter of the daughter branches is smaller than that of the parent branch. This means that the diameter of the airways becomes progressively smaller as one proceeds from the trachea to the periphery; this also holds for the length of the segments, in principle.

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Ref. 16

High-Resolution CT of the Lung

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CHAPTER 4

Diffusion and convection in intrapulmonary gas mixing

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CHAPTER CONTENTS

BECAUSE LUNGS CONTAIN a large volume of gas at end expiration (functional residual capacity), inspired gas cannot reach the alveolar-capillary membrane by bulk flow alone (i.e., by displacement of the inspired gas/lung gas boundary toward the lung periphery); therefore other mechanisms must intervene to achieve mixing with resident gas. Thus the gas transport between the atmosphere and the alveolar-capillary membrane is provided not only by alveolar ventilation but also by intrapulmonary gas mixing. This mixing step is usually not particularly considered in analysis of pulmonary gas transport, where it is tacitly assumed that mixing in the alveolar region is virtually complete and thus does not limit gas transport. In the last decade, however, the completeness of intrapulmonary gas mixing has been questioned, mainly on the basis of experimental data obtained by refined gas-monitoring techniques.

Evidently intrapulmonary mixing is not complete, as shown by the presence of series or anatomical dead space, which diminishes with breath holding, but is never entirely suppressed. When axial (longitudinal) gas-concentration gradients in airways are designated as *stratification*, dead space undoubtedly is a manifestation of stratification. Stratification or stratified inhomogeneity (127) in the proper sense, however, means presence of gradients within the gas-exchange zone of the lungs (i.e., in the alveolar space).

Dead space and alveolar space have an anatomical background (conducting airways vs. alveolated airways) but are mainly defined functionally as non-gas-exchanging and gas-exchanging or as nonmixing and well-mixing volumes. The dead space and the alveolar space are neither anatomically nor functionally separated by a sharp boundary. This is reflected in the expirogram (plot of concentration vs. expired volume or time) by a somewhat gradual change from phase II (steep concentration change) to phase III (alveolar plateau). This transition region may be regarded as due to dead space (flattened, e.g., by distributed transit times) or to stratification in the proximal region of the alveolar space. Therefore the delimitation of

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CHAPTER 82

Design and Morphometry of the Pulmonary Gas Exchanger

Ewald R. Weibel

Gas exchange in the lung must be very efficient. As the blood is pumped through the lung, it takes up all the O_2 the body needs and releases the CO_2 produced; in heavy exercise, when an average human consumes about 2.5 liters of O_2 every minute, this must be achieved in a fraction of a second. This calls for a high level of bioengineering design of a gas exchanger with a high diffusion conductance. We find that the human lung establishes air–blood contact over a surface approaching that of a tennis court and uses a tissue barrier 50 times thinner than a sheet of air-mail stationery for support. But further problems need to be solved at the same time. This large area must be adequately ventilated and perfused and sufficiently stable in spite of the minimal amount of tissue available as mechanical support, and it must be viable, capable of self-maintenance and repair throughout the entire lifetime of the individual. In fact, no man-made extracorporeal oxygenizer nearly approaches the lung's performance in all these respects.

In this chapter, I review the human pulmonary gas exchanger's basic design features, its cell and tissue structure, and its architecture. I then present a model for pulmonary diffusing capacity by which the effect of design on gas exchange can be estimated, and finally I discuss the validity of its assumptions and simplifications.

DESIGN OF THE PULMONARY MICROVASCULAR UNIT

Alveolar Walls Contain a Dense Network of Capillaries

Alveolar septa are about 5–8 μm thick and are bounded by an alveolar surface on each side (Fig. 1). About half this thin wall is occupied by blood that flows through a very dense meshwork of capillaries. The other half is tissue that must provide mechanical support and form a suitable barrier for controlled fluid exchange.

By forming about 300 million alveoli as outpocketings of the most peripheral airways, the lung establishes a very large internal surface that is directly connected to the airway tree (1,2). Two adjoining alveoli share their wall but each alveolus adjoins several alveoli, some of which are connected to different alveolar ducts. The alveolar walls, therefore, form a three-dimensional continuum, similar to the lamellae in a foam. Each alveolar septum meets, with the exception of the free edges facing the alveolar duct (see Chapter 81), with two other septa along each of its edges (Fig. 2b). This is significant because it explains why the capillary network, though appearing like a flat sheet in each alveolar wall facet, in fact, forms a complex spatial continuum that extends over a space at least as large as an acinus or lobule (3–5). Thus, while each capillary meshwork unit is exposed to two alveoli (one on each side of the septum), the capillary path extends over a large number of alveoli.

It is not easily possible to properly define the microvascular unit (i.e., that part of the capillary network that extends from an arteriole to a venule); such units may not exist at all, at least not anatomically. Rather, we find that arterioles feed into the capillary network at more or less regular distances (Fig. 2) and that venules tap this network in much the same way (4–6). The distances between arterioles and venules are on the order of 0.5–1 mm and, therefore, extend over several alveoli (7). To define a *microvascular gas-exchange unit* as the functional unit of this three-dimensional maze is, therefore, not only rather difficult, it is quite arbitrary. The picture one likes to present—namely, that of one capillary unit associated with one alveolus—is therefore, rather fictitious but it serves the purpose of modeling, as long as we realize that the

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CHAPTER 104

Collateral Ventilation

Wayne Mitzner

ANATOMIC CONSIDERATIONS

Definition

The term *collateral ventilation* refers to ventilation of a region of lung through collateral airways. Within this context, the word *collateral* has several relevant definitions, including "accompanying, but secondary or subordinate" and "corresponding in rank or function." (1). All previous reviews of collateral ventilation have emphasized its secondary nature, ignoring the "corresponding" aspect of the collateral airways. This has led to a widespread intuition that not only are the specific collateral airways that are responsible for collateral ventilation in some way different from the normal airways, but also that they take no part in normal ventilation. In the present chapter, we will emphasize that, based on their anatomic location, the collateral airways are in fact normal airways that are normally ventilated with each breath. The secondary nature of ventilation through these collateral airways arises only when a larger airway becomes obstructed. Then, ventilation to the obstructed region can only occur via flow through a limited number of collateral airways.

For a working definition of collateral ventilation, consider an anatomic region of lung parenchyma served by a given bronchus. Within this region, ventilation normally occurs through that bronchus via the standard airway branching pattern from larger to smaller airways. Collateral ventilation to this given region then refers to any ventilation that arrives from a neighboring airway branching structure. Collateral ventilation can thus be defined at any level of airway branching. In pathologic conditions where airway obstruction might occur at any level of airway branching, collateral ventilation may serve partially to bypass the obstruction. However, in the common practical measurement of collateral ventilation with a bronchoscope or wedged catheter, the collateral communications are those that occur between distinct segmental bronchi.

The first measurements of collateral ventilation were by Van Allen et al. in 1930 (2). In this initial work, a catheter was wedged in a segmental bronchus, and ventilation in and out of this catheter was measured as the surrounding lung was ventilated. They also showed that a whole atelectatic lobe could be inflated by air infusion through the segmental bronchus. Measurement of collateral ventilation in humans was first done in 1948 by Baarsma et al. (3), using a wedged balloon-tipped catheter. Several other physiological studies by VanAllen and associates were carried out in the early 1930s (4–6), but it was not until the late 1960s that physiological interest was renewed by Macklem and associates (7,8). Hogg et al. (7), demonstrated that resistance to collateral flow in excised human emphysematous lungs was greatly decreased, suggesting an important role for collateral flow in lung disease. A comprehensive review of collateral ventilation was published by Macklem in 1971 (9), and the reader is referred to that for additional details regarding much of the older literature.

Pathways for Collateral Flow

There exist three possible pathways for collateral ventilation—channels of Lambert, alveolar pores, and channels of Martin. The potential contributions of these are discussed separately.

Channels of Lambert

In 1955, Lambert (10) described accessory bronchiole alveolar communications in normal human and cat lungs. These channels consisted of epithelialized tubular com-

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Ventilation–Perfusion Relationships

Peter D. Wagner and John B. West

I. INTRODUCTION

It would be natural to suppose that if a lung were supplied with adequate amounts of fresh gas and mixed venous blood, and if complete equilibration occurred between alveolar gas and pulmonary capillary blood in every lung unit, then normal pulmonary gas exchange would be assured. As is well known, however, this is not the case. Unless the proportion of the total ventilation and blood flow going to each gas-exchanging unit is the same, overall gas exchange becomes inefficient and, other things being equal, the arterial P_{O_2} falls and the P_{CO_2} rises.

A full understanding of how mismatching of ventilation and blood flow

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CHAPTER 126

Ventilation–Perfusion Relationships

John B. West and Peter D. Wagner

HISTORICAL BACKGROUND

Most of the hypoxemia and carbon dioxide retention seen in patients with lung disease is caused by mismatching of ventilation and blood flow within the lung. The importance of the ratio of ventilation to blood flow in determining gas exchange in any lung region was first recognized nearly 80 years ago. However, developing a comprehensive and quantitative appreciation of the effects of ventilation–perfusion inequality on pulmonary gas exchange has proved to be very demanding, and it has only been in the last few years that many important aspects have been clarified.

From a historical point of view, we can identify three phases in the advance of knowledge in this difficult area. This first was the recognition that the gas exchange that takes place in any lung unit is determined not only by the ventilation or the blood flow, but by the ratio of one to another. Perhaps Krogh and Lindhard (1) were the first to state this specifically. In 1917 they wrote, "if the different lobes of the lungs are not equally dilated during inspiration the air in them must obtain a different composition and this must be true both with respect to O_2 and CO_2 during normal breathing and with regard to other gases during special mixing respirations." They then added in a footnote, "Unless, indeed, the circulation through each lobe should be in proportion to its ventilation." Shortly after this, Haldane (2) recognized that ventilation–perfusion inequality could cause hypoxemia, but, unfortunately, he also stated that carbon dioxide retention would not occur. This was an important misconception that still surfaces from time to time, even in the thickest textbooks of respiratory medicine.

The second phase began in the late 1940s following the resurge of interest in respiratory physiology that occurred during World War II. Fenn et al. (3) and Riley and Cournand (4) tackled the qualitative relationships between ventilation, blood flow, and gas exchange. Because these depend on the nonlinear oxygen and carbon dioxide dissociation curves, they introduced graphical analysis of these relationships that were not amenable to algebraic manipulation. The third phase began in the mid-1960s, when Kelman (5–7) and Olszowka and Farhi (8) introduced computer procedures to describe the oxygen and carbon dioxide dissociation curves. This stimulated the development of numerical techniques for describing the gas-exchange behavior of distributions of ventilation–perfusion ratios (9). Shortly after this, the multiple inert-gas elimination technique was introduced (10,11), which allowed distributions of ventilation–perfusion ratios to be recovered from normal subjects and patients with various types of lung disease. The extensive use of this technique has greatly clarified both the physiological aspects and the clinical implications of ventilation–perfusion inequality over the last 20 years. Readers who want a more extensive discussion of the topic than can be accommodated in the space available here are referred to more extensive reviews (12,13).

GAS EXCHANGE IN A SINGLE LUNG UNIT

Basic Equation

The P_{O_2}, P_{CO_2}, and P_{N_2} in any gas-exchanging unit of the lung are uniquely determined by three major factors: (a) ventilation–perfusion ratio, (b) composition of inspired gas, and (c) composition of mixed venous blood. Additional minor factors alter the "chemical" status of the blood and therefore the shapes or positions of the O_2 and CO_2 dissociation curves. These include the temperature, hemoglobin, hematocrit, and acid-base status of the blood.

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Numerical Analysis of Gas Exchange

Albert J. Olszowka and Peter D. Wagner

I. NUMERICAL ANALYSIS IN STEADY STATE GAS EXCHANGE

A. Introduction

Of all the organs, the lungs are possibly the most amenable to mathematical modeling and a major part of this is related to gas exchange. There are both structural and functional reasons behind the rational applicability of such modeling. The lung is made (structure) up of a large number of anatomical units, each of which is qualitatively similar. In each unit, ventilation via the airways and perfusion via the blood vessels lead to exchange of gases between blood and gas phases that are separated by a tissue sheet of an average thickness of less than 1 μm. It is possible to calculate with relatively few assumptions how gas exchange occurs in such units (function) and to determine the factors that influence such gas ex-

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Mathematical Analysis of Compartmental Lung Models

John W. Evans

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CHAPTER 8

Measurement of the Distribution of Ventilation–Perfusion Ratios

PETER D. WAGNER

I. INTRODUCTION

The idea that maldistribution of either inspired gas or pulmonary arterial blood within the lungs can interfere with gas exchange is not new. Early in this century, Krogh and Lindhard (1917) discussed the conse-

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Ventilation-Perfusion Inequality & Gas Exchange During Exercise in Lung Disease

Peter D. Wagner

In comparing gas exchange during exercise and rest, it is apparent that a large number of factors, which by themselves each affect the arterial P_{O_2} and P_{CO_2}, may change simultaneously. Usually, oxygen uptake ($\dot{V}_{O_2}$) increases as does cardiac output ($\dot{Q}_T$) and minute ventilation ($\dot{V}_E$), mixed venous P_{O_2} falls while mixed venous P_{CO_2} rises, and the distribution of ventilation and perfusion may be altered. It is also believed that the average contact time of the red cell for gas exchange falls and consequently a gas exchange unit in which partial pressure equilibration between alveolar gas end-capillary blood is marginal even at rest is likely to develop alveolar-end capillary differences during exercise attributable to incomplete diffusion equilibration.

It is clearly a difficult problem to sort out the quantitative interactions occurring in individual patients so as to arrive at a complete explanation for the arterial P_{O_2} and P_{CO_2} during exercise. At the center of this problem lies the difficulty in identifying the nature and amount of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality on the one hand, and the amount of hypoxemia due to failure of diffusion equilibration on the other. This is particularly so when both abnormalities co-exist. Exchange of "diffusion-limited" gases such as carbon monoxide is seriously affected by $\dot{V}_A/\dot{Q}$ inequality; conversely any increase in the alveolar-arterial P_{O_2} difference ($A_aD_{O_2}$) during exercise cannot be assumed to be due to failure of diffusion equilibration on one hand or to worsening $\dot{V}_A/\dot{Q}$ relationships on the other.

A partial solution to these problems is offered by the method of multiple inert gas elimination (4,6). Under steady-state conditions it is possible to derive considerable quantitative information about the functional distribution of ventilation and blood flow and with this information it is possible to predict quantitatively the exchange of O_2 and CO_2 on the explicit assumption that diffusion equilibration is complete. Since the other interacting factors are allowed for in this prediction scheme, application of the inert gas method can test the hypothesis that incomplete diffusion equilibration is a significant factor in the genesis of hypoxemia in a given patient. The physiological basis of this scheme is the known order of magnitude difference in the rates of diffusion equilibration of inert gases on the one hand and oxygen on the other. Inert gases reach alveolar-capillary partial pressure

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A GRAPHICAL ANALYSIS OF THE RESPIRATORY GAS EXCHANGE

The O_2-CO_2 Diagram

BY

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Ref. 95

CHAPTER 12

:fusing-capacity heterogeneity

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PTER CONTENTS

SUREMENTS OF THE PULMONARY diffusing capac- f O_2 and of CO have had a major influence in iological studies and in the practice of clinical cine. However, these measurements often have difficult to interpret because of the many physi- cal components that interact to comprise the final ured value. The classic approach has been to yze separately the membrane diffusing capacity) and the red blood cell components (70) by use homogeneous lung model and to interpret physi- cal and clinical findings within this restricted ework. The results and interpretations are af- d by heterogeneity in alveolar ventilation ($\dot{V}_A$), olar volume (V_A), alveolar perfusion ($\dot{Q}$), and pul- ary diffusing capacity (D_L). The relative impor- e of each of these heterogeneities and of their actions varies according to individual character- s and the particular method chosen to measure In general, measured D_L usually underestimates D_L (actual D_L of the lung); however, there are nples of heterogeneities that can result in an estimate of true D_L. Recently some new ap- ches have been developed to permit reexamination of the familiar concept of diffusing capacity in an attempt to understand better the physiological information contained in these measurements. This chapter first addresses the interrelationships among blood flow, ventilation, gas solubility, and diffusing capacity in a homogeneous lung, then considers data demonstrating the importance of heterogeneities on measured D_L, and finally considers the influence of gas-phase diffusion limitation.

Several terms have been used to express deviation from uniform behavior in the lung, including *heterogeneity*, *inhomogeneity*, *nonhomogeneity*, *nonuniformity*, and *maldistribution*. Because these terms are generally considered synonymous, the term *heterogeneity* is used throughout this chapter. The modifier L (referring to the whole lung) is dropped; D means D_L unless specifically noted.

GAS EQUILIBRATION ACROSS ALVEOLAR-CAPILLARY MEMBRANE

Movement of gas between the alveolar gas phase and pulmonary capillary blood is thought to be a passive process governed by the simple laws of diffusion. Equilibration of gas in pulmonary capillary blood flowing past the alveolus and separated by a diffusion barrier is described by the homogeneous lung model shown in Figure 1. Over any increment of distance along the capillary, the flux of gas into the blood is defined by Fick's law of diffusion

$$d\dot{M} = dDx(P_A - Pb) \quad (1)$$

where $d\dot{M}$ is the uptake of gas by blood in the infinitesimal capillary element dx, dDx is the diffusing capacity of the element of diffusion barrier, and P_A and Pb are the partial pressures of the gas in the alveolus and in capillary blood. The flux of gas across the barrier increment creates an infinitesimal change in blood gas content (C) in the element

$$d\dot{M} = \dot{Q} \cdot dC = \dot{Q}\beta b \cdot dPb \quad (2)$$

where βb is the capacitance coefficient (effective solubility) of the gas in blood. Many investigators have used such basic principles to describe the equilibration

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Pulmonary Pathophysiology —the essentials

2nd edition

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THE LUNG

PHYSIOLOGIC BASIS OF PULMONARY FUNCTION TESTS

THIRD EDITION

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We adopted three articles written in Japanese (published by the first author) as the reference in the current review. The reason is that we have not found the English papers good enough for replacing our Japanese papers.

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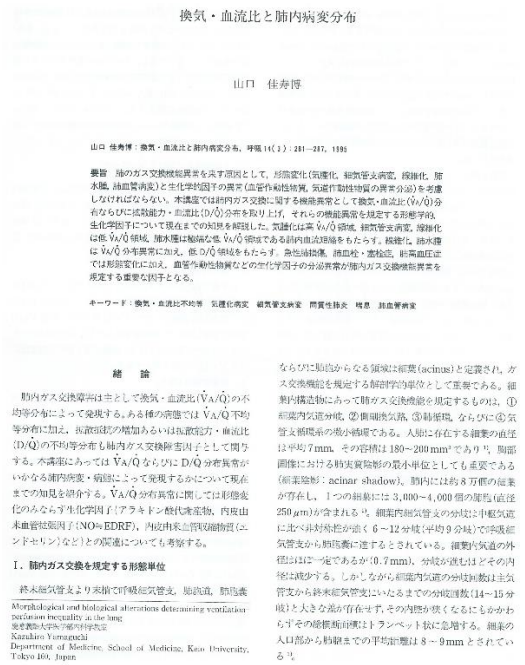

換気・血流比と肺内病変分布

山口　佳寿博

山口 佳寿博：換気・血流比と肺内病変分布．呼吸 14(2)：281—287，1995

要旨　肺のガス交換機能異常を来す原因として，形態変化（気腫化，細気管支病変，線維化，肺水腫，肺血管病変）と生化学的因子の異常（血管作動性物質，気道作動性物質の異常分泌）を考慮しなければならない．本講座では肺内ガス交換に関する機能異常として換気・血流比（$\dot{V}_A/\dot{Q}$）分布ならびに拡散能力・血流比（$D/\dot{Q}$）分布を取り上げ，それらの機能異常を規定する形態学的，生化学的因子について現在までの知見を解説した．気腫化は高 $\dot{V}_A/\dot{Q}$ 領域，細気管支病変，線維化は低 $\dot{V}_A/\dot{Q}$ 領域，肺水腫は極端な低 $\dot{V}_A/\dot{Q}$ 領域である肺内血流短絡をもたらす．線維化，肺水腫は $\dot{V}_A/\dot{Q}$ 分布異常に加え，低 $D/\dot{Q}$ 領域をもたらす．急性肺梗塞，肺血栓・塞栓症，肺高血圧症では形態変化に加え，血管作動性物質などの生化学因子の分泌異常が肺内ガス交換機能異常を修飾する重要な因子となる．

キーワード：換気・血流比不均等　気腫化病変　細気管支病変　間質性肺炎　喘息　肺血管病変

緒　論

肺内ガス交換障害は主として換気・血流比（$\dot{V}_A/\dot{Q}$）の不均等分布によって発現する．ある種の病態では $\dot{V}_A/\dot{Q}$ 不均等分布に加え，拡散障害の増加あるいは拡散容量・血流比（$D/\dot{Q}$）の不均等分布も肺内ガス交換障害因子として関与する．本講座においては $\dot{V}_A/\dot{Q}$ ならびに $D/\dot{Q}$ 分布異常がいかなる肺内病変・病態によって発現するかについて現在までの知見を紹介する．$\dot{V}_A/\dot{Q}$ 分布異常に関しては形態変化のみならず生化学因子（アラキドン酸代謝産物，内皮由来血管拡張因子（NO≒EDRF），内皮由来血管収縮物質（エンドセリン）など）との関連についても考察する．

I．肺内ガス交換を規定する形態単位

終末細気管支より末梢で呼吸細気管支，肺胞道，肺胞嚢ならびに肺胞からなる領域は腺房（acinus）と定義され，ガス交換機能を規定する解剖学的単位として重要である．細胞内構造物にあって肺ガス交換機能を規定するものは，①腺房内気道分岐，②傍細気路，③動脈環，ならびに④気管支循環系の微小循環である．人肺に存在する腺房の直径は平均7mm，その容積は180～200 mm³ であり[1]，胸部画像における肺実質陰影の最小単位としても重要である（腺房陰影：acinar shadow）．肺内には約8万個の腺房が存在し，1つの腺房には3,000～4,000個の肺胞（直径250 μm）が含まれる[1]．腺房内細気管支の分岐と中枢気道に比べ非対称性が強く6～12分岐（平均9分岐）で呼吸細気管支から肺胞嚢に達するとされている．腺房内気道の外径は1/1に一定であるが（0.7mm），分岐が進むほどその内径は減少する．しかしながら腺房内気道の分岐回数は主気管支から終末細気管支にいたるまでの分岐回数（14～15分岐）と大きな差が存在せず，その内径が狭くなるにもかかわらずその総横断面積はトランペット状に急増する．腺房の入口部から肺胞までの平均距離は8～9mm とされている[1]．

Morphological and biological alterations determining ventilation-perfusion inequality in the lung
肺実質陰影型呼吸病変
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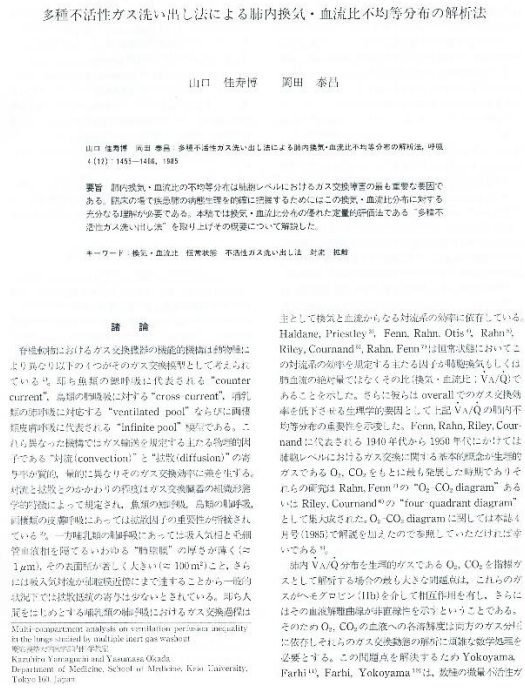

多種不活性ガス洗い出し法による肺内換気・血流比不均等分布の解析法

山口　佳寿博　　岡田　泰昌

山口 佳寿博　岡田 泰昌：多種不活性ガス洗い出し法による肺内換気・血流比不均等分布の解析法．呼吸 4(12)：1451—1456，1985

要旨　肺内換気・血流比の不均等分布は肺胞レベルにおけるガス交換障害の最も重要な要因である．肺疾患の病態生理を的確に把握するためにはこの換気・血流比分布に対する充分な理解が必要である．本稿では換気・血流比分布の優れた定量的評価法である“多種不活性ガス洗い出し法”を取り上げその概要について解説した．

キーワード：換気・血流比　正常状態　不活性ガス洗い出し法　対流　拡散

諸　論

脊椎動物におけるガス交換器官の機能的機構は物理的により異なり以下の4つがその代表型として考えられている[1]．即ち魚類の鰓呼吸に代表される“counter current”，鳥類の肺呼吸に対する“cross current”，哺乳類の肺呼吸に対応する“ventilated pool”ならびに両棲類肺呼吸に代表される“infinite pool”様型である．これら異なった機構ではガス輸送を規定する主たる物理的因子である“対流（convection）”と“拡散（diffusion）”の寄与率が質的，量的に異なりそのガス交換効率に差を生ずる．対流と拡散とのかかわりの形態はガス交換肺胞の組織形態学的方法によって規定され，魚類の鰓呼吸，鳥類の肺呼吸，両棲類の皮膚呼吸にあっては拡散因子の重要性が明確されている[2]．一方哺乳類の肺呼吸にあっては吸入気相と毛細管血液相を隔てるいわゆる“肺胞膜”の厚さが薄く（≒1 μm），その表面積が著しく大きい（≒100 m²）こと，さらには吸入気対流の循環時間にまで達することから一般的状況下では拡散性の寄与は少ないとされている．即ち人肺を主体とする哺乳類の肺呼吸におけるガス交換過程は主として換気と血流からなる対流系の効率に依存している．Haldane, Priestley[3]，Fenn, Rahn, Otis[4]，Rahn[5]，Riley, Cournand[6]，Rahn, Fenn[7]は生理状態においてこの対流系の効率を規定する主たる因子が肺胞換気もしくは肺血流の絶対量ではなくその比（換気・血流比；$\dot{V}_A/\dot{Q}$）であることを示した．さらに彼らは overall でのガス交換効率を低下させる生理学的要因として上記 $\dot{V}_A/\dot{Q}$ の肺内不均等分布の重要性を示唆した．Fenn, Rahn, Riley, Courand に代表される1940年代から1950年代にかけては肺胞レベルにおけるガス交換に関する基本的概念が生理的ガスである O_2，CO_2 をもとに満も発展した時期であり[8]それらの研究は Rahn, Fenn[7]の“O_2-CO_2 diagram”あるいは Riley, Cournand[6]の“four-quadrant diagram”として集大成された．O_2-CO_2 diagram に関しては本誌6月号（1985）で解説を加えたので参照していただければ幸いである[9]．

肺内 $\dot{V}_A/\dot{Q}$ 分布を生理的ガスである O_2，CO_2 を指標ガスとして解析する場合の最も大きな問題点は，これらのガスがヘモグロビン（Hb）を介して相互作用を有し，さらにはその血液解離曲線が非直線性を示すということである．そのため O_2，CO_2 の血液への各溶解度は両方のガス分圧に依存しそれらのガス交換動態の解析に煩雑な数学処理を必要とする．この問題点を解決するため Yokoyama, Farhi[10]，Farbi, Yokoyama[11]は，数種の微量不活性ガ

Multi-compartment analysis on ventilation perfusion inequality in the lungs studied by multiple inert gas washout
多種不活性ガス洗い出し法
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O_2-CO_2 ダイアグラム
—その呼吸生理学的意義—

山口 佳寿博

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要旨　O_2-CO_2 ダイアグラムは肺胞レベルにおけるガス交換機構を理解するうえで最も基本となる概念である。臨床の場で肺内ガス交換障害の程度を的確に把握するためにはこのダイアグラムに対する充分なる理解が必要である。本稿では O_2-CO_2 ダイアグラム上に表現される換気・血流比曲線を取り上げ，その意義ならびにその作成に必要な諸仮定とそれらによりもたらされる生理学的諸問題を中心に言及した。さらに換気・血流比曲線上に定義される理想肺胞気なる指標の概念とその臨床的意義および評価法について解説した。

キーワード：換気・血流比曲線　恒常状態　理想肺胞気　不活性ガス・ガス交換
換気・血流比不均等分布　直列抵抗　死腔　拍動流　往復換気

はじめに

1946年 Fenn, Rahn, Otis[1]は，海面レベルおよび高地における肺胞気組成の変化を含む肺内ガス交換機構の理論的解析を目的として，O_2-CO_2 ダイアグラム（Fenn diagram）の原形を提案した。その後このダイアグラムを基礎として，Rahn[2]および Riley, Cournand[3]は肺胞気組成を決定する主たる機能的要因の一つは肺胞換気量と肺毛細管血流量との比（換気・血流比）であることを示し，それ以後の呼吸生理学を飛躍的に発展させた。以上の集大成として1955年 Rahn, Fenn[4]は，"A graphical analysis of the respiratory gas exchange : The O_2 CO_2 diagram" を発表し，種々の条件下での肺内ガス交換機構に関する解析を O_2-CO_2 ダイアグラム上で示した。彼ら近代呼吸生理学者によって提出された一連の理論体系は，その後約40年にわたって数多くの生理学者により吟味・検討され，呼吸生理学ならびに呼吸器臨床において最も標準的な理論として繁用されてきた。

本稿では O_2-CO_2 ダイアグラム上に表現される換気・血流比曲線を取り上げ，その妥当性ならびに問題点を整理した。呼吸器病態下の場にあって肺内ガス交換障害の的確な定量的把握の手助けとなれば幸いである。

O_2-CO_2 diagram and its physiological significance
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I．恒常状態におけるガス交換

O_2-CO_2 ダイアグラム上に換気・血流比曲線を作成するためにはいくつかの仮定が必要である。これら仮定の持つ生理学的意義については次項以降で検討するものとして，まず本項では図1に示されるような "均一な肺一組織モデル" を基礎として "steady state（恒常状態）" という概念とその状態下で成立する基本的な関係式について考察を加えたい。指標ガスを x とし組織代謝によって単位時間に消費，もしくは生成される割合を $\dot{M}x$ とする。肺血流量を $\dot{Q}$，吸入気肺胞換気量を $\dot{V}_{AI}$，呼気肺胞換気量を $\dot{V}_A$ とし，有効組織容積（effective tissue volume），有効肺容積（effective lung volume），肺胞血容積ならびに動脈血容積をそれぞれ V_t, V'_A, $V_{\bar{v}}$, V_a で表すものとする。さらにガス x の吸入気ならびに肺胞気組成を F_{Ix}, F_{Ax} とし，組織内，動脈血および静脈血含量を C_{tx}, C_{ax}, $C\bar{v}_x$ で表すも